# Poster Session I – Sunday, 23 June - 12.30-14.30

<table>
<thead>
<tr>
<th></th>
<th>Title</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Unravelling the Role of Niaspan in Peripheral Nerve Regeneration</td>
<td>Stefano Previtali</td>
</tr>
<tr>
<td>2</td>
<td>Neuropathy related genes as possible modifiers of PMP22 related neuropathies</td>
<td>Anneke van der Kooi</td>
</tr>
<tr>
<td>3</td>
<td>Genetic and clinical finding in a cohort of 341 Chinese patients with Charcot-Marie-Tooth disease</td>
<td>Ruxu Zhang</td>
</tr>
<tr>
<td>4</td>
<td>The Polygenic Architecture of Carpal Tunnel Syndrome</td>
<td>Akira Wiberg</td>
</tr>
<tr>
<td>5</td>
<td>Rab35 GTPase is an inhibitor of mTORC1 and regulates myelination in the PNS</td>
<td>Federica Grandi</td>
</tr>
<tr>
<td>6</td>
<td>Dominant mutations of a Notch pathway component cause type 2 Charcot-Marie-Tooth disease</td>
<td>Jeremy Sullivan</td>
</tr>
<tr>
<td>7</td>
<td>Mutations In The Small Heat Shock Proteins HSPB1 And HSPB8 Impair The Autophagic Flux</td>
<td>Angela Sisto</td>
</tr>
<tr>
<td>8</td>
<td>Molecular mechanisms of impaired sensory nerve regeneration in diabetes</td>
<td>Sung-Tsang Hsieh</td>
</tr>
<tr>
<td>9</td>
<td>Mutations in SCL25A46 cause a spectrum of clinical phenotypes including axonal CMT with optic atrophy.</td>
<td>Carolynne Doherty</td>
</tr>
<tr>
<td>10</td>
<td>Clinical heterogenity of p.Val30Met mutation in transthyretin-related familial amyloid polyneuropathy in Turkey</td>
<td>Hacer Durmus</td>
</tr>
<tr>
<td>11</td>
<td>Impact of Inotersen on Functioning for Patients with hATTR Amyloidosis: Results from a Placebo-Controlled Trial</td>
<td>Spencer Guthrie</td>
</tr>
<tr>
<td>12</td>
<td>CMT1 with nerve conduction blocks caused by a homozygous mutation in the LITAF gene</td>
<td>Marion Masingue</td>
</tr>
<tr>
<td>13</td>
<td>Morphometric Analysis of Peripheral Myelinated Nerve Fibers through Deep Learning</td>
<td>Jun Li</td>
</tr>
<tr>
<td>14</td>
<td>A cellular model of iPS-derived motor neurons to investigate a GDAP1-associated form of Charcot-Marie-Tooth disease</td>
<td>Federica Miressi</td>
</tr>
<tr>
<td>15</td>
<td>A diagnostic challenge: 10-year-old boy with leucoencephalopathy, bulbar dysfunction, optic atrophy, nystagmus and motor neuronopathy.</td>
<td>Shaimaa Elaidy</td>
</tr>
<tr>
<td>16</td>
<td>Lipodystrophy in CMT1A points out a new inborn error of lipid metabolism</td>
<td>Davide Visigalli</td>
</tr>
<tr>
<td>17</td>
<td>The Role of TTR in Health and Disease</td>
<td>Laura Obici</td>
</tr>
<tr>
<td>18</td>
<td>Reliability of the CMTPedS Training and Quality Assurance Program</td>
<td>Timothy Estilow</td>
</tr>
<tr>
<td>19</td>
<td>A novel family with axonal Charcot-Marie-Tooth disease caused by a mutation in the EGR2 gene.</td>
<td>Stefano Tozza</td>
</tr>
<tr>
<td>20</td>
<td>The role of defective endoplasmic reticulum-mitochondria relationship in CMT2A pathology</td>
<td>Nathalie Bernard-Marissal</td>
</tr>
<tr>
<td>21</td>
<td>Phenotypic and neurophysiological variability in two related female patients with CMTX1</td>
<td>Catarina Falcão de Campos</td>
</tr>
<tr>
<td>22</td>
<td>Longitudinal Assessment of Iowa FAP Cohort Treated with siRNA</td>
<td>Shawna Feely</td>
</tr>
<tr>
<td>23</td>
<td>Digitally assessed real-world diversity in people with Charcot-Marie-Tooth disease in the UK and US</td>
<td>Mark Larkin</td>
</tr>
<tr>
<td>24</td>
<td>A Comprehensive Update of the Inherited Neuropathies Consortium of the Rare Diseases Clinical Research Network</td>
<td>Chelsea Bacon</td>
</tr>
<tr>
<td>25</td>
<td>SOLVING FAMILIES ON THE GENESIS PLATFORM: A DIAGNOSTIC FLOWCHART BASED ON CLINVAR STATUS</td>
<td>Vivian Cintra</td>
</tr>
<tr>
<td>26</td>
<td>Temporal dispersion in CMTX1 nerve conduction studies</td>
<td>Rodrigo Diniz da Gama</td>
</tr>
<tr>
<td>27</td>
<td>Hereditary Transthyretin-Mediated (hATTR) Amyloidosis: French Perspective on the Patient Journey</td>
<td>David Adams</td>
</tr>
<tr>
<td>Page</td>
<td>Title</td>
<td>Author</td>
</tr>
<tr>
<td>------</td>
<td>----------------------------------------------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>28</td>
<td>Autosomal Dominant, Late Onset Scapulotibial Motor Neuropathy/Neuronopathy: Expanding the Spectrum of DCTN1-Related Disorders.</td>
<td>Matthew Burford</td>
</tr>
<tr>
<td>29</td>
<td>Early PXT3003 therapy delays disease onset in a rat model of Charcot-Marie-Tooth disease 1A (CMT1A)</td>
<td>Thomas Prukop</td>
</tr>
<tr>
<td>30</td>
<td>Nerve excitability properties of upper limb sensory and motor axons: a comparative study</td>
<td>Antonia Carroll</td>
</tr>
<tr>
<td>31</td>
<td>A molecularly characterised CMT cohort in the West of Scotland</td>
<td>Kathryn Brennan</td>
</tr>
<tr>
<td>32</td>
<td>TTR mutations in patients diagnosed as having CIDP</td>
<td>Wilson Marques Jr.</td>
</tr>
<tr>
<td>33</td>
<td>Hereditary transthyretin amyloidosis (hATTR): description of the first cohort of V122I patients from South Italy</td>
<td>Anna Mazzeo</td>
</tr>
<tr>
<td>34</td>
<td>Variation in Ankle Dynamics During Gait in Youth with Charcot-Marie-Tooth Type 1A</td>
<td>Sylvia Ounpuu</td>
</tr>
<tr>
<td>35</td>
<td>Emilin1 Defect In Distal Lower Limb Laxity And Motor Neuropathy</td>
<td>Chiara FIORILLO</td>
</tr>
<tr>
<td>36</td>
<td>Peripheral Nerves Impairment in Idiopathic Parkinson’s Disease</td>
<td>Ani Antia</td>
</tr>
<tr>
<td>37</td>
<td>Two 173 point mutations in HMBS gene causing acute intermittent porphyria</td>
<td>Jie Lin</td>
</tr>
<tr>
<td>38</td>
<td>Transthyretin Familial Amyloid Polyneuropathy: Impact of mutation type on symptoms</td>
<td>Christopher Gibbons</td>
</tr>
<tr>
<td>39</td>
<td>Predictive modeling reveals threonyl-tRNA synthetase (TARS) as a candidate gene for axonal peripheral neuropathy</td>
<td>Anthony Antonellis</td>
</tr>
<tr>
<td>40</td>
<td>NEXT-GENERATION SEQUENCING (NGS) BY A GENE-PANEL APPROACH IN INHERITED PERIPHERAL NEUROPATHIES.</td>
<td>Moreno Ferrarini</td>
</tr>
<tr>
<td>41</td>
<td>Studying the role of HINT1 as a transcriptional regulator and its involvement in peripheral neuropathies</td>
<td>Silvia Amor-Barris</td>
</tr>
<tr>
<td>42</td>
<td>Molecular diagnosis approach of Hereditary Peripheral Neuropathies in a French reference center.</td>
<td>Guillemette Beaudonnet</td>
</tr>
<tr>
<td>43</td>
<td>Extending the Scope of Diagnostic Gene Panels in CMT Improves Diagnostic Yield</td>
<td>Menelaos Pipis</td>
</tr>
<tr>
<td>44</td>
<td>AHNAK2 mutations in a Malaysian family with autosomal recessive demyelinating CMT</td>
<td>Azlina Ahmad-Annuar</td>
</tr>
<tr>
<td>45</td>
<td>Real-world Effectiveness of Tafamidis in Patients with Transthyretin Amyloidosis with Polyneuropathy in THAOS</td>
<td>Laura Obici</td>
</tr>
<tr>
<td>46</td>
<td>Modern Gene and Allele Discovery, Evaluation in CMT: The Genesis Platform and the Variant Browser</td>
<td>Lisa Abreu</td>
</tr>
<tr>
<td>47</td>
<td>NARS As A Candidate Gene In A Dominant CMT2 Family</td>
<td>Willem De Ridder</td>
</tr>
<tr>
<td>48</td>
<td>Comparative transcriptomics of aminoacyl-tRNA synthetases mutations in an induced neural progenitor cell model</td>
<td>Matthew Jennings</td>
</tr>
<tr>
<td>49</td>
<td>A Novel SPTLC1 Mutation In Potentially Treatable Hereditary Sensory And Autonomic Neuropathy Type I.</td>
<td>Federica Boso</td>
</tr>
<tr>
<td>50</td>
<td>CMT1A AND IMPAIRED PATIENT MOBILITY: EXPRESSIONS, REMEDIES AND IMPACT ON QUALITY OF LIFE</td>
<td>Allison Moore</td>
</tr>
<tr>
<td>51</td>
<td>c.2125_2133del is a new mutation in MFN2 gene resulting in a Heterogeneous Phenotypic Spectrum</td>
<td>Fernanda Figueiredo</td>
</tr>
<tr>
<td>52</td>
<td>F WAVE PERSISTENCE IN THE DIFFERENTIAL DIAGNOSIS OF SENSORY POLYNEUROPATHIES AND NEUROPATHIES</td>
<td>Fabricio Diniz de Lima</td>
</tr>
<tr>
<td>53</td>
<td>Targeting a core axonal degeneration program to treat vincristine and bortezomib-induced axonal degeneration</td>
<td>Stefanie Geisler</td>
</tr>
<tr>
<td>54</td>
<td>Impact of Multidisciplinary Intensive Neurorehabilitation on Peripheral Neuropathies: a Retrospective Study</td>
<td>Elda Judica</td>
</tr>
<tr>
<td>55</td>
<td>Prevalence of Central and Peripheral Nervous System Disorders in Hemophiliacs</td>
<td>Francisco Gondim</td>
</tr>
<tr>
<td>56</td>
<td>Associations of falls in cancer patients with chemotherapy-induced peripheral neurotoxicity (CIPN).</td>
<td>Andreas Argyriou</td>
</tr>
<tr>
<td>61</td>
<td>Transplantation of Human iPSC-derived Motor Neurons for Denervation Induced Muscle Atrophy</td>
<td>Robert Baloh</td>
</tr>
<tr>
<td>62</td>
<td>Repeater F-waves In Carpal Tunnel Syndrome</td>
<td>Akiko Hachisuka</td>
</tr>
<tr>
<td>63</td>
<td>Schwann Cell- and Neuronal- Specific Translatome in Diet-Induced Allodynia Mouse Model</td>
<td>Virginie Aubert</td>
</tr>
<tr>
<td>64</td>
<td>NONcNZO and Tallyho Mice: Novel Mouse Models of Type 2 Diabetes that Develop Peripheral Neuropathy</td>
<td>John Hayes</td>
</tr>
<tr>
<td>65</td>
<td>Folate Deficiency is Associated with Distal Symmetric Polyneuropathy in Zambia: Results from a Case-Control Study</td>
<td>Michelle Kvalsund</td>
</tr>
<tr>
<td>66</td>
<td>MRI and Triple Stimulation Technique to detect brachial plexus abnormalities in Multifocal Motor Neuropathy</td>
<td>Emilien Delmont</td>
</tr>
<tr>
<td>67</td>
<td>Role of Supportive Diagnostic Criteria in Chronic Inflammatory Demyelinating Polyradiculoneuropathy: Data from the Italian Database</td>
<td>Eduardo Nobile-Orazio</td>
</tr>
<tr>
<td>68</td>
<td>Guillain-Barré Syndrome following Arboviral Infection in Northeast Brazil: a Case Series</td>
<td>Sonja Leonhard</td>
</tr>
<tr>
<td>69</td>
<td>Biallelic Neurofascin variants affect paranodal axoglial junctions causing neurodevelopmental impairment and central and peripheral demyelination</td>
<td>Stephanie Efthymiou</td>
</tr>
<tr>
<td>70</td>
<td>Peripheral Nervous System (PNS) Toxicity Induced by Immune-checkpoint Inhibitors in Cancer Patients: Single Centre Experience.</td>
<td>Silvia Bocci</td>
</tr>
<tr>
<td>71</td>
<td>Rare and Challenging case of Guillain- Barre syndrome associated with stroke secondary to spotted fever</td>
<td>Anomali Vidanagamage</td>
</tr>
<tr>
<td>72</td>
<td>Ten Year Plateau in HIV-Induced Motor Neurone Disease: a First Case from Sub-Saharan Africa.</td>
<td>Marieke Dekker</td>
</tr>
<tr>
<td>73</td>
<td>Updated CSF Total Protein Reference Values Improve CIDP Diagnosis</td>
<td>Ari Breiner</td>
</tr>
<tr>
<td>74</td>
<td>The effect of phosphodiesterase-2 inhibitor on CX3C chemokine axis in experimental autoimmune neuritis</td>
<td>Toshiki Fujioka</td>
</tr>
<tr>
<td>75</td>
<td>Toscana virus associated with Guillain-Barré Syndrome: A case-control study</td>
<td>Sevim Erdem-Ozdamar</td>
</tr>
<tr>
<td>76</td>
<td>The Utility of Guillain-Barré Syndrome Prognostic Models in Malaysian Patients</td>
<td>Cheng-Yin Tan</td>
</tr>
<tr>
<td>77</td>
<td>A multicenter prospective study aimed to validate sphingomyelin as a biomarker for acquired dysimmune neuropathies</td>
<td>Giovanna Capodivento</td>
</tr>
<tr>
<td>78</td>
<td>Enhanced Proinflammatory T cell pathology in Chronic Inflammatory Demyelinating Polyneuropathy</td>
<td>Karissa Gable</td>
</tr>
<tr>
<td>79</td>
<td>Fc-gamma ReceptorIIa Polymorphism is Associated with Severity in Guillain-Barré Syndrome</td>
<td>Shoma Hayat</td>
</tr>
<tr>
<td>80</td>
<td>Clinical Response and Progression over time for Multifocal Motor Neuropathy (MMN) Treated with Intravenous Immunoglobulin (IVIG)</td>
<td>Peck Kee Chia</td>
</tr>
<tr>
<td>81</td>
<td>Natural History of Lumbosacral Radiculoplexus Neuropathy</td>
<td>P James Dyck</td>
</tr>
<tr>
<td>82</td>
<td>Risk factors for Lumbosacral Radiculoplexus Neuropathy</td>
<td>P James Dyck</td>
</tr>
<tr>
<td>83</td>
<td>Peripheral Nerve Involvement in Malignancies: an Overview on Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) and Cancer.</td>
<td>Marta Campagnolo</td>
</tr>
<tr>
<td>84</td>
<td>Targeting Axonal or Glial Membranes with Anti-GM1 Antibody to Model Axonal and Demyelinating Peripheral Neuropathies</td>
<td>Clare Campbell</td>
</tr>
<tr>
<td>85</td>
<td>Immuno-mediated polyneuropathies: A 15-year experience of a tertiary neuromuscular center</td>
<td>Luca Gentile</td>
</tr>
<tr>
<td>86</td>
<td>Working up peripheral neuropathy in under-resourced regions- a case in point</td>
<td>Habibul rahman Habib</td>
</tr>
<tr>
<td>87</td>
<td>Therapeutic response and long-term outcomes in Lewis-Sumner patients: revisiting the syndrome three decades later</td>
<td>Guillaume Fargeot</td>
</tr>
<tr>
<td>88</td>
<td>Clinical and Electrophysiological profile of patients with CIDP</td>
<td>Pravallika Dutta</td>
</tr>
<tr>
<td>89</td>
<td>Microscopic Polyangiitis Presenting with Extensive PNS and CNS Manifestations</td>
<td>Seok-Jin Choi</td>
</tr>
<tr>
<td>Page</td>
<td>Title</td>
<td>Author(s)</td>
</tr>
<tr>
<td>------</td>
<td>----------------------------------------------------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>90</td>
<td>Clinical and treatment patterns of CIDP across India- Questionnaire Based study</td>
<td>Meena AK</td>
</tr>
<tr>
<td>91</td>
<td>Depression, Quality-of-Life and Health Status During Long-Term IVIG (Gamunex® 10%) Therapy in CIDP Patients</td>
<td>Juliane Klehmet</td>
</tr>
<tr>
<td>92</td>
<td>Serum BAFF Levels In Chronic Inflammatory Demyelinating Polyneuropathy</td>
<td>Luuk Wieske</td>
</tr>
<tr>
<td>93</td>
<td>Restless legs syndrome affects multiple life domains in patients with chronic inflammatory demyelinating polyradiculoneuropathy</td>
<td>Ivana Basta</td>
</tr>
<tr>
<td>94</td>
<td>Bortezomib/Dexamethasone therapy in 20 patients with POEMS syndrome</td>
<td>Hiroshi Amino</td>
</tr>
<tr>
<td>95</td>
<td>Subcutaneous Immunoglobulin maintenance therapy in inflammatory neuropathy: longterm efficacy and tolerability</td>
<td>Aisling Carr</td>
</tr>
<tr>
<td>96</td>
<td>A Case of a Rapidly Progressive Motor Neuropathy-Neuronopathy ? Paraneoplastic</td>
<td>Zaheer Bagha</td>
</tr>
<tr>
<td>97</td>
<td>IMMUNORM: an observational study on safety and tolerability of subcutaneous immunoglobulin treatment in auto-immune diseases.</td>
<td>Patrick Chérin</td>
</tr>
<tr>
<td>98</td>
<td>Anti-ganglioside antibodies classification and correlation with the clinical manifestations in the inflammatory peripheral neuropathy patients</td>
<td>So Hyun Ahn</td>
</tr>
<tr>
<td>99</td>
<td>Nationwide Long-term Outcome in Treated Chronic Inflammatory Demyelinating Polyneuropathy</td>
<td>Ali Al-Zuhairy</td>
</tr>
<tr>
<td>100</td>
<td>OPTIC Trial: Intravenous Immunoglobulin And Intravenous Methylprednisolone As Induction Treatment In CIDP – study update</td>
<td>Sander Bus</td>
</tr>
<tr>
<td>101</td>
<td>Guillain-Barré Syndrome associated with influenza A H1N1 virus: a parainfectious disorder?</td>
<td>Stefano Giuseppe Grisanti</td>
</tr>
<tr>
<td>102</td>
<td>Efficacy and Safety of different Dosages of IVIG (panzyga®) in Patients with CIDP- ProCID Study-Update</td>
<td>David Comblath</td>
</tr>
<tr>
<td>103</td>
<td>Assessing the Best MCID Threshold for Grip Strength in Chronic Inflammatory Neuropathies</td>
<td>Robert Hadden</td>
</tr>
<tr>
<td>104</td>
<td>MYD88 and CXCR4 Mutational Profile in IgM Paraproteinemic Neuropathy with Anti- MAG Antibody.</td>
<td>Marta Ruiz</td>
</tr>
<tr>
<td>105</td>
<td>The impact of prioritization measures on the use of IVIG in the French neuromuscular network.</td>
<td>Shahram ATTARIAN</td>
</tr>
<tr>
<td>106</td>
<td>Granulomatous Neuropathy of Unknown Cause Presenting as Distal Multiplex Neuropathy</td>
<td>Anna Grisold</td>
</tr>
<tr>
<td>107</td>
<td>Frequent central nervous system, pachymeningeal and plexus MRI changes in POEMS syndrome</td>
<td>Stephen Keddie</td>
</tr>
<tr>
<td>108</td>
<td>A novel ‘at home’ protocol for the hand rehabilitation of patients with Guillain-Barré Syndrome</td>
<td>Prada valeria</td>
</tr>
<tr>
<td>109</td>
<td>Antibodies Against Peripheral Nerve Antigens in Chronic Inflammatory Demyelinating Polyradiculoneuropathy in a Turkish Cohort</td>
<td>Ayse Nur Ozdag Acarli</td>
</tr>
<tr>
<td>110</td>
<td>Autoimmune hepatitis-related sensory neuronopathy: Frequency and clinical profile</td>
<td>Alberto Martinez</td>
</tr>
<tr>
<td>111</td>
<td>Small fiber involvement in anti-MAG demyelinating neuropathy – data from a small cohort</td>
<td>Nicolae Grecu</td>
</tr>
<tr>
<td>112</td>
<td>Carfilzomib ameliorates chronic neuritis in ICAM-deficient NOD mice</td>
<td>Anne Mausberg</td>
</tr>
<tr>
<td>113</td>
<td>Clinical and epidemiological profile of a Brazilian’s cohort of patients with Chronic Inflammatory Demyelinating Polyradiculoneuropathy</td>
<td>Osvaldo Nascimento</td>
</tr>
<tr>
<td>114</td>
<td>TOPIRAMATE PREVENTS OXALIPLATIN NEUROTOXICITY IN A RAT MODEL</td>
<td>PAOLA ALBERTI</td>
</tr>
<tr>
<td>115</td>
<td>PRDM12 is required for initiation of the nociceptive neuron lineage during neurogenesis</td>
<td>Luca Bartesaghi</td>
</tr>
<tr>
<td>116</td>
<td>Cheiralgia Paresthetica In A Sri Lankan Coconut Plucker.</td>
<td>Sathyajith Ambawatte</td>
</tr>
<tr>
<td>117</td>
<td>A novel tissue-selective β2-adrenoceptor agonist with minimized cardiovascular effects, 5-HOB, attenuates neuropathic pain in mice</td>
<td>Shinji Hatakeyama</td>
</tr>
<tr>
<td>118</td>
<td>Intravenous Immunoglobulin Therapy For Small Fiber Neuropathy</td>
<td>Margot Geerts</td>
</tr>
<tr>
<td>Page</td>
<td>Title</td>
<td>Author</td>
</tr>
<tr>
<td>------</td>
<td>-------------------------------------------------------------------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>119</td>
<td>Interpretation of quantitative sudomotor axon reflex test results comparing the Korean and Western normative data</td>
<td>EUN BIN CHO</td>
</tr>
<tr>
<td>120</td>
<td>Psychological Approach To Control The Pain In Small Fiber Neuropathy</td>
<td>Aysun Damci</td>
</tr>
<tr>
<td>121</td>
<td>Skin Biopsy Evaluations in Adolescents with Juvenile Fibromyalgia and Healthy Controls</td>
<td>Anne Oaklander</td>
</tr>
<tr>
<td>122</td>
<td>The value of the Sudoscan™ in detecting autonomic dysfunction in small fiber neuropathy.</td>
<td>Amir Far</td>
</tr>
<tr>
<td>123</td>
<td>Ratio of Distal to Proximal Epidermal Nerve Fiber Density as Predictor of Small Fiber Neuropathy</td>
<td>Mamatha Pasnoor</td>
</tr>
<tr>
<td>124</td>
<td>Ulnar neuropathy at the elbow: reappraisal of the latency difference between ulnar and median nerves</td>
<td>thierry Kuntzer</td>
</tr>
<tr>
<td>125</td>
<td>Antibodies against PlexinD1 and peripheral nerve structures in patients with small-fiber neuropathy</td>
<td>Elba Pascual-Goñi</td>
</tr>
<tr>
<td>126</td>
<td>Transcriptomic analysis of dorsal root ganglia in a mouse model of vincristine-induced peripheral neuropathy</td>
<td>Aurore Danigo</td>
</tr>
<tr>
<td>127</td>
<td>Different mouse models of neuropathy induced by oxaliplatin: acute and chronic neurotoxicity</td>
<td>Hichem Bouchenaki</td>
</tr>
<tr>
<td>128</td>
<td>Circadian Variability Of Pain Features In Possible Small Fiber Neuropathy Patients</td>
<td>Daniele Cazzato</td>
</tr>
<tr>
<td>129</td>
<td>Nerve involvement associated to GNE gene mutations: expanding the clinical spectrum</td>
<td>Nicolae Grecu</td>
</tr>
<tr>
<td>130</td>
<td>DRG Mitochondrial Homeostasis and its Alteration by CXCR4 Signaling in Painful Diabetic Neuropathy (PDN)</td>
<td>Sandra Hackelberg</td>
</tr>
<tr>
<td>131</td>
<td>The Validation of Neuroactive Drug Selection Based On Combinatorial Screening In Bortezomib-Induced Neurotoxicity Models</td>
<td>Cristina Meregalli</td>
</tr>
<tr>
<td>132</td>
<td>Test-retest reliability of the human immunodeficiency virus/acquired immunodeficiency syndrome-associated neuropathic pain questionnaire</td>
<td>Alagoma Iyagba</td>
</tr>
<tr>
<td>133</td>
<td>A Candidate Gene for Autosomal Recessive Cerebellar Ataxia with Axonal Neuropathy</td>
<td>Ayse Candayan</td>
</tr>
<tr>
<td>134</td>
<td>Combination of a new EGR2 missense variant with LITAF T49M polymorphism in Charcot-Marie-Tooth type 1</td>
<td>Maria Empar Blanco-Cantó</td>
</tr>
<tr>
<td>135</td>
<td>Slowly progressive familial ALS caused by an hnRNPA1 missense mutation</td>
<td>Nicolas Dubuisson</td>
</tr>
<tr>
<td>136</td>
<td>Case report of diagnosis of Congenital Disorder of Glycosylation in 65-year-old followed for Myasthenia Gravis</td>
<td>Tiffany Grider</td>
</tr>
<tr>
<td>137</td>
<td>WITHDRAWN</td>
<td></td>
</tr>
<tr>
<td>138</td>
<td>Small-fibre sensory and sudomotor neuropathy as early and stage-dependent biomarkers of transthyretin-amyloid neuropathy</td>
<td>Chi-Chao Chao</td>
</tr>
<tr>
<td>139</td>
<td>A Natural History and Outcome Measure Discovery Study of Charcot-Marie-Tooth 4J</td>
<td>Diana Castro</td>
</tr>
<tr>
<td>140</td>
<td>Genetic Cohort Study in Korean Inherited Peripheral Neuropathy Patients</td>
<td>Yu Jin Choi</td>
</tr>
<tr>
<td>141</td>
<td>Dietary phospholipids as a therapeutic strategy in Charcot-Marie-Tooth Disease 1A</td>
<td>Robert Fledrich</td>
</tr>
<tr>
<td>142</td>
<td>Genetic Heterogeneity of Autosomal Recessive Charcot-Marie-Tooth Disease in a Turkish Cohort</td>
<td>Esra Battaloglu</td>
</tr>
<tr>
<td>143</td>
<td>Myopathies and neuropathies associated with Pro209 mutations in BAG3 have comparable molecular deficits</td>
<td>Elias Adrienssens</td>
</tr>
<tr>
<td>144</td>
<td>Follow up of hereditary transthyretin neuropathy at early stages : new clinical and electrophysiological scores</td>
<td>Chrystel Chéraud Bonfort</td>
</tr>
<tr>
<td>145</td>
<td>Resolving the Pathogenic Mechanism of the GJB1 5’ UTR c.-103C&gt;T Mutation</td>
<td>Bianca Grosz</td>
</tr>
<tr>
<td>146</td>
<td>Experience with Patisiran in the treatment of hereditary Transthyretin amyloidosis neuropathy</td>
<td>Lucia Galan</td>
</tr>
<tr>
<td>147</td>
<td>Transthyretin-induced cytoskeleton remodeling: a double-edged sword</td>
<td>Jessica Eira</td>
</tr>
<tr>
<td>Page</td>
<td>Title</td>
<td>Author</td>
</tr>
<tr>
<td>------</td>
<td>----------------------------------------------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>148</td>
<td>Sleep Disorders in Charcot-Marie-Tooth Disease</td>
<td>Silvia Fenu</td>
</tr>
<tr>
<td>149</td>
<td>Charcot-Marie-Tooth Neuropathy Type 1B with Clinical Response to Immunomodulatory Therapy related to Inflammatory Overlap</td>
<td>Davide Cardellini</td>
</tr>
<tr>
<td>150</td>
<td>Prevalence And Characterization Of Pain In CMT1A Patients.</td>
<td>Helen Azevedo</td>
</tr>
<tr>
<td>151</td>
<td>Phosphor proteomic studies in DI-CMTC</td>
<td>Maria-Luise Erfurth</td>
</tr>
<tr>
<td>152</td>
<td>Progress of the Paediatric Charcot-Marie-Tooth Disease Clinical Practice Guidelines</td>
<td>Paula Bray</td>
</tr>
<tr>
<td>153</td>
<td>Synovial Sarcoma of the Median Nerve in a Pediatric Patient: A Case Report</td>
<td>Robert Allman</td>
</tr>
<tr>
<td>154</td>
<td>Eventual death of diabetic neuropathy</td>
<td>Masayuki Baba</td>
</tr>
<tr>
<td>155</td>
<td>A Prospective Study of Neuropathic Symptoms Preceding Clinically Diagnosed Diabetic Polyneuropathy: ADDITION-Denmark</td>
<td>Signe Andersen</td>
</tr>
<tr>
<td>156</td>
<td>Exploratory Study about the Molecular Mechanisms Underlying the Development of Cisplatin-Induced Peripheral Neuropathy</td>
<td>Aina Calls</td>
</tr>
<tr>
<td>157</td>
<td>Chemotherapy-induced peripheral neuropathy involves specific cellular targets. The case of Cisplatin, Taxol and Vincristine.</td>
<td>Noelle Callizot</td>
</tr>
<tr>
<td>158</td>
<td>Should we prevent thrombosis related to Intravenous Immunoglobulin infusions with systematic anticoagulant prophylaxis?</td>
<td>Robin Arcani</td>
</tr>
<tr>
<td>159</td>
<td>Contactin-1 connects CIDP and nephrotic syndrome</td>
<td>Janev Fehmi</td>
</tr>
<tr>
<td>160</td>
<td>Effects of Intravenous Immunoglobulin (IVIG) on Cardiovascular Function, Cytokines and Complement Activation in Cynomolgus Monkeys</td>
<td>Ann Fancher</td>
</tr>
<tr>
<td>161</td>
<td>Neuromuscular complications following target therapy in cancer patients: beyond Immune Checkpoint Inhibitors.</td>
<td>Chiara Demichelis</td>
</tr>
<tr>
<td>162</td>
<td>Multicenter Study Investigating the Association of GBS with Flavivirus and other Arbovirus in Asia-organizational challenges.</td>
<td>Sherwin Joy Agustin</td>
</tr>
<tr>
<td>163</td>
<td>Does F chronodispersion reflect the conduction variability of the motor neurons?</td>
<td>Elisabeth Chroni</td>
</tr>
<tr>
<td>164</td>
<td>Safety and Tolerability of panzyga® (human normal immunoglobulin - IVIG) in Patients with CIDP</td>
<td>Steven Baker</td>
</tr>
<tr>
<td>165</td>
<td>High-resolution mapping identifies HLA associations with multifocal motor neuropathy</td>
<td>Jeroen Bos</td>
</tr>
<tr>
<td>166</td>
<td>Guillain-Barré Syndrome: A Review of Epidemiology, Clinical Findings, and Outcomes at an Academic Children's Hospital</td>
<td>Kaitlin Batley</td>
</tr>
<tr>
<td>167</td>
<td>Riximab for treatment of treatment resistant chronic inflammatory demyelinating polyradiculoneuropathy: a retrospective chart review</td>
<td>Mazen Dimachkie</td>
</tr>
<tr>
<td>168</td>
<td>Nerve Conduction Studies in Patients Included in the International Guillain-Barré Syndrome Outcome Study (IGOS).</td>
<td>Samuel Arends</td>
</tr>
<tr>
<td>169</td>
<td>Serbian validation of the I-RODS questionnaire in patients with chronic inflammatory demyelinating polyneuropathy</td>
<td>Ivo Bozovic</td>
</tr>
<tr>
<td>170</td>
<td>Role of Comorbidities on Clinical Presentation, Treatment Choice, Response to Treatment and Disability in CIDP.</td>
<td>Pietro Dondendu</td>
</tr>
<tr>
<td>171</td>
<td>Economic Evaluation Of Subcutaneous Vs Intravenous Immunoglobulin Therapy In Chronic Inflammatory Demyelinating Polyneuropathy:Real Life Study</td>
<td>Bernardo Maria De Martino</td>
</tr>
<tr>
<td>172</td>
<td>GD1a/GT1a Ganglioside Complex Antibody in Guillain-Barré Syndrome: Case Report and Studies on the Epitope Formation.</td>
<td>Atsuro Chiba</td>
</tr>
<tr>
<td>173</td>
<td>Safety and Tolerability of High Infusion Rates of Intravenous Immunoglobulin in Patients with CIDP</td>
<td>Carolina Barnett</td>
</tr>
<tr>
<td>174</td>
<td>Propensity modelling as a means to advance treatment in GBS</td>
<td>Amy Davidson</td>
</tr>
<tr>
<td>175</td>
<td>INCbase, A Prospective International CIDP Registry, Infrastructure And Timeline</td>
<td>Filip Eftimov</td>
</tr>
<tr>
<td>176</td>
<td>Multicentre Study Investigating Association of Guillain-Barre Syndrome with Flaviviruses and other Arboviruses in Sri Lanka</td>
<td>Asitha Goonetilleke</td>
</tr>
<tr>
<td>Page</td>
<td>Title</td>
<td>Author</td>
</tr>
<tr>
<td>------</td>
<td>-------------------------------------------------------------------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>177</td>
<td>Ibrutinib in Neuropathy with Anti-Myelin-Associated Glycoprotein (MAG) Antibody.</td>
<td>Francesca Castellani</td>
</tr>
<tr>
<td>178</td>
<td>Four-Month Response Rate In Patients With CIDP Treated With Intravenous Immunoglobulins 5%. The Neurotrack Cohort</td>
<td>Jerome FRANQUES</td>
</tr>
<tr>
<td>179</td>
<td>Update of International CIDP Outcome Study (ICOS): A Prospective Study on Predictors of Disease Course</td>
<td>Carina Bunschoten</td>
</tr>
<tr>
<td>180</td>
<td>Phase 3 Study of HyQvia for Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP): ADVANCE CIDP-1 Infusion Protocol</td>
<td>Shabbir Hasan</td>
</tr>
<tr>
<td>181</td>
<td>Dermal neovascularization as early biomarker in POEMS syndrome: a preliminary case-control study</td>
<td>Camille Guibert</td>
</tr>
<tr>
<td>182</td>
<td>A Scale for Evaluation of Muscle Cramps: Development of the Toronto Cramp Impact Index (TCII)</td>
<td>Hans Katzberg</td>
</tr>
<tr>
<td>183</td>
<td>Genetic and Histological Investigation of CAMKK2 in HIV-Associated Sensory Neuropathy – A New Candidate?</td>
<td>Jessica Gaff</td>
</tr>
<tr>
<td>184</td>
<td>Heme and Sensory Neuropathy: Insights From Novel Mutations in the Heme Exporter FLVCR1</td>
<td>Deborah Chiabrando</td>
</tr>
<tr>
<td>185</td>
<td>Ignoring Clustering Effect in Multi-Site PAIN-CONTRoLS: A Patient-Informed Cryptogenic Polyneuropathy Clinical Trial. Reasonable Assumption?</td>
<td>Alexandra Brown</td>
</tr>
<tr>
<td>186</td>
<td>Nav1.7 Expression in Keratinocytes and Skin Nerve Fibers</td>
<td>Mirna Anđelić</td>
</tr>
</tbody>
</table>
Unravelling the Role of Niaspan in Peripheral Nerve Regeneration

Stefano Previtali, Alessio Gioia, Silvia Cipriani, Emanuela Porrello, Valeria Alberizzi, Roberta Di Guardo, Francesca Bianchi, Ubaldo Del Carro, Alessandra Bolino

Institute of Experimental Neurology (InSpe), IRCCS Ospedale San Raffaele, Milano, Italy

Introduction: Charcot-Marie-Tooth (CMT) neuropathies are highly heterogeneous disorders caused by mutations in more than 100 genes, with no available treatment. Thus, it is difficult to envisage a single suitable treatment for all pathogenetic mechanisms. Axonal Neuregulin-1 type III (Nrg1t3) drives Schwann cell myelination and determines myelin thickness. Nrg1t3 is inhibited by the α-secretase TACE, which negatively regulates PNS myelination. We hypothesized that modulation of Nrg1 levels and/or secretase activity may constitute a unifying treatment strategy for CMT neuropathies with focal hypermyelination as it could restore normal levels of myelination. We recently reported that in vivo delivery of Niaspan, a FDA approved drug known to enhance TACE activity, efficiently rescues myelination in two models of CMT neuropathy: the Mtmr2 KO mouse, a model of CMT4B1 with myelin outfoldings, and in the Pmp22 +/- mouse, which reproduces HNPP with tomacula. As Nrg1 may also influence axonal regeneration and remyelination, which are key events in the progression of CMTs, we investigated whether Niaspan can influence peripheral nerve regeneration in CMT mouse models.

Methods: We performed nerve crush injury in adult Pmp22 +/- and Mtmr2-KO mice. Niaspan was administered once a day starting the day after the crush. We carried out morphologic, morphometric, and histochemical analyses to evaluate the regeneration status (T21; 21 days post injury) and the achievement of both structural and functional repair (T45).

Results: Preliminary results obtained in the Pmp22 +/- model suggest that Niaspan treatment does not negatively influence nerve regeneration/remyelination, but rather it may ameliorate neurophysiology. We are evaluating Niaspan effect also in Mtmr2-KO mice. Of note, we observed defects in regeneration in both Pmp22 +/- and Mtmr2-KO mice, which have not previously reported.

Conclusions: Understanding the role of Niaspan in peripheral nerve regeneration will provide new insights to the use of this drug for the therapy of CMT neuropathy.

References: None.

Keywords: Axonal Regeneration, Pre-clinical Studies, Schwann Cell, Axonal Biology, CMT

Grant Support: Italian Ministry of Health RF-2016-02361246
Neuropathy related genes as possible modifiers of PMP22 related neuropathies

Anneke van der Kooi1, Barbara van Paassen2, Fred van Ruissen1, Marianne de Visser1, Camiel Verhamme1, Frank Baas3

1Amsterdam University Medical Center, location Academic Medical Center, Amsterdam, Netherlands, 2Erasmus Medical Center, Rotterdam, Netherlands, 3Leiden University Medical Center, Leiden, Netherlands

Charcot-Marie-Tooth disease type 1A (CMT1A) and hereditary neuropathy with liability to pressure palsies (HNPP) are autosomal dominantly inherited peripheral neuropathies caused by copy number variation of the PMP22 gene. Considerable phenotypic variation is known for both disorders, suggesting modifiers.

We undertook a search for genetic modifiers of PMP22 related neuropathies by selecting the extremes of the spectrum of CMT1A and HNPP patients, based on disability assessed by the Overall Neuropathy Limitation Scale (ONLS). The ONLS data of 287 patients (184 CMT1A and 103 HNPP patients) showed a Gaussian distribution for both disorders. The median score for CMT1A patients was 4 and for HNPP patients 3. Twenty-one mild CMT1A (ONLS <2), 26 severe CMT1A (ONLS >5), 25 mild HNPP (ONLS <2) and 25 severe HNPP patients (ONLS >4) were clinically evaluated to further characterize disease severity. A next generation sequencing gene panel containing 147 genes related to neuropathies and hereditary motor syndromes was tested in this selection of patients.

Missense, frameshift, nonsense and intronic mutations possibly affecting splicing were selected. No significant difference was found in the mean number of variants (mutation burden) per patient between the mild and severe groups. Further selection of variants with an allele frequency of ≤4% in a control population was done. A significant difference between the mild and the severe HNPP group was found. In several patients double trouble was found (another likely pathogenic mutation in a neuropathy related gene). Replication of these results in a larger cohort are needed.

References: None.

Keywords: CMTR, Human Genetics

Grant Support: None.
Genetic and clinical finding in a cohort of 341 Chinese patients with Charcot-Marie-Tooth disease

Ruxu Zhang¹, Zhiqiang Lin¹, Beisha Tang², Stephan Zuchner³

¹the third Xiangya Hospital, Central South University, Changsha, Hunan, China, ²Xiangya Hospital, Central South University, Changsha, Hunan, China, ³John P. Hussman Institute for Human Genomics, University of Miami Miller School of Medicine, Miami, FL, USA

We are reporting the genetic and clinical profile of a cohort of 341 Chinese CMT patients and analyze the mutational distributions according to geographic location and age of participants. CMT patients were enrolled between 2006 and 2018. MLPA, Sanger sequencing or gene panel testing was applied to detect sequence variants. Genotype-phenotype analysis was carried out in the cohort, where 159 patients live in Hunan province. The percentage of CMT1 and CMT2 patients were 50.1% and 49.9%, respectively. The genetic diagnosis rate was 54.0% and the most common four genes accounted for 85% of diagnosed patients. EGR2 and NEFL were relatively common in CMT1. GDAP1, IGHMBP2 and HSPB1 were commonly observed in CMT2 patients. The CMT1 genetic diagnosis rate was 59.6% in children and 66.2% in adults. PMP22, GJB1 and MPZ were the most frequently mutated genes. The CMT2 genetic diagnosis rate was 66.2% in children and 27.5% in adults. Twenty-five previously unreported pathogenic variants in ten CMT genes were identified. Three simultaneous heterozygous mutations in MFN2 and GDAP1 were detected and related to severe CMT2 phenotypes with early age of onset. This study represents the largest cohort of Chinese CMT patients to date. We are significantly expanding the phenotype and genotype spectrum of CMT.

References: None.

Keywords: Human Genetics

Grant Support: National Natural Science Foundation of China (81771366), the Hunan Provincial Natural Science Foundation (2017JJ2365), the Science Foundation of Health and Family Planning Commission of Hunan Province (A2017001)
INTRODUCTION: Carpal tunnel syndrome (CTS) is the commonest entrapment neuropathy. Despite its high heritability of 0.46 [1], very little is known about the genetic aetiology of CTS. METHODS: We undertook a genome-wide association study (GWAS) of CTS using 12,312 cases and 389,344 controls of white British ancestry from the UK Biobank resource. We then performed RNA-Seq to investigate whether genes implicated in the GWAS were expressed in tenosynovium surgically resected from the carpal tunnels of CTS patients. We also performed a two-sample Mendelian randomisation analysis using height as the exposure and CTS status as the outcome, using 601 single nucleotide polymorphisms (SNPs) as instrumental variables for height, taken from a large meta-analysis of adult height GWAS [2]. RESULTS: We discovered genome-wide significant associations (p<5e-8) at 16 loci across the genome. Of the associated variants, rs72755233 (p=2.3e-15) is a missense variant in ADAMTS17, rs62621197 (p=7.5e-14) is a missense variant in ADAMTS10, and rs3791679 (p=2.0e-12) lies within an enhancer region of EFEMP1. All three genes are important in extracellular matrix modulation, and we demonstrated expression of these genes at high levels in surgically resected tenosynovium. These variants have been reported in previous GWAS to be associated with human height, and we found that on average, UK Biobank CTS patients are ~2cm shorter than controls. The Mendelian randomisation analysis demonstrated that a 1 S.D. increase in height is associated with an odds ratio of 0.79 for the development of CTS. CONCLUSIONS: We performed the first ever GWAS in CTS, and identified likely causal genes in its pathogenesis, all of which are highly expressed in carpal tunnel tenosynovium. Our findings support the idea that the genetic susceptibility to CTS may arise from aberrant connective tissue architecture or from altered musculoskeletal growth, and implicates an inverse causal role of height in the aetiology of CTS.


Keywords: Human Genetics, CMTR, Pain

Grant Support: Medical Research Council (MRN001524/1) Wellcome Trust (097152/Z/11/Z and 202747/Z/16/Z) Swiss National Science Foundation (P00P3-158835)
Poster 5

Rab35 GTPase is an inhibitor of mTORC1 and regulates myelination in the PNS

Federica Grandi1, Linda Sawade2, Marianna Mignanelli3, Roberta Di Guardo3, Genaro Patiño-López4, Steve Shaw5, Kerstin Klinkert6, Francina Langa Vives7, Arnaud Echard7, Volker Haucke2, Alessandra Bolino1

1IRCCS Ospedale San Raffaele, Milano, Italy, 2Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP), Berlin, Germany, 3IRCCS Ospedale San Raffaele, Milan, Italy, 4Hospital Infantil de México, Ciudad de México, Mexico, 5National Institutes of Health, 10 Center Dr., Bethesda, MD, USA, 6Institut Pasteur, 25-28 rue du Dr Roux, Paris, France, 7Institut Pasteur, 25-28 rue du Dr Roux, Paris, France

Introduction. Charcot-Marie-Tooth type (CMT) 4B1 and B2 are characterized by recessive inheritance, early onset, severe course, slowed nerve conduction, and myelin outfoldings, redundant loops of myelin. CMT4B1 and B2 neuropathies are caused by loss-of-function mutations in the MTMR2 and MTMR13, the Myotubularin related 2 and 13 genes, respectively. MTMR2 is a phosphatase which dephosphorylates PtdIns3P and PtdIns(3,5)P2 phosphoinositides, potent signaling molecules regulating endo-lysosomal trafficking. On the contrary, MTMR13, which is catalytically inactive, is thought to assist MTMR2 in its sub-cellular localization and to increase enzymatic activity. How decreased phospholipid levels cause CMT4B with myelin outfoldings still remains to be clarified. Interestingly, we found that MTMR2/MTMR13 interact with Rab35, which likely activates the myotubularin complex. Rab35 is a small GTPase known to recruit and activate effectors involved in vesicle formation or in cytoskeleton regulation. Methods. To examine the role of Rab35 in nerve development and myelination, we generated Rab35 conditional Knock-out mice with ablation of Rab35 specifically in Schwann cells (Rab35 cKO). Results. Interestingly, nerves of Rab35 cKO are characterized, in addition to myelin outfoldings, by the presence of abundant tomacula and myelin degeneration, which are not observed in nerves of either Mtmr2 or Mtmr13 mutant mice. Since myelin outfoldings and tomacula in the PNS could be associated with overactivation of mTORC1, we analyzed the mTORC1 pathway in Rab35 cKO nerves. Consistent with this, we found that mTORC1 signaling is up-regulated in Rab35 cKO nerves. Conclusions. Our data indicate that Rab35 is a novel regulator of myelination in the PNS. Of note, our data also suggest that PtdIns3P and PtdIns(3,5)P2 phospholipids, regulated by Rab35/Mtmrs, induce mTORC1 pathway activation in the nerve.

References: None.

Keywords: CMTR, Schwann Cell

Grant Support: None.
Dominant mutations of a Notch pathway component cause type 2 Charcot-Marie-Tooth disease

Jeremy Sullivan¹, William Motley¹, Janel Johnson², William Aisenberg¹, Katy Barwick³, Jennifer Huh¹, Meriel McEntagart⁴, Marie-Helene Marion⁵, Lucy Hicklin⁵, Hamid Modarres⁵, Emma Baple³, Aamir Zuberi⁶, Cathleen Lutz⁵, Rachelle Gaudet⁷, Bryan Traynor⁸, Andrew Crosby³, Charlotte Sumner¹

¹Johns Hopkins University School of Medicine, Baltimore, MD, USA, ²National Institutes of Health, Bethesda, MD, USA, ³RILD Wellcome Wolfson Centre, Royal Devon and Exeter NHS Foundation Trust, Exeter, United Kingdom of Great Britain and Northern Ireland, ⁴St. George’s University of London, London, United Kingdom of Great Britain and Northern Ireland, ⁵St. George’s Hospital, London, United Kingdom of Great Britain and Northern Ireland, ⁶The Jackson Laboratory, Bar Harbor, ME, USA, ⁷Harvard University, Cambridge, MA, USA, ⁸National Institutes of Health, Johns Hopkins Hospital, Bethesda, MD, USA

The Notch pathway is a highly conserved cell-cell signaling mechanism with pleiotropic roles in normal tissue development and homeostasis. Dysregulated Notch signaling has also been implicated in the pathogenesis of a multitude of human diseases, including neurodegenerative disorders and cancer, and represents an emerging therapeutic target. Despite this pivotal pathogenic role, only a small number of monogenic disorders (e.g. CADASIL) have been shown to be caused by mutations in Notch pathway components. Here, we describe two missense mutations in a Notch pathway component, that segregate with Charcot-Marie-Tooth disease type 2 (CMT2) in two unrelated families with strikingly similar clinical features, including severe vocal fold paresis. In transfected cells, both mutant proteins exhibited impaired complex glycosylation and reduced plasma membrane expression. Knock-in mice harboring homozygous CMT2-associated mutations in the endogenous mouse gene exhibit embryonic lethality by mid-gestation, confirming a clear functional relevance of the amino acid substitution. Together, these findings broaden the spectrum of neurological disorders associated with alterations in the Notch pathway, and further point to a key role for Notch signaling in peripheral nerve function¹.


Keywords: Human Genetics, Axonal Biology

Grant Support: This work was supported in part by NIH (NINDS) R01NS062869, the Intramural Research Program of the National Institutes of Health (NIH), NINDS intramural research funds, the National Institute on Aging (Z01-AG000949-02), Medical Research Council (G1002279), and by the Jackson Laboratory’s Genetic Engineering Technologies Scientific Service. WWM was supported in part by NIH (NINDS) R25NS065729.
Mutations In The Small Heat Shock Proteins HSPB1 And HSPB8 Impair The Autophagic Flux

Angela Sisto¹, Mansour Haidar², Bob Asselbergh³, Elias Adriaenssens², Vicky De Winter², Jean-Pierre Timmermans⁴, Michaela Auer-Grumbach⁵, Manisha Juneja², Vincent Timmerman²

¹Pheripheral Neuropathy Research Group, University of Antwerp, Antwerp, Belgium, ²Peripheral Neuropathy Research Group, University of Antwerp, Antwerp, Belgium, ³VIB-UAntwerp Center for Molecular Neurology, Antwerp, Belgium, ⁴Laboratory of Cell Biology & Histology, Antwerp Centre for Advanced Microscopy, University of Antwerp, Antwerpen, Belgium, ⁵Department of Orthopaedics, Medical University of Vienna, Vienna, Austria

Autophagy is a crucial process for the cellular homeostasis, as it promotes the removal and recycling of misfolded proteins and damaged organelles. Therefore, impairments of this pathway leads to the accumulation of toxic species and neurodegeneration. Indeed, mutations in HSPB1 and HSPB8, ubiquitously expressed molecular chaperones, cause axonal CMT (CMT2) or distal hereditary motor neuropathy (dHMN). HSPB1 knock-out cells reported impairments in autophagosome formation, which is rescued by the reintroduction of wild-type HSPB1. Through proteomic analysis, we revealed that HSPB1 directly interacts with sequestosome1 (P62/SQSTM1), main autophagy modulator, which mediates the recruitment of ubiquitinated proteins and promote the nucleation of autophagic vesicles. Mutations in HSPB1 lead to a decrease in the formation of p62 bodies, and subsequent impairment of phagophore formation, suggesting a regulatory role for HSPB1 in autophagy via interaction with SQSTM1. Moreover, in patient iPSC-derived motor neurons we confirmed impairment in the autophagic flux with reduction of P62 bodies and autophagosomes (1). The HSPB8 protein belongs to the chaperone-assisted selective autophagy (CASA) complex, composed of HSPB8-BAG3-HSP70, that recruits SQSTM1 and ubiquitinated chaperone-bound cargo. It was shown that depletion of HSPB8 impairs the formation of P62 bodies. We confirmed the autophagic impairment in our homozygous Hspb8K141N knock-in mouse model (2). Evidently mutant HSPB1 and HSPB8 share the same mechanism as their activities merges in SQSTM1 modulation, providing a scaffold for autophagosome formation.


Keywords: Axonal Biology, CMTR

Grant Support: None.
molecular mechanisms of impaired sensory nerve regeneration in diabetes

Sung-Tsang Hsieh, Hung-Wei Kan, Chi-Chao Chao

National Taiwan University Hospital, Taipei, Taiwan, National Taiwan University, Taipei, Taiwan

Sensory neuropathy of the small fiber type is a major complication of diabetes and a critical factor leading to painless injury. The pathology hallmarks include skin denervation with reduced intraepidermal nerve fiber (IENF) density and degeneration of dermal nerve fibers. Although peripheral nerves are able to regenerate, this potential is impaired in diabetes and underlying mechanisms remain elusive. We aimed to address this issue by investigating the molecular mediators underlying extrinsic and intrinsic factors of nerve regeneration in 2 systems: (1) human skin biopsies and (2) a cell model of dorsal root ganglia (DRG) neurons co-cultured with human dermal fibroblast exposed to high-glucose medium. The expression of regenerating markers (growth-associated protein 43) was similar between diabetic patients and control subjects. The collagen composition was altered in diabetes and its expression was increased in diabetic skin compared with control skin due to upregulation of Sec31a, a key molecule in the transit between ER and Golgi apparatus for collagen synthesis. In the cell model, Sec31 was upregulated in human dermal fibroblast exposed to high-glucose medium. Under such molecular interactions, neurite outgrowth of cultured DRG neurons was retarded. The silencing of Sec31a reduced collagen protein expression and rescued neurite outgrowth of DRG neurons. The study established molecular mechanisms and scenario of poor nerve regeneration in diabetic neuropathy.


Keywords: Axonal Biology, Small Fibers, Diabetes

Grant Support: MOST 107-2320-B-002-043-MY3
Mutations in SCL25A46 cause a spectrum of clinical phenotypes including axonal CMT with optic atrophy.

Carolynne Doherty¹, Menelaos Pipis¹, Andrea Cortese¹, Roy Poh², James Polke², Robert Pitceathly¹, Alexander Rossor¹, Mary Reilly¹

¹MRC Centre for Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, United Kingdom of Great Britain and Northern Ireland, ²Neurogenetics unit, UCL Queen Square Institute of Neurology, London, United Kingdom of Great Britain and Northern Ireland

Introduction: Optic atrophy is seen in association with a number of inherited neuropathies, particularly those who have mutations associated with abnormalities of mitochondrial fusion. We present a case of axonal CMT with optic atrophy.

Clinical presentation: At age 6 this now 20-year-old female was noted to have atrophy of the distal legs with bilateral foot drop. A length dependent axonal motor and sensory neuropathy was demonstrated by neurophysiological evaluation. A deterioration of visual acuity 3/36 right and 6/60 left occurred at age 16 and the borderline visual evoked potentials were felt to be compatible with optic neuropathy. Her medical history includes attention deficit disorder. Clinical examination at age 18 showed pale optic discs. There was mild scoliosis. A positive knee bob sign was evident along with distal atrophy and weakness in a length dependent manner. Upper limb and knee reflexes were brisk except for absent ankle jerks and absent plantar responses. Pinprick was reduced below the ankle and vibration perception impaired at knee on Rydell testing.

Investigations: Mutations in OPA1, OPA3, POLG, ATPase 6 and 8 were sought but not identified. Whole Exome Sequencing identified compound heterozygous mutations in the SCL25A46 gene (p.A322D and p.Y386C), one of each was subsequently demonstrated in the parents.

Discussion: A spectrum of disorders of varying severity has been described associated with mutations in SCL25A46. These include CMT2 with optic atrophy (HMSN type 6B) sometimes with additional features including spasticity and ataxia, Leigh syndrome and pontocerebellar hypoplasia. The gene encodes a mitochondrial solute carrier protein and is thought to have a role in mitochondrial fusion/fission dynamics. We present a discussion of the literature alongside a case presentation of axonal neuropathy with optic atrophy.

References: None.

Keywords: CMTR, Human Genetics

Grant Support: Dr Carolynne Doherty and Professor Mary Reilly are grateful to the Muscular Dystrophy Association for their grant support.
Clinical heterogeneity of p.Val30Met mutation in transthyretin-related familial amyloid polyneuropathy in Turkey

Hacer Durmus1, Arman Çakar1, Oya Uyguner2, Zeliha Matur3, Feza Deymeer1, Piraye Ofazer1, Yesim Parman1

1Istanbul University, Istanbul Medical Faculty, Neurology Department, Istanbul, Turkey, 2Istanbul University, Istanbul Medical Faculty, Department of Medical Genetics, Istanbul, Turkey, 3İstanbul Bilim Üniversitesi Tıp Fakültesi Nöroloji Anabilim Dalı, Istanbul, Turkey

Transthyretin-related familial amyloid polyneuropathy (TTR-FAP) is a rare autosomal dominant disorder caused by mutations of the transthyretin (TTR) gene. The mutant amyloidogenic transthyretin protein causes the systemic accumulation of amyloid fibrils that results in organ dysfunction. TTR-associated FAP is a progressive and fatal disease, if left untreated, and should be considered in the differential diagnosis of any person presenting with a progressive polyneuropathy, particularly with accompanying autonomic involvement. The clinical, electrophysiological, histopathological, and genetic characteristics of nine patients from Turkey (1 female, 8 male) from eight unrelated families with polyneuropathy and p.Val30Met mutation in TTR were evaluated. Two patients were homozygous for the mutation. Mean age at disease onset was 51.56±10.59 years (range 37–66 years). Four of them were early onset (onset before age 50), but only two siblings from middle Anatolia presented before the age of 40 years. The most commonly reported initial complaint was paresthesia in the feet. Two patients presented with distal upper extremity weakness (asymmetrical in one). One patient had orbital amyloidosis. The patient with upper extremity presentation had bilateral ptosis and mild ophthalmoparesis for three years, he also had tongue atrophy. Hypophonia due to vocal cord involvement was detected in two patients. Only one male patient had bilateral carpal tunnel syndrome. Three patients died during the period of follow-up as a result of systemic involvement. In eight patients, electrophysiological findings at presentation were compatible with sensory-motor axonal polyneuropathy and autonomic neuropathy. EMG showed demyelinating sensory and motor asymmetrical polyneuropathy syndrome accompanied by signs of axonal lossing one patient. Although Turkey is a non-endemic region for TTR-FAP, we observed both early and late onset patients. In comparison to late onset cases from other non-endemic regions, late onset patients from Turkey had more frequent family history, high penetrance and more severe accompanying autonomic symptoms.

References: None.

Keywords: Amyloidosis, Human Genetics

Grant Support: None.
Impact of Inotersen on Functioning for Patients with hATTR Amyloidosis: Results from a Placebo-Controlled Trial

Spencer Guthrie¹, Aaron Yarlas², Giampaolo Merlini³, Michelle White², Asia Sikora Kessler², Andrew Lovley², Michael Pollock¹, Morie Gertz⁴

¹Akcea Therapeutics, Boston, MA, USA, ²Optum, Johnston, RI, USA, ³Amyloidosis Center, University of Pavia, San Matteo, Italy, ⁴Mayo Clinic, Rochester, NY, USA

Introduction: Hereditary transthyretin (hATTR) amyloidosis is a rare, systemic, progressive condition where misfolded proteins deposit in muscle and organ tissues leading to symptoms of peripheral neuropathy, possible cardiomyopathy, and autonomic neuropathy. The Norfolk Quality of Life (QOL)-Diabetic Neuropathy (DN) questionnaire is a patient-reported measure that has been validated for capturing neuropathy-specific QOL in patients with hATTR amyloidosis. The current objective is to describe item-level responses on the Norfolk QOL-DN questionnaire by patients with hATTR amyloidosis with polyneuropathy to determine the impact of inotersen on functioning and daily activities.

Methods: Data were from a multinational, double-blind, placebo-controlled trial of inotersen for 172 adults with hATTR amyloidosis (NCT01737398). The Norfolk QOL-DN was administered to patients at baseline, week 35, and week 66. Nineteen items from the scale elicit concrete information about functioning and daily activities. These items use five response options: “no problems”, “very mild problems”, “mild problems”, “moderate problems”, and “severe problems”. Response options were dichotomized, with the latter two options coded as indicating substantial impairment.

Results: At week 66, fewer patients receiving inotersen than those receiving placebo indicated they had substantial impairment on several aspects of functioning and activities: pain keeping them awake at night (16% vs. 37%); difficulty moving fingers (46% vs 64%); feeling unsteady on their feet (49% vs 67%); difficulty getting out of a chair (50% vs. 62%), walking (41% vs 60%), walking down stairs (42% vs. 58%), bathing (23% vs. 35%), dressing (21% vs 35%), getting on/off the toilet (23% vs. 37%), and utensil use (19% vs. 31%).

Conclusion: Patients with hATTR amyloidosis receiving inotersen for 66 weeks less frequently reported substantial impairment in many aspects of functioning and activities of daily living than those receiving placebo. Ability to engage in these functions and activities was better preserved in patients treated with inotersen than placebo.

References: None.

Keywords: Amyloidosis, Clinical Trials

Grant Support: None.
CMT1 with nerve conduction blocks caused by a homozygous mutation in the LITAF gene

Marion Masingue¹, Bénédicte Chassande¹, Tanya Stojkovic¹, Philippe Latour²

¹Centre de Référence de pathologie neuromusculaire Paris-Est, Institut de Myologie, GHU Pitié-Salpêtrière, Paris, France, ²Département de Neurobiologie, Centre de Biologie Est, Hospices Civils de Lyon, Bron, France

Dominant mutations in the LITAF gene (an ubiquitous endosomal protein) have been described in mild demyelinating neuropathies (Charcot Marie Tooth (CMT 1C). We describe here the first case of a patient with a homozygous LITAF mutation, with a particular phenotype. The patient, a female aged 32 years old, born of probable consanguineous parents, complained since age 30 of lower limbs pain, cramps and fatigability. Clinical examination revealed pes cavus, distal sensorimotor deficiency in all four limbs. There was no areflexia. ENMG showed diffuse slowed conduction velocities (20m/s), compatible with a demyelinating profile, but also, interestingly, diffuse nerve conduction blocks. Sensory action potentials were abolished in the lower limbs. Screening of the PMP22 gene was negative and genetic analysis were expanded to a CMT panel that revealed a homozygous (c.479G>A (p.Arg160His)) mutation in the LITAF gene. Her mother was heterozygous for the mutation, and was asymptomatic. This is the first homozygous LITAF mutation described so far, indicating that it should also be looked for in recessive CMT1. So far, to our knowledge, only one heterozygous mutation has been described in the exon 160 of the LITAF gene (p.Arg160Cys). The change in amino acids of the p.Arg160His mutation is less pathogenic but would explain, at the homozygous state, the mild phenotype of our patient. CMT1 can be caused by homozygous mutation in the LITAF gene, presenting with mild demyelinating neuropathy with nerve conduction blocks, sometimes mimicking chronic inflammatory demyelinating polyneuropathy on ENMG, as previously described.

References: None.

Keywords: CMTR

Grant Support: None.
Morphometric Analysis of Peripheral Myelinated Nerve Fibers through Deep Learning

Jun Li, Daniel Moiseev
Wayne State University, Detroit, MI, USA

Introduction: Most neurological diseases produce one of two key pathological changes – axonal loss or demyelination – or a combination of the two. Therefore, studying these disorders requires rigorous quantification of myelin and axon pathology. Traditional manual quantification is time-consuming and may suffer from inter-observer variation. Deep-learning has been utilized to automate image analysis. The aim of the present study is to develop a Convolutional Neural Network (CNN) – based approach to segment images of mouse nerve. Methods: We used Keras, a deep-learning library, to create a CNN based on U-net architecture for improved localization of image features. Training data included 280 microscopic images of mouse sciatic nerve cross-sections paired with their respective segmentation masks obtained in previous studies of neuropathy mouse models. Results: After training, accuracy plateaued at 0.91 dice coefficient and the validation dice coefficient varied between 0.81 and 0.85. Compared to the manual method, the CNN-based automated method exhibited a 2.5% decrease of nerve fiber density, 4.2% lower axonal diameter, 2.0% larger myelin thickness, and 2.6% lower G-ratio. Distribution of myelinated fiber diameters was very similar between the two methods, thus no size of nerve fibers was disproportionately affected by the automation. After training, measurements took 16-20 minutes per image while manual segmentation took 65-76 minutes. Conclusions: We have developed a CNN-based method to analyze nerve morphometrics. Previously acquired nerve images were used to train the model to recognize atypical myelin structures, including severe pathological changes. The trained model decreased analysis time with excellent accuracy in axonal density and g-ratio. We were not able to eliminate manual refinement of the automated segmentation product, but our data have provided alternative methods for improvement. Overall, greatly increased efficiency in the automation outweighs minor limitations, thus justifying our confidence in its prospects.


Keywords: Schwann Cell, Axonal Biology

Grant Support: Supported by: NINDS (R01NS066927).
Poster 14

A cellular model of iPS-derived motor neurons to investigate a GDAP1-associated form of Charcot-Marie-Tooth disease

Federica Miressi¹, Marion Rassat¹, Nicolas Vedrenne¹, Laurence Richard², Cécile Laroche³, Laurent Magy⁴, Corinne Magdelaine⁵, Steven Naud⁶, Sylvie Bourthoumieu⁷, Frédéric Favreau⁸, Franck Sturtz⁵, Pierre-Antoine Faye⁶, Anne-Sophie Lia⁵

¹University of Limoges, MMNP, EA 6309, F-87000 Limoges, France, Limoges, France, ²CHU Limoges, Service de Neurologie, F-87000 Limoges France, Limoges, France, ³CHU Limoges, Service de Pédiatrie, F-87000 Limoges France, Limoges, France, ⁴University of Limoges, MMNP, EA 6309, CHU Limoges, Service de Neurologie, F-87000 Limoges France, Limoges, France, ⁵University of Limoges, MMNP, EA 6309, CHU Limoges, Service Biochimie Génétique Moléculaire, F-87000 Limoges France, Limoges, France, ⁶CHU Limoges, Service Biochimie Génétique Moléculaire, F-87000 Limoges France, Limoges, France, ⁷University of Limoges, MMNP, EA 6309, CHU Limoges, Service de Cytogénétique, F-87000 Limoges France, Limoges, France, ⁸University of Limoges, MMNP, EA 6309, CHU Limoges, Service Biochimie Génétique Moléculaire, F-87000 Limoges France, Limoges, France

Charcot-Marie-Tooth (CMT) disease is the most common inherited peripheral neuropathy in humans. Among all the CMT-associated genes, GDAP1, which codes for the ganglioside-induced differentiation protein 1, has often been linked to axonal forms of CMT. The role of GDAP1 protein, which is located in the mitochondrial outer membrane, and its involvement in CMT pathophysiology still remain unclear. Despite the teething difficulties in developing appropriate cellular models, in recent years, iPS (induced-pluripotent stem) cells became one of the most employed strategy to investigate motor neurons dysfunctions in genetic peripheral disorders. For our study, we obtained human dermal fibroblasts, from two unaffected controls and one CMT-patient carrying a homozygous non-sense GDAP1 mutation, and we dedifferentiated them into iPS cells. iPSc were then differentiated into motor neurons according to an established differentiation protocol. Here we show the results of our morphological and functional analysis, conducted at fibroblasts, iPS and motor neurons levels, with the purpose of better understand the molecular mechanisms impaired by GDAP1 dysfunction in CMT patient.

References: None.

Keywords: CMTR

Grant Support: Région Nouvelle-Aquitaine, University of Limoges
Poster 15

A diagnostic challenge: 10-year-old boy with leucoencephalopathy, bulbar dysfunction, optic atrophy, nystagmus and motor neuronopathy.

Shaimaa Elaidy¹, Terrence Thomas², Tchoyoson Lim³, Wai-Yung Yu³, Umapathi Thirugnanam³

¹Zagazig University, Zagazig, Egypt, ²KK Women’s and Children’s Hospital, Singapore, Singapore, ³National Neuroscience Institute, Singapore, Singapore

A 10-year-old boy of Arab origin, born of consanguineous parents in Egypt, presented with a 4-year history of progressive weakness of upper and lower extremities. Within the first year of symptoms, he developed bulbar and respiratory weakness that required tracheostomy and mechanical ventilation. In the last 6 months the mother has noticed diminution of vision in both eyes. His medical history is otherwise unremarkable. He was born full-term via a normal virginal delivery; he attained normal motor and mental milestones. There is no genetic disorders in the family. Examination reveals a child, with no dysmorphic features, on nasogastric feeding and tracheostomy. He has intact cognition, hearing and reflexive eye movements. There is no light perception in both eyes. Fundoscopy reveals bilateral optic atrophy without cherry red spots or retinitis pigmentosa. Gaze evoked nystagmus was noted earlier when his vision was better. Prominent wasting and fasciculations of tongue are present. Limb examination reveals severe hypotonia, areflexia, distal more than proximal weakness of limbs and distal vibratory sensory loss. General examination reveals ichthyosis, scoliosis and mild hepatomegaly. Routine laboratory studies are all normal. Nerve conduction studies reveal severe axonal neuropathy-neuronopathy with sparing of sensory potentials. MRI shows distinctive periventricular cystic leukomalacia with T2 signal changes in the brainstem. Various leukodystrophies and genetic leukoencephalopathies are considered, including mitochondrial cytopathies such as complex 1 deficiency and LBSL (leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation); vanishing white matter disease and Alexander’s disease. The investigative approach has to be restricted in view of resource limitation. Hence, the case is presented to solicit opinions from peripheral nerve society members for a targeted, cost-effective diagnostic approach.

References: None.

Keywords: Human Genetics, CMTR, Other, Schwann Cell, Axonal Biology

Grant Support: None.
Lipodystrophy in CMT1A points out a new inborn error of lipid metabolism

Davide Visigalli¹, Giovanna Capodivento¹, Abdul Basit², Roberto Fernandez³, Zeeshan Hamid², Barbora Pencova³, Chiara Gemelli¹, Daniela Marubbi³, Adrienne Luoma⁵, Christian Riekel⁶, Daniel Kirschner⁵, Angelo Schenone¹, José Fernández⁷, Andrea Armirotti², Daniela Marubbi⁴, Adrienne Luoma⁵, Christian Riekel⁶, Daniel Kirschner⁵, Angelo Schenone¹, José Fernández⁷, Andrea Armirotti², Lucilla Nobbio¹

¹DINOGMI University of Genoa, IRCCS San Martino Hospital, Genoa, Italy, ²Analytical Chemistry Lab Fondazione Istituto Italiano di Tecnologia, Genoa, Italy, ³Department of Physical Chemistry Faculty of Science and Technology University of the Basque Country, Leioa, Spain, ⁴DIMES University of Genoa, IRCCS San Martino Hospital, Genoa, Italy, ⁵Department of Biology Boston College, Chestnut Hill, MA, USA, ⁶The European Synchrotron ESRF, Grenoble, France, ⁷Department of Physical Chemistry Faculty of Science and Technology University of the Basque Country, Leioa, Spain

Charcot-Marie-Tooth type 1A (CMT1A) is the most frequent hereditary dysmyelinating neuropathy in which the well-defined genetic cause has not yet been paralleled by the comprehension of the underlying molecular mechanisms. In fact, whether myelin maturation is arrested or delayed is still an open question and evidences about the composition of the myelin membrane during disease course are still lacking. Here, we find an early and altered sphingo- and phospholipid composition and ultrastructure abnormalities of the myelin sheath to demonstrate the failure of its correct assembly in CMT1A. The same biochemical derangement even emerges in rat and human biological fluids implying a systemic lipid metabolic dysfunction. Actually, the untimely lipid defect in CMT1A resembles the features of an inborn error of metabolism pointing to potentially shared therapeutic approaches. Overall, our results identify new pathomechanisms and promising serum biomarkers to effectively impact CMT1A and other CMT neuropathies in which lipid biosynthesis and remodelling are compromised.

References: None.

Keywords: CMTR, Metabolic, Schwann Cell

Grant Support: None.
The Role of TTR in Health and Disease

Laura Obici¹, Vittorio Bellotti², Teresa Coelho³, Jeffery Kelly⁴, Marcia Liz⁵

¹Amyloidosis Research and Treatment Center, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, ²National Amyloidosis Centre, Royal Free Hospital, University College London, London, United Kingdom of Great Britain and Northern Ireland, ³Unidade Corino Andrade, Hospital Santo António, Centro Hospitalar Universitário do Porto, Porto, Portugal, ⁴The Scripps Research Institute, La Jolla, CA, USA, ⁵Instituto de Biologia Molecular e Celular (IBMC) and Instituto de Inovação e Investigação em Saúde (i3S), Porto, Portugal

Background: The complete array of physiological roles of transthyretin (TTR), a protein produced primarily in the liver, eye and choroid plexus and the aggregation of which is associated with ATTR amyloidosis, is yet to be determined. With the evolving landscape of treatment options for ATTR polyneuropathy that prevent TTR production through pharmacological mRNA suppression, it is vital to understand the roles of TTR in normal health and the impact of knockdown.

Methods: Following a comprehensive literature search, a group of experts with different background knowledge in TTR function and metabolism and in ATTR amyloidosis met to discuss the biological activity of TTR based on animal and human models and to identify gaps in knowledge to determine areas of further study.

Results: TTR was proposed to have biological functions independent of its carrier role for thyroid hormones and retinol. TTR appears to have an important neurotrophic effect, supported by several studies in TTR knockout mice, which present with sensory impairment and decreased locomotor activity, ¹behavioural abnormalities,² age-related memory deficits² and impaired spatial memory.³ TTR is also involved in nerve regeneration⁴ and axonal growth.⁴ Moreover, experimental evidence points to a neuroprotective role of TTR in cerebral ischaemia⁴ and in transgenic mice for Alzheimer’s disease (AD),⁵ with several studies indicating a direct interaction between TTR and amyloid β protein, either in its soluble or aggregated form.⁶,⁷ The putative proteolytic activity of TTR against amyloid β and possible other substrates may also contribute to its neuroprotective role in AD.⁸,⁹

Conclusions: TTR is likely to have a more significant role in health than previously thought, possibly modulating processes associated with aging, neuroprotection and nerve regeneration. It is therefore critical to achieve a greater understanding of the need for TTR, especially in the era of TTR knockdown treatments.


Keywords: Amyloidosis, Human Genetics, Pre-clinical Studies

Grant Support: None.
Poster 18

Reliability of the CMTPedS Training and Quality Assurance Program

Timothy Estilow¹, Allan Glanzman¹, Kristy Rose², Linda Lowes³, Megan Iammarino⁴, Natalie Miller⁴, Zarife Sahenk³, Joshua Burns⁵

¹The Children's Hospital of Philadelphia, Philadelphia, PA, USA, ²University of Sydney, Children's Hospital at Westmead, Sydney, Australia, ³Center for Gene Therapy Nationwide Children's Hospital, Department of Pediatrics The Ohio State University, Columbus, OH, USA, ⁴Center for Gene Therapy Nationwide Children's Hospital, Columbus, OH, USA, ⁵University of Sydney, The Children's Hospital at Westmead, Sydney, Australia

Introduction: Consistent and accurate administration of clinical outcome assessments (COA) is essential for clinical trial success. The Charcot-Marie-Tooth disease Pediatric Scale (CMTPedS) is a valid, sensitive, and responsive measure of disability in children, adolescents and young adults with CMT. Training and quality assurance methodology has been developed to ensure reliability across clinical evaluators in preparation for upcoming trials. Methods: Two clinical evaluators new to the CMTPedS completed training in preparation for a gene therapy trial (ClinicalTrials.gov Identifier: NCT03520751). Initially, self-directed training via www.cmtpeds.org was completed using the CMTPedS Equipment and Training Resource kit, links to relevant publications and background on test development, and an online video library demonstrating item administration and scoring to ensure familiarity with the scale. Face-to-face training was then provided by a master trainer consisting of: a guided review of CMTPedS items, live demonstration, and hands on practice. Inter-rater reliability of the clinical evaluators against the ‘gold standard’ master trainer was assessed in two patients with CMT and one healthy control. Results: Inter-rater reliability for the CMTPedS total score was excellent (ICC 0.98). Inter-rater reliability was also excellent for all individual CMTPedS items: Functional Dexterity Test (ICC 0.86), Nine Hole Peg Test (ICC 0.90), hand grip strength (ICC 0.94), ankle plantarflexion strength (ICC 0.98), ankle dorsiflexion strength (ICC 0.85), pinprick (ICC 1.0), vibration (ICC 0.83), balance (ICC 0.96), gait (ICC 0.97), and long jump (ICC 0.97). Note, multiple six-minute walk tests not assessed to avoid fatigue. Conclusions: A thorough review of the CMTPedS online resources combined with face to face training was adequate in establishing clinical evaluator reliability. Training and reliability is a necessary prelude to multi-site clinical trials.

References: None.

Keywords: CMTR, Clinical Trials, Other

Grant Support: This study was supported by grant U54NS065712 from the National Institutes of Neurological Diseases and Stroke and office of Rare Diseases.
A novel family with axonal Charcot-Marie-Tooth disease caused by a mutation in the EGR2 gene.

Stefano Tozza¹, Stefania Magri², Elena Pennisi³, Erika Schirinzi⁴, Chiara Pisciotta⁵, Francesca Balistreri², Daniele Severi¹, Giulia Ricci², Gabriele Siciliano⁴, Franco Taroni², Lucio Santoro¹, Fiore Manganelli¹

¹Department of Neuroscience, Reproductive Sciences and Odontostomatology, University of Naples "Federico II", Naples, Italy, ²Unit of Medical Genetics and Neurogenetics, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, ³Neurology Unit, San Filippo Neri Hospital, Rome, Italy, ⁴Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, ⁵Rare Neurodegenerative and Neurometabolic Disease Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

EGR2 is one of the most important transcription factors involved in myelination in the peripheral nervous system. EGR2 mutations typically cause different form of demyelinating neuropathy, i.e. Charcot-Marie-Tooth type 1D (CMT1D), Dejerine-Sottas Neuropathy (DSN) and Congenital Hypomyelinating Neuropathy (CHN). However, recently the EGR2 gene has been associated to axonal phenotype in a single large CMT family. Herein, we report the first Italian CMT family associated to EGR2 mutation and axonal phenotype.

Five patients belonging to a large CMT family underwent genetic, clinical and electrophysiological analysis and one of them underwent sural nerve biopsy.

Neurological evaluation showed a classical CMT phenotype and clinical impairment as assessed by CMT Neuropathy Score (CMTNS) was variable ranging from mild (CMTNS= 6) to moderate (CMTNS= 16).

Electrophysiological examination was consistent with a motor-sensory axonal neuropathy. Motor and sensory action potentials were absent or reduced at lower limbs and normal or reduced at upper limbs, and nerve conduction velocity, when applicable, was mildly reduced. Needle electromyography showed chronic axonal changes in distal muscles.

Sural nerve biopsy was compatible with a chronic axonal neuropathy and showed a loss of large myelinated nerve fibers without de-remyelinating signs or onion bulbs.

Genetic analysis through NGS approach identified in the proband a missense change (c.1235A>G; p.Glu412Gly) in the EGR2 gene, and the segregation within the family was confirmed by Sanger sequencing.

This description expands the phenotypical heterogeneity of EGR2-related neuropathy, suggesting that EGR2 gene should be tested in patients with axonal CMT. However, why mutations in a gene involved in myelination may result in primary axonal neuropathy remains to be elucidated.

References: None.

Keywords: CMTR

Grant Support: None.
Charcot-Marie-Tooth (CMT) disease represents one of the most frequent genetic diseases affecting the nervous system resulting from defects either in Schwann cells or in neurons/axons. Despite a relatively high frequency of CMT (1/2500), there is still no effective treatment. CMT2A is the most common axonal form, characterized by a peripheral neuropathy involving both sensory and motor neurons. Autosomal dominant inheritance of CMT2A is linked to missense mutations in the MFN2 gene encoding Mitofusin-2 (MFN2). MFN2 is a GTPase originally identified at the outer membrane of mitochondria and more recently, at the interface between the endoplasmic reticulum (ER) and the mitochondria. ER-mitochondria contacts, known as mitochondria-associated-membranes (MAMs), mainly regulate transfer of calcium and lipids between the two organelles. However, the effects of mutated MFN2 on MAMs in diseased neurons have not been studied so far.

To study the pathophysiology of CMT2A, we used primary neuronal cultures infected with AAV6-hsynapsin vectors encoding either MFN2WT or MFN2R94Q as well as CMT2A patient-derived fibroblasts. In vivo, we used a transgenic mouse model of CMT2A that we developed previously (CMT2A Tg; Cartoni et al., 2010).

We observed that the presence of MFN2R94Q led to axonal degeneration without inducing neuronal death both in vitro and in vivo. Remarkably, the presence of mutant protein led to reduction in MAMs, in primary neurons, in CMT2A patient-derived fibroblasts as well as in vivo, in motoneurons of CMT2A mice. These modifications occurred concomitantly with activation of ER stress response, dysregulated calcium handling, and alterations in mitochondrial morphology and transport, collectively contributing to axonopathy.

Importantly, drugs reinforcing the ER-mitochondria cross-talk and/or reducing ER stress restored mitochondria morphology and prevented axonal degeneration. Our work thus revealed a new mechanism implicated in CMT2A pathology which may provide a relevant therapeutic target in axonal forms of CMT disease.

References: None.

Keywords: Axonal Biology, Metabolic

Grant Support: None.
Charcot-Marie-Tooth (CMT) disease is a clinical and genetically heterogeneous group of hereditary motor and sensory neuropathies characterized by slowly progressive distal muscle weakness and atrophy, foot deformities, distal sensory loss and depressed tendon reflexes. CMTX1 is due to mutations in the GJB1 gene. It typically presents with an earlier and more severe phenotype in males, while females have a milder phenotype being either asymptomatic or oligosymptomatic. We describe the clinical and electrophysiological findings in two sisters with CMTX1 diagnosis with a variable severity phenotype.

Two Portuguese affected sisters presented at our Department at the age of 57 years old and 55 years old respectively with a late-onset neuropathy, at 6th decade of life. A family history compatible with autosomal dominant or X-linked inheritance (father, grand-mother and cousin) was evoked. The younger sister presented a mild phenotype. She complained of neuropathic pain in both feet with no other symptoms. Neurological examination revealed exclusively absence of achilles reflexes. Neurophysiological study revealed a sensory-motor demyelinating polyneuropathy. The discrepancy between the clinical and neurophysiological features evoked a hereditary etiology. Genetic screening for CMT1A and CMT1B were negative. The older sister carried a more severe phenotype. Neurological examination reported distal motor weakness (MRC score 3/5), algic hypoesthesia with sock distribution, pes cavus and absent deep tendon reflexes. Neurophysiological study showed axonal sensory-motor polyneuropathy with mild demyelinating features. In both patients a heterozygous mutation c.397T>C (p.Trp133Arg) in the GJB1 gene was found confirming the CMTX1 diagnosis.

This report illustrates the phenotypic and neurophysiological variability associated to CMTX1 even between two related patients harboring the same mutation. It also emphasizes that female patients can present a more severe phenotype similar to male patients. In conclusion, screening of GJB1 gene should be performed in both male and female patients with no male-to-male transmission with CMT.

References: None.

Keywords: CMTR

Grant Support: None.
Poster 22

Longitudinal Assessment of Iowa FAP Cohort Treated with siRNA

Shawna Feely, Nicole Kressin, Emilee Gibson, Jeri Sieren, Heena Olalde, Andrea Swenson, Michael Shy

University of Iowa, Iowa City, IA, USA

Transthyretin (TTR) mutations cause Familial Amyloidosis Polyneuropathy (FAP) and are associated with a range of symptoms such as peripheral neuropathy, autonomic neuropathy, cardiomyopathy, central nervous system and vision abnormalities. Clinical trials for FAP have utilized a variety of outcome measures, Neuropathy Impairment Score of the Lower Limb (NIS-LL), Polyneuropathy Disability Score (PDS), and Karnofsky Performance Status (KPS), to assess for change. We evaluated 14 subjects over 24 months of treatment with siRNA in an Early Access Program (EAP) using the NIS-LL, KPS, PDS, and the Charcot Marie Tooth Disease Exam Score version 2 (CMTESv2). Two subjects switched to different treatment sites and one died of an unrelated malignancy. At 6 months, all outcome measures showed an average improvement in scores overall, with the exception of the KPS which showed slightly worse averaged scores. The most significant improvement shown at 6 months was with the CMTESv2. At 12 months, this cohort continued to show improvement in averaged scores, particularly when using the NIS-LL and CMTESv2. The only score that did not show improvement was the PND which showed no change. At 18 months, both the NIS-LL and CMTESv2 showed improvement in scores. The KPS showed no change. By 24 months, there was only one subject left in EAP, so scores could not be compared. Overall the outcome measures used to assess neuropathy in this cohort showed a stabilization or improvement in neuropathy symptoms during the course of treatment. This data suggests that the CMTESv2 may also be useful as an outcome measure for patients with FAP and that it may be as or more sensitive than other measures. Rasch modified CMTESv2 may prove more sensitive than the CMTESv2.

References: None.

Keywords: Amyloidosis, Clinical Trials, CMTR

Grant Support: None.
Poster 23

Digitally assessed real-world diversity in people with Charcot-Marie-Tooth disease in the UK and US

Mark Larkin¹, Tjalf Ziemssen², Shahram Attarian³, Florian Thomas⁴, Allison Moore⁵, Daniel Tanesse⁶, Xavier Paoli⁷, Viviane Bertrand⁷, Youcef Boutalbi⁷, Emma Bagshaw¹, Hara Kousoulakou¹

¹Vitaccess Ltd., Oxford, United Kingdom of Great Britain and Northern Ireland, ²Universitätsklinikum Carl Gustav Carus an der Technischen Universität, Dresden, Germany, ³Assistance Publique - Hopitaux de Marseille, Marseille, France, ⁴Hackensack University Medical Center, Hackensack, USA, ⁵Hereditary Neuropathy Foundation, New York, USA, ⁶CMT France, Fougères Cedex, France, ⁷Pharnext SA, Issy-les-Moulineaux, France
Introduction:

The objectives of this analysis were to explore the demographics of UK and US participants enrolled in a real-world observational study of Charcot-Marie-Tooth disease (CMT), and to investigate differences between the overall study population and those reporting participation in clinical trials for CMT.

Methods:

Adults with CMT were recruited to a two-year international observational study exploring the real-world impact of the disease. Data were collected via CMT&Me, a ‘bring your own device’ app specifically developed for this study, through which participants were asked questions about demographic, CMT management-related and quality-of-life variables. This interim analysis examined the demographics of UK and US participants. Differences between the overall study population and those who reported having participated in clinical trials were examined.

Results:

Diversity of study participants was high across all demographic parameters. At the time of reporting, more females than males were enrolled. Participant age distribution was well-balanced. Around half of participants in both countries had CMT Type 1A, with Type 2 and ‘unknown’ being the next most commonly reported subtypes. Participants received their CMT diagnosis at a wide range of ages, with the median being around adolescence. The most common employment statuses were ‘working for pay’ and ‘unable to work due to disability’.

A small proportion reported having participated in clinical trials for CMT. Rates were similar between UK and US respondents, and demographics for trial participants were largely comparable with those of the overall study population. The majority were female and had CMT Type 1A. Similar age distributions and employment statuses were observed in both groups.

Conclusions:

Diversity was high among UK and US participants in this observational study of CMT. Demographics were similar between those who reported clinical trial participation and those who did not. This ongoing registry will provide further real-world insights to increase understanding of CMT.

References: None.

Keywords: Other

Grant Support: None.
Poster 24

A Comprehensive Update of the Inherited Neuropathies Consortium of the Rare Diseases Clinical Research Network

Chelsea Bacon

University of Iowa, Iowa City, IA, USA

The INC is composed of 21 sites that evaluate patients with Charcot-Marie-Tooth disease (CMT) and maintain data pulled from clinical visits in a standardized manner. Clinical information from patient visits is electronically submitted and maintained in a database housed at the University of South Florida at the Data Management and Coordination Center. All 21 sites are actively seeing patients, and University of Miami houses and researches DNA samples from INC sites for testing on potential new forms of CMT and genetic modifiers of CMT1A. Current projects include: Natural History Evaluation of Charcot-Marie-Tooth disease (with particular emphasis on CMT1B, CMT2A, CMT4A, and CMT4C), Genetics of CMT, Creation and Validation of a CMT Pediatric Scale and Infant Scale, Creation and Validation of a Disability Severity Index for CMT, Analysis of Symptomatic Domains Most Relevant to CMT. These projects have helped to create validated outcome measures to use in clinical trials. In addition, over the past five years, the INC has been able to identify over half of all the genes currently known to cause CMT. The INC has evaluated 10,633 patients overall, with 5,570 patients for the Natural History Evaluation of CMT, and 2,451 patients participating in the Genetics of CMT. The INC partners with patient advocacy groups in order to bring knowledge to patients establish connections between patients and researchers and physicians. These groups include the Muscular Dystrophy Association, the Charcot Marie Tooth Association, CMTUK, CMTA Australia, and Telethon from Italy. Additionally, the INC maintains a Contact Registry housed at the University of South Florida, which allows patients to self-register in a disease-specific registry that corresponds to each consortia. Patients are notified when they are able to participate in research, when new sites become available, and are provided with updates about the consortium of choice.

References: None.

Keywords: CMTR

Grant Support: This consortium Inherited Neuropathy Consortium is part of the NIH Rare Diseases Clinical Research Network (grant #1U54NS065712-01)
In order to manage large scale CMT exome and genome data, we had previously introduced the GENESIS platform, a collaborative web-based software where researchers across the globe are able to analyze, archive and share genomic data. To date, data from more than 5,100 families from 44 countries are included in GENESIS, but less than 10% of them have a reported genetic diagnosis. Although, 3,724 variants in GENESIS are classified as 'pathogenic' or 'likely pathogenic' in ClinVar. Here we propose a systematic flowchart to solve families on this platform in a standardized and structured manner. The workflow follows recommendations developed by the American College of Medical Genetics – Association for Molecular Pathology (ACMG–AMP) combined with the Sherloc criteria. The filters applied on the GENESIS platform included classification as pathogenic or likely pathogenic in ClinVar, population frequency equal to or below 8 alleles in gnomAD, and minimal read depth above 20x. After filtering, we verified the phenotype, clinical inheritance pattern, literature reports, and absence of misalignments in BLAT. Among 3,000 GENESIS families that carry a variant classified as pathogenic/likely pathogenic in ClinVar and based on our current proportion estimate, we can expect to solve an additional ~20% of families. We are currently implementing a semi-automatic diagnostic reporting system that will provide a more efficient genetic diagnosis of the families under research studies. Our approach will build a step toward establishing a common framework for the consistent diagnoses of families in GENESIS, facilitating the analysis for researchers.

References: None.

Keywords: Human Genetics

Grant Support: None.
Temporal dispersion in CMTX1 nerve conduction studies

Rodrigo Diniz da Gama, Pedro Tomaselli, Carolina Moreira, Patricia Toscano, Vanessa Marques, Wilson Marques Jr

University of São Paulo, Ribeirão Preto Medical School, Ribeirão Preto, Brazil

**Background:** Nerve conduction studies are a useful tool to characterize Charcot-Marie-Tooth disease. The presence of temporal dispersion (TD) may be a confounding factor between CMTX1 and inflammatory neuropathies.

**Aims.** The objective of the present study was to characterize TD in CMTX1 by comparing these findings with nerve conduction among patients with CIDP, CMT1A and healthy controls.

**Methods:** CMAPs were analyzed among patients with CMTX1, CIDP, CMT1A, and controls. TD were identified when: 1. duration between proximal and distal potential (P-D) was either between 30% and 60% (mild increase), or above 60% (sharp increase); 2. multiphasic or 3. duration of distal potential was over 9 ms.

**Results:** A total of 99 nerves of 21 patients (14 women and 7 men) were described in CMTX1 group. 28.28% of all nerves had TD. On average, each patient had 30.84% of nerves with this finding. Eight patients (38%) presented at least 2 nerves with TD. In 57.14%, potential increase was mild, while in 39.28%, it was sharp; 42.85% presented multiphasic nerves. 3.57% presented distal duration over 9 ms. Six patients (28.57%) presented at least one multiphasic nerve. Among women, 22 of the 64 nerves described (34%) had TD. Six women (27%) presented at least 2 nerves with this characteristic. Among men, 6 of the 35 nerves described (17%) has TD. Two men (28%) presented at least TD in 2 nerves. The number of nerves with TD (p = 0.018), of multiphasic nerves (p = 0.018), and nerves with sharp TD (p = 0.034) was significantly higher in CIDP. No abnormality was observed in CMT1A and the control group.

**Conclusions:** CMTX1 presented more frequently TD than CMT1A and the control group. However, patients presented less nerves with TD, multiphasic nerves, and nerves with sharp increase in P-D duration than patients with CIDP.

**References:** None.

**Keywords:** CMTR, Other, Inflammatory

**Grant Support:** None.
Hereditary Transthyretin-Mediated (hATTR) Amyloidosis: French Perspective on the Patient Journey

David Adams¹, Geraldine Nonnez¹, Marieke Podevin², Shahram Attarian³, Pascal Cintas⁴, Olivier Lairé⁵, Cyrla Hababou⁶, Jérôme Carey¹

¹Département de Neurologie, Hôpital Bicêtre AP-HP, Le Kremlin Bicêtre, France, ²Fondatrice et Dirigeante du Cabinet ARGO SANTE, Saint-Denis-en-Val, France, ³Service des Maladies Neuromusculaires et la SLA Hôpital de la Timone, Marseille, France, ⁴Centre de Référence de Pathologie Neuromusculaire, Hôpital Pierre Paul Riquet, Toulouse, France, ⁵Centre d’Imagerie Cardiaque, Hôpital de Rangueil, Toulouse, France, ⁶Alnylam Pharmaceuticals, Paris, France

Introduction: hATTR amyloidosis is a rapidly progressive, life-threatening disease where amyloid fibrils accumulate in multiple tissues. The majority of patients develop a mixed phenotype including polyneuropathy and cardiomyopathy. Nonspecific symptomology can delay diagnosis. A survey was conducted to better understand issues facing the French hATTR amyloidosis community.

Methods: Qualitative survey on disease management conducted in France (1/2/2018-3/29/2018) utilizing semi-structured interviews with 7 healthcare professionals (HCPs) with expertise in hATTR amyloidosis (including neurologists and cardiologists), 17 patients with hATTR amyloidosis and 5 caregivers. 15 patients had polyneuropathy with 7 showing a mixed phenotype (of these, 14 received tafamidis, the only approved treatment at the time for patients with hATTR amyloidosis with polyneuropathy, 1 had a liver transplant), 1 was asymptomatic and 1 had only cardiomyopathy. Semi-quantitative textual analysis was performed to interpret responses: simple lexical analysis counted vocabulary and content analysis by topic categorization to quantify the intensity of concerns and cross-reference them.

Results: HCPs deemed hATTR amyloidosis as a severe, debilitating disease with delayed diagnosis that led to missed treatment opportunities. Patients described a lengthy diagnosis journey during which they began experiencing multisystem manifestations. 60% of patients reported disease progression, of which 56% reported rapid progression. Most struggled to walk and were unable to continue with activities they had engaged in prior to their illness (walks, trips, etc.) leading to isolation and depression. Considerable burden was placed on caregivers, who became responsible for assisting with most daily activities (shopping, housework, showering, dressing, etc.).

Conclusions: hATTR amyloidosis is described as a severe and “imprisoning” disease. HCPs recognize need for coordination of multidisciplinary teams and early diagnosis and treatment. Patients require significant support from caregivers. They report poor quality of life due to difficulties with various activities, loss of autonomy which directly impacts caregivers, and fear for themselves and their families.

References: None.

Keywords: Amyloidosis

Grant Support: None.
Purpose: To expand the phenotypic spectrum of dynactin 1 (DCTN1)-related disease in a family with late-onset spinal muscular atrophy (SMA) with prominent scapular and tibial weakness.

Family Presentation: The proband is a 70-year-old woman with 20 years of slowly progressive, symmetric, proximal upper more than lower extremity weakness. She endorsed upper extremity fasciculations but no cramping, sensory, autonomic, bulbar, or respiratory symptoms.

Examination showed reduced tone, weakness of neck flexion, scapular winging most prominent on arm abduction, proximal more than distal weakness of the upper extremities most prominent in shoulder external rotation, proximal lower extremity weakness, and inability to stand on toes with preserved ankle dorsiflexion. Hyporeflexia was noted throughout with absent ankle jerks. Cranial nerve, sensory, and coordination testing was normal.

Lab testing revealed elevated CK (611 U/L). NCS/EMG was consistent with diffuse, chronic denervation with reinnervation. Genetic testing for 5q SMA (SMN1/2) was normal. Whole exome sequencing showed a heterozygous, splice site variant in DCTN1 (c.279+1G>T).

The 43-year-old daughter presented with a milder phenotype with proximal upper extremity weakness and fasciculations. Examination showed mild shoulder external rotation weakness. NCS/EMG was consistent with chronic denervation with reinnervation. Variant testing confirmed that she had the DCTN1 variant.

Family history revealed multiple paternal family members with progressive weakness, consistent with an autosomal dominant inheritance pattern.

Significance: Mutations of DCTN1 have been described distal hereditary motor neuropathy with vocal cord paralysis (dHMN7b) as well as neurodegenerative disorders (Perry syndrome, ALS-FTD). We describe a family with a late-onset, proximal-predominant motor neuropathy/neuronopathy associated with scapulotibial weakness, expanding the phenotypic spectrum. A DCTN1 variant within the same splice site (c.279+2T>C) has been reported in a patient with progressive muscle wasting, weakness, and fasciculations. We are currently pursuing variant testing in asymptomatic family members and functional testing.


Keywords: Human Genetics, CMTR, Other

Grant Support: None.
Early PXT3003 therapy delays disease onset in a rat model of Charcot-Marie-Tooth disease 1A (CMT1A)

Thomas Prukop¹, Jan Stenzel², Stephanie Wernick², Theresa Kungi², David Ewers², Serguei Nabirotchkin³, Klaus-Armin Nave², Rodolphe Hajji³, Daniel Cohen³, Michael Sereda¹

¹Max-Planck-Institute of Experimental Medicine, University Medical Center, Goettingen, Germany, ²Max-Planck-Institute of Experimental Medicine, Goettingen, Germany, ³Pharnext, Issy-Les-Moulineaux, France

The most common type of Charcot-Marie-Tooth disease is caused by a duplication of PMP22 leading to dysmyelination, axonal loss and progressive muscle weakness (CMT1A). Currently, no approved therapy is available for CMT1A patients. A novel polytherapeutic proof-of-principle approach using PXT3003, a low-dose combination of baclofen, naltrexone and sorbitol, slowed disease progression after long-term dosing in adult Pmp22 transgenic rats, a known animal model of CMT1A. Here, we report an early postnatal, short-term treatment with PXT3003 in CMT1A rats that delays disease onset into adulthood. CMT1A rats were treated from postnatal day 6 to 18 with PXT3003. Behavioural, electrophysiological, histological and molecular analyses were performed until 12 weeks of age. Daily oral treatment for approximately 2 weeks ameliorated motor deficits of CMT1A rats reaching wildtype levels. Histologically, PXT3003 corrected the disturbed axon calibre distribution with a shift towards large motor axons. Despite dramatic clinical amelioration, only distal motor latencies were improved and correlated with phenotype performance. On the molecular level, PXT3003 reduced Pmp22 mRNA overexpression and improved the misbalanced downstream PI3K-AKT / MEK-ERK signalling pathway. The improved differentiation status of Schwann cells may have enabled better long-term axonal support function. We conclude that short-term treatment with PXT3003 during early development may partially prevent the clinical and molecular manifestations of CMT1A. Since PXT3003 has a strong safety profile and is currently undergoing a phase III trial in CMT1A patients, our results suggest that PXT3003 therapy may be a bona fide translatable therapy option for children and young adolescent patients suffering from CMT1A.

References: None.

Keywords: Pre-clinical Studies, Schwann Cell, Axonal Biology

Grant Support: This trial was financially supported by Pharnext who provided support in the form of salaries for authors SN, RH and DC, but did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.
Nerve excitability properties of upper limb sensory and motor axons: a comparative study

Antonia Carroll1, James Howells2, Cindy Lin2, Neil Simon3, Susanna Park2, Mary Reilly4, Steve Vucic5, Matthew Kiernan2

1Brain and Mind Centre, University of Sydney Westmead Clinical School, University of Sydney, Sydney, Australia, 2Brain and Mind Centre, University of Sydney, Sydney, Australia, 3St Vincent's Hospital Clinical School, University of NSW, Sydney, Australia, 4MRC Centre for Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, UK., London, Australia, 5Western Clinical School, University of Sydney, Sydney, Australia

Introduction: The excitability properties of sensory and motor nerves are varied. The reason for this is myriad, including alterations in function, size and anatomy of the respective nerves. In order to characterise these differences and provide a reference guide for future studies of excitability parameters in disease groups, often limited by concurrent median neuropathy at the wrist, we characterised the motor and sensory axon excitability properties of the major distal upper limb nerves.

Methods: Axonal excitability studies were performed on 20 healthy controls, assessing the median and ulnar motor and sensory nerves as well as the superficial radial nerve.

Results: Depolarising threshold electrotonus (TE) at 10-20 ms was significantly increased in median compared to ulnar motor axons (p=0.01). This was accompanied by an increase in hyperpolarizing TE at 10-20 ms (p=0.01) and 20-40 ms (p<0.05). Separately, “fanning in” of TE along with increased resting current/threshold gradient (P < 0.001) were evident in the superficial radial nerve when compared to the median and ulnar sensory axons. Interestingly, ulnar sensory axons exhibited a higher threshold for activation when compared to the superficial radial (p<0.001) and median sensory axons (P= 0.04), there was, however, no difference in activating threshold for median and ulnar motor nerves (p= 0.06).

Discussion: The present study has established significant differences in axonal excitability between upper limb motor and sensory nerves, with the superficial radial nerve exhibiting a greater degree of slow K+ channel conductance. The differences in biophysical axonal properties could account for the vulnerability of specific upper limb nerves in peripheral nerve disorders. This study demonstrates the feasibility and utility of radial and ulnar nerves for peripheral nerve excitability studies, particularly in the context of concurrent median neuropathy.

References: None.

Keywords: Axonal Biology, Node Biology, Other

Grant Support: AC acknowledges the Brain Foundation for providing postgraduate support
A molecularly characterised CMT cohort in the West of Scotland

Kathryn Brennan

Queen Elizabeth University Hospital, Glasgow, United Kingdom of Great Britain and Northern Ireland

Charcot Marie Tooth Disease (CMT) is the most common form of inherited peripheral neuropathy. Mutations in over 100 genes have been identified as causal in this clinically and genetically diverse group of hereditary neuropathies. We have collected a cohort of 101 patients from 80 families with molecularly characterised Charcot Marie Tooth Disease attending a peripheral neuropathy clinic between 2015-2019 in the West of Scotland. This clinic captures a population of circa 2 million. We wanted to determine the population of molecularly confirmed CMT patients attending the clinic and to characterise their phenotypes.

Our testing in Scotland (depending on phenotype) involves MLPA of PMP22 first then targeted sequencing of specific genes according to phenotype. We also have access to inherited neuropathy gene panels and genome sequencing via the Scottish Genomes Project when indicated. We identified mutations in only 11 genes in this population. We observed the following groups: CMT1A n=52, CMT1X n=21, HNPP (n=7) and CMT1E (n=4). We also identified 5 patients with MFN mutations (2 of whom had AR mutations), 5 with MP0 mutations and 2 siblings with DNM2 mutations. Single patients with mutations identified in the following genes were also observed: NEFL, FIG4, AARS, GDAP and TRPV4. CMT1A was the most common form of inherited peripheral neuropathy observed representing just over 50% of the cohort. Indeed genetic interrogation of only 2 genes (PMP22 and GJB1) accounted for 83% of cases (84/101). Significant clinical heterogeneity was observed in the various groups especially in the CMT1A cohort. Autosomal recessive disease was rare with only 3 patients showing this pattern of inheritance (1 FIG4 and 2 MFN2). This small study contributes to the evolving literature on the genetic epidemiology of CMT.

References: None.

Keywords: Human Genetics, Other

Grant Support: None.
TTR mutations in patients diagnosed as having CIDP

Wilson Marques Jr.,1, Fernanda Figueiredo1, Silmara Gouvea1, Alex Silva1, Carolina Moreira1, Patricia Toscano1, Vanessa Marques1, Acary Oliveira2, Marcondes França Jr.1, Osvaldo Nascimento4, Mario Emilio Dourado Jr.5, Pedro Tomaselli1, Wilson Marques Jr.6

1Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, SP, Brazil., Ribeirão Preto, Brazil, 2Paulista School of Medicine, Federal University of São Paulo, São Paulo, SP, Brazil., São Paulo, Brazil, 3Faculty of Medical Science-State University of Campinas, Brazil, Campinas, Brazil, 4Federal Fluminense University, Antônio Pedro University Hospital, Niterói, Rio de Janeiro, Brazil, Rio de Janeiro, Brazil, 5Federal University of Rio Grande do Norte – UFRN, Natal, Brazil, Natal, Brazil, 6Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, SP, Brazil, Ribeirão Preto, Brazil

Introduction: Familial Amyloid Polyneuropathy (PAF) due to TTR mutations is caused by deposition of the TTR variant in the peripheral nerve. It is an autosomal dominant disease with incomplete penetrance. The most common onset manifestation is a length-dependent sensory neuropathy with preferential involvement of the small diameter sensory fibers and the autonomic nervous system, progressing over the years to a sensory and motor polyneuropathy, leading to severe disability. Neurophysiological studies demonstrate primarily an axonal neuropathy, but not infrequently nerve conduction studies fulfill CIDP criteria, resulting in wrong diagnosis and unnecessary treatment.

Objective: to analyse the presence of TTR mutations in patients previously diagnosed and treated as having CIDP.

Methods: We analysed retrospectively 62 patients diagnosed and treated as having CIDP. Their clinical and EMG data were reviewed. After informed consent the TTR coding region was sequenced on both directions.

Results: We identified two patients carrying the p.Val50Met (c.148G>A, rs 28933979) variant, a well recognized pathogenic TTR mutation and five patients carrying the p.Gli26Ser (c.76G>A, rs1800458) benign polymorphism.

Discussion: in this study we confirmed that patients with TTR mutations may be misdiagnosed as having CIDP. Interestingly the polymorphism p.Gli26Ser was present in a high frequency. This finding must be confirmed in large series, before being considered to have any role CIDP predisposition.


Keywords: Amyloidosis

Grant Support: FEPA, INCT Translational Medicine
Hereditary transthyretin amyloidosis (hATTR): description of the first cohort of V122I patients from South Italy

Anna Mazzeo, Luca Gentile, GianLuca Di Bella, Massimo Russo, Antonio Toscano, Giuseppe Vita

1 Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy, Messina, Italy
2 Clinical and Experimental Medicine Department, University of Messina, AOU "Policlinico G. Martino", Messina, Italy, 3 Nemo Sud Clinical Centre for Neuromuscular Disorders, Messina University Hospital, Messina, Italy, Messina, Italy

Introduction. V122I is one of more than 100 mutations in transthyretin (TTR) gene associated with hereditary TTR amyloidosis (hATTR). It has, as main clinical expression, a hypertrophic restrictive cardiomyopathy with mild or no neurological symptoms (1). It is particularly common among African Americans, with prevalence as high as 3.9%. Instead, a prospective study performed in an American urban population showed only two of 453 DNA samples from Caucasian newborns being positive for V122I (0.44%). Patients. We report here four unrelated Caucasian families (6 subjects) hailing from Sicily and carrying V122I mutation. All the subjects underwent neurologic/neurophysiologic evaluation and cardiologic baseline tests; in 4 of them, (99 m) Tc-DPD scintigraphy and/or cardiac magnetic resonance were performed. Results. In 2/6 subjects both neurological and cardiologic tests were negative, so they were classified as asymptomatic carriers. Of the remaining 4 patients, in three of them we found a classical cardiac phenotype, with a hypertrophic restrictive cardiomyopathy and cardiac failure. No signs of neuropathy were detected, except for carpal tunnel syndrome. The last case presented an axonal polyneuropathy and no cardiac involvement. Conclusions. Although in the US V122I prevalence in individuals without documented African origin is very low, subjects of uncertain African descent, carrying this mutation, have been identified in the United Kingdom, Italy, and France. A study from five cardiological center in France revealed that, among 300 consecutive patients with a diagnosis of hypertrophic cardiomyopathy who underwent exomic sequencing of TTR gene, 15% had a pathogenic TTR variant and the most common mutation was V122I. Our report describes the first cohort of V122I patients from South Italy confirming the possible underestimation of this mutation in the non-African population. The heterogeneity in the genotype–phenotype suggests that other factors may interact with disease causing mutations.

References: None.

Keywords: Amyloidosis

Grant Support: None.
Abnormal ankle dynamics during gait in CMT typically falls within three distinct patterns: equinus/cavus foot, cavovarus foot and flail foot(1). The purpose of this study was to determine if all three ankle phenotypes are present in CMT1. A consecutive series of 22 patients (44 limbs, 9 females, 12.8 ± 3.0 years) with a diagnosis of CMT Type 1A were analyzed. All patients underwent a comprehensive gait analysis following standard procedures. Differences between groups for selected parameters were analyzed using ANOVA with Tukey Post Hoc Testing (alpha = 0.05).

Patients with CMT1A presented with all three ankle phenotypes based on peak ankle dorsiflexion in terminal stance with 16 limbs (36%) in the equinus/cavus foot (7±3 degrees), 19 limbs (43%) in the cavovarus foot (14±11 degrees) and 9 limbs (20%) in the flail foot/ankle (20±2 degrees) groups. Seven patients had feet that were classified into different groups. Significant differences were also found between the ankle-based subgroups in knee (mean flexion in stance: 5±7, 11±5 and 14±11 degrees for the equinus/cavus, cavovarus and flail groups, respectively, p=0.009) and hip kinematics and kinetics. The results of this study show substantial variation in gait function within CMT1A including all three ankle phenotypes. Therefore, treatment options to address gait issues will vary among youth with CMT1A. Summarizing a specific treatment path based on CMT type may not be possible. Patients in the flail group would need AFO support to correct excessive and delayed peak ankle dorsiflexion in terminal stance. Asymmetry in some of the patients suggests that treatment options would need to vary depending on the side. Computerized gait analysis is a reliable method for characterizing abnormal walking in CMT and predicting specific treatment needs. Natural history studies should also determine the changes of gait phenotype over time for improved understanding of therapeutic outcomes.


Keywords: Other, Other, Other, Other, Other

Grant Support: Harold and Rebecca Gross Foundation
Elastin microfibril interface-located proteins (EMILINs) are extracellular matrix glycoproteins implicated in elastogenesis and cell proliferation.

Recently, a missense mutation in **EMILIN1** gene has been associated to autosomal dominant connective tissue disorder and sensory-motor neuropathy in a single family.

We report on a novel heterozygous **EMILIN1** mutation c.748C>T [p.R250C] located in the coiled coil forming region of the protein, identified by WES in a further family of 4 members, all presenting a more specific phenotype with severe laxity and motor neuropathy selectively affecting distal lower limbs. Immunofluorescence study of muscle biopsy documented the presence of EMILIN-1 in nerve bundles and perimysial connective tissue. Nerve biopsy showed unspecific alteration in the myelin folds in one case. Skin fibroblasts from two affected patients displayed a reduced extracellular deposition of EMILIN-1 protein with a disorganized network of poorly ramified fibers. Zebrafish model presented altered locomotion and diminished axonal sprouting from spinal cord.

Our data endorse the role of **EMILIN1** in human disease of connective tissue and peripheral nerves and expands the related clinical spectrum.


**Keywords:** Human Genetics

**Grant Support:** None.
Peripheral Nerves Impairment in Idiopathic Parkinson's Disease

Ani Antia¹, Nato Bokuchava², Maia Beridze³, Nana Kvirkvelia⁴

¹Pineo - Medical Ecosystem, Tbilisi, Georgia, ²High Technology Medical Center - University Clinic, Tbilisi, Georgia, ³The First University Clinic of Tbilisi State Medical University, Tbilisi, Georgia, ⁴Petre Sarajishvili Institute of Neurology, Tbilisi, Georgia

Background and aims: Parkinson’s disease (PD) is a neurodegenerative disorder that affects motor system. Peripheral nerves are frequently involved in patients with PD that negatively influences on their quality of life.

Our aim was to assess the frequency and type of peripheral neuropathy (PNP) in PD patients.

Methods: The study comprised 46 patients with PD (28 males, 18 females aged 64-82 years, disease duration was 2-10 years) and 46 age and gender matched controls. Nerve conduction studies were performed in median, ulnar, peroneal, tibial and sural nerves of both limbs. Statistics performed by SPSS -14.0.

Results: Electrophysiological abnormalities consistent with a diagnosis of PNP were found in 25 PD patients (54.6%), who were older (76.3±6.1 vs 70.5±6.3 years) and had a longer duration of PD, compared to 13 healthy controls (28.2%). The most common type of PNP in PD patients was motor demyelinating (33.2%) axonal motor and sensory PNP detected in 21.4%. The most common type of PNP in healthy controls was axonal motor and sensory PNP and in 17.4% and sensory PNP in 10.8% (p<0.01).

Conclusion: PNP is common in PD patients compared to healthy controls. The most common type is the motor demyelinated PNP. Polyneuropathy is rarely found. Our results suggest the correlation between the presence of motor neuropathy in PD and age of patients (P<0.5). No correlation was found between the presence of PNP and gender.

References: None.

Keywords: Other

Grant Support: None.
Two 173 point mutations in HMBS gene causing acute intermittent porphyria

Jie Lin

Fudan University, Huashan Hospital, Shanghai, China

Abstract: Acute intermittent porphyria (AIP) is a rare inherited disorder due to mutations in HMBS gene. These mutations usually lead to severe HMBS enzymatic activity deficiency. The classical manifestations of AIP include acute abdominal pain, neuropsychiatric symptoms and red urine. Here, we reported two unrelated patients who had specific manifestations respectively and the same mutation point with different amino acid changes. One patient was a young male whose brain, peripheral nerve and skin were involved. De novo mutation p.Arg173Trp was found in this patient. The other patient with p.Arg173Gln mutation in HMBS gene was a woman of reproductive stage. Her symptoms and physical signs were typical but the biochemical tests were negative. These two cases extend the spectrum of AIP.

References: None.

Keywords: Human Genetics, Metabolic, Small Fibers

Grant Support: None.
Introduction: hATTR amyloidosis is due to one of many mutations in the transthyretin (TTR) gene, resulting in a progressive fatal disease with sensory, motor and autonomic involvement.

Objective: To characterize the symptoms, signs and skin biopsy neuropathological findings in a cohort of individuals with TTR mutations.

Methods: Individuals with a variety of TTR mutations underwent detailed neurological examinations including the Neuropathy Impairment Score in the Lower Limb (NIS-LL), the Utah Early Neuropathy Score (UENS), Coutinho staging, autonomic testing, symptom scores (using the EuroQol, Brief Pain Symptom Inventory, and the Orthostatic Hypotension Questionnaire). All subjects had 3mm punch skin biopsies at the distal leg and distal thigh with analysis of amyloid burden by Congo Red, and neuropathy severity by staining with protein gene product 9.5.

Results: A total of 88 subjects participated with the following TTR mutations: 43- Val30Met, 30- Ser50Arg, 6- Gly47Ala, 5- Ser52Pro, 2- F64L, 1- I73V and 1 with Y136H. Coutinho staging included 47 stage 0, 32 stage 1, 8 stage 2 and 1 stage 3. For example, at Coutinho stage 1, compared to other mutations, V30M mutations had the greatest orthostatic intolerance (P<0.01, ANOVA), pain (P<0.01, ANOVA) and disability (P<0.01, ANOVA). A radar-plot approach will be used to compare neuropathy features across mutations and Coutinho stages.

Conclusion: Symptoms of neuropathy, both somatic and autonomic, vary by mutation type and across Coutinho staging. S50R mutations have greater symptom burden with early disease classification, while the V30M mutations have the largest increase in symptom burden with disease progression. These findings have implications for the types of screening used in individuals with different hTTR mutations.

References: None.

Keywords: Amyloidosis

Grant Support: Acknowledgement: Funded by Pfizer (RF)
Predictive modeling reveals threonyl-tRNA synthetase (TARS) as a candidate gene for axonal peripheral neuropathy

Anthony Antonellis

University of Michigan Medical School, Ann Arbor, MI, USA

Aminoacyl-tRNA synthetases (ARSs) charge tRNA molecules with cognate amino acids, a critical step in translating the genetic code. Mutations in five genes encoding an ARS cause autosomal dominant, axonal peripheral neuropathy. Neuropathy-associated ARS mutations decrease enzyme function in biochemical and yeast complementation assays, and are dominantly toxic when modeled in C. elegans. These functional studies provide important evidence for determining the pathogenicity of newly identified mutations in patient populations, suggesting that such models have considerable predictive power. Here, we use the above model systems to determine if mutations in any ARS gene can cause peripheral neuropathy, beginning with threonyl-tRNA synthetase (TARS), which has not been associated with any human disease. Like the five ARS enzymes previously implicated in peripheral neuropathy, TARS is homodimeric and charges tRNA in the cytoplasm, making it a strong candidate for testing our predictive models. We first performed a loss-of-function screen in yeast by testing 10 TARS missense mutations that affect highly conserved amino-acid residues in critical regions of the enzyme. Three mutations (N412Y, R433H, and G541R) reduce or ablate yeast cell growth, indicating impaired enzyme function. We then modeled these loss-of-function TARS mutations in the C. elegans ortholog tars-1 and tested each variant for dominant toxicity. From these assays, we identified one TARS variant (G541R) that is loss-of-function in yeast and dominantly toxic in worm. These findings make G541R TARS similar to HARS and AARS variants that are implicated in neuropathy. Toward assessing G541R TARS for a role in peripheral neuropathy, we generated and validated a knock-in mouse strain for this variant. Here, we present unpublished yeast, C. elegans, mouse, and human genetic data indicating that human TARS mutations may cause axonal peripheral neuropathy. This work provides a framework to proactively identify ARS loci and alleles that contribute to axonal peripheral neuropathy.

References: None.

Keywords: CMTR, Human Genetics

Grant Support: None.
NEXT-GENERATION SEQUENCING (NGS) BY A GENE-PANEL APPROACH IN INHERITED PERIPHERAL NEUROPATHIES.

Moreno Ferrarini¹, Silvia Testi¹, Federica Taioli¹, Tiziana Cavallaro², Sergio Ferrari², Gian Maria Fabrizi ¹

¹Verona University, Verona, Italy, ²Verona Hospital, Verona, Italy

Charcot-Marie-Tooth (CMT) disease is associated with up to 100 genes. NGS is a cost-effective tool of mutational screening; nevertheless, many patients, especially those affected with the axonal CMT (CMT2) or with Hereditary Motor Neuropathies (HMN), still remain undiagnosed.

We report the yield of targeted NGS for the diagnosis of CMT-related neuropathies using a PGM Ion Torrent platform. By the ampliseq™ tool we implemented three custom gene panels: Neuro1_routine panel (18 genes), Neuro1_extension panel (45 genes) and Neuro2 panel (62 genes); panels were designed based upon presumptive mutational frequencies. By using 318 chips, the capacity of analysis was 40 patients on Neuro1_routine, 10 patients on Neuro1_extension, and 4 patients on Neuro2. Targeted resequencing was performed after ruling out Copy Number Variations in the more common PMP22, MPZ, GJB1 genes.

One hundred eighty-seven patients were analyzed by the Neuro1_routine, 124 by the Neuro1_extension, and 20 patients by the Neuro2 panel. We obtained 68 variants individually classified into classes 5 (pathogenic), 4 (likely pathogenic) or 3 (Variant of Uncertain Significance - VUS), according to the American College Medical Genetics and Genomics criteria. The diagnostic yield was 32% (60 index cases) including class 3 variants, and 12.3% (23 index cases) considering only class 4-5 variants. Variants occurred in 29 genes, the most frequent being: MFN2 (five class 4-5 and four class 3 variants); Hspb1 (two class 4-5 and four class 3 variants); GJB1 (two class 4-5 and three class 3 variants); MPZ (four class 4-5 variants); GARS (one class 4 and three class 3 variants), LRSAM1 (three class 3 variants), DYNc1h1 (three class 3 variants), GDAP1 (one class 5 and one class 3 variants).

The report emphasizes difficulties in variants interpretation, due to the lack of ready-to-use functional tests in vitro, of feasible co-segregation analysis and of an open access to disease-specific databases.

References: None.

Keywords: Human Genetics

Grant Support: None.
Poster 41

**Studying the role of HINT1 as a transcriptional regulator and its involvement in peripheral neuropathies**

Silvia Amor-Barris, Ligia Mateiu, Kristien Peeters, Albena Jordanova

*VIB Center for Molecular Neurology, University of Antwerp, Antwerp, Belgium*

In 2012 our group described *HINT1* as one of the most common genes causing autosomal recessive hereditary peripheral neuropathy. Since then, 16 pathogenic mutations have been identified leading to loss of HINT1 function due to three different mechanisms: 1) protein instability, followed by proteasomal degradation; 2) loss of enzymatic activity; 3) premature stop codon triggering putative nonsense-mediated mRNA decay.

HINT1 is a ubiquitously expressed purine phosphoramidase but its function in the peripheral nerves is still uncharacterized. One of the many roles assigned to HINT1 is transcriptional regulation of important cellular pathways, like apoptosis, tumor suppression, etc. In order to study the effect of HINT1 mutations on this function, quantitative differential transcriptome profiling was performed using lymphoblast cultures of patients carrying different HINT1 mutations. We performed 3' polyadenylated RNA next generation sequencing using QuantSeq library generation. In this way, we generated only one read per mRNA transcript allowing us to reliably quantify and compare transcriptomes of healthy individuals and patients. We then performed gene set enrichment and gene ontology analyses to determine misregulated molecular pathways. We were able to identify: 1) already known pathways regulated by HINT1; 2) pathways previously linked to CMT; 3) pathways involved in the general maintenance of the cell which might have an important impact in sensitive cells such as peripheral neurons. This study provides clues for deciphering the pathomechanisms leading to HINT1-neuropathies.

**References:** None.

**Keywords:** CMTR

**Grant Support:** None.
Poster 42

Molecular diagnosis approach of Hereditary Peripheral Neuropathies in a French reference center.

Guillemette Beaudonnet¹, Bruno Francou², Christine Barnerias³, Marion Brisset⁴, Cécile Cauquil⁵, Isabelle Desguerre⁶, Marion Gerard⁶, Cyril Gitiaux⁷, Arnaud Isapof⁷, Céline Labeyrie⁸, Pierre Lozeron⁸, Sarah Léonard-Louis⁹, Michèle Mayer⁷, Guillaume Nicolas⁴, Adeline Not⁵, Marie-Christine Nougues⁷, Pascal Sabouraud¹⁰, Tanya Stojkovic⁹, Jérôme Bouligand², Alexis Proust¹¹, David Adams¹², Anne Guiochon-Mantel¹¹, Andoni Echaniz-Laguna¹²
Introduction

Hereditary motor and sensory neuropathies (HMSN), i.e. Charcot-Marie-Tooth disease (CMT), are a group of heterogeneous disorders with various clinical, electrophysiological and genetic presentations. Molecular diagnostic strategy usually consists in screening first the PMP22 gene duplication responsible for the most frequent CMT, i.e. CMT1A. If PMP22 analysis is negative, next generation sequencing (NGS) is used to simultaneously analyze the remaining CMT-linked genes.

Patients, Materials and Methods

After exclusion of the CMT1A-related PMP22 duplication, we used an in-home panel of 95 genes to analyze 355 CMT index cases from 7 French University Hospitals. Clinical and genetic results were systematically discussed in multidisciplinary meetings (MM) involving both clinicians and geneticists. Genetic variants of interest were investigated using Sanger sequencing.

Results

17p12 duplication was found in 16% of cases (n=68). NGS analysis found a CMT-causative mutation in 25% of cases (n=89). In 33% of cases (n=117), a variant of uncertain significance (VUS) was identified. No genetic cause has been identified in 42% of cases (n=149).

Conclusion

In our series, NGS led to definite molecular diagnosis in 25% of CMT cases, and VUS were found in 33% of cases. NGS effectiveness was low in patients with late-onset CMT (>60 years old) and patients with no family history. MM were crucial to classify variants and steer care management, including fine-tuning diagnosis, providing genetic counseling, identifying families in need of genome-wide analysis, and re-classifying diagnosis.

References: None.

Keywords: Human Genetics, CMTR

Grant Support: None.
Extending the Scope of Diagnostic Gene Panels in CMT Improves Diagnostic Yield

Menelaos Pipis1, Alaa Khan1, Nandini Badarinarayan2, James Polke2, Roy Poh2, Matilde Laura1, Alexander Rossor1, Henry Houlden3, Mary Reilly1

1MRC Centre for Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, United Kingdom of Great Britain and Northern Ireland, 2Neurogenetics Unit, UCL Queen Square Institute of Neurology, London, United Kingdom of Great Britain and Northern Ireland, 3MRC Centre for Neuromuscular Diseases, Neurogenetics Unit, UCL Queen Square Institute of Neurology, London, United Kingdom of Great Britain and Northern Ireland

Targeted CMT gene panels have become the commonest next-generation sequencing (NGS) technique used in CMT clinical practice. Such panels employ specific capture kits which ensure that only the genomic regions of known CMT genes are targeted and sequenced and although subtype-specific panels exist such as demyelinating or axonal, there is a move towards the use of single unified CMT panels. The preparation of CMT panels usually falls within a greater NGS library preparation that may also include genes of other hereditary neurological conditions such as hereditary spastic paraplegia (HSP), hereditary ataxias and myopathies.

Bearing in mind the significant intergenic and intragenic phenotypic heterogeneity of CMT, we analysed the banked sequenced data from 700 CMT cases that had an initial negative CMT panel. In unrelated cases whose phenotype we will detail, we identified pathogenic (ACMG Class 5) and likely pathogenic variants in genes including MFN2, NEFH, KIF5A, MPV17 and FXN and further variants of unknown significance (VUS) in SACS and POLG. The pre-existing phenotype-genotype correlations in specific cases have aided in the interpretation of novel variants.

Our findings highlight the phenotypic and genetic heterogeneity of CMT as well as the increasingly recognised phenotypic overlap between axonal CMT and the hereditary spastic paraplegias (HSP), ataxias and distal myopathies. Therefore, in genetically unclassified cases of CMT in which the CMT panel is negative, investigators should consider testing a HSP or ataxia panel depending on the phenotype.

References: None.

Keywords: CMTR, Human Genetics

Grant Support: None.
AHNAK2 mutations in a Malaysian family with autosomal recessive demyelinating CMT

Azlina Ahmad-Annuar\textsuperscript{1}, Shelisa Tey\textsuperscript{1}, Nortina Shahrizaila\textsuperscript{1}, Alexander Drew\textsuperscript{2}, Sarimah Samulong\textsuperscript{1}, Khean-Jin Goh\textsuperscript{1}, Esra Battaloglu\textsuperscript{4}, Derek Atkinson\textsuperscript{6}, Yesim Parman\textsuperscript{6}, Albena Jordanova\textsuperscript{5}, Ki-Wha Chung\textsuperscript{7}, Byung-ok Choi\textsuperscript{8}, Yi-Chung Li\textsuperscript{9}, Michaela Auer-Grumbach\textsuperscript{10}, Garth Nicholson\textsuperscript{11}, Marina Kennerson\textsuperscript{11}

\textsuperscript{1}University of Malaya, Kuala Lumpur, Malaysia, \textsuperscript{2}University of Sydney, The Kinghorn Cancer Centre, Sydney, Australia, \textsuperscript{3}University of Malaya, Kuala Lumpur, Malaysia, \textsuperscript{4}Bogazici University, Istanbul, Turkey, \textsuperscript{5}University of Antwerp, Antwerp, Belgium, \textsuperscript{6}Istanbul University, Istanbul, Turkey, \textsuperscript{7}Kongju National University, Gongju, Korea (Republic of), \textsuperscript{8}Sungkyunkwan University School of Medicine, Seoul, Korea (Republic of), \textsuperscript{9}National Yang-Ming University School of Medicine, Taipei, Taiwan, \textsuperscript{10}Medical University of Vienna, Vienna, Austria, \textsuperscript{11}University of Sydney, Sydney, Australia

We are studying a Malaysian family of a consanguineous marriage with two sons who are affected with autosomal recessive CMT. Mutations in all known recessive genes have been excluded and genome-wide linkage analysis mapped the likely disease locus to a 7.48Mb region on chromosome 14q31.11-q32.33. Whole exome sequencing identified two non-synonymous mutations in the \textit{AHNAK2} gene (p.T40P and p.H915Y) that segregated with the disease in the family. Studies with patient fibroblasts indicate the mutation results in a significant loss of AHNAK2 protein expression. Expression studies and localization studies of AHNAK2 are currently being conducted to understand more about this poorly characterized gene. In addition, functional studies will help to determine how this loss of expression interferes with cell survival and function.

\textbf{References:} None.

\textbf{Keywords:} Human Genetics

\textbf{Grant Support:} This work was supported by the University of Malaya High Impact Research grant (HIR-MOHE MED/08/02) awarded to A.A.A; the National Health and Medical Research Grant (APP104668) awarded to M.L.K and G.A.N; the Korean Health Technology R&D Project, Ministry of Health & Welfare (HI15C1560) awarded to B-O.C and K-W.C, Ministry of Science and Technology, Taiwan, ROC (MOST105-2628-B-075-002-MY3) awarded to Y-C.L, Research Fund of the University of Antwerp (TOP BOF 29069) awarded to A.J. Austrian Science Fund (FWF, P27634FW) awarded to M.A-G.
Modern Gene and Allele Discovery, Evaluation in CMT: The Genesis Platform and the Variant Browser

Lisa Abreu¹, Dana Bis¹, Adriana Rebelo¹, Steve Courel², Matt Danzi¹, Eric Powell¹, Stephan Zuchner¹

¹University of Miami, Miami, FL, USA, ²University of Miami, Miami, FL, USA

Over 120 CMT and related genes have been identified; yet, nearly 50% of CMT patients do not currently receive a genetic diagnosis. This will clearly hamper access to clinical trials and especially gene therapy approaches. The latter will require certainty about variant pathogenicity. To address these challenges, we have created two web-based tools: the GENESIS analysis and archiving platform and the Inherited Neuropathy Variant Browser (INVB). The continuously improving GENESIS platform with now over 9,000 genomic datasets has grown to include most of the INC and many AOINC investigators. With support from this platform, these investigators have collectively identified more than 50% of all CMT genes discovered globally. Prominent examples include BSCL2, ATP1A1, MME, and WARS. To date, over 140 publications have cited GENESIS, with 65 from the CMT or related fields. The concept of user-driven data sharing and matchmaking has allowed researchers from across the globe to connect candidate genes with additional families. Active development includes structural variation and multi-OMICS analysis and statistical analysis features. Complementary, the INVB tool is focused on evaluation of pathogenicity of variation in CMT genes. The large number of Variants of Unknown Significance has created major challenges for genetic counseling. Additionally, fewer individual variants in known genes are being published as the academic merit is decreasing, and most testing now happens in clinical laboratories, which typically do not correlate their variants with clinical phenotypes. With INVB, we aim to encourage and facilitate the global capture of variant data to gain a large collection of alleles in CMT genes, ideally in conjunction with phenotypic information. Geneticists, physicians, and genetic counselors can enter variants detected by clinical tests or in research studies in addition to genetic variation gathered from published literature. In conclusion, these resources will help maintaining the pace of diagnostic improvements for CMT patients.

References: Inherited Neuropathy Consortium

Keywords: Human Genetics, Pre-clinical Studies

Grant Support: None.
Poster 47

NARS As A Candidate Gene In A Dominant CMT2 Family

Willem De Ridder¹, Tine Deconinck², Danique Beijer², Peter De Jonghe³, Stefan Züchner⁴, Anthony Antonellis⁵, Jonathan Baets⁶

¹University of Antwerp, Antwerp University Hospital, Edegem, Belgium, ²University of Antwerp, Edegem, Belgium, ³Antwerp University Hospital, Edegem, Belgium, ⁴University of Miami, Miami, FL, USA, ⁵University of Michigan Medical School, Ann Arbor, MI, USA, ⁶University of Antwerp, Antwerp University Hospital, Edegem, Belgium

Introduction: Mutations in genes encoding aminoacyl-tRNA synthetase (ARS) enzymes have been implicated in a broad spectrum of recessive and dominant human genetic disorders. ARSs are enzymes that charge tRNA molecules with cognate amino acids in the cytoplasm and mitochondria. Recessive mutations in different ARS enzymes typically cause severe, early-onset diseases affecting different tissues. Interestingly, dominantly inherited mutations in cytoplasmic ARSs are exclusively linked to an axonal peripheral neuropathy (CMT2). As of yet, 28 of the 37 human ARS enzymes have been implicated in Mendelian disorders and phenotypes linked to the remaining ARSs are expected to be documented.

Methods: We studied the clinical, genetic, and electrophysiological details of a family in which multiple individuals of different generations present with a CMT2 phenotype. We performed whole-exome sequencing on genomic DNA of the index patient and performed segregation studies of an identified heterozygous candidate variant in NARS. Additional experiments encompassing yeast complementation assays are being planned to study the functional effect of the identified variant on NARS function. Additional families with rare NARS variants are investigated.

Results: We identified the heterozygous p.Ser461Phe variant in NARS, a missense variant absent from the gnomAD control database, affecting a highly conserved amino-acid residue of the encoded cytoplasmic enzyme NARS. In silico prediction algorithms were in favor of pathogenicity and the variant co-segregates with disease in multiple affected individuals. Two other NARS variants are currently investigated with regard to pathogenicity.

Discussion: We identified a putative mutation in NARS, segregating with disease in a dominant CMT2 family. Additional pedigrees as well as functional studies will potentially strengthen the association of NARS with CMT2. We propose NARS as a new member of the ARS gene family involved in the pathophysiology of PNS axonal degeneration.

References: None.

Keywords: Human Genetics

Grant Support: None.
Comparative transcriptomics of aminoacyl-tRNA synthetases mutations in an induced neural progenitor cell model

Matthew Jennings¹, Denisa Hathazi², Patricia Prada Dacasa³, Helen Griffin⁴, Veronika Boczonadi⁴, Rita Horvath⁵

¹Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK, United Kingdom of Great Britain and Northern Ireland, ²Leibniz-Institut für Analytische Wissenschaften, ISAS, Dortmund, Germany, ³Universitat Autònoma de Barcelona, Barcelona, Spain, ⁴Wellcome Centre for Mitochondrial Research, Institute of Genetic Medicine, Newcastle University, Newcastle, United Kingdom of Great Britain and Northern Ireland, ⁵Department of Clinical Neurosciences, University of Cambridge, Cambridge, United Kingdom of Great Britain and Northern Ireland

Mutations in aminoacyl-tRNA synthetase (ARS) genes cause a range of neurological diseases. Heterozygous missense mutations in cytosolic ARS typically result in axonal peripheral neuropathy (CMT2) or distal hereditary motor neuropathy (dHMN). Proposed mechanisms of ARS-related CMT include loss-of-function affecting aminoacylation, as well as toxic gain-of-function. Furthermore, there is evidence to suggest that non-canonical functions of the bifunctional mitochondrial glycyl-ARS (GARS) and lysyl-ARS (KARS) may additionally play a role in the pathology of these disorders. In contrast, autosomal recessive mutations in ARS cause multisystemic disorders predominantly affecting the brain, heart and skeletal muscle.

To delineate the effect of these mutations in the nervous system we developed an in vitro model by direct conversion of fibroblasts into induced neuronal progenitor cells (iNPCs) of patients carrying dominant or recessive mutations in cytosolic (AARS, NARS), bifunctional (GARS, KARS) and mitochondrial (AARS2, EARS2, RARS2) ARS genes. We performed RNA sequencing (RNAseq) of these iNPCs to investigate the evidence supporting or contradicting common mechanisms in these disorders, and further incorporated proteomic data in the GarsC20R1+/− mouse model.

Cellular pathway analysis of RNAseq data indicates that processes involved in neurite extension and interaction with extracellular matrix proteins are altered in cells from cytosolic and bifunctional ARS-related CMT, whereas processes associated with protein translation are affected in iNPCs carrying recessive mutations. Defects in mitochondrial-ARS proteins typically alter mitochondrially encoded electron transport chain complexes, distinct from that seen in bifunctional ARS-mutant cells.

Proteomic analysis in the GarsC20R1+/− mouse detected significant changes in proteins involved in axon development, dendritic transport, myelin sheet formation and maintenance, but also in mitochondrial proteins involved in fatty acid oxidation, acetyl Co-A biosynthetic process, mitochondrial biogenesis and fission. Integration of these data indicates mutations in cytosolic, bifunctional and mitochondrial ARS genes lead to disease by distinct pathomechanisms, which may explain the different clinical manifestations.

References: None.

Keywords: Axonal Biology, Human Genetics

Grant Support: None.
A Novel SPTLC1 Mutation In Potentially Treatable Hereditary Sensory And Autonomic Neuropathy Type I.

Federica Boso1, Andrea Armirotti2, Federica Taioli1, Moreno Ferrari1, Lucilla Nobbio3, Tiziana Cavallaro1, Gian Maria Fabrizi1

1University of Verona and Department of Neurosciences, Verona, Italy, 2Analytical Chemistry Lab - Fondazione Istituto Italiano di Tecnologia, Genova, Italy, 3University of Genova, Genova, Italy

Hereditary Sensory and Autonomic Neuropathy type I (HSANI) generally present with early sensory loss, lancinating pain and variable motor and autonomic involvement. Most patients carry Serine Palmitoyl-Transferase (SPT) Long Chain base subunit 1 (SPTLC1) mutations that affect the first step in sphingolipids biosynthesis by modifying SPT substrate specificity to produce atypical neurotoxic deoxysphingoid bases (DSB) [1].

We identified a novel SPTLC1 mutation in a patient with fairly typical phenotype, comprised of progressive loss of superficial and deep sensation on lower limbs, pronated feet with hammer toes, repetitive ulcerations with osteomyelitis and cutaneous dystrophy. Interestingly he reported neither pain or positive sensory symptoms nor difficulties in motor performances throughout adolescence. Anamnesis was negative, except for isoniazid/pyridoxine chemoprophylaxis, not reaching neurotoxic cumulative doses.

Neurophysiological studies disclosed an axonal, sensory-motor, length-dependent neuropathy with unrecordable laser-evoked potentials. Sural nerve biopsy showed a chronic axonal process with severe fiber loss and denervated Schwann cell processes; no active degeneration, collagen pockets or clusters of regenerating fibers were detectable. Targeted-resequencing demonstrated a c.398G>T heterozygous transversion in exon 5 leading to a likely pathogenic p.Cys133Phe substitution, since it was absent in reference databases, probably damaging in-silico and it was originating de-novo at cosegregation analysis. As suggested by untargeted lipidomic analysis, this mutation could affect SPT specificity: indeed abnormally high plasma levels of aberrant m18:0 DSB (22:0, 23:0, 24:0) reinforced the hypothesis of heightened metabolization of Alanine and subsequent atypical DSB production.

Pathogenic mechanisms are still unanswered, but elevated DSB levels have also been linked to similar clinical entities such as diabetic and paclitaxel induced neuropathies. Most importantly, DSB measures could become a diagnostic and prognostic marker to aid the recognition of patients with atypical mutations, since a recent trial suggested that SPTLC1-HSAN might be treatable as L-serine could limit DSB accumulation, thus reducing disease severity and progression [2].


Keywords: Other

Grant Support: None.
CMT1A AND IMPAIRED PATIENT MOBILITY: EXPRESSIONS, REMEDIES AND IMPACT ON QUALITY OF LIFE

Allison Moore¹, Robert Moore¹, Joy Aldrich²

¹Hereditary Neuropathy Foundation, New York, NY, USA, ²Hereditary Neuropathy, Seattle, WA, USA

OBJECTIVES: Impaired mobility is cited by CMT1A patients as the #1 pheno-typical expression of their disease, significantly impacting daily activities and QoL. This study assessed the most prevalent symptoms that cause mobility impairments of CMT1A patient and their associated impact on QoL. In addition, it identifies the remedies patients use to cope with their mobility impairment.

METHODS: HNF created the Global Registry for Inherited Neuropathies (GRIN), to capture detailed Inherited Neuropathy (IN) patient history via an online, IRB approved patient survey from 2013Q1-2019Q1. IN patients (N=2,142) were surveyed, yielding a 34% CMT1A (N=770) cohort. This cohort was queried against a subset of questions to test for causal relationships between disease state, level of impairment and QoL.

RESULTS: CMT1A patients (N=770) identify mobility (63%) as the Activity of Daily Life (ADL) impacted most by their disease. Multiple expressions of their disease that have an impact on their mobility, with the most common response being weak ankles 79%. 58% of patients can neither walk on their heels or toes, indicating a significant degree of impairment. 48% reported using some type of orthotic device (leg braces, foot orthotics) or mobility device (cane, walker, wheelchair, scooter) to assist with mobility. 51% of CMT1A patients have had orthopedic surgery as a remedy to gain additional mobility or to reduce loss of function. Maintaining balance and walking stamina were cited as most challenging by 28% of patients. A significant by-product of mobility challenges is fatigue, reported by 85% of CMT1A patients. Pain is cited by 77%.

CONCLUSIONS: Mobility impairments are represented in a large cohort of CMT1A patients, affecting their physical and psychological well-being. While use of orthotics, mobility devices, and surgery can have a positive impact on mobility, CMT1A patients need a more cohesive and comprehensive approach to addressing mobility impairment.

References: None.

Keywords: Other, CMTR, Pain, Other

Grant Support: Pharnext Pharmaceuticals
c.2125_2133del is a new mutation in MFN2 gene resulting in a Heterogeneous Phenotypic Spectrum

Fernanda Figueiredo, Pedro Tomaselli, Silmara Gouvea, Adriana Genari, Carolina Moreira, Vanessa Marques, Wilson Junior

University of São Paulo, Ribeirão Preto, Brazil

Background: Mutations in the MFN2 gene are the most frequent cause of the axonal neuropathies. They are associated to a large spectrum of clinical manifestations, including an autosomal dominant CMT (CMT2A), a recessive subtype, a severe early onset axonal neuropathy (SEOAN), a dominant CMT associated to pyramidal features, a dominant CMT associated to optic atrophy, CMT associated to cognitive impairment, and a sensory neuropathy associated to anhidrosis.

Aim: To present a new MFN2 mutation associated to phenotypic variability inside the family.

Case report: In a screening study of our axonal CMT patients, by Sanger sequence, we found a novel deletion variant (NM_014874: c.2125_2133del) in 3 patients of the same family. This variant eliminates 3 amino acids located in C-terminus of the protein, an important domain necessary for MFN2 function. Family pedigree is typically autosomal dominant. We had the opportunity to study 3 sibs born from an affected mother. The first sibling is a 47 years old woman affected by an early onset (4 years old) severe motor and sensory neuropathy associated to hoarseness and severe findings on NCS (SAP: radial = 4.7 uV, 43 m/s; ulnar = absent; CMAP: ulnar = 0.5 mV, 47.3 m/s). The second sibling is a woman with a milder CMT disease (SAP: radial = 8.7 uV, 53.8 m/s; ulnar = 2.4 uV, 52.8 m/s; CMAP: ulnar = 3.27 mV, 54.9 m/s). The last sibling is a man showing a mild phenotype (CMTNS v2 = 9) restricted to the motor fibers – dHMN (SAP: sural = 15.8 uV, superficial peroneral = 9.1 uV; CMAP: peroneal = 0.4 mV, 36.6 m/s).

Discussion/Conclusion: We present a new mutation on MFN2 gene that seems to be associated to a large spectrum of clinical manifestations, including a severe early onset CMT2 a much milder CMT2 phenotype and a milder dHMN.


Keywords: Human Genetics, Other, Other, Other, Other

Grant Support: CAPES; PRONAS; INCT Translational Medicine and FAPESP and FAEPA
F WAVE PERSISTENCE IN THE DIFFERENTIAL DIAGNOSIS OF SENSORY POLYNEUROPATHIES AND NEURONOPATHIES

Fabricio Diniz de Lima¹, Alberto Rolim Muro Martinez¹, Antonio Jose Garbino², Anamarli Nucci³, Marcondes Cavalcante França Junior¹

¹State University of Campinas, Campinas, Brazil, ²Lauro de Souza Lima Institute, Bauru, Brazil

Introduction: The distinction among sensory polyneuropathies (SP) and neuronopathies (SN) is important for etiologic investigation and for prognosis estimation. However, this task is often challenging for the clinical neurophysiologist. In this scenario, we hypothesize that F wave assessment might be helpful, since it is able to detect subtle signs of motor involvement, which are found in SP, but not in SN. The aim of this study was to determine whether lower limb F waves are useful in the differential assessment of SP and SN.

Methods: Sixty-nine patients were selected: 21 with SP - 12 diabetic, 4 familial amyloidosis and 5 with systemic diseases - , 22 with leprosy neuropathy (LN) and 26 with SN - caused by Sjögren's syndrome, autoimmune hepatitis, HTLV or idiopathic. We collected data on height for every subject. For each patient, we obtained 20 supramaximal distal stimuli in the peroneal and tibial nerves to record F waves using a Neuropack M1 unit (Nihon Kohden Co., Japan). The values of F wave latencies (minimum, mean and maximal) and persistence for the peroneal and tibial nerves in both groups were compared. Non-parametric tests were used and p values < 0.05 were considered significant.

Results: The mean age of patients was 52 years and there were 36 men. There were no significant between-group differences regarding ages (p=0.3598), the F wave latencies adjusted for height (p=0.2704) and persistences of SP compared to LN groups. The F waves persistence for the left ulnar (p = 0.0235), right ulnar (p=0.023), left peroneal (p=0.001), right peroneal (p=0.0025), left tibial (p=0.0005) and right tibial nerves (p=0.0365) was significantly lower in the SP group compared to SN.

Conclusion: The ulnar, peroneal and tibial F waves may be useful in the differential diagnosis between SP and SN. The persistence of responses is the most sensitive parameter.

References: None.

Keywords: Axonal Biology, Diabetes, Metabolic

Grant Support: No.
Targeting a core axonal degeneration program to treat vincristine and bortezomib-induced axonal degeneration

Stefanie Geisler¹, Ryan Doan², Shay Huang², Galen Cheng², Jeffrey Milbrandt², Aaron DiAntonio²

¹Washington University School of Medicine in St. Louis, St. Louis, MO, USA, ²Washington University School of Medicine in St. Louis, Saint Louis, MO, USA

Peripheral axonal polyneuropathy is a common side effect of many chemotherapeutic agents despite disparate mechanisms of action, suggesting that the axon destructive properties of various chemotherapies converge on a common axon degeneration (AxD) program. We discovered that genetic deletion of SARM1 protects axons from degeneration after axotomy and prevents neuropathy induced by the commonly used chemotherapeutic agent vincristine in a mouse model. It remains unknown whether the same upstream regulators and downstream effectors of SARM1 act in vincristine-induced AxD and axotomy, and whether the protective effects of SARM1 deletion are also realized by chemotherapeutics with different mechanisms of action. To address these questions, we used cultured mouse dorsal root ganglion neurons and the two chemotherapeutic agents vincristine and bortezomib (BTZ). Vincristine acts by stabilizing tubulin polymerization and interfering with intracellular trafficking, whereas BTZ inhibits the proteasome. We demonstrate that genetic deletion of SARM1 strongly decreases not only vincristine-induced AxD, but also AxD following administration of BTZ. In axotomy, SARM1 is activated by loss of NMNAT and acts through catastrophic decrease of NAD⁺. As in axotomy, AxD after vincristine and BTZ is preceded by loss of NAD⁺. Maintaining NAD⁺ levels by overexpression of nicotinamide riboside kinase and supplementation with nicotinamide riboside strongly protect from vincristine and BTZ-induced degeneration. Furthermore, as in axotomy, overexpressing cytNMNAT1 prevents degeneration following both vincristine and BTZ. However, while inhibiting the same MAP-kinase pathway that regulates SARM1 in axotomy protects from vincristine-induced AxD, it does not decrease BTZ-induced AxD. BTZ induced degeneration instead is transcriptionally regulated and mediated by axonal caspases. These findings indicate that different upstream pathways converge on SARM1. Excitingly, we are able to inhibit this program and, thus pathological AxD in vitro, by expressing a SARM1-dominant/negative mutant. We suggest that targeting SARM1 may have great therapeutic value in the prevention of multiple variants of chemotherapy-induced neuropathy.

References: None.

Keywords: Axonal Biology, Pre-clinical Studies, Other

Grant Support: NIH K08 NS091448
Impact of Multidisciplinary Intensive Neurorehabilitation on Peripheral Neuropathies: a Retrospective Study

Elda Judica¹, Antonio Caronni², Irma Sterpi¹, Michela Picardi¹, Massimo Corbo¹

¹Casa di Cura del Policlinico, Milan, Italy, ²IRCCS Santa Maria Nascente Fondazione Don Gnocchi Onlus., Milan, Italy

Neurorehabilitation strategies for neuropathies are vague and not standardized. Our primary objective was to evaluate the effects of neurorehabilitation therapies and interventions in patients affected by neuropathies of different etiologies in order to assess the functional outcome.

We retrospectively analyzed a sample of 185 patients with neuropathies admitted to the Neurorehabilitation Department of our clinical center in the previous five years (2014-2018) who underwent intensive goal-oriented treatment for five weeks using various modalities including gait training, strengthening and stretching exercises, balance and occupational therapy. We classified our sample in five groups as follows: Inflammatory Neuropathies (29 patients, with ten Guillain Barré Syndrome and nineteen Chronic Inflammatory Demyelinating Polyneuropathy), Diabetic Polyneuropathies (34 patients), Hereditary Neuropathies (ten patients), Toxic Neuropathies (eight alcohol and chemotherapy related neuropathies), and miscellaneous forms (104 patients including dysmetabolic, vasculitic and idiopathic forms related to other medical conditions). Static posturography, instrumental Timed Up and Go (TUG) test, 10 m walking test and mini-BESTest scale were also performed on a subgroup of 25 patients with axonal neuropathy for gait and balance instrumental evaluation.

All groups of patients, except for the hereditary one, showed significant gain both for motor FIM score and global FIM score at discharge. In particular, Inflammatory and Diabetic neuropathies showed significant changes in motor FIM score and global FIM score (p<0.0001). Similarly, Toxic neuropathies showed significant motor and global FIM score change (p<0.0001 and p 0.001 respectively). In addition, even the subgroup of patients with axonal neuropathy significantly improved gait speed, TUG, turning angular velocity and mini-BESTest scores.

These overall findings suggest encouraging evidence of patient-tailored rehabilitation potential for peripheral neuropathies. Patients with neuropathies benefit from multidisciplinary approach and intensive goal-oriented rehabilitation program on functional and motor outcome particularly on gait improvement. Hereditary neuropathies could need a more specific approach such as orthotics and surgical intervention.


Keywords: Inflammatory, Diabetes, Metabolic, CMTR, Other

Grant Support: None.
Prevalence of Central and Peripheral Nervous System Disorders in Hemophiliacs

Francisco Gondim¹, Jose Fernandes², Vicente Pinto², Antonia Dias³

¹Federal University of Ceara, Brazil, Fortaleza, Brazil, ²Federal University of Ceara, Brazil, Sobral, Ceara, Brazil, ³Hemocentro Regional Norte, Sobral, Ceara, Brazil

Patients with hemophilia may suffer from several types of central and peripheral nervous system diseases. Intracranial bleeding is a leading cause of death, but data about the prevalence of those conditions is limited. We prospectively evaluated the prevalence of central and peripheral nervous system disorders in all patients with hemophilia seen at the Hemocentro Regional Norte, Brazil. Seventy-five hemophilia A patients (no type B patient was found) were prospectively evaluated (prevalence of 4.61 hemophiliacs/100,000 inhabitants in this area). 13.3% (N=10) had either central (N=5) or peripheral nervous system disorders (N=5) secondary to bleeding. Patients with CNS disease had their neurological event at a significantly earlier age than patients with PNS disorders: 12.2±6.6 versus 32.5±5 (P<0.05). Three patients had subdural hematomas, one intracerebral and one subarachnoid hemorrhage. Overall, the outcome of those conditions was good, although one patient underwent intracerebral hemorrhage drainage (patient #3) and 3 were left with epilepsy or behavior disorders. Prophylactic factor VIII therapy replacement prevented all new cases of CNS disease, and decreased the prevalence of PNS dysfunction. The most commonly affected peripheral nerve was the femoral (N=3). One patient had a right sciatic neuropathy and one tardive right ulnar neuropathy related to right elbow hemophilic arthropathy. Most of the patients had predominant residual sensory involvement, although 2 had more significant motor involvement. In summary, to our knowledge, this is the first prospective description of clinically relevant central and peripheral nervous system disorders in hemophiliac patients prior and after the prophylactic factor VIII replacement era.

References: None.

Keywords: Axonal Regeneration, Human Genetics

Grant Support: None.
Associations of falls in cancer patients with chemotherapy-induced peripheral neurotoxicity (CIPN).

Andreas Argyriou1, Jordi Bruna2, Pantelis Litsardopoulos3, Roser Velasco4, Garifalia Anastopoulou5, Haralabos Kalofonos6

1Neurological Department, Saint Andrew’s General Hospital of Patras, Patras, Greece, 2Unit of Neuro-Oncology, Hospital Universitari de Bellvitge-IDIBELL, Barcelona, Spain, Barcelona, Spain, 3Neurological Department, Saint Andrew’s General Hospital of Patras, Patras, Greece, 4Unit of Neuro-Oncology, Hospital Universitari de Bellvitge-IDIBELL, Barcelona, Barcelona, Spain, 5Department of Medicine-Oncology Unit, Saint Andrew’s General Hospital of Patras, Patras, Greece, 6Department of Medicine, Division of Oncology, Medical School, University of Patras, Patras, Patras, Greece

Aim: To explore the associations of falls in a well characterized cohort of cancer patients with chemotherapy-induced peripheral neurotoxicity (CIPN).

Patients and methods: We studied 122 cancer patients experiencing any grade of CIPN, following completion of treatment with oxaliplatin, paclitaxel, cisplatin or their combination (paclitaxel+cisplatin) containing regimens for various non-hematological malignancies. The results of the clinical examination were summarized by means of the Total Neuropathy Score – clinical version (TNSc). Neurophysiological examination was also carried out. Descriptive statistics and logistic regression analyses were conducted to examine our data.

Results: Among 122 patients, 21 (17.2%) of them reported falls. They were 7 males and 14 females with a mean age of 57.3±8.1 years. All of them (21; 100%) had grade 3 CIPN, according to TNSc with a median value of 15 (range: 15-18). Univariate analysis showed that the following variables were strongly associated with falls: TNSc score of >14 corresponding to grade 3 CIPN, evidence of motor impairment, evidence of sensory ataxia with positive Romberg sign and decrease of sural a-SAP>50% of the baseline value (p<0.001 for all the latter parameters). Multivariate regression analysis failed to define independent predictors of falls. However, ROC analysis demonstrated that a discriminative TNSc cutoff value of >14 (p<0.001) predicted falls with a Sensitivity of 100% and Specificity of 87%, whereas sensory ataxia (p<0.001) predicted falls with a Sensitivity of 95% and Specificity of 83%.

Conclusion: Grade 3 CIPN, as assessed with TNSc, and evidence of sensory ataxia with positive Romberg sign were strongly associated with increased risk of falls. Although our results need further validation, the TNSc scale appears a practical and easy tool to identify patients at higher risk of falling.

References: None.

Keywords: Other

Grant Support: None.
Poster 61

Transplantation of Human iPSC-derived Motor Neurons for Denervation Induced Muscle Atrophy

Robert Baloh\(^1\), A.K.G.M. Muhammad\(^1\), Berhan Mandefro\(^2\), Shaughn Bell\(^1\), Jesse Landeros\(^1\), Dhruv Sareen\(^1\)

\(^1\)Cedars-Sinai Medical Center, Los Angeles, CA, USA, \(^2\)Cedars-Sinai Medical Center, Los Angeles, USA

Skeletal muscles that lose neural innervation, as occurs in motor neuron diseases (MND) peripheral nerve injury, undergo atrophy. We hypothesized that transplantation of human induced pluripotent stem cell-derived motor neurons into peripheral nerve near the target muscle, has the potential to reinnervate muscle and maintain muscle mass. We utilized a previously established experimental axotomy model in adult immunosuppressed or nude rats by transecting the sciatic, tibial, sural, peroneal nerves to prevent reinnervation by endogenous axons. Subsequently RFP-tagged iPSC derived motor neurons were transplanted into tibial nerve distal to the axotomy site near the intact muscular branch to medial gastrocnemius muscle. After 1, 2 or 6 weeks, the rats were euthanized and the distal tibial nerve stump along with medial gastrocnemius was harvested. Immunohistochemistry revealed human cells and RFP in injection site indicating graft survival at all time points, and class III beta-tubulin (TUBB3) immuno-positive axonal processes extending from the graft into medial gastrocnemius muscle; co-staining of RFP with \(\alpha\)-bungarotoxin showed apposition of distal axons with neuromuscular junctions supporting that the human graft innervated rat muscle. Additionally, the wet weight ratio of medial gastrocnemius (weight of muscle from treated side/contralateral naive side) in the group treated with motor neurons was significantly higher than that in vehicle treated controls (P <0.05; two-tailed unpaired t test). In rats followed for 6 months, the graft was stable and no tumor formation was apparent. The findings suggest that the transplanted human iPSC-derived motor neurons in axotomized tibial nerve survive up to 6 weeks, and can innervate the medial gastrocnemius and attenuate the denervation-induced muscle atrophy without tumorigenicity. Further studies are warranted to determine whether such cell transplantation strategy can function as a “relay” between brain and muscle, result in restoration of voluntary muscle function, and usher novel treatment strategies for MND or peripheral nerve injury.

References: None.

Keywords: Axonal Regeneration, Pre-clinical Studies

Grant Support: None.
Repeater F-waves In Carpal Tunnel Syndrome

Akiko Hachisuka¹, Yoshiaki Yamanaka², Akinori Sakai³, Satoru Saeki⁴

¹Department of Rehabilitation Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan, ²Department of Orthopedic surgery, University of Occupational and Environmental Health, Kitakyushu, Japan, ³Department of Orthopedic surgery, University of Occupational and Environmental Health, Kitakyushu, Japan, ⁴Department of Rehabilitation Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan

Background: Carpal tunnel syndrome (CTS) is the most common form of peripheral nerve injury characterized by pain, tingling, numbness, and muscle weakness. Delay of the distal motor latency (DML) is a major electrodiagnostic finding of CTS. However, little has been reported on repeater F-waves in patients with CTS. We have previously reported that repeater F-waves increased and correlated negatively with motor unit number estimation (MUNE) on the median nerve in polio survivors. This study aimed to identify the characteristics of repeater F-waves in CTS.

Methods: In this study, seventeen hands of patients with moderate to severe CTS (13 female, 4 male, age 67±6.9 (mean±SD)) were analyzed. Symptom severity and hand function were assessed using the Boston Carpal Tunnel Questionnaire (BCTQ), DASH, pinch, and electrophysiological examinations including nerve conduction studies, MUNE, and F-wave elicited by 100 stimulations. The occupancy rate of repeater F-waves (ORF) was calculated as follows: ORF = total number of repeater F-waves/total number of F-waves × 100 (%).

Results: Repeater F-waves and ORF were increased in patients with CTS (23.9 ± 12.9%, 35.9 ± 25.2%, respectively). F-wave persistence was normal (69.3 ± 29.3%). F-wave minimal latency was prolonged (31.6 ± 10.5 ms). Nerve conduction study findings were as follows: MCV, 48.2 ± 4.6 m/s; DML 6.7 ± 2.1 ms; CMAP, 6.2 ± 2.8 mV; SCV, 34.3 ± 13.2 m/s; DSL, 5.4 ± 3.1 ms; and SNAP, 6.8 ± 8.1 uV. Repeater F-waves were correlated with DML (r = 0.385, p < 0.05), but not with MUNE (r = 0.002, p< 0.05). MUNE was decreased and correlated with BCTQ (114 ± 72.5, r = 0.305, p< 0.05).

Conclusion: Repeater F-waves and ORF were increased in CTS. Repeater F-waves may be considered as a parameter of CTS severity.

References: Hachisuka, A. Komori, T. Abe, T. Hachisuka, K. Repeater F-waves are signs of motor unit pathology in polio survivors, Muscle Nerve, 51, 680-685

Keywords: Other

Grant Support: This study was supported by JSPS KAKENHI Grant Number JP18K17701. 18K17701 18K17701
Diabetic neuropathy is one the most common complication of diabetes, affecting ~ 50% of obese individuals with type II diabetes. Recent clinical evidence indicates that onset of type II diabetic neuropathy is associated with altered lipid metabolism in sensory neurons and also Schwann cells. The molecular and cellular neurophysiology underlying these observations is not clear because the PNS is a complex system involving multiple cell types such as neurons, Schwann cell or immune cells. We used Western-diet (WD) fed mice to induce neuropathy and we performed cell-specific translatomic analysis using Ribo-tag and cre-lox technology. Our translatomic analysis performed in regular chow and WD-fed mice at different times points unmasks a cell specific reprogramming aiming at stimulating the communication between sensory neurons and Schwann cell in neuropathic mice. Our studies will begin to decipher the in vivo cell-specific events underlying the progression of obesity-induced neuropathy. The results are expected to inform future in vivo basic and mechanistic research and drug development aimed at addressing an unmet clinical need.

References: None.

Keywords: Schwann Cell, Axonal Biology

Grant Support: NIH NIDDK 5R01DK117404
Diabetic peripheral neuropathy (DPN) is one of the most common complications of type 2 Diabetes (T2D). For a better understanding of disease pathogenesis, mouse models that accurately reflect the features present in the human condition are essential. Traditionally, monogenic leptin-based models (leptin receptor deficient, \( db/db \); leptin deficient, \( ob/ob \)) have been used extensively to study DPN as they develop a severe T2D and DPN phenotype. However, a limitation of these models is that impaired leptin-signaling disrupts endocrine/neuroendocrine signaling that can drastically affect mouse metabolism. The NONcNZO and Tallyho mouse strains have recently been identified as polygenic mouse models of T2D that better reflect human disease. As both strains have only recently become available, the goal of this study was to characterize the DPN phenotype in each to assess their usefulness as an alternate model of T2D induced DPN.

Male mice were obtained from Jackson Labs and placed on a standard diet for 12 weeks. When compared to non-diabetic controls, both strains display a gradual increase in body weight and fasting glucose over time and at study conclusion both strains show an increase in hemoglobin A1c, plasma insulin, triglycerides and phospholipids. We report that both strains develop DPN to a similar degree at study termination evaluated by significant deficits in motor and sensory nerve conduction velocities, thermal hyperalgesia and increased small fiber loss.

Compared to \( db/db \) and \( ob/ob \) mice, our preliminary data demonstrate that NONcNZO and Tallyho mice develop a moderate metabolic and neuropathic phenotype and thus can serve as a more appropriate model of understanding the gradual development of DPN. Such models may also aid in identifying therapies for DPN that have not proved successful in the more aggressive leptin-based models of T2D.

References: None.

Keywords: Diabetes, Metabolic, Small Fibers

Grant Support: None.
Poster 65

Folate Deficiency is Associated with Distal Symmetric Polyneuropathy in Zambia: Results from a Case-Control Study

Michelle Kvalsund¹, Violet Kayamba², Cleopatra Mwansa-Thurman³, Paul Kelly⁴, Gretchen Birbeck⁵, David Herrmann⁵

¹Michigan State University, University of Zambia, East Lansing, MI, USA, ²University of Zambia, Lusaka, Zambia, ³Michigan State University, East Lansing, MI, USA, ⁴Barts & the London School of Medicine, London, United Kingdom of Great Britain and Northern Ireland, ⁵University of Rochester, Rochester, NY, USA
Introduction.

Low serum vitamin B12 and folate levels were recently found in 60% of Zambian HIV+ and HIV- persons with distal symmetric polyneuropathy (DSP), but the population prevalence of these micronutrient deficiencies are unknown. We sought to estimate the risk of these deficiencies among DSP cases compared to age (+/- 5 years), sex, HIV, and clinic-matched controls from five public clinics in Zambia.

Methods.

Participants were adults (18 years or older) identified from general and antiretroviral clinics. DSP diagnosis was based on having at least one DSP symptom and sign, as confirmed by physician examination utilizing validated screening instruments. HIV- controls were identified among patient companions. HIV+ controls were collecting antiretrovirals without a medical complaint. Participants were interviewed regarding sociodemographic, dietary, and medical characteristics and underwent renal and liver function, serum vitamin B12 and folate, erythrocyte folate, homocysteine, and methylmalonic acid (MMA) assessments. HIV and CD4 testing were also performed.

Results.

109 consenting case-control pairs enrolled. Participants were 65% female, 52% HIV-infected, with mean age of 47.6 (SD 13.5) years. Among HIV+ participants, mean CD4 count was 484 (SD 221) and 482 (SD 236) for cases and controls, respectively (p=0.93). DSP symptoms and signs were similar between HIV+ and HIV- cases (p’s>0.05). Height, prior tuberculosis treatment, alcohol use, education, asset index, dietary diversity, and nutritional supplement use did not differ between cases and controls (p’s>0.05). Cases had at least 3:1 odds of having low serum folate (p=0.002), severely low erythrocyte folate (p=0.014), and elevated homocysteine (p=0.001) compared to controls. Serum vitamin B12 and MMA were not associated with case status (p’s>0.05).

Conclusions.

Markers of folate deficiency are highly associated with DSP in Zambia, suggesting either undernutrition or under-absorption of folate may be driving high DSP rates. Future studies should investigate a broader range of nutritional deficiencies and strategies for interventions.


Keywords: Metabolic, Other

Grant Support: U.S. State Department Fulbright African Regional Research Award, World Federation of Neurology, and the Michigan State University Clinical and Translational Sciences Institute
MRI and Triple Stimulation Technique to detect brachial plexus abnormalities in Multifocal Motor Neuropathy

Emilien Delmont¹, Thomas Le Corroller², Aude-Marie Grapperon¹, Giovanni Corazza¹, Shahram Attarian¹

¹Referral Centre for Neuromuscular diseases and ALS, Hôpital La Timone, Marseille, France, ²Department of Radiology, Institute for Locomotion, Hôpital Sainte-Marguerite, Marseille, France

Introduction
Conduction blocks (CB) are the diagnostic hallmark of multifocal motor neuropathy (MMN). Classical nerve conduction study cannot detect CB above the Erb's point. Plexus MRI and motor evoked potential with triple stimulation (MEP-TST) detect abnormalities of the brachial plexus. The aim of this study was to compare the performance of MEP-TST and plexus MRI to detect brachial plexus abnormalities in MMN.

Methods
Twenty-six patients underwent MEP-TST bilaterally performed on median and ulnar nerves and brachial plexus MRI using 3DT1-weighted and 3DT2-weighted short tau inversion recovery (STIR) imaging.

Results
Median age was 54 years and median disease duration was 3.5 years. IgM anti GM1 antibodies were detected in 13/26 patients. Intravenous immunoglobulins were efficient in 23/26 patients. Seven patients never had CB on classical nerve conduction studies. MEP-TST detected proximal CB in 19/26 patients (73%). Plexus MRI showed T2 hyperintensity in 18/26 patients (69%) and nerve enlargement in 14/18 patients (54%). A combination of the two techniques increased significantly the sensitivity to 96% of the patients (25/26). Among patients without CB, MEP-TST and plexus MRI were respectively abnormal in 5/7 (71%) and 4/7 patients (57%).

Conclusions
MEP-TST provides information on the nerve conduction and MRI on the morphology of the brachial plexus. The combination of both examinations adds value to the current diagnosis criteria of MMN especially in MMN without CB on conventional nerve conduction studies.

References: None.

Keywords: Inflammatory, Other

Grant Support: None.
Role of Supportive Diagnostic Criteria in Chronic Inflammatory Demyelinating Polyradiculoneuropathy: Data from the Italian Database

Eduardo Nobile-Orazio¹, Pietro Doneddu², Dario Cocito³, Fiore Manganelli⁴, Chiara Briani⁵, Raffaella Fazio⁶, Massimiliano Filosto⁷, Luana Benedetti⁸, Anna Mazzeo⁹, Girolama Marfia¹⁰, Giovanni Antonini¹¹, Laura Piccolo¹², Giuseppe Cosentino¹³, Stefano Jann¹⁴, Maurizio Clerici¹⁵, Marinella Carpo¹⁶, Marco Luigetti¹⁷, Gabriele Siciliano¹⁸, Tiziana Rosso¹⁹, Giuseppe Lauria²⁰, Guido Cavaletti²¹, Giuseppe Liberatore²², Erdita Peci³, Lucio Santoro⁴, Marta Ruiz²², Stefano Tronci⁶, S Cotti Piccinelli²³, Angelo Schenone²⁴, Antonio Toscano²⁵, Giorgia Mataluni²⁶, Luca Leonardi¹¹, Andrea Cortese²⁷
**Objective:** A number of supportive criteria are considered by the EFNS/PNS to help in the diagnosis of CIDP even if their relative utility is not established.

**Material and methods:** We reviewed the data from the Italian CIDP database to determine the frequency and utility of supportive criteria in the diagnosis of CIDP.

**Results:** We enrolled 545 patients with a clinical diagnosis of CIDP including 437 with definite (405), probable (24), possible (6) CIDP or CISP (2) according to EFNS/PNS criteria. The diagnosis of definite CIDP was possible with only motor nerve conduction studies (NCS) in 346 patients (85%), with the addition of one supportive criteria in 20 (5%) patients and two in 39 (10%) patients. In five patients the diagnosis of probable CIDP was made with only NCS while 19 required one supportive criteria. Abnormality consistent with demyelination in at least two motor nerves were found on conduction velocity in 177 patients (51%), conduction block in 157 (45%), increased temporal dispersion in 122 (35%), in distal latency in 69 (20%) and in F-wave in 32 (9%). Among the 78 patients who improved the definition of their diagnosis, 51 (65%) had increased CSF proteins, 23 (29%) demyelinating features on sensory NCS or evoked potentials, while 3 had demyelinating findings on nerve biopsy and 6 nerve ultrasound/MRI abnormalities. The same abnormalities in the whole CIDP group, were 258/336 (77%) for increased CSF proteins, 150/394 (38%) for demyelinating sensory NCS/evoked potentials, 21/35 (60%) for nerve biopsy and 50/65 (77%) for US or MRI. In 38 patients (49%) response to immune therapy was necessary to improve diagnostic definition.

**Discussion:** In 82% of patients with CIDP the diagnosis can be made with only NCS while supportive diagnostic tests are often unnecessary to improve the diagnosis even if they are extensively made in the current practice.

**References:** None.

**Keywords:** Inflammatory

**Grant Support:** Research Grants from Regione Lombardia, Italy, GBS-CIDP Foundation International, USA, Humanitas Clinical Institute, Italy, Kedrion Biopharma, Italy, CSL Behring, Italy
Guillain-Barré Syndrome following Arboviral Infection in Northeast Brazil: a Case Series

Sonja Leonhard¹, Suzannah Lant², Livia Brito Bezerra de Albuquerque³, Lais Cordero Diniz da França⁴, Vanessa Fragoso Cassiano⁴, Marcela Lopes Santos⁵, Roberta da Paz Melo⁶, Bart Jacobs¹, Maria Pessoa Militão de Albuquerque⁵, Maria Brito Ferreira⁴

¹Erasmus University Medical Center, Rotterdam, Netherlands, ²Institute of Infection and Global Health, University of Liverpool, Liverpool, United Kingdom of Great Britain and Northern Ireland, ³Federal University of Pernambuco (UFPE), Recife, Brazil, ⁴Hospital da Restauração, Recife, Brazil, ⁵Fiocruz, Recife, Brazil

Introduction

Zika virus (ZIKV) has been associated with the Guillain-Barré syndrome (GBS). Other arthropod-borne viruses (arboviruses), including Chikungunya (CHIKV) and Dengue virus (DENV), have also been linked to GBS. We describe a large cohort of GBS patients with evidence of a preceding arbovirus infection in Northeast Brazil.

Methods

Adult GBS patients with preceding arboviral symptoms were recruited in our center between December 2014 and January 2017. Diagnostic evidence of recent ZIKV, CHIKV, or DENV infection was defined as presence of viral RNA or specific IgM in serum or cerebral spinal fluid (CSF).

Results

Of the 73 included patients, 51 (70%) had a recent arboviral infection: 53% with ZIKV, 33% with CHIKV, and 11% with DENV. Recent infection with multiple arboviruses was found in 20 patients. Median time between start of systemic and neurological symptoms was 8 days (IQR 5-24). Clinical features included: limb weakness (97%), sensory signs (85%), facial palsy (58%), dysautonomia (26%), and respiratory insufficiency (16%). Nerve conduction studies showed a demyelinating neuropathy in 14 (64%) and an axonal neuropathy in 6 (29%) of 21 tested cases. Fourteen cases (19%) were admitted to the intensive care unit (ICU). Sensory signs during admission and complete recovery at last follow-up were significantly more frequent in arbovirus-positive compared to -negative cases.

Conclusion

Our results suggest that besides infection with ZIKV, infection with CHIKV, DENV, or recent sequential or co-infection with more than one of these three viruses, may trigger GBS. Post-infectious instead of (para) infectious pathophysiology is most likely in the majority of cases. GBS related to arbovirus infection is characterized by a classic sensorimotor demyelinating neuropathy with facial palsy, respiratory insufficiency and dysautonomia, and has a relatively favorable outcome. It is advised to consider multiple arboviruses in GBS patients in endemic regions and to be aware of complications that necessitate ICU admission.

References: None.

Keywords: Inflammatory, Other

Grant Support: Horizon 2020, ZikaPLAN Grant Agreement No. 734584
Biallelic Neurofascin variants affect paranodal axoglial junctions causing neurodevelopmental impairment and central and peripheral demyelination

Stephanie Efthymiou¹, Vincenzo Salpietro¹, Jerome Devaux², Maria Nolano³, Henry Houlden¹

¹UCL Queen Square Institute of Neurology, London, United Kingdom of Great Britain and Northern Ireland, ²INSERM U1051, Institut de Neurosciences de Montpellier, Montpellier, France, ³Istituti Clinici Scientifici Maugeri, Naples, Italy

Axon pathfinding and synapse formation are essential processes for nervous system development and function. The assembly of myelinated fibres and node of Ranvier is mediated by a number of cell adhesion molecules of the immunoglobulin superfamily including the Neurofascin (NFASC) alternative isoforms Nfasc186 and Nfasc140, located in the axonal membrane at the node of Ranvier, and Nfasc155, a glial component of the paranodal axoglial junction. We identified 8 individuals from 5 unrelated families, exhibiting a neurodevelopmental disorder characterized a spectrum of central (intellectual disability, developmental delay, motor impairment, speech difficulties) and peripheral (early onset demyelinating neuropathy) involvement, who were found by exome or genome sequencing to carry one frameshift and four different homozygous non-synonymous variants in NFASC. Expression studies using immunostaining-based techniques identified absent expression of the Nfasc155 isoform as a consequence of the frameshift variant and a significant reduction of expression was also observed in association with two non-synonymous variants affecting the fibronectin type III domain. Cell aggregation studies revealed a severely impaired Nfasc155-CNTN1/CASPR1 complex interaction as a result of the identified variants. Immunofluorescence staining of myelinated fibres from two affected individuals showed a severe loss of myelinated fibres and abnormalities in the paranodal junction morphology. Our findings establish that recessive variants affecting the Nfasc155 isoform can affect the formation of paranodal axoglial junctions at the nodes of Ranvier. The genetic disease caused by biallelic NFASC variants includes neurodevelopmental impairment and a spectrum of central and peripheral demyelination as part of its core clinical phenotype. Our findings support possible overlapping molecular mechanisms of paranodal damage at peripheral nerves in both the immune-mediated and the genetic disease, but the observation of prominent central neurological involvement in NFASC biallelic variant carriers highlights the importance of this gene in human brain development and function.

References: None.

Keywords: Node Biology, Human Genetics

Grant Support: We greatly appreciate the financial support provided by The Wellcome Trust and strategic award (Synaptopathies) funding (WT093205 MA and WT104033AIA).
Peripheral Nervous System (PNS) Toxicity Induced by Immune-checkpoint Inhibitors in Cancer Patients: Single Centre Experience.

Silvia Bocci¹, Laura Insana¹, Riccardo Danielli², Liana Africa¹, Federica Ginanneschi¹, Laura Franci¹, Luana Calabrò², Anna Maria Di Giacomo², Michele Maio², Fabio Giannini¹

¹Department of Medicine, Surgery and Neurosciences - University of Siena, Siena, Italy, ²Medical Oncology and Immunotherapy, Istituto Toscano Tumori - University Hospital of Siena, Siena, Italy

Introduction. Immunomodulating monoclonal antibodies (ImAb) against cytotoxic T-lymphocyte antigen-4 (CTLA4), programmed death-1 (PD1) and its ligand (PDL1) have been approved for treatment of metastatic melanoma, lung and renal cancer. By unbalancing the immune system, ImAbs may generate several multi-organ immune-related Adverse Events (irAEs), including neuromuscular manifestations.

Case reports. We describe five patients suffering from metastatic melanoma and one from non-small-cell lung cancer that received ImAbs and experienced PNS-irAEs. Three patients presented sensory-motor axonal polyneuropathies, two of which with mild and slow course (CTCAE grade 1), onset 13 and 16 weeks after anti-CTLA4 and anti-CTLA4/anti-PD1 combination treatment and followed by spontaneous recovery in 4 and 12 months respectively. Third patient presented subacute course (grade 2) with associated myopathy, beginning after one week of anti-CTLA4/anti-PD1 therapy and partially improved after ImAb discontinuation and steroid therapy. Fourth patient presented rapidly ascending tetraparesis (grade 3) at week 6 of anti-PD1 therapy. Lab tests and EDX were diagnostic for AIDP. Full recovery was obtained after IVIg treatment. Fifth patient presented focal onset in left lower limb followed by severe spreading of signs and loss of deambulation (grade 3) after anti-CTLA4 and anti-PDL1 administration in sequence. EDX showed CIDP-like abnormalities. ImAb withdrawal and IVIg plus steroids administration caused moderate benefit. Last patient presented oftalmoparesis and diffuse limb weakness (grade 2) developing after 3 weeks of anti-PD1 therapy. EDX were consistent with CIDP plus ocular nerve involvement. Immunotherapy was discontinuated and steroids were administered without benefit. Anti-gangliosides and anti-onconeural antibodies were negative in all patients.

Conclusions. PNS-irAEs are reported in less than 1% of patients. The current series quite represents the whole clinical spectrum of them, ranging from mild and spontaneously or treatment reversed to poorly responsive complications. Increasing use of ImAbs needs a joined specific alert by oncologists and neurologists, to promptly recognize and treat PNS-irAEs.


Keywords: Inflammatory, Other

Grant Support: None.
Poster 71

Rare and Challenging case of Guillain- Barre syndrome associated with stroke secondary to spotted fever

Anomali Vidanagamage¹, Amila Chandrasekara¹, Chamali Aluwihare¹, Sujatha Pathirage², Anil De Silva¹, Arjuna Fernando¹

¹National Hospital, Colombo, Sri Lanka, ²Medical Research Institute, Colombo, Colombo, Sri Lanka

Introduction

Spotted fever is a rare disorder rarely manifesting as Guillain- Barre syndrome (GBS) and stroke.

A 44 years old man, from Deraniyagala, Sri Lanka presented with intermittent low-grade fever for two weeks with arthralgia, myalgia, and frontal headache. On admission to local hospital, bilateral lower limb weakness was noted and he went into respiratory paralysis requiring intubation and ICU care. On examination, there was global areflexia and the pupils were normal.

During the stay, a transient erythematous macular rash over the medial surface of the right elbow with a healed eschar on the right lower leg was noted.

His CSF study showed high protein of 86 g/dl with a cytoprotein dissociation compatible with GBS.

Nerve conduction study showed Sensory motor axonal polyneuropathy suggestive of AMSAN type GBS.

Weil-Felix test was OXK 1:160, OX2- 1:160 and OX-19 Negative. IFA for spotted fever was positive supporting the diagnosis of spotted fever.

Persistent spiking fever did not respond to empirical antibiotics and showed marked improvement following doxycycline. With plasma exchange, he recovered from GBS and right hemiplegia became apparent. Following rehabilitation for the stroke, he had a good recovery with a modified ranking scale of 2.

Non-contrast imaging on admission revealed bilateral basal ganglia infarctions later confirmed by MRI and MRA suggestive of vasculitis. T2 FLAIR, DWI and ADC images demonstrate bilateral T2 FLAIR high signal intensities involving left internal capsule, right globus pallidus, and bilateral external capsules. These showed diffusion restriction suggesting acute infarcts.

The MRA demonstrate subtle irregularity of the right posterior cerebral arteries suggesting a vasculitic irregularity. No occlusions or luminal filling defects are noted.

Rest of the brain appears normal.

Conclusion

Although rare, rickettsia infection should be considered in febrile strokes as well as in atypical manifestations of Guillain- Barre syndrome.

References: None.

Keywords: Inflammatory

Grant Support: None.
Ten Year Plateau in HIV-Induced Motor Neurone Disease: a First Case from Sub-Saharan Africa.

Marieke Dekker¹, Emmanuel Assey¹, Asha Osman¹, William Howlett², Kajiru Kilonzo¹

¹Kilimanjaro Christian Medical Centre, Moshi, Tanzania, United Republic of, ²Kilimanjaro Cristian Medical Centre, Moshi, Tanzania, United Republic of

Introduction Human Immune Deficiency (HIV)-induced Motor Neuron Disease (MND) is an Amyotrophic Lateral Sclerosis (ALS)-mimic which can be arrested and even partially reversed upon initiation of antiretroviral therapy. It is the reason why in the analysis of suspected MND, HIV infection always ought to be ruled out. Opportunistic infection by a human endogenous retrovirus (HERV) in HIV patients has been associated with motor neuron disease variants which are arrested by antiretroviral therapy and are paralleled by reduction in viral load of HIV as well as HERV. This can be regarded a ‘guilty bystander’ phenomenon. Methods A case study with over ten years of neurological, virological and electromyographic follow up. Results We report a case of a male with quickly progressive motor neurone disease, phenotypically compatible with Amyotrophic Lateral Sclerosis (ALS). The patient proved positive for HIV and was initiated on first-line antiretroviral therapy. His symptoms partially improved upon which he reached a plateau phase with ongoing fasciculations yet unchanged muscle mass suggesting less denervation activity than seen in non-HIV related MND. The patient’s progression of motor neurone disease then virtually arrested for over a decade and he was lost to follow up. He then came to medical attention again for another likely HIV-related condition. By EMG, denervation was demonstrated in all three segments which is compatible with definite ALS according to Awaji Shima criteria. In our setting as well as in other associated higher resource institutions, HERV testing was not available. Conclusions MND always requires ruling out treatable disease mimics, amongst which HIV. The improvement in response to antiretroviral therapy confirms that ALS/HIV is a treatable entity also in Africa. Together with the other reported cases, it raises the tantalizing suggestion that more types of MND may be related to activated central nervous system retroviruses, some as yet undiscovered.


Grant Support: none
Updated CSF Total Protein Reference Values Improve CIDP Diagnosis

Ari Breiner¹, Pierre Bourque¹, Jeffrey Allen²

¹The Ottawa Hospital, University of Ottawa, Ottawa, Canada, ²University of Minnesota, Minneapolis, MN, USA

Background: Recent publications have demonstrated that CSF total protein (CSF-TP) upper reference limits should be higher, and stratified by age. However, most hospital laboratories continue to use the antiquated 0.45g/L cutoff value, and do not adjust for the effect of age.

Objectives: We sought to apply new, data-driven upper reference limits to the analysis of a cohort of correctly and incorrectly diagnosed CIDP patients.

Methods: CSF-TP values were tested for normality, and descriptive statistics were calculated. Exploratory analyses were used to assess the effect of different CSF-TP upper reference limits on sensitivity and specificity of CIDP diagnosis.

Results: Among correctly diagnosed patients (n=47), the median CSF protein was 1.05g/L. The use of a higher and age-dependent CSF-TP URL reduced the sensitivity of CSF analysis slightly (from 95% to 84-86%), but did not change the overall CIDP detection rate, as patients met other supportive criteria, and fulfilled clinical or electrodiagnostic criteria. Among incorrectly diagnosed patients, the median CSF protein was 0.53g/L. 12/36 (33%) false positive diagnoses occurred with CSF-TP elevation as the sole supportive criteria. By using data-driven CSF-TP URL, the specificity of CSF analysis increased from 39% to 57%-64%.

Conclusions: The widespread adoption of data-driven and age-dependent CSF-TP upper reference limits improves the specificity of CIDP diagnosis, without a clinically meaningful compromise in sensitivity. Application of more stringent CSF protein reference values has the potential to lessen the occurrence of CIDP misdiagnosis.

References: None.

Keywords: Inflammatory

Grant Support: None.
The effect of phosphodiesterase-2 inhibitor on CX3C chemokine axis in experimental autoimmune neuritis

Toshiki Fujioka1, Wataru Hagiwara1, Hideo Kihara1, Takafumi Uchi1, Masashi Inoue1, Shingo Konno1, Mayumi Murata2, Tomomi Imamura2, Miyuki Matsumoto2, Mari Matsushima2, Hideki Sugimoto1

1Toho University Graduate School of Medicine, Toho University Ohashi Medical Center Department of Neurology, Tokyo, Japan, 2Toho University Ohashi Medical Center Department of Neurology, Tokyo, Japan

BackgroundCX3C chemokine plays a pivotal role in inflammation and neuropathic pain via its specific receptors expressed on microglia or dorsal ganglion cells in spinal cord injury model, however, its role in inflammatory neuritis remains to be elucidated. ObjectiveTo investigate sequential RNA expression of CX3C chemokine fractalkine (Flk) and its specific receptor (FR) in cauda equina (CE) of experimental autoimmune neuritis (EAN) rats treated with either phosphodiesterase-3 inhibitor (PDE3-I) or vehicle. Material and MethodsFemale Lewis rats (110~130gm, Charles River, Yokohama) were immunized with synthetic peptide from bovine P2 protein to induce EAN. PDE3-I cilostazol (CLZ), 30 mg/kg/day, was administered daily from one day post immunization (dpi). CE were removed at 7, 11, 14, 21, 28 dpi, extracted RNA were reverse transcribed to obtain cDNA, analyzed using real-time PCR (∆∆CT method) for Flk or FR expression. This experiment was approved by Toho University Animal Experiment Committee (#13-51-215, 14-52-215, 15-53-215). ResultsMotor paralysis developed in all rats at 11 dpi, however, subsequent paralysis was suppressed in CLZ group. Real-time PCR analysis revealed transient up-regulation of Flk messages in CE of vehicle-treated EAN at 7-11 dpi (preclinical ~ acute stage). Reciprocally, in CLZ-treated rats in same phase, Flk expression was decreased compared to vehicle group (p<0.05 by Mann-Whitney U test). On the other hand, expression of FR during entire course of EAN was identical in CLZ and vehicle-treated rats with weak decrease in acute phase followed by weak increase. ConclusionCLZ treatment ameliorates motor impairment of EAN rats via Flk down-regulation in peripheral nervous system.

References: None.

Keywords: Inflammatory

Grant Support: None.
Toscana virus associated with Guillain-Barré Syndrome: A case-control study

Sevim Erdem-Ozdamar¹, Serhat Vahip Okar¹, Can Ebru Bekircan-Kurt¹, Sabri Hacıoğlu², Aykut Özkul², Koray Ergünay³

¹Hacettepe University Neurology Department, Ankara, Turkey, ²Ankara University; Faculty of Veterinary Medicine, Department of Virology, Ankara, Turkey, ³Hacettepe University; Department of Medical Microbiology, Ankara, Turkey

Background: Guillain-Barré syndrome (GBS) is an acute-onset, immune-mediated polyradiculoneuropathy, often precipitated by an antecedent infection. An association of GBS with vector-borne viral infections have been suggested, with evidence for the involvement of Zika, Dengue, Chikungunya and West Nile virus (WNV). Objectives: This prospective case-control study was conducted to identify vector-borne viral infections in GBS. Study Design: Thirteen individuals newly-diagnosed as GBS were enrolled. Disease severity, prognostic factors and nerve conduction patterns were assessed. Eleven individuals with non-infectious conditions requiring cerebrospinal fluid (CSF) analysis were included as controls. Plasma, CSF and urine specimens were evaluated via nucleic acid amplification assays aimed to detect a broad spectrum of viruses. WNV and Toscana virus (TOSV) IgM/IgG antibodies were screened using commercial immunofluorescence assays, and confirmed via virus neutralization tests (VNT). Results: Partial TOSV nucleocapsid and genotype 1 polymerase sequences were detected in CSF of a patient with normal pressure hydrocephalus. Two control subjects had VNT-confirmed TOSV IgM in plasma. VNT-confirmed WNV and TOSV IgG were detected in 15.4% and 61.5% of GBS patients, respectively. Variations in WNV IgG and TOSV IgM detection rates were not statistically-significant among study cohorts. However, TOSV IgG was significantly more frequent in GBS patients. No difference was observed for disease form or prognostic scores for virus markers. Follow-up serological profiles were identical to the initial findings. Conclusions: We have identified TOSV as a potential precipitating agent in GBS, with some rare clinical presentations of symptomatic TOSV infection.

References: None.

Keywords: Inflammatory, Other

Grant Support: The study was supported by the Hacettepe University Scientific Research Projects Coordination Unit funds (Project ID:15364: THD-2017-15364).
The Utility of Guillain-Barré Syndrome Prognostic Models in Malaysian Patients

Cheng-Yin Tan, Siti Nur Omaira Razali, Khean-Jin Goh, Nortina Shahrizaila

University of Malaya, Kuala Lumpur, Malaysia

Introduction: Guillain-Barré syndrome (GBS) is an acute immune-mediated neuropathy that has variable course and outcome. The Erasmus GBS Outcome Score (EGOS), modified EGOS (mEGOS) and Erasmus GBS Respiratory Insufficiency Score (EGRIS) are prognostic models designed to predict the functional outcome of GBS patients at 6 months (EGOS and mEGOS) and the need for mechanical ventilation within a week of admission (EGRIS). In the current study, we aim to validate mEGOS, EGOS and EGRIS in Malaysian GBS patients. Methods: Consecutive patients presenting with features supportive of GBS were recruited. All patients with outcome data available at 6 months were included. Outcome was determined by GBS disability score (GDS) with good outcome when GDS < 3 and poor outcome when GDS ≥ 3. Patients with GBS and Miller Fisher syndrome (MFS) were analysed separately. Results: Between 2010 and 2018, 89 patients with complete data were recruited. 61 (68.5%) patients had GBS and 28 (31.5%) patients had MFS. In the GBS cohort, high mEGOS on admission and day 7 of admission were significantly correlated with poor outcome (r = 0.383, p = 0.002; r = 0.482, p < 0.001; respectively). There were no significant correlations between mEGOS or EGOS and outcome in patients with MFS (mEGOS on admission: r = 0.104, p = 0.598; mEGOS at day 7 of admission: r = -0.008, p = 0.968; EGOS: r = 0.031; p = 0.877). The EGRIS for GBS patients with mechanical ventilation were significantly higher than those patients without mechanical ventilation (4 ± 2 vs 2 ± 1; p < 0.001). Conclusions: MEGOS is clinically useful and relevant to the Malaysian GBS population but not in patients with MFS. EGRIS could be used to predict the need of mechanical ventilation in our local GBS patients.


Keywords: Inflammatory

Grant Support: Dr. CY Tan receives research grant from the University of Malaya (BK074-2017).
A multicenter prospective study aimed to validate sphingomyelin as a biomarker for acquired dysimmune neuropathies

Giovanna Capodivento¹, Chiara De Michelis¹, Davide Visigalli¹, Elisabetta Capello², Alessandro Beronio³, Marco Luigetti⁴, Giovanni Antonini⁵, Diego Franciotta⁶, Marinella Carpo⁷, Angelo Schenone¹, Luana Benedetti², Lucilla Nobbio¹

¹Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili UNIGE, Genoa, Italy, ²Dipartimento di Neuroscienze ed Organi di Senso Ospedale Policlinico San Martino, Genoa, Italy, ³Neurologia Ospedale S. Andrea, La Spezia, Italy, ⁴Department of Geriatrics Neurosciences Head and Neck surgery and Orthopedics Fondazione Policlinico Gemelli, Rome, Italy, ⁵Unit of Neuromuscular Diseases, Department of Neurology Mental Health and Sensory Organs ‘Sapienza’ University, Rome, Italy, ⁶Fondazione Istituto Neurologico Nazionale C. Mondino, Pavia, Italy, ⁷UOC Neurologia, Treviglio, Italy

We recently demonstrated the clinical relevance of sphingomyelin (SM) dosage as a myelin biomarker in a retrospective study performed on the CSF of 262 neurological patients. Indeed, SM is extremely higher in GBS/CIDP patients compared to subjects affected by non-demyelinating disorders and patients with blood brain barrier dysfunction but not overt demyelination. Our results represent a proof-of-principle that this biomarker might greatly improve the management of dysimmune demyelinating neuropathies. Among practical implications, we envisage: i) the correct identification of GBS variants (i.e. demyelinating vs axonal) at the onset, to overcome the current delay of neurophysiology; ii) the clustering of CIDP patients in well-defined subgroups to improve the diagnostic accuracy, to define disease severity and to determine the most suitable therapy either in pre-clinical and clinical trials. In the present study, we planned to test and validate sphingomyelin dosage as a clinically acceptable biomarker, in a prospective multicenter study involving most of the main italian centers devoted to the management of patients affected by GBS and CIDP. At the moment we have enrolled about fifty GBS/CIDP patients and a comparable number of patients affected by non-demyelinating disorders to be used as control subjects. All patients have been analysed within the first two weeks of their admission in each center and they underwent a complete neurological and neurophysiological evaluation. Recommended outcome measures to evaluate strength, sensitivity, gait and disability of patients affected by GBS/CIDP were used. We correlated SM levels for each patient with demographical data, disease duration, CSF indexes, clinical scores and complete neurophysiological evaluations. We are confident that, upon completion, this study will allow to candidate SM dosage, a simple, fast and inexpensive test, as a novel CSF biomarker to be routinely used in the clinical practice of dysimmune neuropathies.

References: Capodivento, Visigalli, Schenone, Nobbio, Sphingomyelin as a myelin biomarker in CSF of acquired demyelinating neuropathies, Scientific reports, 7, 7831, 2017

Keywords: Inflammatory

Grant Support: GMN 2018 GBS-CIDP Foundation International Research Grant 2018
Enhanced Proinflammatory T cell pathology in Chronic Inflammatory Demyelinating Polyneuropathy
Karissa Gable, John Yi, Melissa Russo, Jeffrey Guptill
Duke University, Durham, NC, USA

Introduction: Chronic inflammatory demyelinating polyneuropathy (CIDP) is an autoimmune disorder of the peripheral nerves, and the underlying autoimmune mechanism is incompletely understood. Prior studies of T-cells in CIDP patients demonstrated dysregulation in regulatory T cells and IL-17 producing CD4+ T cells (Th17 cell).1, 2 Overall Th17 cell frequencies and IL-17 levels appear to correlate with disease activity.3, 4 However, in depth simultaneous characterization of B-cell and T-cell maturation and function has not been reported in CIDP.

Methods: Cryopreserved peripheral blood mononuclear cells from EFNS/PNS probable or definite CIDP patients (N=10) and healthy controls (N=10) were analyzed by a flow cytometry immune profiling panel to evaluate B-cell and T cell phenotypes that includes their activation, maturation and functional status.

Results: We found significantly reduced B cell frequencies in CIDP patients (p<0.001), although percentages of naïve and memory B-cells and plasmablasts were similar between controls and CIDP patients. We also found decreased naïve (p<0.01) and increased memory (p<0.05) and effector (p<0.05) CD4+ T cell frequencies in CIDP patients. This increase in effector and memory CD4 T cells paralleled an increase in the frequency of CD4 T cells co-producing IFN-g, TNF-a, and IL-2 (p=0.037) and IFN-g and IL-2 (p<0.001). We also observed an increase in Th17 cell frequencies (p<0.001). The increase in pro-inflammatory cytokines was also observed in CD8 T cells, where the frequency of terminal effector T cells and pro-inflammatory cytokine production including IFN-γ (p<0.05), IL-2 (p< 0.01), and IL-17 (p< 0.01) were also increased.

Conclusions: This B and T cell profiling study extends current knowledge of strong T cell mediated immunopathology in CIDP. Enhancement of Th17 cell frequencies, pro-inflammatory cytokine production, and effector T cell populations are consistent with loss of self-tolerance and previous studies showing decreased Tregs in CIDP. Future studies could explore T cell directed therapies in CIDP.


Keywords: Inflammatory, Other

Grant Support: None.
Fc-gamma ReceptorIlla Polymorphism is Associated with Severity in Guillain-Barré Syndrome

Shoma Hayat¹, Md. Babu¹, Israt Jahan¹, Avizit Das¹, Ishtiaq Mahmud², Zahirul Islam¹

¹icddrb, Dhaka, Bangladesh, ²University of Dhaka, Dhaka, Bangladesh

Immunoglobulin G Fc-gamma receptors (FcγRs) mediate and regulate diverse effector functions by bridging humoral and cell-mediated immune responses that has been involved in the pathogenesis of Guillain-Barré syndrome (GBS). FcγR polymorphisms FcγRIIa: H/R131 (rs1801274), FcγRIIIa: V/F158 (rs396991), FcγRIIIB: NA1/NA2 and their haplotype patterns may affect the affinity of IgG-FcγR interactivity and may influence disease development. We determined FcγR polymorphisms in 303 patients with GBS and 302 ethnically matched healthy individuals in Bangladesh by allele-specific polymerase chain reaction. Pair wise linkage disequilibrium (LD) and haplotype patterns were analyzed based on D' statistics. Haplotype analysis revealed 27 different patterns from FcγRIIa, FcγRIIIa and FcγRIIIB polymorphic loci. Nine common patterns (Haplotype 1-9, frequency >5%) comprises 61.5% of the total variation were included in the analysis. FcγR genotypes and haplotype patterns did not show association with susceptibility to GBS. FcγRIIa-V158F was significantly associated with severely affected patients with GBS (P=0.005, OR=2.24, 95% CI=1.28-3.91). FcγRIIa-F/F158 genotype was more likely found in mildly affected patients (P=0.03, OR=0.55, 95% CI=0.32-0.94). Haplotype 1 (FcγRIIa-H131R- FcγRIIa-V158F- FcγRIIIB-NA1/2) and FcγRIIIB-NA2/2 genotype were most prevalent among anti-GM1 antibody (Ab) sero-positive patients with GBS (P=0.031, OR=9.61, 95% CI=1.24-74.77 and P=0.027, OR=1.62, 95% CI=1.06-2.5 respectively) compared to sero-negative patients. FcγRIIIB-NA1/2 and FcγRIIIB-NA2/2 were associated with recent Campylobacter jejuni infection (P=0.027, OR=1.5, 95% CI=1.05-2.10 and P=0.004, OR=1.70, 95% CI=1.18-2.44). In addition, FcγRIIa-V/V158 was less likely found in anti-LOS-Ab positive patients (P=6.20e-06, OR=0.36, 95% CI=0.23-0.56) whereas, FcγRIIa-F/F158 (P=0.038, OR=1.5, 95% CI=1.02-2.11) and FcγRIIa-V158F (P=0.025, OR=1.5, 95% CI=1.05-2.10) were significantly prevalent among anti-LOS-Ab positive patients. No association was evident between FcγR genotypes and disease outcome, but patient with haplotype 1 (FcγRIIa-H131R- FcγRIIa-V158F- FcγRIIIB-NA1/NA2) was associated with slow recovery (P=0.04, OR=0.41, 95% CI=0.18-0.96). Finally, FcγRIIa polymorphisms play a pivotal role in disease severity as well as in the pathogenesis of GBS in Bangladesh.

References: N/A

Keywords: Inflammatory, Human Genetics, Axonal Biology, Axonal Regeneration, Other

Grant Support: N/A
Clinical Response and Progression over time for Multifocal Motor Neuropathy (MMN) Treated with Intravenous Immunoglobulin (IVIG)

Peck Kee Chia¹, Stefanie Kar Yan Hung², Fu Liong Hiew²

¹Kuala Lumpur General Hospital, University Putra Malaysia, Kuala Lumpur, Malaysia, ²Kuala Lumpur General Hospital, Kuala Lumpur, Malaysia

We determine the clinical progression, disability and outcome of all MMN patients treated with IVIg in our centre. Retrospective study of patients referred to neurology department Kuala Lumpur Hospital between year 2009 to 2018. Eleven patients were diagnosed MMN during the study period. The mean age was 46.8 (SD 13.3), mean disease duration of 108.0 months (SD 80.2). All were reported with unilateral limb onset (upper limb 7, 63.6%). At diagnosis, after mean delay of 49.9 months (SD 73.5), seven (63.6%) had 2 limbs and three (27.3%) had 3 limbs involvement. Ten patients received standard induction IVIg dose of 2.0gm/kg, average 3.6 cycles (range 1-5) over an average 30.6 weeks (SD 19.1). Nine (90%) responded, demonstrated improvement in MRCSS of > 2 points, and 8 improved in mRS score of >1 point. Four (57.1%) out of seven recently treated patients improved in total ONLS of >1 point, six (85.7%) improved in MMN-RODS, and all had improvement in hand grip strength (mean 4.7kg, SD 2.1). Nine patients received maintenance therapy for at least 2 years. We observed a 38.5% drop of IVIg treatment dose in 2nd year, and a further 34.8% drop in 3rd year of treatment. This corresponded to the continuous improvement in all above parameters up to 3rd year of treatment except MMN-RODS (stopped after 2nd year). Following that, patients received increasing dose of IVIg for 9 years with average dose increment of 0.12gm/kg/year (SD 0.09, 11.2%). One patient received treatment up to 14th years. MRCSS and mRS continued to deteriorate over time with mean deterioration of 0.9 points/year and 0.3 points/year respectively. ONLS, MMN-RODS and grip strength stabilised after the third year of treatment. From our experience, IVIg stabilised progression of MMN after 3 years, but an increasing dose of IVIg is required to maintain sustained improvement.

References: None.

Keywords: Inflammatory, Other

Grant Support: None.
Objective: To characterize the natural history (clinical outcome and survival) in a population-based cohort of Lumbosacral Radiculoplexus Neuropathy (LRPN). Background: Recently, we found that the incidence of LRPN (Olmsted County, Minnesota) is 4.16/100,000/year, which is 3 times more common than CIDP or AIDP and it occurs 8 times more frequently among diabetics. Although LRPN clinical, pathological and neurophysiological findings have been described, its long-term natural history has not been systematically characterized. Materials/Methods: 62 LRPN episodes in 59 patients defined by clinical and electrophysiological criteria were identified over 16 years (2000-2015) using Rochester Epidemiology Project. Demographic, clinical and survival data were extracted. Survival and mortality risk factors were compared to age-gender matched controls. Results: At diagnosis, LRPN patients median age was 70 (24-88) years, median neuropathy impairment score (NIS) 22 points (1-102), pain and weakness were present in 92% and 95% respectively, 24% were wheel-chair bound and median modified Rankin scale (mRS) was 3 (1-4). The median time from diagnosis to last neurological follow-up was 8 (4-49) months, and the median NIS had improved to 17 points (0-56) (p<0.001). 56% (had NIS improvement of ≥4 points, 12% remained wheel-bound, 55% had pain and 83% weakness and median mRS was 2 (0-4). LRPN survival after 5 and 10 years was 86% and 55% respectively. Compared to age-gender matched controls, LRPN persons had a 76% increased mortality rate (p=0.016). In multivariate mortality risk factor analysis, diabetes mellitus, chronic kidney disease, stroke and advanced-age were significant risk factors for death but LRPN was not. There were no significant survival differences between diabetic and non-diabetic LRPN. Conclusions: LRPN usually improves over time but people are often left with problematic functional impairment. Although having LRPN increases mortality risk, this is likely due to higher prevalence of diabetes mellitus and other comorbidities rather than LRPN itself.

References: None.

Keywords: Inflammatory, Metabolic, Diabetes

Grant Support: None.
Objective: To investigate the risk factors for Lumbosacral Radiculoplexus Neuropathy (LRPN).

Background: Recently, our group found significantly higher frequency of diabetes mellitus in patients with LRPN compared to age-gender matched controls (66.1% vs 19.8%) from Olmsted County, Minnesota, USA. Within the same population, we found diabetics have odds of 7.91 for developing LRPN compared to non-diabetics. However, the influence of anthropomorphic variables or other comorbidities were not studied. Methods: Demographic and clinical data from 59 LRPN patients and 177 age-gender matched controls were extracted from the Rochester Lumbosacral Radiculoplexus Neuropathy study. Categorical variables are presented as % and differences between groups were compared by Chi-square/fisher test. Univariate and multivariate logistic regression analysis were performed. Results: LRPN patients compared to controls had more frequently: hypertension (64.4% vs 44.6%; p=0.009), stroke/TIA (13.6% vs 4%; p=0.009), obesity (53.6% vs 36%; p=0.02), dementia (6.8% vs 1.1%; p=0.017), dyslipidemia (66.1% vs 40.7%; p=0.0007), and other auto-immune disorder (15.3% vs 6.2%; p=0.031). Factors predictive of LRPN on univariate logistic regression were hypertension (OR 2.25; CI 1.22-4.13), obesity (OR 2.05; CI 1.11-3.8), stroke/TIA (OR 3.81; CI 1.31-11.01), dementia (OR 6.36; CI 1.13-35.67), dyslipidemia (OR 2.84; CI 1.53-5.27) and other auto-immune disorder (OR 2.71; CI 1.07-6.93). Multivariate logistic regression analysis, that included diabetes mellitus in the model, showed that diabetes mellitus (OR 8.36; CI 4.01-17.42), BMI (OR 1.07; CI 1.01-1.13), stroke (OR 4.08; CI 1.18-14.17) and other auto-immune disorder (OR 4.58; CI 1.43-14.65) are independent risk factors for LRPN. Conclusions: Diabetes Mellitus is the strongest LRPN risk factor, and most others like hypertension, renal dysfunction, dyslipidemia, obesity and dementia are likely intrinsically related to diabetes. Interestingly, previous diagnosis of an auto-immune disorder is also an independent risk factor for LRPN. Immune dysfunction and chronic hyperglycemia seems to be the most influence factors for the development of this immune-mediated neuropathy.

References: None.

Keywords: Inflammatory, Metabolic, Diabetes

Grant Support: None.
Poster 83

Peripheral Nerve Involvement in Malignancies: an Overview on Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) and Cancer.

Marta Campagnolo1, Marta Ruiz2, Mario Cacciavillani3, Gregorio Barilà4, Tamara Berno4, Alessandro Salvalaggio2, Francesca Castellani2, Andrea Visentin4, Livio Trentin4, Renato Zambello4, Chiara Briani 2

1Department of Neurosciences, University of Padova, Padova, Italy, Padova, Italy, 2Department of Neurosciences, University of Padova, Padova, Italy, Padova, Italy, 3CEMES-EMG Lab, Data Medica Group, Padova, Italy, Padova, Italy, 4Hematology and Clinical Immunology Unit, Department of Medicine, University of Padova, Padova, Italy, Padova, Italy

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) has been associated with malignancies, particularly hematological disorders, especially non-Hodgkin lymphoma (NHL).

In a cohort of 61 consecutive patients (38 males, mean age 63.9±15 yrs) with CIDP we identified 16 patients (11 men, mean age 67.1±10.1, mean disease duration 7.1±7.1 yrs) with malignancies (mean duration 7.5±8.2 yrs). We report on their clinical characteristics and response to therapies.

Twelve patients had an associated hematological disorder (4 MM, 4 CLL, one essential thrombocythemia, 2 NHL, one AL amyloidosis), 4/16 had solid tumor (3 breast, one prostate cancer). CIDP preceded the hematological disease in 5 patients (median interval 5.5 yrs, range 1-21); in 8/16 the cancer (3 CLL, one MM, 4 solid malignancies) was followed by the neurological diagnosis (median interval 9 yrs, range 1-28). Three patients presented concomitant onset of the hematological and neurological diseases. Cerebrospinal fluid (available in 11/16), disclosed albumin-cytological dissociation in 7/11 (mean values of proteins 1±0.2 g/L) and a mirror pattern in 6/11 patients (one with breast cancer, 5 with hematological disorders). Therapies for CIDP included intravenous immunoglobulins (IVIg) (7/10 patients with benefit), steroids (4/6 patients with benefit), plasma exchange (partial response in 2 patients). Two patients with underlying NHL underwent rituximab, with clinical improvement in one. One of the MM patients presented consistent stabilization of neurological picture only after autologous stem cell transplant, and is now off from any maintenance therapy for CIDP.

In conclusion, 26.2% of our cohort had a history of malignancy. The mechanism underlying this concurrence is unclear, and a coincidental association may be possible. In 50% of our patients, CIDP preceded or was concomitant with the hematological disease, supporting the hypothesis of a correlation (especially in those with shorter intervals), and suggesting the need for a closer follow-up to promptly diagnose a possible underlying malignancy.

References: None.

Keywords: Inflammatory

Grant Support: None.
Targeting Axonal or Glial Membranes with Anti-GM1 Antibody to Model Axonal and Demyelinating Peripheral Neuropathies

Clare Campbell, Rhona McGonigal, Denggao Yao, Madeleine Cunningham, Hugh Willison

University of Glasgow, Glasgow, United Kingdom of Great Britain and Northern Ireland

It is established that antibodies to gangliosides, particularly GM1, are involved in the pathogenesis of the axonal variant of Guillain-Barré syndrome (GBS). These antibodies cause deposition of complement and activation of calpain resulting in nerve terminal injury and disruption of proteins and ion channels at the nodes of Ranvier, leading to conduction block. In the demyelinating variant of GBS, segmental demyelination along the internodes and detachment of the paranodal loops occur. In some cases, secondary axonal degeneration develops, but the pathogenic mechanisms of this variant are unknown.

We wanted to compare injury outputs at the nodes of Ranvier following targeted injury to either the paranodal Schwann cell membrane or the axonal membrane. Transgenic mice were generated with restricted expression of complex gangliosides to either neuronal membranes (GalNAcT-/-Tg(neuronal)) or glial membranes (GalNAcT-/-Tg(glial)). This allowed us to specifically target the axonal or glial membranes with anti-GM1 antibody with the aim to establish in vivo mouse models representative of the axonal or demyelinating variants of GBS, respectively. Axon integrity, measured by the structural protein neurofilament, is reduced by 61% in GalNAcT-/-Tg(neuronal) mice compared to control, as expected. This is due to calpain cleaving the neurofilament. Interestingly, neurofilament intensity is reduced by 32% in GalNAcT-/-Tg(glial) mice compared to control, suggesting an impairment of axonal integrity. One possible explanation for this could be secondary degenerative mechanisms resulting as a consequence of glial membrane injury. Analysis of axo-glial adhesion molecules at the node and paranode are currently ongoing to assess the status of the axo-glial junction and the outcome will be presented at the conference. Preliminary work shows that the GalNAcT-/-Tg(neuronal) and GalNAcT-/-Tg(glial) transgenic mice offer the potential to model the axonal and demyelinating variants of GBS, respectively, which will help elucidate the downstream mechanisms that occur following autoantibody injury.

References: None.

Keywords: Schwann Cell, Node, Node Biology, Inflammatory

Grant Support: Funded by the Wellcome Trust
Poster 85

Immuno-mediated polyneuropathies: A 15-year experience of a tertiary neuromuscular center

Luca Gentile, Anna Mazzeo, Anna Maria Barone, Giuseppe Vita, Antonio Toscano

UOC di Neurologia - Policlinico G.Martino, University of Messina, Italy, Messina, Italy

Peripheral neuropathy is a common neurological disorder facing neurologists. Immune-mediated, diabetic, hereditary, infectious, systemic/metabolic/toxic (not diabetic) and cryptogenic are the major categories of neuropathy in which almost all patients can be included. Among them, the immune-mediated group is one of the most representative. Some reviews report that the 18-20% of all the neuropathies diagnosed in a neuromuscular referral center are immuno-mediated. We revised all the cases of neuropathy (n: 650) diagnosed at our tertiary neuromuscular centre in the last 15 years (2004-2019). 176 (27%) of them were consistent with an immuno-mediated neuropathy (CIDP typical and atypical, GBS, MMN, Miller-Fischer syndrome, vasculitic neuropathy, polyneuropathy associated to monoclonal gammopathy, Parsonage-Turner syndrome and sensory neuronopathy). Diagnosis were based on clinical examination, neurophysiological evaluation, lab test and, when necessary, lumbar puncture and nerve biopsy. Intravenous immunoglobulin (IVIG) were the most used first line treatment, with high rate of effectiveness and safety, followed by intravenous or oral steroids. IVIG and steroids were often used as chronic treatment. Since 2010, the majority of patients are treated with subcutaneous immunoglobulin (SCIG) treatment which successfully implemented patient’s health and quality of life.

References: None.

Keywords: Inflammatory

Grant Support: None.
A 38 year-old male car mechanic from the northern region of Afghanistan presented 1 year ago with distal numbness of the right toes that ascended and, over the next 6 weeks, progressed to cause weakness and numbness of the both legs. A papulovesicular rash on the legs, extending to lower trunk, and fever were noted at that time. The rash resolved in 2-3 weeks. He had ischaemic discoloration of left index and right little finger associated with numbness and weakness of both hands two months later. He also complained of distal burning sensations and poor vision. A few weeks later he lost left eye vision acutely. He has been wheelchair bound for the last 9 months. Examination revealed distal predominant asymmetric weakness with worse foot drop on the right. Both ankle reflexes were absent. There was marked glove and stocking sensory loss, and thermal skin injuries in the leg. The distal ends of left hand digits II and V showed dry gangrene. Multiple vasculitic skin lesions were seen in the pulps of the right fingers. Vision was only counting fingers on the left. There were no overt symptoms or signs of dysautonmia. Nerve conduction studies showed severe, asymmetric sensorimotor axonal polyneuropathy. Routine urine analysis and blood work-up were unremarkable except for raised CRP but normal ESR ANA, dsDNA, ANCA, Anti CCP, RF, C3, C4, HIV, HCV serologies were negative. Hepatitis B viral count was very high. Other tests, including cryoglobulinaemia and sural nerve biopsy, were not available locally. Patient could not afford to travel elsewhere for these. The clinical diagnosis considered was Hepatitis B-related vasculitic mononeuritis multiplex. The differential diagnosis of leprosy was deemed less likely. The patient has been started on entecavir. In view of his progressive symptoms we are planning to start high dose corticosteroids empirically.
Therapeutic response and long-term outcomes in Lewis-Sumner patients: revisiting the syndrome three decades later

Guillaume Fargeot¹, Thierry Maisonobe², Dimitri Psimaras², Rabab Debs², Timothee Lenglet², David Adams¹, Christophe Vandendries³, Céline Labeyrie¹, Karine Viala²

¹CRMR Neuropathies Amyloïdes Familiales et autres Neuropathies Périphériques Rares, Hôpital Bicêtre, APHP, Le Kremlin Bicêtre, France, ²Département de Neurophysiologie Clinique, Hôpital Pitié Salpêtrière, APHP, Paris, France, ³Service d’imagerie, Fondation Ophtalmologique Adolphe de Rothschild, APHP, Paris, France, Paris, France

Background and purpose: Early differentiation of Lewis-Sumner syndrome (L-SS) from other types of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP-ot) is critical to effective treatment. We compared the clinical/electrophysiological characteristics, and long-term outcomes of L-SS and CIDP-ot.

Methods: Between 2002 and 2018, we retrospectively analyzed data from 45 consecutive patients with asymmetric sensory or sensory-motor neuropathy involving ≥2 nerve trunks with ≥1 overt conduction block (CB) on a motor nerve and compared them to 35 CIDP-ot.

Results: In the L-SS group, asymmetric (P<0.001) and monomelic involvement (P=0.03) of the upper limbs (P<0.001) was significantly more frequent; paucisymptomatic forms (ONLS ≤1) were less frequent (P<0.001); and electroneuromyography showed that CB in intermediate nerve segments was the main demyelinating feature, with little evidence of abnormal distal latencies or conduction velocity but frequent F-wave abnormalities on nerves without CB (44%). Plexus MRI and somatosensory evoked potentials found similar proximal abnormalities in both L-SS and CIDP-ot (70%/84% and 67%/87%). Long-term prognosis was globally poorer in the L-SS group with more frequent aggravation during treatment (P =0.017), less frequent treatment withdrawal (P=0.037), and longer time to achieve successful withdrawal (39 versus 15 months). Response to first-line treatment was poorer in the L-SS group due to the inefficacy of corticosteroids and plasma exchange.

Conclusions: L-SS patients appear to have a more severe disease course with a less favorable therapeutic response rate and long-term outcomes. Rapid differentiation of L-SS from other forms of CIDP is crucial to effective patient-management. Better understanding of the pathophysiology of L-SS and the development of new treatment strategies are essential.

References: None.

Keywords: Inflammatory

Grant Support: None.
Poster 88

Clinical and Electrophysiological profile of patients with CIDP

Pravallika Dutta, Meena AK, Sireesha Yareeda, Neeharika Mathukumalli, Jabeen Shaik.Afshan, Rupam Borgohain

nizam's institute of medical sciences, hyderabad, India
Introduction and Background:

CIDP is a chronic progressive demyelinating neuropathy. Several clinical variants of CIDP have been reported widening the spectrum of this neuropathy. Natural course of the disease is variable. We aim to study the clinical and electrophysiological profile of patients with CIDP seen in our hospital.

Material and methods:

All patients clinically suspected to have CIDP and confirmed by EFNS/PNS diagnostic criteria were included. Patients with confirmed positive paraprotein and other mimics were excluded. The demographic, clinical, laboratory, histopathology, electrophysiological analysis and imaging data were recorded. INCAT and MRC scoring was used to assess the functional outcomes.

Results:

A total of 46 patients were included in the study. The mean age was 44 (51-60) years, male to female ratio was 3:1(36,12). Three patients { MGUS(2) and POEMS syndrome(1)} were excluded. Three patients had GBS like presentation. Thirteen (29%) patients had underlying diabetes mellitus. Out of whom one patient was a renal transplant recipient on tacrolimus and mycophenolate. Most common phenotype was classic variant of CIDP with relapsing remitting course. Two were found to have MADSAM variant and one was found to have pure sensory form of CIDP (CISP). Twelve(26%) patients had facial weakness. Forty four patients met the EFNS/PNS ENMG criteria and most common electrophysiological criteria being prolonged distal latency. CSF albuminocytological dissociation was seen in 18(40%) patients. Steroids was the common immunosuppressant used as a first line agent. Two patients refractory to treatment received rituximab and 3 received PLEX as a rescue for exacerbation. The maximum INCAT score was 12 seen in 2 patients only. Twenty four (52%) patients went into remission in 6 months duration.

Conclusion:

Classical CIDP with a relapsing remitting course of illness is the most common clinical phenotype. EFNS criteria was sensitive electrophysiological criteria. Outcome was good in most of the patients.

References: None.

Keywords: Inflammatory

Grant Support: None.
Microscopic Polyangiitis Presenting with Extensive PNS and CNS Manifestations

Seok-Jin Choi¹, Jin Ah Kim², Yoon-Ho Hong³, Je-Young Shin², Jung-Joon Sung²

¹Inha University Hospital, Incheon, Korea (Republic of), ²Seoul National University Hospital, Seoul, Korea (Republic of), ³Seoul National University-Seoul Metropolitan Government Boramae Medical Center, Seoul, Korea (Republic of)

Microscopic polyangiitis (MPA) is an idiopathic autoimmune disease associated with anti-neutrophil cytoplasmic antibodies (ANCA) which is characterized by necrotizing systemic vasculitis involving small-caliber blood vessels. A 63-year-old man presented with progressive swallowing difficulty, significant weight loss (-15 kg over one month), and bilateral hearing loss following non-traumatic subdural hematoma (SDH). Neurological examination showed flaccid dysarthria, depression of the soft palate, and neck flexor weakness (MRC grade IV). Deep tendon reflexes were hypoactive, but showed exaggerated response after isometric contraction. The results of laboratory tests were as follows: white blood cell (WBC) 8,440/μL (eosinophils 2.8%), hemoglobin 11.2 g/dL, platelet 364,000/μL, C-reactive protein 7.5 mg/dL, erythrocyte sedimentation rate 128 mm/hr, blood urea nitrogen 12.1 mg/dL, and creatinine 0.88 mg/dL. Urinalysis showed WBC 3-5/high power field (HPF), red blood cell 11-15/HPF, and proteinuria (276 mg/day, normal range < 140 mg/day). Perinuclear ANCA (p-ANCA) measured by a direct immunofluorescence assay was positive, but cytoplasmic ANCA (c-ANCA) was negative. Brain computed tomography (CT) showed increased amount of SDH in the right cerebral convexity compared to the CT scan performed 2 weeks prior. Nerve conduction study showed right median neuropathy. On needle electromyogram, profuse denervation and reinnervation potentials were observed in the left masseter and genioglossus muscles. The results of high-frequency repetitive nerve stimulation test suggested a dysfunction of presynaptic neuromuscular junction transmission. Head-up tilt test showed severe orthostatic hypotension (systolic/diastolic blood pressure -31/17 mmHg at 30 seconds). Temporal bone CT showed acute and chronic otitis media with effusion. Pure tone audiogram and speech audiogram demonstrated bilateral sensorineural hearing loss. He was diagnosed as having MPA after kidney biopsy, and successfully treated with oral prednisolone and intravenous cyclophosphamide therapy. In summary, we report a rare case of ANCA-associated MPA with extensive neurological manifestations including both CNS and PNS (cranial nerves, motor/sensory/autonomic nervous system, and neuromuscular junction).

References: None.

Keywords: Inflammatory

Grant Support: None.
Clinical and treatment patterns of CIDP across India- Questionnaire Based study

Meena AK¹, Balaji Patil²

¹nizam’s institute of medical sciences, hyderabad, India, ²Eisai pharmaceuticals India Pvt limited, hyderabad, India

Introduction: Chronic inflammatory demyelinating polyneuropathy (CIDP) is a chronic, proximal and distal, asymmetrical or symmetrical, motor and sensory demyelinating polyneuropathy with a progressive course for at least 2 months. This study is planned to understand the clinical features, treatment, diagnosis and management of CIDP in India.

Method: This study was questionnaire based study conducted among CIDP specialist in India. Questionnaires were Web-based (https://docs.google.com/forms), with access provided through an e-mail link. The questionnaire consisted of 16 questions and was designed to help us better understand the presentation of CIDP, diagnosis, treatment strategies, and management of CIDP. Participants were asked to respond to the question on the basis of their experience of CIDP and management paradigm.

Results: Total 83 participants responded to all the questions. In a time frame of one month, 30.1% participants were practicing neurology more than 20 years and 22.9% participants practicing more than 10 years in the domain of Neurology. 31.3% participants are seeing 5-10 CIDP patients every year, 19.3% participants are seeing 10-15 patients/year while 16.9% participants are seeing more than 20 CIDP patients/year. Eighty five% participants trust on prolonged distal latency, 84.3% participants trust on slowing of conduction velocity and 74.3% participants trust on conduction block. For the treatment of CIDP, 55.4% specialists utilizes steroids, 27.7% use steroids in addition to immunosuppressant and 21.7% utilize IVIG in addition to steroid as first choice of treatment of CIDP.

Conclusion: Steroids remain as first line choice of therapy for the treatment of CIDP followed by IVIG. Plasma exchange use in the treatment of CIDP is still not been recognized among the experts.

References: None.

Keywords: Inflammatory

Grant Support: None.
Depression, Quality-of-Life and Health Status During Long-Term IVIG (Gamunex® 10%) Therapy in CIDP Patients

Juliane Klehmet¹, Bernd Kieseier², Judith Haas³, Björn Tackenberg⁴

¹NeuroCure Clinical Research Center Berlin, Charité Universitätsmedizin, Berlin, Germany, ²Neurologische Klinik, Heinrich-Heine Universität, Düsseldorf, Germany, ³Jüdisches Krankenhaus Berlin, Berlin-Mitte, Germany, ⁴Klinik und Poliklinik für Neurologie, Marburg, Germany

Purpose: Chronic inflammatory demyelinating polyneuropathy (CIDP) is often accompanied by anxiety/depression and daily activity impairment affecting patients’ quality of life. Here we describe the dynamics of these symptoms in patients receiving intravenous immunoglobulin (IVIG) therapy in routine clinical practice.

Methods: GAMEDIS was a multi-centre, prospective, non-interventional study performed on CIDP patients aged ≥18 years treated with IVIG (Gamunex® 10%), who were followed-up for 2 years. Beck Depression Inventory II (BDI), Short form-36 health survey (SF-36), and Work Productivity and Activity Impairment score attributable to general health (WPAI-GH), forms were fulfilled by the patients at baseline and each quarterly visit. Safety profile was also assessed.

Results: 148 patients (93.7% of the total enrolled patients) were evaluable during a mean period of 83.3 weeks. All patients displayed minimal or no depression at baseline (mean BDI score <14), with no variation across the study. SF-36 mean scores remained stable during the study, with slight improvement of the physical and physical role functioning, bodily pain and mental health dimensions. The mean activity impairment scores, representing daily work and non-work activities, were reduced at the end of the study respect to baseline visits. A total of 34 potentially-treatment related adverse events were reported, mostly headache [n=5], hypersensitivity, rash and diarrhoea [n=2 each]).

Conclusion: Patients’ QoL and depression were shown to be stable during long-term treatment with Gamunex® 10% in clinical practice. The overall activity impairment slightly improved. Gamunex® 10% good tolerability and safety was confirmed by this study in daily clinical practice condition.

References: None.

Keywords: Inflammatory

Grant Support: None.
Poster 92

Serum BAFF Levels In Chronic Inflammatory Demyelinating Polyneuropathy

Luuk Wieske¹, Gwen van Lieverloo¹, Camiel Verhamme¹, Marleen Koel-Simmelink², Ivo van Schaik¹, Charlotte Teunissen², Filip Eftimov¹

¹department of Neurology, Amsterdam Neuroscience, Amsterdam UMC, Amsterdam, Netherlands, ²department of Clinical Chemistry, Amsterdam Neuroscience, Amsterdam UMC, Amsterdam, Netherlands
Purpose:

B-cell activating factor (BAFF) plays an important role in several autoimmune disorders as an essential cytokine for B-cell activation, maturation and survival. Anti-BAFF directed therapy is approved for SLE. Increased BAFF serum levels that decrease within hours or days after IVlg have been found in CIDP. We investigated the correlation between serum BAFF levels and disease activity, treatment response and outcome measures in CIDP.

Methods:

Three prospective cohorts of CIDP patients were studied: 1) patients starting induction treatment (IT cohort, N:30) measured at baseline and six months after starting treatment; 2) patients on maintenance treatment starting IVlg withdrawal (MT cohort, N:24) measured at baseline and six months after IVlg withdrawal or at time of relapse and 3) patients in long-term remission without treatment (N:26). Serum BAFF was measured using Luminex® assay. Age matched healthy controls (N:33) were used for comparison. Treatment response was defined as improvement by at least the minimal clinical important difference (MCID) on the I-RODS; and/or an increase of ≥8 kPa on grip strength. Relapse was defined as any deterioration requiring retreatment.

Results:

BAFF levels were higher in CIDP patients compared to healthy controls (median 785 pg/ml [IQR 658- 965] vs 660 pg/ml [IQR 620-740]; p<0.01). BAFF levels did not differ between IT, MT and remission patients. Changes in BAFF levels did not differ between patients responding or not responding to induction treatment and patients with or without a relapse after treatment withdrawal. BAFF levels did not correlate with I-RODS or grip strength in any of the cohorts.

Conclusion:

In an unselected cohort of CIDP patients, BAFF levels were higher compared to controls but did not correlate with disease activity, treatment response, grip strength or I-RODS. The role of BAFF in specific subgroups of CIDP patients with predominant B-cell mediated autoimmunity needs to be investigated.

References: None.

Keywords: Inflammatory

Grant Support: None.
Restless legs syndrome affects multiple life domains in patients with chronic inflammatory demyelinating polyradiculoneuropathy

Ivana Basta¹, Stojan Peric¹, Ivo Bozovic¹, Aleksandra Kacar¹, Vesna Martic², Aleksandra Dominovic-Kovacevic³, Zoran Vukojevic³, Miroslav Stojanovic⁴, Vidosava Rakosevic-Stojanovic¹, Dragana Lavnic¹, Zorica Stevic¹

¹Neurology Clinic, Clinical Center of Serbia, Belgrade, Serbia, ²Military Medical Academy, Belgrade, Serbia, ³Neurology Clinic, Clinical Center of Banja Luka, Banja Luka, Bosnia and Herzegovina, ⁴Neurology Clinic, Clinical Center of Kragujevac, Kragujevac, Serbia

Background: Restless legs syndrome (RLS) was described in patients with different types of polyneuropathies. Our aim was to analyze frequency of RLS in CIDP patients and its influence on patients’ sleep, daily affairs, mood and quality of life (QoL).

Methods: Study included 58 patients with CIDP (57% males, age 58±16), who attended tertiary clinics in Serbia and Republic of Srpska during 2017. RLS was diagnosed in accordance with the NIH criteria. RLS Rating Scale, INCAT disability score and SF-36 questionnaire were also used.

Results: RLS was present in 18 (31%) CIDP patients and its mean severity was moderate (18.3±7.9). Medications for RLS were not prescribed in any of them. RLS symptoms were present at least two days per week in 72% of patients and duration of symptoms was at least one hour per day in 50% of them. Age at CIDP onset and at the moment of testing was higher in patients with RLS (56±12 vs. 46±15 and 65±14 vs. 55±16 years, respectively, p<0.05). Eleven (61%) of 18 patients with RLS had moderate to very severe sleep disturbances, six (33%) had moderate to very severe tiredness and sleepiness during day, seven (39%) had moderate to severe influence of RLS on daily affairs, and nine (50%) had moderate to severe mood disturbances. We did not observe significant association between QoL measured with SF-36 and presence of RLS.

Conclusions: RLS was found in one third of our CIDP patients. RLS had influence on sleep, daily affairs, and patients’ mood. Routine screening of RLS in CIDP patients should be introduced.

References: None.

Keywords: Inflammatory

Grant Support: None.
Bortezomib/Dexamethasone therapy in 20 patients with POEMS syndrome

Hiroshi Amino, Sonoko Misawa, Tomoki Suichi, Kazumoto Shibuya, Yukari Sekiguchi, Atsuko Tsuneyama, Yoichi Suzuki, Satoshi Kuwabara

Department of Neurology, Graduate School of Medicine, Chiba University, Chiba, Japan

POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome is an important cause of progressive demyelinating neuropathy associated with monoclonal plasma cell proliferation. Treatment for multiple myeloma, such as autologus stem cell transplantation and immune modulating drugs have been applied to POEMS, leading to better prognosis. Bortezomib, a proteasome inhibitor, is one of the mainstay drugs for myeloma, but it has not been aggressively applied to POEMS probably due to concern with its neurotoxic side effect. The aim of this study is to investigate the safety and efficacy of bortezomib for POEMS syndrome. We reviewed medical records of 20 consecutive POEMS patients (10 men, mean age 53 years old), who were treated with bortezomib and dexamethasone. The reasons to choose bortezomib were acute worsening (n=7), refractory to thalidomide/lenalidomide (n=4) or life-threatening condition (n=10) such as massive pleural effusions. The patients received 1-4 cycles of subcutaneous bortezomib (1.0-1.3mg/m², 21-day cycle of twice weekly or 35-day cycle of weekly) and dexamethasone. After treatment with bortezomib, serum VEGF levels rapidly decreased in 10 patients (50%) and clinical symptoms improved in 11 patients (55%). 10 of the 20 patients (50%) could achieve remission (normalization of serum VEGF levels) and mean time to remission was 2 months (SD:2.4). Four patients were resistant to bortezomib and required alternative treatment. One patient died of POEMS syndrome during the initial cycle. Mild neuropathy was seen in 25% of the patients, and ileus, thrombocytopenia, and constipation were seen in 10% of the patients. However, no patients discontinued the treatment due to these side effects. Bortezomib and dexamethasone can be a safe and effective therapeutic option for POEMS syndrome and they could rapidly lead to remission even in patients who are acutely worsened or severely affected.

References: None.

Keywords: Clinical Trials

Grant Support: None.
Subcutaneous Immunoglobulin maintenance therapy in inflammatory neuropathy: longterm efficacy and tolerability

Aisling Carr¹, Ryan Keh², Sarah Morrow¹, Laura Compton¹, Mahima Kapoor¹, Mike Lunn¹, Mary Reilly ³, Dave Gosal², Tim Lavin²

¹Centre for Neuromuscular Diseases, 8-11 Queen Square, National Hospital of Neurology and Neurosurgery, London, United Kingdom of Great Britain and Northern Ireland, ²Greater Manchester Neuroscience Department, Salford Royal Hospital, Manchester, United Kingdom of Great Britain and Northern Ireland, ³Centre for Neuromuscular Diseases, 8-11 Queen Square, National Hospital for Neurology and Neurosurgery, London, United Kingdom of Great Britain and Northern Ireland

Introduction

The PATH trial provides RCT evidence for efficacy of SCIg in CIDP with more, previously IVIg-dependent, patients relapsing on placebo than SCIg. Maintenance IVIg regimen was fractionated to weekly SCIg at equivalent g/kg/month dose (1:1). In practice we titrate dose to clinical response and actual SCIg requirements are not known.

Aim

To examine for change in maintenance dose requirements in patients with inflammatory neuropathy transferred from regular IVIg to longterm regular SCIg. To examine tolerability in real-life clinical practice.

Methods

Database review of all patients treated with SCIg for inflammatory neuropathy in 2 UK specialist peripheral neuropathy centres.

Results

37 patients received SCIg for inflammatory neuropathy up to April 2018; 46% female; age (mean, S.D.):57.8 (13.7) years, range=25-77 years. Duration IVIg prior to transfer: 52.9(35.6) months, range:10months-11years. Previous IVIg maintenance= 79.9(31.1) g/month; 1.2 (0.45) g/kg/month, frequency: 4 weekly. Reasons for transfer: Lifestyle/convenience:17/37(45.9%), CV risk:2/37(4.6%), Headache:3/37(6.9%), not known:6/37(13.8%). Duration SCIg=52.9(35.6)months, range:10.2-105 months; maintenance:22.1(7.5)g/week, range:4.8-36g;86.4 (31.5)g/month; 1.44 (0.5)g/kg/month. Difference: +6.35 (22.4) g/month; +0.1(0.4)g/kg/month. 23/37 stable on 1:1 ratio, 8/37 ↑dose due to clinical deterioration, 3/37 ↓dose due to clinical stability, 4 stopped. No Adverse reactions.

Conclusion

Clinical practice experience over an extended time period supports efficacy and safety of SCIg in the inflammatory neuropathy cohort.

References: None.

Keywords: Inflammatory

Grant Support: None.
Poster 96

A Case of a Rapidly Progressive Motor Neuropathy-Neuronopathy ? Paraneoplastic

Zaheer Bagha¹, Thirugnanam Umapathi²

¹Coast Province General Hospital, Mombasa, Kenya, ²National Neuroscience Institute, Singapore, Singapore

A 54 year old male presented to a public hospital in Kenya with a 3 month history of left upper limb paralysis followed by painless progressive lower limb weakness resulting in inability to walk unassisted and then distal weakness of the right upper limb. There were no sensory complaints. He had been having low grade fever, night sweats, unintentional weight loss (70 kg to 55 kg over past 3 months). Review of systems did not reveal any symptoms suggestive of a specific infection or neoplasm. He had normal tone but reduced reflexes in all the limbs. Power was grade 3 in both lower limbs, 0 in the left upper limb, 2 distally and 4 proximally in the right upper limb. All sensory modalities were intact. Cranial nerves and bulbar muscles were uninvolved. General examination was remarkable for pallor, bilateral ankle oedema, bilateral crepitations, enlarged liver 12 cm below the costal margin without splenomegaly or lymphadenopathy. Routine investigations were remarkable for microcytic anaemia, raised white cell count, CRP and procalcitonin. HIV, Hepatitis B and C serologies were negative. ALP and GGT were raised at 563 and 616 U/l respectively. CA 19-9 was 472 u/ml (0-37) and CEA 9.56 ug/l (0-3.4). Serum protein electrophoresis was normal. CT abdomen revealed multiple non-enhancing cystic lesions in the liver, some with fine internal septae and minimal ascites. Spinal fluid showed normal cell count, protein and glucose. TB PCR (Gene Xpert) was negative. Nerve conduction studies showed severe generalized axonal motor neuropathy-neuronopathy. A biopsy of the liver masses was planned but the patient’s condition worsened from sepsis, and the patient passed on before a definitive diagnosis could be made. The pure motor peripheral neuropathy-neuronopathy was presumed to be paraneoplastic. Facilities to test for paraneoplastic antibodies were not available and the family declined for a postmortem.

References: None.

Keywords: Inflammatory

Grant Support: None.
IMMUNORM aims to evaluate the safety and efficacy of Gammanorm®, a 16.5% subcutaneous immunoglobulin (SCIG), in auto-immune disease and neuropathy care. In France, off label use has been reported for the treatment of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Multifocal Motor Neuropathy (MMN), Dermatomyositis (DM), Polymyositis (PM), Inclusion-Body Myositis (IBM), Necrosing Myositis (NM) and Idiopathic Thrombocytopenic Purpura (ITP). IMMUNONORM aims to enroll 80 adults with such auto-immune diseases and to follow their SCIG treatment for 2 years after their initial prescription. The primary objective is to determine the number of adverse drug reactions (ADR). Efficacy is examined using disease specific scores during quarterly follow-up visits.

To date, 31 patients have been registered across 11 French hospitals. At inclusion, patients were 57.3 years old (SD:14.8, [28.81–82.13]), 67.7% were women including 9 CIPD, 6 PM, 4 IBM, 3 MMN, 2 DM, 2 NM cases, the remainder having “other” auto-immune pathologies. All but 1 patient had received prior treatments, 27 (from n=30, 90%) patients were reported to have previously received intravenous immunoglobulins (IVIG), approximately half had received corticoids (56.7%) or immunosuppressors (46.7%). Initial biological exams revealed elevated levels of creatine phosphokinase (CPK; n=15; 610 IU, SD: 1079, [68–4358]). The mean dose prescribed was 109 g/month (SD: 43.5, [15– 176]), 24 patients received home-based infusions. Only 1 ADR has been reported to date (hypergammaglobulinemia), and only 3 patients have terminated the study, 1 of whom has continued SCIG treatment. At 3 months of SCIG therapy, CPK levels were reduced in those 5 reported patients.

Preliminary results indicate that SCIG treatment of these rare conditions is safe and well tolerated. As most patients (n=24) were recruited in 2018 and early 2019, efficacy data from their initial follow-up visits is currently being collected.

References: None.

Keywords: Inflammatory, Pain, Small Fibers, Schwann Cell, Other

Grant Support: None.
Poster 98

Anti-ganglioside antibodies classification and correlation with the clinical manifestations in the inflammatory peripheral neuropathy patients

So Hyun Ahn¹, Yoon-Ho Hong², Jin-Ah Kim¹, Jung-Joon Sung¹, Ah Won Kim¹, Min Ju Cha¹, Je-Young Shin¹, Young-Nam Kwon¹, Hyun Seok Baek¹

¹Seoul National University Hospital, Seoul, Korea (Republic of), ²Seoul Metropolitan Government Boramae Medical Center, Seoul National University College of Medicine, Seoul, Korea (Republic of)

In this study we investigated the anti-ganglioside antibodies classification and correlation with the clinical manifestations in the inflammatory peripheral neuropathy patients. Method: Samples from 89 patients diagnosed with inflammatory peripheral neuropathy including CIDP(72), GBS(8) and MMN(6) were prospectively enrolled. We used a multiplex immunochromatography to detect anti-ganglioside antibodies and compared them with previous results by ELISA. Results: Anti-ganglioside antibodies were found in 13.5%(12/89) by ELISA and 4.5%(4/89) by immunochromatography. Serum IgG anti-ganglioside antibodies were detected in 9.7% of the CIDP patients and in 12.5% of the AIDP patients done by ELISA, however, in 1.4% of the CIDP patient and in 12.5% of the AIDP patients done by immunochromatography. Serum IgM anti-ganglioside antibodies were detected in 33% of MMN patients and 1.4% of the CIDP patient and in 12.5% of the AIDP patients done by ELISA. Serum IgM anti-ganglioside antibodies were detected in 2.8% of CIDP patients done by immunochromatography. Immunochromatography method showed lower detection rate compared to ELISA, which may be related with the blood sampling time (acute or chronic) and accuracy of method. Conclusions: These results suggest that IgM anti-GM1 antibodies are associated with CIDP, and that IgG anti-GM2 associated with AIDP and CIDP.

References: None.

Keywords: Inflammatory

Grant Support: None.
Poster 99

Nationwide Long-term Outcome in Treated Chronic Inflammatory Demyelinating Polyneuropathy

Ali Al-Zuhairy\(^1\), Søren Sindrup\(^2\), Henning Andersen\(^3\), Johannes Jakobsen\(^4\)

\(^1\)Department of Neurology, Neuroscience Center, Copenhagen University Hospital (Rigshospitalet), Copenhagen, Denmark, \(^2\)Department of Neurology, Odense University Hospital, Odense, Denmark, \(^3\)Department of Neurology, Aarhus University Hospital, Aarhus, Denmark, \(^4\)Department of Neurology, Neuroscience Center, Copenhagen University Hospital (Rigshospitalet), Copenhagen, Denmark

Purpose: To evaluate the effect of long-lasting immune modulating therapy in patients with chronic inflammatory demyelinating polyneuropathy (CIDP).

Methods: A population-based cross-sectional study was conducted in patients referred to the Danish healthcare system between 1985 and 2006 using the Danish National Patient Register.

Results: One-hundred-twenty-nine patients had CIDP, 23 had died (1 death caused by CIDP), 39 were excluded and 16 rejected participation. The remaining 51 patients had a mean disease duration of 16.9 years and 27 patients (53%) were in remission. Forty-six patients walked independently and three had no walking function. The Inflammatory Rasch-built Overall Disability Scale (I-RODS) score was reduced by 17% as compared to 20 matched control subjects, isokinetic strength (IKS) decreased by 20%, the Neuropathy Impairment Score (NIS) was doubled, the Timed 25-Foot Walk was prolonged by 23% and the EQ-5D-5L-Index Value was 20% lower. Mood and aerobic capacity were mildly impaired. Pain, social adjustment, and working capacity were not different from controls. There was a close relationship between the I-RODS scores and NIS ratings and of both scores to all other primary study parameters. Regression analysis showed that a substantial part of the long-term disability was directly related to time until start of initial therapy.

Conclusion: Long-term prognosis in treated CIDP is characterized by moderate disability with proportional loss of strength, functions and quality of life but 10% of patients are severely disabled. It is suggested that the long-term disability in CIDP can be further reduced if initial therapy is started earlier.

References: None.

Keywords: Inflammatory

Grant Support: The study was supported by a research grant from Baxter/Baxalta, now part of Shire covering the expenses for a PhD-study, without providing personal benefits to any of the authors.
OPTIC Trial: Intravenous Immunoglobulin And Intravenous Methylprednisolone As Induction Treatment In CIDP – study update

Sander Bus1, Laura Zambreanu2, Ahmed Abbas3, Yusuf Rajabally3, Rob Hadden2, Rob de Haan4, Corianne de Borgie4, Michael Lunn2, Ivo van Schaik5, Filip Eftimov5

1Amsterdam UMC, University of Amsterdam, Department of Neurology, Amsterdam Neuroscience, Amsterdam, Netherlands, Amsterdam, Netherlands, 2Centre for Neuromuscular Disease, National Hospital for Neurology and Neurosurgery, London, United Kingdom of Great Britain and Northern Ireland, 3Regional Neuromuscular Service, University Hospitals of Birmingham, Birmingham, United Kingdom of Great Britain and Northern Ireland, 4Amsterdam UMC, University of Amsterdam, Clinical Research Unit, Amsterdam, Netherlands, 5Amsterdam UMC, University of Amsterdam, Department of Neurology, Amsterdam Neuroscience, Amsterdam, Netherlands

Introduction: The OPTIC trial (ISRCTN15893334) is a investigator-initiated randomized double blind placebo-controlled trial designed to assess whether combined induction treatment with intravenous immunoglobulins (IVIg) and methylprednisolone (IVMP) leads to more remissions than IVIg treatment alone.

Methods: Adults diagnosed with definite or probable CIDP according to the EFNS/PNS criteria will be included, comprising three categories: 1) Treatment naïve patients; 2) Relapse patients following a year or more of stable disease; 3) Patients having received a single loading dose of IVIg in the last three months with initial improvement and subsequent deterioration. Patients are randomized to receive IVIg + IVMP (1000 mg) or IVIg + placebo (sodiumchloride 0.9%) every three weeks for 18 weeks. IVIg treatment consists of a 2 g/kg loading dose over 3-5 days and six maintenance courses of 1 g/kg over 1-2 days. Primary outcome is the number of patients in remission at 52 weeks. Remission is defined as sustained improvement between week 18 - 52 without need for further treatment. Improvement is assessed at week 18 and defined as an increase of at least the minimal clinically important difference (MCID) on the Inflammatory Rasch-Built Overall Disability Scale (I-RODS) and/or improvement of ≥ 1 point on the Inflammatory Neuropathy Cause and Treatment (INCAT) disability scale compared to baseline. Follow-up is 2 years and includes long term safety and clinical assessments, including an extended economic evaluation.

Results: First patient was enrolled in February 2018. Fourteen patients (out of 96) are enrolled. Six patients completed the 18 week treatment protocol as of March the 1st 2019. Eight centers in the Netherlands are currently including and six more centers in United Kingdom are expected to include patients from summer 2019 onwards. Results are expected in 2022.

References: None.

Keywords: Inflammatory, Clinical Trials

Grant Support: ZonMW, Prinses Beatrix Spierfonds, Sanquin
Poster 101

Guillain-Barré Syndrome associated with influenza A H1N1 virus: a parainfectious disorder?

Stefano Giuseppe Grisanti¹, Chiara Demichelis², Luana Benedetti²

¹University of Genoa and IRCCS Policlinico San Martino, Genoa, Genoa, Italy, ²University of Genoa and IRCCS Policlinico San Martino, Genova, Genoa, Italy

Introduction

Guillain–Barré syndrome (GBS) is an acute, acquired, monophasic, immune-mediated disorder of the peripheral nervous system that develops in susceptible individuals after infection or after immunisation. In this fashion, exposure to influenza virus via infection or vaccination has been associated with GBS. Regardless of the triggering factor, the infectious event or the vaccination are usually reported several weeks before the disease onset. Herein, we report three GBS cases in which the respiratory infection and the immune-mediated neurological symptoms appeared almost simultaneously.

Case report

The first patient was a 15-years old man who developed acute lumbar pain and paresthesias in the lower limbs concomitant with the development of fever and cough. Neurological examination demonstrated absence of deep tendon reflexes. The second patient and the third patient were a 53-years old and a 61-years old women who developed quadriplegia and areflexia, with respiratory failure currently with the finding a viral pneumoniae. In all the patients, CSF analysis demonstrated albuminocytological dissociation, while nerve conduction studies were congruous with the diagnosis of demyelinating GBS. Influenza A (H1N1) infection was confirmed by PCR on nasopharyngeal swab. The first and the second patients recovered spontaneously; because of the severity of the disease course, the third patient was treated with intravenous immunoglobulin (IVIg) with improvement.

Discussion

Several studies indicated that influenza viruses could act as trigger factors for GBS. In this scenario, molecular mimicry and a cross-reactive immune response are thought to play a major role in the pathogenesis of GBS. Usually, the trigger infection precedes by several weeks the appearance of the neurological symptoms. These three cases demonstrate that GBS could appear with a short delay after influenza A H1N1 infection, and this could be related to the triggering of a strong immune response to the virus. Further investigations are needed to clarify these findings.


Keywords: Inflammatory

Grant Support: None.
Efficacy and Safety of different Dosages of IVIG (panzyga®) in Patients with CIDP–ProCID Study-Update

David Cornblath¹, Pieter van Doorn², Hans Hartung³, Hans Katzberg⁴, Ingemar Merkies⁵, and the ProCID Investigators⁶

¹Johns Hopkins University, Baltimore, MD, USA, ²Erasmus University Medical Center, Rotterdam, Netherlands, ³Heinrich Heine University, Dusseldorf, Germany, ⁴University of Toronto, Toronto, Canada, ⁵Maastricht University Medical Center, Maastricht, Netherlands, ⁶[NOT FOUND]]

The ProCID study is a prospective, double-blind, randomized, parallel group, multi-center phase III efficacy and safety study of 3 doses of IVIg (Panzyga®) in patients with CIDP. The ProCID study aims to confirm published clinical trial results obtained with the standard dose of 1.0 g/kg every 3 weeks, and will in addition evaluate efficacy and safety of a higher and a lower maintenance dose, with the aim to offer CIDP patients more adequately dose and effective treatment options. A lower dose might be beneficial for patients resulting in less risk of adverse drug reactions. On the other hand, a higher dose might reduce the number of treatment non-responders.

The study began in May 2017 and is ongoing in 25 centres in Ukraine, Romania, Russia, Czech Republic, Poland, Bulgaria, Hungary, Germany, and Canada. The study protocol specified that 140 adult patients with definite or probable CIDP according to the EFNS/PNS Criteria will be enrolled and randomized 1:2:1 to receive either 0.5 g/kg, 1.0 g/kg or 2.0 g/kg IVIg for seven maintenance infusions at 3-week intervals during the Dose-Evaluation Phase, after a loading dose of 2.0 g/kg IVIg. The primary efficacy is the percentage of responders (at least 1 point decrease in the adjusted INCAT disability score) in the 1.0 g/kg IVIg arm (given every 3 weeks) at Week 24. The most important secondary efficacy endpoint is the percentage of responders at Week 24 in the 0.5 g/kg and 2.0 g/kg arms relative to baseline and compared to the 1.0 g/kg arm.

As of 28 February 2019, 171 patients were enrolled/screened, 137 patients were randomized, and 65 patients had completed the study. Further updates will be presented at the meeting. We expect the last patient to complete the study in Q3/2019 and final study results to be available in Q2/2020.

References: None.

Keywords: Inflammatory, Clinical Trials

Grant Support: ProCID is an Octapharma sponsored interventional Phase III study
To determine a practical minimum clinically important difference (MCID) for grip strength in an individual patient with chronic inflammatory neuropathy. Fifteen patients with chronic inflammatory neuropathies (10 CIDP, 5 MMN) on regular long-term intravenous immunoglobulin (IVIg) measured their grip strength using the Martin Vigorimeter at home every day from one IVIg treatment until the next (median 28 days), to assess objective improvement between hospital visits. We analyzed grip strength changes from baseline in the weaker hand, comparing published MCID thresholds of 8 kPa and 14 kPa (1). Most patients showed a slow treatment-related fluctuation with superimposed fast ‘random’ daily fluctuations. We smoothed the data as a rolling 5-day mean to minimize random fluctuations, and quantified the random fluctuations as the difference between smoothed and raw data on each day. Random fluctuations of ≥8 kPa occurred in four patients (27%) on a mean 6% of days, but never reached ≥14 kPa. Therefore 8 kPa increase is not specific for true improvement. The random fluctuations in the left hand were only weakly correlated with the right hand on the same day (r=0.33). Smoothed grip strength increased by ≥8 kPa in 11 (73%) patients and by ≥14 kPa in 6 (40%) patients. Unsmoothed grip strength increased by ≥14 kPa in 7 (47%) patients. Grip strength increases agreed well with patients’ subjective health improvement and with RODS. All these results are from analysis of the mean grip strength on each day, but maximum daily grip strength was only slightly less sensitive and more convenient. To detect improvement of grip strength in an individual patient, we suggest a threshold of 8 kPa (smoothed data) or 14 kPa (raw data).


Keywords: Inflammatory, Other

Grant Support: None.
MYD88 and CXCR4 Mutational Profile in IgM Paraproteinemic Neuropathy with Anti-MAG Antibody.

Marta Ruiz1, Andrea Visentin2, Marta Campagnolo1, Cinzia Candiotto3, Francesca Castellani1, Alessandro Salvalaggio4, Renato Zambello5, Francesco Piazza5, Livio Trentin5, Roberta Bertorelle3, Chiara Briani1

1University of Padova, Department of Neurosciences, Padova, Italy, 2Hematology and Clinical Immunology Unit, Department of Medicine, University of Padova, Padova, Italy, 3Immunology and Molecular Oncology, Veneto Institute of Oncology IOV - IRCCS, Padova, Italy, 4University of Padova, Department of Neurosciences, Padova, Italy, 5Hematology and Clinical Immunology Unit, Department of Medicine, University of Padova, Padova, Italy

Neuropathy with antibodies to myelin-associated glycoprotein (MAG) is the most common IgM paraproteinemic neuropathy. Although the paraprotein is commonly a monoclonal gammopathy of undetermined significance (MGUS), the monoclonal IgM may underscore lymphoproliferative disorders, Waldenstrom’s Macroglobulinemia (WM) but also lymphoma or chronic lymphocytic leukemia (CLL). Recently, the discovery of the mutational profile of the MYD88 and CXCR4 genes have radically changed the prognostic evaluation of IgM monoclonal gammapathies. MYD88L265P has been found to be the most common mutation in WM and IgM-MGUS. Somatic mutations in the C-terminal domain of CXCR4 have been shown to be associated with a more aggressive WM disease. MYD88/CXCR4 status has been shown to be predictive of response to ibrutinib (the first-in-class inhibitor of Bruton’s tyrosine kinase) in WM. In a single center study we assessed the mutational profile of MYD88 and CXCR4 genes in anti-MAG antibody neuropathy patients. Eighteen patients (5 women, mean age 68±9 years, 7 previously treated with rituximab) with anti-MAG antibody neuropathy were enrolled. Seven had IgM MGUS, 9 WM, 2 CLL. Molecular analysis was performed on DNA extracted by an automated system from bone marrow mononuclear cells after density gradient separation by Ficoll Hypaque. MYD88L265P mutation was searched by allele specific-PCR. For detecting the most common CXCR4 mutation (S338X) a highly sensitive allele specific-PCR assay was developed while Sanger sequencing (less sensitive) was required for both nonsense and frameshift mutations of the C-terminal domain in S338X negative samples. In the first 18 patients studied, 15 turned out to carry the MYD88 mutation, namely all the 9 WM patients, 5/7 MGUS patients and one of the two CLL and all the patients were negative for CXCR4 mutations. The results helped identify the presence of a mutational target for a potential new and effective therapy, such as ibrutinib, for anti-MAG antibody neuropathy.

References: None.

Keywords: Inflammatory

Grant Support: None.
Poster 105

The impact of prioritization measures on the use of IVIG in the French neuromuscular network.

Shahram ATTARIAN¹, Karine VIALA², Guilhem SOLE³, Francoise BOUHOUR⁴, frerderic TAITHE⁵, Julien CASSEREAU⁶, raul Juntas Morales⁷, Yann PEREON⁸, Jean Baptiste CHANSON⁹, Francoise LEBEAU¹⁰, Alain CREANGE¹¹, Pascal CINTAS¹², Guillaume NICOLAS¹³, francoise CHAPON¹⁴, Clément BARON¹⁵, Agnes JACQUIN¹⁶, Pauline REACH¹⁷, Olivier FLABEAU¹⁸, Evelyne FENEUIL¹⁹, Sylvain LACHAUD²⁰, Mathilde LEFILLIATRE¹⁴, Laurent TATU²¹, David ADAMS²²
Introduction:

There is a growing imbalance between the production of IVIg and their indications. IVIg consumption increases by 7% each year.

In 2017, faced with national challenges in immune globulin supply, French National Agency for Drug and Health Product Safety (ANSM) developed a prioritization table for the use of IVIg in partnership with the neuromuscular disease network (FILNEMUS).

Methods:

To assess the impact of the recommendations by ANSM on their practice during 2018 and on the use of IgIV, a survey was carried out with the FILNEMUS reference centers (FRC) questioning in main indications: GBS, CIDP, MMN, Lewis-Sumner, Myasthenia Gravis.

Results

22 FRC answered the questionnaire. 96% FRC encountered supply difficulties in IVIg and 60% of them observed a temporary interruption of supply. There was 1293 new patients requiring IVIg in 2018; and an active file of 4025 with dysimmune neuropathy. The recommendations were applied in 83.5% of FRC. IVIg consumption decreased by 5% in 2018.

For CIDP, first-line treatment is IVIg in 71%, plasma exchanges in 16.5% and steroids in 9%. The ONLS score is mainly used to prescribe IVIG (83.5%). IVIg are prescribed in 91% of definite CIDP, and 58% of possible CIDP. The therapeutic test is practiced in majority (79%) at the rate of 2 g/kg on 3 monthly courses. Rhythms of neurological evaluation on the effectiveness of IgIV being before IVIg and after 3 months (100%). The improvement of one point of the ONLS score at 3 months is the chosen to assess response (91.5%).

For long term therapy with IgIV, spacing courses with constant dose is used (87%). IVIG are most often substituted by steroids. Savings strategies in IgIV are sometimes used in 87.5%.

Conclusion:

A global IVIg prescribing strategy is necessary, the development of IVIG savings treatments is urgent.
References: None.

Keywords: Inflammatory, Other

Grant Support: None.
Granulomatous Neuropathy of Unknown Cause Presenting as Distal Multiplex Neuropathy

Anna Grisold1, Stefan Meng2, Romana Höftberger3, Ellen Gelpi3, Wolfgang Grisold4

1Department of Neurology, Medical University of Vienna, Vienna, Austria, 2Department of Radiology, Kaiser Franz Josef Hospital, Vienna, Austria, 3Institute of Neurology, Medical University of Vienna, Vienna, Austria, 4Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Vienna, Austria

Introduction

Granulomatous neuropathy is a rare type of peripheral neuropathy. Associations with sarcoidosis, autoimmune diseases (e.g. Sjögren syndrome) and lymphoma have been described.

Methods

Case report and review of the literature.

Results

A 55-year old previously healthy female presented with numbness between the second and third finger of her right hand, which had gradually developed over several months. She also noted weakness when spreading her fingers. On clinical examination, the thenar and hypothenar muscles appeared normal. Nerve ultrasound revealed thickened right interdigital nerves. Only focal nerve changes have been detected in electrophysiology. The patient refused any treatment at this point. However, within several months, she developed a severe atrophy of the right hand. One year after symptom onset, she also reported numbness of her right lateral foot. The sural nerve appeared thickened on ultrasound and was biopsied. Histology revealed granulomatous nerve tissue. Serial sections showed no evidence for acid-fast bacilli, and staining for monoclonal lymphocytes was negative. Extensive work-up ruled out sarcoidosis, Sjögren syndrome and neoplastic causes. Subsequently, clinical symptoms progressed and about 16 months after onset, a therapeutic trial with intravenous immunoglobulins and weekly methotrexate was initiated. This regimen has been continuously applied within the past year, and atrophy as well as sensory impairment have not progressed. Even a mild improvement of muscle strength in her hand was noted. This treatment attempt was based on the exclusion of a malignancy and histologic findings suggestive of an inflammatory process.

Conclusion

We report a patient with a slowly progressive distally pronounced neuropathy with evidence of a granulomatous nerve inflammation. Despite extensive diagnostic work-up the etiology remained unclear. In this case, the exclusion of malignancy supported an auto-inflammatory cause. A combined treatment of intravenous immunoglobulins and methotrexate led to a mild improvement, which further corroborates an underlying autoimmune phenomenon.

References: None.

Keywords: Inflammatory, Other

Grant Support: None.
Objective

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes (POEMS) syndrome is a rare multisystem disease associated with a plasma-cell dyscrasia. Although pachymeningeal involvement has occasionally been described, MRI of the central nervous system (CNS) has not yet been extensively investigated.

Methods

We retrospectively evaluated CNS MRI in Europe's largest single-center cohort of POEMS syndrome. Of 77 patients who have been formally diagnosed with POEMS, 41 had MRI brain and 29 had MRI spine. A control group of 33 patients with chronic inflammatory demyelinating polyneuropathy (CIDP) was used as this is the major differential diagnosis. Of these CIDP patients, 12 underwent both MRI brain and spine, 7 had solely MRI brain and 14 had MRI spine.

Results

In 41 POEMS patients with MRI brain, we identified frequent smooth, diffuse meningeal thickening of the cerebral convexities and falx (n = 29, 71%), of which 4 had meningeal collections. 17 (41%) had vascular abnormalities including white-matter disease, of which 4 had established infarcts. Of 29 patients with MRI spine, 17 (59%) had thickening of the brachial and lumbosacral plexus. Conversely in 19 CIDP patients with MRI brain, none had meningeal thickening (p < 0.0001); however, 8 (42%) had vascular abnormalities (p = 0.85). Of 26 patients with MRI spine, 9 (35%) had brachial or lumbosacral plexus thickening (p = 0.06).

Conclusions

In contrast to CIDP, POEMS patients frequently have pachymeningeal thickening. Vascular abnormalities and plexus thickening were also common but not statistically different to CIDP.

Keywords: Inflammatory, Other, Other

Grant Support: Dr Keddie is funded by the Association of British Neurologists and the Guarantors of Brain
A novel ‘at home’ protocol for the hand rehabilitation of patients with Guillain-Barré Syndrome

Prada Valeria¹, Grandis Marina¹, Beronio Alessandro², Mannironi Antonio², Schenone Angelo³, Benedetti Luana⁴

¹Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics and maternal/child Sciences, Genova, Italy, ²Sant’andrea Hospital, La Spezia, La spezia, Italy, ³Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics and Maternal/Child sciences, Genova, Italy, ⁴San Martino Hospital, Genova, Italy

Guillain-Barré syndrome (GBS) is an inflammatory polynuropathic disease, which is characterized by the acute or subacute onset of motor deficit, generally with distal and symmetric distribution with a hypo or osteotendinous areflexia, to which sensible disorders can be added. Long-term patients still could present sensory and/or motor problems even in the upper limbs, impairing the quality of life. The aim of this study is to evaluate the efficacy of a new at home protocol of hand rehabilitation with an engineered glove and with a novel compliance questionnaire.

We selected 10 long-term patients with GBS diagnosis. We performed a first evaluation (T0) with dynamometer (hand grip and tripod pinch), thumb opposition test and the Hand Test System, an engineered glove which evaluates the frequency of movement (MR) in 2 tasks: finger tapping (FT) and index-medium-ring-little sequence (IMRL). The protocol requested daily exercises for 2 months and then patients has been re-evaluated (T1). A compliance questionnaire has been performed by a phone call every week for 8 weeks.

We compared all the results at T0 with normal subjects and all patients’ data are statistically impaired. All patients answered to the questionnaire every week and they felt spurred to do the exercises. The evaluation at T1 showed a statistically significant improvement of TOT and HTS tasks, strength improved but not in both hands and in both tasks statistically.

We can conclude that long-term GBS patients shows an impairment of strength, articularity and dexterity if compared to normal subjects at baseline. Moreover, our questionnaire has been useful to monitor the daily commitment of the patients and spur them to do their best. Furthermore, the at home protocol is effective, even if strength test is not perfectly reliable. Despite the good results of this pilot study, it is necessary to increase the number of patients involved.


Keywords: Inflammatory, Clinical Trials, Other

Grant Support: None.
Antibodies Against Peripheral Nerve Antigens in Chronic Inflammatory Demyelinating Polyradiculoneuropathy in a Turkish Cohort

Ayse Nur Ozdag Acarli, Atay Vural, Vuslat Yilmaz, Nermin Gorkem Sirin Inan, Hacer Durmus Tekce, Guher Saruhan Direskeneli, Bianca Fiebig, Kathrin Doppler, Claudia Sommer, Edgar Meinl, Erdem Tuzun, Yesim Parman

1Istanbul University, Istanbul Medical Faculty, Istanbul, Turkey, 2Koç University, Ludwig-Maximilians-Universität München, Institute of Clinical Neuroimmunology, Istanbul, Turkey, 3Istanbul University, Institute of Experimental Medicine, Istanbul, Turkey, 4University Hospital Würzburg, Würzburg, Germany, 5University Hospital Würzburg, Wuerzburg, Germany, 6Ludwig-Maximilians-Universität München, Institute of Clinical Neuroimmunology, Muenchen, Germany

Objective: To investigate the frequency and clinical features of anti-nodal/paranodal antibodies in Turkish CIDP patients.

Methods: Fifty consecutive CIDP patients (mean age 42.7±14.8 years), all fulfilling the 2010 EFNS/PNS diagnostic criteria for definite CIDP but one for probable CIDP, 13 patients with CMT1A (mean age 38.9±13.3), and 10 healthy controls (mean age 37.5±10.5) were included into the study. Sera from the participants were investigated with binding assays on murine teased fibers and measured for anti-neurofascin 155 (NF155), anti-NF186, and anti-contactin-1(CNTN1) by ELISA. Epitope and IgG subtype analysis for anti-NF155 reacting serum was performed by using live TE671 cells stably expressing human NF155 and its truncated forms.

Results: Anti-NF155 IgG4 antibodies reacting to Fn3-Fn4 domain were identified in one patient (2%) with CIDP, but not in CMT1A or normal participants. No antibodies against NF186 or CNTN1 or reactivity to murine nerve fibers were detected in other patients of CIDP cohort. The anti-NF155 positive CIDP patient was a 31-year-old male when presented with predominant distal weakness, tremor, and sensory ataxia. His impairment continued with steroid therapy and he had partial response to IVIg and azathioprine. After three years on treatment his clinical findings became stable with atrophy of the foot and calf muscles, and treatment was stopped. After six years of follow-up without treatment, patient reported headache, and transient episodes of visual loss at age 40. His eye exam revealed papilledema, and visual field constriction. His brain MRI showed bilateral mild parietal atrophy. Investigation of the CSF showed slightly elevated opening pressure, and high protein (226 mg/dL). He was diagnosed with pseudotumor cerebri. Acetazolamide was administered for two years, his symptoms improved. His neurologic examination is stable, MRC sum score is 56, and INCAT is 4 after 15 years from onset.

Conclusion: The proportion of anti-nodal/paranodal antibodies seropositivity among Turkish CIDP patients in our cohort was lower than published reports. The unique patient with anti-NF155 antibody showed a distinct concomitant neurologic disorder with CIDP, although he had no risk factors for idiopathic intracranial hypertension.

References: None.

Keywords: Node Biology, Inflammatory

Grant Support: None.
Autoimmune hepatitis-related sensory neuronopathy: Frequency and clinical profile


University of Campinas, Campinas, Brazil

Introduction: Autoimmune hepatitis (AIH) is characterized by several extrahepatic manifestations, including neurological syndromes. Most reports described central nervous system affection; very few addressed peripheral nervous system involvement. There are anecdotal reports of the association between AIH and sensory neuronopathy (SN), but no systematic evaluation has been performed to date.

Objective: To investigate the frequency of the AIH-SN association and to describe the phenotypic profile of those patients.

Methods: Seventy consecutive AIH patients were enrolled and evaluated with neurological exam and nerve conduction exam/electromyography (NCS/EMG). Their findings were compared to a 52-hepatitis B group. Student’s t-test and chi-square with p-values <0.05 considered significant, were done for group comparisons.

Results: Mean age and gender proportion were slightly different between groups (42.2±16.3 vs 51.7±13.6 years and male/female of 14:56 and 29:23, p values <0.01 respectively). Considering the NCS/EMG findings polyneuropathy, radiculopathy and carpal tunnel syndrome rates were similar to both groups. SN was diagnosed in five AIH patients and in none of the Hepatitis B patients (p=0.04).

Considering only these five patients an average profile may be delineated: a woman in her 40’s with neurological sensory deficits asymmetric and associated with dysautonomia and sensory ataxia. Signs of hepatic damage and neurological disability did not follow a similar course after immunosuppressant therapy.

Conclusion: SN was present in 7% of this AIH cohort. These conditions seem to hold a significant association and should be kept in mind when SN patients present with signs of hepatocellular damage or when patients with AIH display sensory asymmetric deficits and ataxia.

References: None.

Keywords: Other, Inflammatory

Grant Support: FAPESP: 2013/26410-0
Small fiber involvement in anti-MAG demyelinating neuropathy – data from a small cohort

Nicolae Grecu, Angela Puma, Luisa Villa, Michele Cavalli, Sabrina Sacconi

Côte d’Azur University, Peripheral Nervous System and Muscle Department, Nice University Hospital, Nice, France, Department of Biomedical Sciences for Health, University of Milan, Milan, Italy

Background: Small fiber involvement in polyneuropathy associated with IgM monoclonal gammopathy and anti-myelin associated glycoprotein (MAG) is thought to be responsible for the dysesthesias encountered in these patients. Currently there is no data from large populations series proving this link.

Materials and methods: Eight consecutive patients with polyneuropathy associated with anti-MAG antibodies were assessed through measurement of electrochemical skin conductance. The work-up for the differential diagnosis suggested no other cause of polyneuropathy in any of the patients.

Results: 5/8 patients were male, median symptom duration at time of diagnosis was 9 months and mean age at diagnosis was 70.5 years. 6/8 patients had paresthesias and/or pain as presenting symptoms and clinical examination revealed a normal examination in 2 patients, sensory-only involvement in 4 patients and weakness and sensory deficits in 2 patients. 7/8 had a demyelinating polyneuropathy pattern on electroneuromyography, with 4 suggestive of distal acquired demyelinating symmetric neuropathy, while one patient had an axonal sensory-motor involvement. Median anti-MAG antibody titer was 47241 Bühlmann Titer Units (BTU). Electrochemical skin conductance measurement showed abnormalities in 7/8 patients in the lower limbs, 4 of which had involvement of all 4 limbs.

Conclusions: Small fiber involvement in polyneuropathy associated with anti-MAG antibodies seems to be present irrespective of disease duration, electrophisiological pattern and clinical manifestations and can be readily assessed with a simple, non-invasive method.

References: Magy L et al, Heterogeneity of polyneuropathy associated with anti-MAG antibodies, Journal of Immunology Research, 2015, 450391, 2015 Luigetti M et al, Neuropathy with predominant small fiber involvement associated with abnormal anti-MAG titer, Internal Medicina, 49(23), 2627-9, 2010

Keywords: Inflammatory

Grant Support: None.
Carfilzomib ameliorates chronic neuritis in ICAM-deficient NOD mice

Anne Mausberg, Fabian Szepanowski, Christoph Kleinschnitz, Mark Stettner

University Medicine Essen, Essen, Germany

Chronic inflammatory neuropathies are still a therapeutic challenge. Glucocorticoids, plasma exchange and intravenous immunoglobulins (IVIg) constitute established treatment options in Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), but do not benefit all patients. Increasing evidence suggests that the introduction of novel agents in multiple myeloma therapies may extent therapeutic options also for autoimmune diseases. Carfilzomib is an immunoproteasome inhibitor reducing the number of plasma cells. However, therapeutic potential in inflammatory neuropathies has not been investigated so far.

To test carfilzomib in an established model of human CIDP, we treated ICAM-deficient NOD mice after onset of clinical signs twice a week with carfilzomib and compared disease progression in placebo-treated affected ICAM-deficient NOD mice. Clinical signs of disease were monitored during the treatment period of 12 weeks.

Compared to placebo treated controls, carfilzomib administration affected the clinical course of the disease. While we observed a continuous disease deterioration in control mice, carfilzomib treated mice showed a reduced disease progression. The positive effect on clinical signs of disease affected paresis as well as ataxia. Further experiments will demonstrate to what extent infiltrating immune cell composition in the PNS is altered in the presence of carfilzomib.

These findings suggest that targeting the immunoproteasome might constitute as novel therapeutic option in chronic inflammatory neuropathies. Furthermore, our data strengthen the important role of B cells and antibodies in chronic inflammatory neuropathies in our animal model.

References: None.

Keywords: Inflammatory, Schwann Cell

Grant Support: None.
Clinical and epidemiological profile of a Brazilian’s cohort of patients with Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Osvaldo Nascimento, Caroline Medeiros, Luis Maia, Arthur Monfredinho, Ivan Abreu, Thiago Rodrigues, Vanessa Lessa, Viviane Carvalho, Camila Pupe

Universidade Federal Fluminense, Rio de Janeiro, Brazil

To analyze the clinico-epidemiological profile of patients with Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in a neuromuscular center.

CIDP is an acquired disorder of peripheral nerves, which is immunologically based. It’s a rare disease and the diagnosis is difficult due to the heterogeneity of the clinical variants.

A retrospective study was performed between March and August 2018, based on 404 patients followed up in the last 35 years. We have reviewed charts with identification, neurological examination, time from onset of symptoms to diagnosis, evolution, clinical grade score (CGS) and electroneuromyography. CIDP’s criteria used were from the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS).

Fourty-six patients had suspected chronic immune-mediated demyelinating neuropathy. Thirty-seven had suspected diagnosis of CIDP. Ten didn’t meet criteria: 2 were excluded (diabetic polyneuropathy) and 8 were atypical (1 CANOMAD; 1 CISP; 2 predominantly distal motor form; 4 predominantly sensory painful form). Twenty-one patients had defined CIDP; 4, probable; and 2, possible. Twenty-one had defined CIDP (19 typical; 2 multifocal acquired demyelinating sensory and motor neuropathy). Four had probable CIDP (2 typical; 1 focal; 1 predominantly sensory form). The 2 with possible CIDP were typical. The mean age was 52. Eight patients had remission; 12, relapsing-remitting form; 10, secondarily progressive form; 2 progressive primary form and 3 remains under investigation. The mean time between onset of symptoms and the date of diagnosis was 54 months. The mean’s CGS at diagnosis was 2.94 and at the last evaluation was of 2.08.

The time between the onset of symptoms and diagnosis is often very long, what impacts the efficacy of treatment. The EFNS/PNS criteria were flawed to identify the atypical forms.

References: None.

Keywords: Inflammatory

Grant Support: None.
TOPIRAMATE PREVENTS OXALIPLATIN NEUROTOXICITY IN A RAT MODEL

PAOLA ALBERTI, CHIORAZZI ALESSIA, ANNALISA CANTA, POZZI ELEONORA, FUMAGALLI GIULIA, LAURA MONZA, CRISTINA MEREGLI, ELISA BALLARINI, Virginia Rodriguez-Menendez, OGGIONI NORBERTO, PAOLA MARMROI, CAVALETTI GUIDO

UNIVERSITY OF MILANO-BICOCCA, MONZA, Italy

PURPOSE. Oxaliplatin (OHP) Induced Peripheral Neurotoxicity (OIPN) is a long-lasting adverse event that burdens cancer survivors. OIPN consists of an acute and chronic syndrome; the first is related to axonal hyperexcitability and the latter to an actual nerve damage causing mainly sensory disfunctions. Acute OIPN is secondary to ion channel dysfunction and it is a predisposing factor to the detrimental chronic one. Thus, a tentative strategy to prevent chronic OIPN could be acting against acute one. We explored this hypothesis using topiramate (TPM). In a preliminary experiment we used Nerve Excitability Testing (NET) confirming the presence of acute OIPN in our chronic OIPN rat model. METHODS. Forty female Wistar rats were divided into 4 groups: control, OHP, OHP+TPM, TPM. OHP was administered iv (5mg/Kg, 2qws4ws) and TPM per os (daily, 100 mg/Kg). Standard neurophysiology was performed at the end of treatment as well as NET. All neurophysiological determinations were performed under deep anesthesia (isoflurane) and body temperature was kept constant (37±0.5° C). Dynamic test was also performed. Skin biopsy and caudal nerves were harvested. RESULTS. Standard neurophysiology and NET confirmed OIPN induction only in OHP group; OHP+TPM group standard neurophysiology was similar to controls and NET showed that the “channelopathy” was contained. IENF and caudal nerve morphology/morphometry showed statistically significant alterations only in OHP group. The same was observed for Dynamic test. CONCLUSION. All outcome measures showed neurotoxicity induction in OHP group, while OHP+TPM was preserved. This a true novelty and a translation in clinical practice can be not a distant future: TPM is a drug yet approved for clinical use with no detrimental interactions with OHP. In a scenario where no cure for OIPN is present this might be a promising evidence to modify OIPN natural history.

References: None.

Keywords: Axonal Biology, Pain, Pre-clinical Studies, Other

Grant Support: None.
The sensation of pain is essential for avoiding harmful risks and preserving the functional integrity of our body. We recently reported that mutations in PRDM12, an epigenetic regulator belonging to the PRDM (PRDI-BF1 and RIZ homology domain) family of putative histone-methyltransferases (HMTs), cause hereditary sensory and autonomic neuropathy type VIII resulting in the absence of pain sensation in affected individuals, yet the mechanistic insights on the causative deficits are missing.

Here we show that in a mouse model lacking PRDM12, nociceptors fail to be generated while other sensory neuron types (A-fiber low-threshold mechanoreceptors, A-LTMRs), remain unaffected. Our data further indicate that PRDM12 is required for initiation of neurogenesis and activation of a cascade of downstream transcription factors, including NEUROD1, BRN3A and ISL1 in the nociceptive lineage. In parallel, an enforced expression of PRDM12 in migrating neural crest cells biases them to localize in the sensory ganglia and to differentiate into sensory neurons. Importantly, while ectopic presence of PRDM12 is not sufficient to seal identity of presumptive pain neurons, it initiates nociceptor development by repressing markers of alternative sensory fates in postmitotic neurons. These data reveal that PRDM12 is necessary for the generation of pain initiating neuron types during development.

References: None.

Keywords: Pain, Human Genetics

Grant Support: None.
Entrapment neuropathies are common. However Cheiralgia paresthetica, isolated superficial branch of radial mononeuropathy is relatively rare. [1] It was first described by Stopford and Matzdorff in 1922 and 1926 respectively. [2, 3] Since Wartenberg’s case series in 1932, this entity is known as Wartenberg syndrome. [4] It is observed that this can be related to occupation [5]. We report the first case of Cheiralgia paresthetica related to coconut plucking. A 33 year old previously healthy gentleman presented with burning pain and numbness over the base of right thumb, index finger and first web space for 6 days without muscle weakness. His occupation as a coconut plucker involved repetitive, vigorous pronation and supination movements and he had been working long shifts recently. There was no history of trauma or surgery. On examination, he had reduced sensation over first web space of right hand. There was no motor weakness to suggest posterior interosseous or proximal radial nerve palsy. There were no hypopigmented lesions or thickened nerves suggestive of leprosy. Rest of the clinical examination was normal. Inflammatory markers, autoantibody screening and retroviral screening were unremarkable. X ray and ultrasound scan of hand and forearm were normal. Nerve conduction studies confirmed isolated right side superficial branch of radial nerve palsy. Based on the above findings, occupation related Cheiralgia paresthetica was diagnosed. He was treated with Amitriptyline and Ibuprofen. He was advised to restrain from his occupation and to use an alternative method for coconut plucking. The patient recovered completely within a week. In conclusion, Cheiralgia paresthetica should be suspected in patients with isolated sensory symptoms of first web space of hand especially if their occupations involve repetitive pronation and supination such as coconut plucking. Exclusion of other possibilities and appropriate timely interventions with avoidance of precipitating movements are essential for successful recovery.


Keywords: Pain, Axonal Biology, Axonal Regeneration

Grant Support: None.
A novel tissue-selective β2-adrenoceptor agonist with minimized cardiovascular effects, 5-HOB, attenuates neuropathic pain in mice

Shinji Hatakeyama, Marie Jourdain

Novartis Institutes for BioMedical Research, Basel, Switzerland

Neuropathic pain is a major type of chronic pain, which is initiated by a lesion in the sensory neuron due to e.g. trauma, postsurgical injuries, anticancer drugs, or by a disease directly affecting the somatosensory system, such as diabetes or cancer. Severe symptoms associated with neuropathic pain can have a significant negative impact on the quality of life and the activities of daily living of the patients. Clinically, tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors are recommended as first-line therapies. Despite its high prevalence, the treatment of neuropathic pain is often challenging due to central nervous system side effects with first-line therapies. Therefore, there is still a high-unmet medical need for a better treatment of neuropathic pain compared the currently available therapies. In the nociceptive system, β2 adrenoceptor is expressed and essential for the anti-neuropathic pain effect of antidepressants such as tricyclics and serotonin-norepinephrine reuptake inhibitors. β2 adrenoceptor agonists are also capable of attenuating allodynia after chronic treatment as effectively as antidepressants. 5-HOB is a novel tissue selective β2 adrenoceptor agonist with minimized cardiovascular effects while retaining efficacy on skeletal muscle in preclinical experiments unlike conventional β2 adrenoceptor agonists, however its effect on the nervous system has not been evaluated yet. Therefore, 5-HOB was evaluated in a mouse model of neuropathic pain. 5-HOB alleviated neuropathic allodynia in a dose dependent manner and reversed the changes in hind paw withdrawal thresholds to the sham control levels. The dose attenuating neuropathic allodynia was slightly lower than the dose inducing skeletal muscle hypertrophy. In conclusion, as reported with known β2 adrenoceptor agonists, 5-HOB was also effective in attenuating neuropathic pain in mice in addition to its effect on skeletal muscle.

References: None.

Keywords: Pre-clinical Studies

Grant Support: None.
Intravenous Immunoglobulin Therapy For Small Fiber Neuropathy

Margot Geerts¹, Bianca de Greef¹, Janneke Hoeijmakers¹, Catharina Faber¹, Ingemar Merkies²

¹Maastricht University Medical Center+, Maastricht, the Netherlands, Maastricht, Netherlands, ²St. Elisabeth Hospital, Willemstad, Maastricht University Medical Center+, Maastricht, The Netherlands,

Small fiber neuropathy (SFN) is a disorder of the thinly myelinated Aδ-fibers and the unmyelinated C-fibers, leading to severe neuropathic pain and autonomic dysfunction. In 53% of patients with SFN, the etiology remains unknown. Because several immune-mediated diseases are associated with SFN, it is conceivable that immunological mechanisms play a role in SFN. In addition, auto-antibodies and inflammatory changes in nerves have been found in patients with SFN. Intravenous immunoglobulins (IVIg) are being used as a treatment for immune-mediated neuropathies. The objective of this study was to investigate the efficacy of IVIg in patients with idiopathic SFN, since no randomized clinical trials have been performed earlier in these patients. The primary objective was to evaluate the efficacy of IVIg versus placebo in patients with skin biopsy proven idiopathic SFN. The secondary objectives were to evaluate the effect of IVIg versus placebo on autonomic symptoms, sleep interference, and quality of life, and the safety and tolerability. The study was a randomized, double-blind, parallel group, placebo-controlled study. Patients received a starting dose IVIg of 2 g/kg body weight over 2–4 consecutive days or matching placebo of 0.9% saline. Subsequently, three additional infusions IVIg with a dose of 1 g/kg body weight or placebo were administered with an interval of 3 weeks. After completion of the 12 week treatment period, a 3-month-extension phase followed for determination of the long-term effect of IVIg. The study was approved by the local medical ethics committee and was funded by Grifols and Lamepro. In total 60 patients were included and treated between July 2016 and November 2018. The (preliminary) results of this study will be presented.

References: None.

Keywords: Small Fibers, Clinical Trials, Pain

Grant Support: Grifols and Lamepro
**Poster 119**

**Interpretation of quantitative sudomotor axon reflex test results comparing the Korean and Western normative data**

**EUN BIN CHO**¹, Jin Myoung Seok², Seunguk Jung¹, Chang Hyo Yoon³, Heejeong Jeong³, Tae-Won Yang³, Ki-Jong Park⁴

¹Neurology, Gyeongsang National University Changwon Hospital, Gyeongsang National University School of Medicine, Jinju, Korea (Republic of), ²Neurology, Soonchunhyang University College of Medicine, Cheonan Hospital, Cheonan, Korea (Republic of), ³Neurology, Gyeongsang National University Changwon Hospital, Gyeongsang National University School of Medicine, Changwon, Korea (Republic of), ⁴Neurology, Gyeongsang National University Changwon Hospital, Gyeongsang National University School of Medicine, Jinju, Korea (Republic of)

**Introduction**

Post-ganglionic sudomotor function might be influenced by age, sex, and ethnicity. However, with lack of Korean normative data, we reported the sudomotor axon reflex test (QSART) results by comparison with normative data derived from the Western countries. Recently, normative values of total sweat volume in QSART were established in the Korean population. In this study, we reported the clinical significance of application of the Korean normative data on QSART.

**Methods**

We retrospectively reviewed the results of QSART performed between March 2016 and June 2018 and reanalyzed the QSART data on the basis of Korean normative data. We group the patients according to age and the combination of abnormal sites (the forearm, proximal leg, distal leg, and foot).

**Results**

We found consecutive 1,202 patients (626 men, 576 women). In men of all age groups, at least 50% percent of previously judged ‘abnormal’ data in each site fell in normal range; the most significant changes (82%) were shown in the forearm. The percentage of normal results in all sites were increased from 26.8% to 66.6%. In women, 25% and 67% of patients with abnormal results in the forearm and foot respectively were reevaluated to have normal results in the same site. However, there were no significant changes of results in the proximal and distal legs with different norms.

**Conclusions**

Koreans had low sweat output compared to Caucasians. Therefore, the data of QSART performed on Korean should be interpreted by comparison with Korean normative data.

**References:** None.

**Keywords:** Other

**Grant Support:** None.
Small fiber neuropathy (SFN) is a condition that is dominated by invalidating neuropathic pain. Both pain and disability are important contributors to a substantial decline in quality of life (QoL). The effect of pharmacological neuropathic pain treatment is often disappointing, since pain reduction is mostly slight and side effects can be debilitating. Psychological factors, such as fear and catastrophizing, appear to play a role in the origin and maintenance of chronic pain and can be influenced by cognitive behavioral treatment. To date no specific cognitive behavioral treatment programs are available for patients diagnosed with SFN. The purpose of this study is to define the psychological factors that are related to disability (or impaired functioning) in patients with SFN and to investigate if a specific treatment strategy based on these factors could result in an improvement of QoL and disability. The study consists of three parts. First, by qualitative focus group interviews the patients' perspectives on pain, QoL, disability and mood will be clarified. Secondly, a retrospective cohort study will be performed supplemented with new questionnaires. Finally, a cognitive behavioral treatment strategy will be developed based upon the psychological factors demonstrated in part one and two. The effect of the newly developed intervention will be investigated with a sequential replicated and randomized single-case experimental ABC-design with multiple measurements. The study will demonstrate which psychological factors are related to disability in patients with SFN. The value of a specific psychological approach in the treatment of SFN will be evaluated. The study protocol will be presented.

References: None.

Keywords: Pain

Grant Support: None.
Epidermal Innervation in Juvenile Fibromyalgia Patients and Healthy Adolescents

Alexis Boneparth MD1, Shan Chen MD2, Daniel B. Horton MD MSCE3, L. Nandini Moorthy MD MS 3, Ian Farquehar BA4, Heather M. Downs BS4, Hang Lee PhD5, Anne Louise Oaklander MD PhD4,6

1 Department of Pediatrics, Columbia University Medical Center, New York, NY, USA
2 Department of Neurology, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA
3 Department of Pediatrics, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA
4 Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA
5 Biostatistics Center, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA
6 Department of Pathology (Neuropathology), Massachusetts General Hospital, Boston, MA, USA

Introduction: Fibromyalgia is a label for illnesses including chronic widespread pain, fatigue and exercise intolerance. Several labs report evidence that ≤40% of adults with fibromyalgia have objective evidence of small-fiber polyneuropathy (SFN),1-3 a plausible biological explanation for many fibromyalgia symptoms. Here we compared skin biopsies and symptoms from adolescents with juvenile fibromyalgia (JFM) and healthy controls.

Methods: With IRB approval we screened 18 participants (13.6-20.6y) with JFM diagnosed by pediatric rheumatologists. All met the American College of Rheumatology modified criteria for JFM, and completed Functional Disability Inventory (FDI; 0-60 range), last-week pain ratings (0-10), and COMPASS-31 dysautonomia-symptom surveys (0-100 range), and were offered standard PGP9.5-immunolabeled lower-calf skin-biopsy tests for SFN. The primary outcome was prevalence of skin biopsies confirming SFN with epidermal neurite densities (END) <5th centile of age/gender/race predicted norms. For comparison, cases were matched by ethnicity, race, sex, and age requirements to healthy controls previously recruited from the community for skin-biopsies. All 23 meeting demographic criteria were included and requested to complete the questionnaires. Data presented as means±SEM.

Results: The 20 JFM patients were on average 16.8±0.43 years old; controls were 17.8±0.42y. The 15 biopsied JFM patients had 273.4±36.3 END/mm2 skin surface area whereas controls had 413.1±86.1 (p<0.01). 47% (8/17) of JFM patients had SFN-confirming biopsies vs. 4% of controls (1/23; p=0.01). FDI scores were 32.6±1.9 in patients vs. 3.1±0.65 in controls (p<0.01). COMPASS-31 scores were 48.7±3.9 in patients vs. 13.4±2.8 in controls (p<0.01). Pain scores were 7.0±0.26 in patients vs. 2.0±0.76 in controls (p<0.01).

Conclusion: As in adults, at least 40% of children with fibromyalgia have skin-biopsy results consistent with SFN. Questionnaires confirmed representativeness of the JFM and healthy-control samples. Because most pediatric SFN is caused by inflammation/autoimmunity or genetic variants—both potentially treatable with disease-modifying therapies4,5—SFN diagnoses should be considered in adolescents labeled with fibromyalgia.

Acknowledgements: Supported in part by a CARRA-Arthritis Foundation Grant (AB), and the National Institutes of Health (R01NS093653, K24NS059892) and the Department of Defense (GW093049) and the Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Advancing Translational Sciences, National Institutes of Health Award UL 1TR002541) and financial contributions from Harvard University and its affiliated academic healthcare centers.
REFERENCES


Poster 122

The value of the Sudoscan™ in detecting autonomic dysfunction in small fiber neuropathy.

Amir Far, Raissa Derckx, Bianca De Greef, Janneke Hoeijmakers, Ingemar Merkies, Catharina Faber

Maastricht University Medical Center+, Maastricht, Netherlands

In small fiber neuropathy (SFN) the smallest myelinated and unmyelinated nerve fibers are dysfunctioning. As a result, patients experience an abnormal pain sensation and various autonomic complaints. Autonomic dysfunction may be an early manifestation in SFN. Currently, the diagnosis of SFN is based on a combination of typical clinical symptoms, with a decreased intra-epidermal nerve fiber density (IENFD) in skin biopsy and/or an abnormal temperature threshold testing (TTT). However, skin biopsy is an invasive, expensive and time-consuming procedure that requires high laboratory skills, and TTT lacks precision. The Sudoscan™ is a device which is developed to identify peripheral autonomic dysfunction by measuring the electrochemical skin conductance (ESC) of the palms and soles, in a fast and noninvasive way. Patients are instructed to place their hands and feet on large stainless-steel plate electrodes during 3 minutes. Subsequently, the results of the test will be directly displayed on a screen.

The aim of this cross-sectional study is to investigate the value of the Sudoscan™ in the diagnostic of SFN. The first objective is to determine whether the normative values of the device correspond with the values of healthy subjects in the Netherlands. Furthermore, the value of the Sudoscan™ in 200 patients diagnosed with SFN will be evaluated, by determining the correlations between the ESC and IENFD, TTT, and different clinical characteristics obtained by questionnaires (including SFN symptoms, neuropathic pain, pain intensity, and daily functioning). The first preliminary results will be presented.

References: None.

Keywords: Pain, Small Fibers, Other

Grant Support: Molecule-to-man pain network (PAIN-Net), H2020 Marie Sklodowska Curie grant.
Ratio of Distal to Proximal Epidermal Nerve Fiber Density as Predictor of Small Fiber Neuropathy

Mamatha Pasnoor, Mark Farrenburg, Duaa Jabari, Constantine Farmakidis, Omar Jawdat, Richard Barohn, Mazen Dimachkie

The University of Kansas Medical Center, Kansas City, KS, USA

Objective: To determine if epidermal nerve fiber density (ENFD) ratio of distal leg to proximal thigh correlates with clinical diagnosis of small fiber neuropathy (SFN).

Background: ENFD assessment has become an important tool for diagnosis of SFN. The usual sites of biopsies include distal leg and proximal thigh. Two site biopsies are performed to assess for length dependency of the neuropathy. Age dependent normative data have been established for distal skin biopsy. In some patients with paresthesias, although the distal and proximal biopsies are normal, the distal ENFD is much less compared to proximal density. There is limited literature looking at the significance of the ratio of distal to proximal biopsy ENFD.

Methods: After IRB approval, we retrospectively evaluated 100 subjects who underwent skin biopsy for evaluation of SFN from January 2016 to January 2018 in the neurology department of KUMC. The distal leg, proximal thigh ENFD information was collected and ratio calculated for all subjects. A neuromuscular physician, blinded to the ENFD data, made the determination of clinical SFN for each subject based on symptoms and neurological exam documented in the chart. Correlation analysis was performed between the ratios and clinical diagnosis.

Results: Total of 100 patient charts were reviewed. The mean age was 46.5 ± 14.7 for those without clinical SFN and 50.4 ± 12.5 for those with clinical SFN. The mean ratio of distal leg to proximal ENFD for subjects with clinical SFN was 0.638 ± 0.495 and without clinical SFN was 0.684 ± 0.325. Paired-t test was used to calculate the difference in means. The mean distal:proximal ENFD ratio was not significantly different in the clinical group vs the group without clinical evidence of SFN.

Conclusions: According to our study, distal:proximal ENFD ratio is not a predictor of clinical SFN.

References: None.

Keywords: Small Fibers

Grant Support: None.
Objectives: To evaluate the sensitivity and specificity of the latency difference (DLat) between ulnar and median nerves of the arm after stimulation at the wrist; one of the easiest techniques proposed for recognizing ulnar neuropathy at the elbow (UNE). As latency difference is not a standardized technique, we set up a multicenter study to recruit large numbers of normal subjects and patients with UNE or generalized neuropathy.

Methods: Six centers participated in the study with data obtained from three groups of participants, controls (CTRLs), patients with UNE and patients with generalized neuropathy (GNP). We first verified the anatomical superposition of the ulnar and median nerves in cadaver examination to allow recording potentials 10 cm above the medial epicondyle. We then standardized the position of the arm with full extension of the elbow. CTRLs were examined on both arms at two consecutive visits.

Results: We recorded 32 idiopathic UNE cases, 44 GNP patients and 62 controls. We demonstrated that a DLat cut-off value of 0.69 ms brings a sensitivity of 0.86 and specificity of 0.89 to discriminate CTRLs from UNE. We also validated that intra-examiner reproducibility is good.

Conclusion: We report a lower normal value for DLat than reported in several non-standardized studies and CTRL and UNE groups have clearly separated DLat values. Significance: Due to its high sensitivity, our standardized technique could be used as a first-line diagnostic tool when UNE is suspected.

References: None.

Keywords: Other, Axonal Biology

Grant Support: None.
Poster 125

Antibodies against PlexinD1 and peripheral nerve structures in patients with small-fiber neuropathy

Elba Pascual-Goñi¹, Amir Far², Cinta Lleixà¹, Margot Geerts², Bianca de Greef³, Ingemar Merkies⁴, Janneke Hoeijmakers², Lorena Martín-Aguilar¹, Isabel Illa¹, Catharina Faber², Luis Querol¹
Introduction:

Small-fiber neuropathy (SFN) has not classically been included within the group of immune-mediated neuropathies, although recent evidence supports an autoimmune mechanism in some cases. First, some GBS variants present as a SFN. Second, autoimmune diseases such as Sjögren's syndrome can associate a SFN. Third, anti-plexinD1 antibodies were described in patients with various neurological disorders and neuropathic pain. Despite this, to date no studies of autoantibody screening were conducted in patients with SFN.

Methods:

We tested serum from 60 skin biopsy-proven idiopathic SFN patients.

PlexinD1 cell-based assays: HEK293 cells transfected with plexinD1, fixed with 4% PFA and incubated with the following solutions in succession: (1) blocking solution (Rabbit serum 1/40 diluted in PBS); (2) patient’s serum (1:1000); (3) commercial anti-plexinD1 Ab (1:1000); (4) RAH IgG AF594 + RAG AF488 (1:1000). Coverslips were mounted with Vectashield and analysed.

Live dorsal root ganglion (DRG) neurons were incubated with patients’ sera diluted in culture medium. Cells were then fixed with 4% PFA and incubated with secondary goat anti-human IgG AF488 antibody. Coverslips were mounted with Vectashield. Fluorescence signal intensity was scored in a 0–3 scale by two independent researchers.

Results:

Cell based-assays did not detect any patient positive for anti-plexinD1 antibodies. Thirteen patients showed mild (score=1), and three moderate (score=2) IgG reactivity against DRG neurons. Immunocytochemistry experiments with SFN patients’ sera over human neurons derived from a neuroblastoma cell-line are under development. Clinical characteristics and treatment response correlations of these patients will be presented at the meeting.

Conclusion:

Anti-PlexinD1 antibodies are absent in painful neuropathies. A proportion of SFN patients IgG react against DRG neurons, but strong reactivity is rare. As far as we know this is the first study of autoantibody screening in SFN.

References: None.

Keywords: Small Fibers, Inflammatory

Grant Support: None.
Poster 126

Transcriptomic analysis of dorsal root ganglia in a mouse model of vincristine-induced peripheral neuropathy

Aurore Danigo, Amandine Bernard, Franck Sturtz, Sylvie Bourthoumieu, Claire Demiot

EA 6309 - Myelin Maintenance & Peripheral Neuropathy, Faculties of Medicine and Pharmacy, University of Limoges, Limoges, France

Background: Neuropathic pain is a major dose-limiting effect of many used chemotherapeutic agents and affects greatly patients’ quality of life. Vincristine (VCR), largely used in pediatric and young adult population for lymphoma treatment, is the most neurotoxic of the vinca-alkaloids. The neurotoxicity of VCR causes a length-dependent sensory peripheral neuropathy (VCR-induced peripheral neuropathy, VIPN) which is frequently limiting for the pursuit of the treatment. The pathophysiological mechanisms of the VCR neurotoxicity are not clearly understood. The aim of this transcriptomic analysis on dorsal root ganglia (DRG) in a mouse model of VIPN is to highlight pathways affected by VCR treatment and discover new targets for the management of VCR-induced pain.

Methods: VCR (100 µg/kg, intraperitoneally (i.p.)) was administered once per day for 7 days in male Swiss mice. DRG were removed after one, three, five, or seven days following the last injection of VCR to evaluate the kinetic of the VCR-induced neurotoxicity on gene expression. The transcriptome analysis was performed using an Agilent gene expression chip.

Results: Mice treated with VCR showed high mechanical allodynia from day 1 until day 7 after the last injection of VCR. Transcriptomic analysis yielded a list of around 800 genes whose expression in DRG was dysregulated by VCR-induced neuropathy (fold change FC > 1.5, p < 0.05). VCR treatment acts on glutamatergic transmission with gnao1, gria4, grik, and prkcg (PKCγ) which were downregulated and grm7, which was upregulated. Several genes involved in synaptogenesis and neuroregeneration were upregulated by VCR (nrcam, nrp2, nlgn1). The nrg1 gene which demonstrated to be upregulated in case of traumatic nerve injury and to be involved in neuropathic pain development, was upregulated by VCR treatment.

Conclusion: Our results may help to elucidate some molecular mechanisms of gene regulation associated with VIPN.

References: None.

Keywords: Pain, Pre-clinical Studies, Axonal Biology, Other

Grant Support: None.
Different mouse models of neuropathy induced by oxaliplatin: acute and chronic neurotoxicity

Hichem Bouchenaki¹, Aurore Danigo¹, Flavien Bessaguet¹, Franck Sturtz¹, Laurent Magy², Claire Demiot¹

¹EA 6309 - Myelin Maintenance & Peripheral Neuropathy, Faculties of Medicine and Pharmacy, University of Limoges, Limoges, France, ²Department of Neurology, Reference Center for Rare Peripheral Neuropathies, University Hospital of Limoges, Limoges, France

**Background:** Neuropathic pain is a major dose-limiting factor of many-used chemotherapeutic agents and greatly affects patients' quality of life. Oxaliplatin (OXP) is an anticancer chemotherapeutic agent used for the treatment of advanced colorectal cancer. OXP treatment induces an acute neurotoxicity, characterized by a reversible cold-induced hypersensitivity in the extremities, and a chronic sensory peripheral neuropathy, characterized by persistent sensory impairment. Development and characterization of animal models mimicking acute and chronic OXP-induced neurotoxicity should help clarifying the mechanisms underlying OXP-related pain and possibly define pain management strategies.

**Methods:** OXP was injected intraperitoneally (i.p.) in male Swiss mice according to three different protocols: 6 mg/kg in one single dose, 15 mg/kg in one single dose, or 5 mg/kg/3d during 2 weeks (cumulative dose = 15 mg/kg). OXP-induced peripheral neuropathy (OIPN) was evaluated by functional tests during seven days.

**Results:** Single injection of 15 mg/kg of OXP induced a high constant mechanical allodynia and cold allodynia, however 50 % of mice died at D5. Single injection of 6 mg/kg of OXP induced no significant mechanical allodynia but moderate transient cold allodynia (p = 0.027 vs. Vehicle at D1). After three injections of 5 mg/kg of OXP, mice developed moderate transient mechanical (p = 0.0003 vs. Vehicle at D1) and cold allodynia (p = 0.019 vs. Vehicle at D1). **Conclusion:** The 15 mg/kg single injection-model, which could mimic chronic neurotoxicity of OXP, was put aside because of the high mortality rate. The 6 mg/kg single injection-model and the 5 mg/kg three injection-model induced a transient cold hypersensitivity reproducing the acute neurotoxicity of OXP experienced by patients. Only 5 mg/kg three injections-model induces a significant mechanical/cold allodynia and reproduces the administration of cycles of chemotherapy in patients. This model can be used as a tool to study the effect of potential pharmacological treatments of OIPN.

**References:** None.

**Keywords:** Pain, Pre-clinical Studies, Other

**Grant Support:** Hichem Bouchenaki is supported by Pharnext SA
Poster 128

Circadian Variability Of Pain Features In Possible Small Fiber Neuropathy Patients

Daniele Cazzato, Grazia Devigili, Patrizia Dacci, Laura Piccolo, Raffaella Lombardi, Erika Salvi, Giuseppe Lauria Pinter

IRCCS Foundation Neurological Institute "Carlo Besta", Milan, Italy

Patients with small fiber neuropathy (SFN) often complain of excruciating burning sensation at hands and feet for which available analgesic treatments still remain unsatisfactory. Despite clinical trials for analgesics in neuropathic pain include a variety of clinical scales, the average daily pain intensity on the 11-point numeric rating scale (NRS) remains the most relevant outcome measure whose change is often chosen as primary endpoint. In this study we examined the circadian variability of pain intensity in a cohort of patients referred for suspected SFN. Patients were asked to report the mean intensity of pain experienced in the 2 preceding weeks in the morning, in the afternoon, in the evening and at night, respectively, as well as an average of whole day using the NRS. NRS comparison in SFN vs non-SFN patients defined using skin biopsy revealed no significant difference, confirming that reduction of IENF does not correlate with pain intensity. Analyzing circadian pattern in SFN patients, NRS showed a slight but significant rising trend from the morning or afternoon to the evening. From 32% to 42% of patients reported a worsening of pain during the day, while only 8% to 15,2% of patients showed a reduction of pain intensity in the afternoon or evening. A >2 points NRS increase occurred in 10% of patients from the afternoon to the evening and in 20% of patients from the morning to the evening while patients reporting a >2 points NRS reduction were 1,7% and 4,6%, respectively. The results of our study revealed, in a significant number of SFN patients, a circadian pattern of pain characterized by an increase of NRS score towards the evening. The circadian NRS variation might therefore represent a possible adjunctive outcome measure in clinical trials for analgesic drugs in SFN related neuropathic pain.

References: None.

Keywords: Pain, Small Fibers, Clinical Trials

Grant Support: None.
Nerve involvement associated to GNE gene mutations: expanding the clinical spectrum

Nicolae Grecu¹, Antoine Ristaino¹, Angela Puma¹, Luisa Villa¹, Michele Cavalli², Ariane Choumert³, Sabrina Sacconi¹

¹Côte d’Azur University, Peripheral Nervous System and Muscle Department, Nice University Hospital, Nice, France, ²Department of Biomedical Sciences for Health, University of Milan, Milan, Italy, ³Rare Diseases Department, La Réunion University Hospital - Site Sud, Saint Pierre, Réunion

Background: Mutations of the GNE gene, encoding an enzyme involved in sialic acid synthesis have been associated with various forms of early-onset myopathy and, more recently, to amyotrophic lateral sclerosis. We report three patients with clinical and electrophysiological evidence of peripheral nerve involvement associated with GNE gene mutations.

Materials and methods: Data from three patients from three distinct families who displayed sensory-motor or distal motor neuropathy in whom GNE gene mutations were identified as the only cause responsible for their pathology was retrospectively examined.

Results: Patient 1 is a 60 year-old male with asymmetric distal lower limb and axial muscle weakness and distal tetramelic touch hypoesthesia evolving since the age of 40; electroneuromyography (ENMG) showed sensory-motor axonal polyneuropathy and muscle biopsy showed both neurogenic changes and rimmed vacuoles; genetic testing found a c.2036T>G (p.Val679Gly) mutation at exon 12 and a c.1442G>C (p.Arg481Pro) mutation at exon 9 of the GNE gene. Patient 2 is a 34 year-old male with asymmetric progressive distal tetramelic muscle weakness for 1 year; EMG showed motor axonal neuropathy and fasciculations at needle examination of the limbs; genetic testing found a c.557A>G (p.His186Arg) mutation at exon 3 (previously undescribed) and a c.717T>G (p.Asp239Glu) mutation at exon 4. Patient 3 is a 63 year-old female from a consanguineous family developing since the age of 48 a progressive symmetric diffuse muscle weakness; ENMG showed a distal axonal motor neuropathy and muscle biopsy showed neurogenic changes; genetic testing found a homozygous c.2114A>G (p.His705 Arg) mutation in the GNE gene.

Conclusions: To date GNE gene mutations have been associated with distal myopathy and amyotrophic lateral sclerosis. Our findings expand the clinical and electrophysiological spectrum of manifestations associated with mutations in the GNE gene.


Keywords: Human Genetics

Grant Support: None.
The most prevalent chronic complication of diabetes is neuropathy, which leads to the development of chronic pain in approximately 25% of patients. Painful Diabetic Neuropathy (PDN) severely impacts patient quality of life and results in economic burden through patient care and workforce loss, but lacks causative treatment options. Achievement of relief is impeded as the underlying mechanisms remain unknown. Our lab has previously shown that chemokine receptor CXCR4 is necessary for the development of neuropathic pain, dorsal root ganglion (DRG) nociceptor hyperexcitability and small-fiber degeneration in the High Fat Diet (HFD) mouse model of Painful Diabetic Neuropathy (Jayaraj et al., 2018). We further found that DRG neurons show increased calcium responsiveness to excitatory stimuli and CXCR4 signaling.

Our hypothesis is that calcium overload induces mitochondrial dysfunction, ultimately leading to axonal degeneration. Our current studies are designed to further illuminate and test the link between calcium and CXCR4 signaling with mitochondrial homeostasis in the HFD model of PDN.

To examine DRG Calcium physiology in vitro and in vivo, we utilized the calcium sensitive dye Fura-2, the genetically encoded calcium sensor GCaMP6 as well as knock out mice for the mitochondrial calcium uniporter (MCU). Mitochondrial homeostasis was further examined with a combination of fluorescent dyes and genetically encoded biosensors such as the redox sensitive mito-roGFP and histology. To specifically study changes in the nociceptor population, we used Nav1.8-cre mice where feasible.

Our preliminary results support a pivotal role of calcium signaling and consequent mitochondria abnormalities in the pathogenesis of neuropathic pain and fiber degeneration in the HFD mouse model of PDN. This contribution is expected to be significant because it identifies novel targets essential to the development of disease modifying therapeutics for PDN.


Keywords: Small Fibers, Diabetes, Pain, Axonal Biology, Inflammatory

Grant Support: Supported by NIH K08 NS079482 and RO1 NS104295-01 to DM Menichella, NU Dixon Young Investigator Grant to DM Menichella
Poster 131

The Validation of Neuroactive Drug Selection Based On Combinatorial Screening In Bortezomib-Induced Neurotoxicity Models

Cristina Meregalli¹, Alessia Chiorazzi¹, Annalisa Canta¹, Giulia Fumagalli¹, Laura Monza¹, Eleonora Pozzi¹, Paola Alberti¹, Alessio Malacrida¹, Elisa Ballarini¹, Norberto Oggioni¹, Guido Cavaletti¹, Peter Bloomingdale², Donald Mager³
Aim: To test the validity of the identification drugs able to prevent bortezomib (BTZ)-induced side effects on the peripheral nervous system using a combinatorial screening of potential pathogenic mechanisms.

Methods: A network-based systems pharmacology model of intracellular signaling and gene regulation in peripheral neurons was constructed using literature information and pathway databases. Cellular signaling pathways specific to drugs that induce peripheral neuropathy were obtained from a prior pharmacological interaction network and used as a foundation for the construction of the systems pharmacology model. The model contains 131 nodes and 252 regulatory interactions. The animal system used to validate the results of the screening is our previously reported and extensively characterized BTZ rat model.

Results: A series of network analyses were conducted to identify novel combinatorial treatment strategies for BTZ-induced peripheral neuropathy. An analysis suggested the combinatorial inhibition of TNFα, NMDA receptors, and reactive oxygen species would completely prevent neuronal apoptosis in the presence of proteasome inhibition. We then became interested in potentially repurposing dexamabolin (DEXA) for the treatment of BTZ-induced peripheral neuropathy, since it has been shown to inhibit all three of the identified targets.

DEXA administration (10 mg/kg i.p, 3 times a week for 8 weeks) was well tolerated in the DEXA-treated rats. As expected, BTZ administration induced significant modifications in nerve conduction studies, associated with behavioral impairments. In the animals co-treated with DEXA and BTZ significant reduction in BTZ-induced mechanical allodynia, while similar trend was also observed in thermal hyperalgesia after 4 weeks of treatment. No effect was observed in DEXA+BTZ-treated rats in nerve conduction studies. Preliminary in vitro data suggest possible synergism of BTZ plus DEXA at microM concentrations against multiple myeloma RPMI cells.

Conclusion: our study confirmed the validity of the proposed combinatorial screening regarding the painful component of BTZ-induced neurotoxic side effects.


Keywords: Pain, Pre-clinical Studies

Grant Support: None.
Poster 132

Test-retest reliability of the human immunodeficiency virus/acquired immunodeficiency syndrome-associated neuropathic pain questionnaire

Alagoma Iyagba1, Mayowa Owolabi2, Adesola Ogunniyi2

1University of Port Harcourt, University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria, 2University of Ibadan, University College Hospital, Ibadan, Nigeria

Introduction: Test-retest reliability analysis is an important psychometric property of a new scale. The HIV/AIDS-associated neuropathic pain questionnaire (HANP-Q) is a newly devised instrument for measuring neuropathic pain in individuals with HIV-AIDS. Our objective was to determine the test-retest reliability of the HANP-Q

Method: We obtained ethical approval before commencement. Test-retest reliability for a pain scale is done by assessing the participants' responses to the questionnaire at baseline and after a 72 hours interval. One-hundred subjects were recruited during the development phase of the questionnaire. The appropriate sample size used for the test-retest reliability was determined using the method described by Walter et al. Thirty-one participants were used for the test-retest reliability analysis. Test re-test reliability was derived by computing a correlation coefficient called coefficient of stability or test-retest reliability coefficient for the two sets of test: T1 at baseline and T2 at 3 days. The coefficient of stability varies between 0 – 1. Criterion for coefficient of stability was set at: ≥ 0.8 < .9 = good reliability. Results were analysed using descriptive and inferential statistics.

Results: There were fourteen males and seventeen females with M: F = 1: 1.2. The mean age, body mass index and CD4+ cell counts of the participants were 40.0 ± 9.0 years, 25.4 ± 5.0 kg/m² and 422.7 ± 300.7 cells/µL respectively. Viral load ranged from 0.0 – 1, 518, 685.0 copies/ml with a median of 384.0 copies/ml. The coefficient of stability was 0.87. There was statistically significant (p = 0.001, r = 0.587) correlation between the two sets of scores

Conclusion: The HANP-Q showed good test-retest reliability. It will be a useful instrument for assessing neuropathic pain among HIV/AIDS individuals.


Keywords: Pain, Small Fibers, Other

Grant Support: None
Inherited ataxias are rare neurodegenerative disorders with clinical and genetic heterogeneity. Their clinical manifestation generally involves progressive gait incoordination, poor coordination of hands, speech and eye movements and frequent atrophy of the cerebellum.

Here we report an isolated patient born to consanguineous parents presenting with cerebellar ataxia with axonal neuropathy. The clinical symptoms of the patient include truncal and gait ataxia, dysdiadochokinesia, intention tremor, and dysmetria with an age of onset at eight years. The clinical features are accompanied by axonal peripheral neuropathy as indicated by electrophysiology studies. Whole exome sequencing, followed by structural variant filtering and segregation analyses, excluded all known genes for inherited ataxias and inherited peripheral neuropathies and suggested a homozygous frameshift variant in the \textit{SEPT11} gene to be potentially disease-causing. Molecular analyses on patient’s skin fibroblasts revealed decreased Sept11 mRNA expression, as well as lack of Sept11 protein in the cell lysates. \textit{SEPT11} encodes a member of the septin family of GTP-binding cytoskeletal proteins and is known to be highly expressed in the Purkinje cells in the molecular layer of cerebellum. Additionally, previous studies show that the knock-down of \textit{SEPT11} in the hippocampal neurons causes reduced dendritic branching and spine density in mice.

Our findings combined with previous knowledge on septin proteins suggest that the loss of Sept11 protein causes an autosomal recessive cerebellar ataxia with axonal neuropathy in this family.

\textbf{References:} None.

\textbf{Keywords:} Human Genetics

\textbf{Grant Support:} TUBITAK Grant number: 215S883
Charcot-Marie-Tooth (CMT) disease is the most common hereditary neuropathy, but with a complex genetic diagnosis in some cases. We report a family with the classical CMT1 phenotype with amyotrophy, weakness and sensory length-dependent loss and demyelinating nerve conduction velocities in the electrophysiological studies. A next generation study of 34 CMT genes have been performed in the proband and identified a novel mutation in EGR2 (p.P397H) and a non-pathogenic polymorphism in LITAF (p.T49M). Other family members were examined clinically and genetically and only the father, that carried both the LITAF T49M and EGR2 P397H mutation, developed the disease. EGR2 is a zinc-finger transcription factor that activates the myelination program in Schwann cells. We have conducted chromatin immunoprecipitation and promoter activity luciferase assays that demonstrated a decrease in transcriptional activity in P397H mutants. LITAF T49M has been described previously as a non-pathogenic polymorphism. However, using heterologous systems and cultured Schwann cells we evidenced decreased protein stability in the T49M mutants compatible with a loss of function mechanism. No direct physical interaction between LITAF and EGR2 could be detected. Therefore, we suggest that the harmful decreased transcriptional activity of EGR2 P397H would be enhanced by LITAF loss of function, interfering with Schwann cell differentiation and myelin development. In this family, these missense mutations would be non-pathogenic in a separate heterozygous state as they were carried by healthy individuals.

References: None.

Keywords: Human Genetics

Grant Support: None.
Poster 135
Slowly progressive familial ALS caused by an hnRNPA1 missense mutation

Nicolas Dubuisson1, Danique Beijer2, Ines Mademan2, Tine Deconinck2, Jonathan Baets3, Peter Van den Bergh1

1Neuromuscular Reference Centre, Department of Neurology, Cliniques Universitaires St-Luc, Belgium, Brussels, Belgium, 2Laboratory of Neuromuscular Pathology, Institute Born-Bunge, University of Antwerp, Belgium, Antwerp, Belgium, 3Neuromuscular Reference Centre, Department of Neurology, Antwerp University Hospital, Belgium, Antwerp, Belgium

Background: Amyotrophic lateral sclerosis (ALS) is a disease of the motor neurons characterized by progressive muscle weakness leading to death within 3–5 years. Approximately 5-10% of cases have a family history (fALS). Over 100 genes have been implicated in ALS pathogenesis. Some encode RNA-binding proteins (RBPs), such as hnRNPA1, which influence pre-mRNA processing and other aspects of mRNA metabolism and transport.

Case report: We report the case of a Moroccan 44-year-old woman, who presented right arm weakness and wasting since the age of 21. Her father and paternal grandmother presented the same phenotype. Both died from respiratory failure around the age of 40. A 43-year-old sister presents with dysarthria, dysphagia, and right hand muscle wasting and weakness since 1 year. Two siblings and three children are presently unaffected.

The diagnosis of a very slowly progressive motor neuron disease was made 4 years after symptom onset, based on typical clinical signs together with supportive neurophysiological findings. Over time, she developed progressive weakness and wasting of the left arm, bulbar symptoms, respiratory insufficiency, and lower limb spasticity. After 22 years of evolution, she is still walking without aid.

Performing the genetic screening of this patient by means of whole-exome sequencing, we detected a novel missense mutation in hnRNPA1 (NM_002136): c.862C>G, p.P288A.

Mutations in the PrLD of hnRNPA1 were recently described in families with multisystem proteinopathies (MSP) and in ALS patients. These mutations were shown to increase the propensity of hnRNPA1 proteins to self-aggregate, which results in cell death and apoptosis.

Conclusion: We report a family with slowly progressive ALS caused by a hnRNPA1 missense mutation. Segregation studies will be presented. hnRNPA1 mutations cause <1% of fALS. Recent data from studies on ALS-linked RBPs suggests that alteration of RBPs which increase their tendency to self-aggregate may lead to a spectrum of motor neuron disorders ranging from classical ALS to distal hereditary motor neuropathy (dHMN), and MSP.


Keywords: Other

Grant Support: NA
Case report of diagnosis of Congenital Disorder of Glycosylation in 65-year-old followed for Myasthenia Gravis

Tiffany Grider, Ludwig Gutmann

University of Iowa Hospitals & Clinics, Iowa City, IA, USA

A 65-year-old woman initially presented with new onset left eye lid ptosis and a history generalized weakness in 1997. She was diagnosed with myasthenia gravis and treated with pyridostigmine with some modest benefit. One year later she underwent thymectomy without improvement. Over the years she had multiple courses of IVIG, plasmapheresis, prednisone, and mycophenolate mofetil, all with only mild transient improvement. Since 2002, she managed without oral medications and required a single course of IVIG in 2013. Carefully reevaluation by her neuromuscular specialist revealed 20 history of muscle weakness and almost no response to extensive treatment over the years. Genetic evaluation revealed two variants of uncertain significance (VUS) in trans in the DPAGT1 gene. One VUS (p.Tyr170Cys) has been described in a patient with congenital disorder of glycosylation (CDG-1J). The other variant (p.Arg121Cys) changes a highly conserved arginine to a cysteine. It is rarely present in population databases (0.005%) and the algorithms predict the change to be disruptive to the function of the protein. To help determine the significance of the genetic variants isoelectric focusing of serum transferrin was completed and was consistent with congenital disorder of glycosylation type 1. CDG Mono-oligo/Di-oligo ratio was 0.24 (normal <=0.06) and CDG A-oligo/Di-oligo ratio was 0.035 (normal <=0.011). Therefore, the clinical evaluation, metabolic studies, and genetic test results are consistent with a diagnosis of Congenital Disorder of Glycosylation Type 1J. Mutations in DPAGT1 gene result in ultrastructural changes in the terminal motor axon and post-synaptic membrane impairing neuromuscular transmission. This case exemplifies the need to reevaluate a long standing diagnosis when potential treatments provide less benefit than expected.

References: None.

Keywords: Human Genetics

Grant Support: None.
INTRODUCTION: Transthyretin amyloid polyneuropathy (ATTR-PN) is a rare, debilitating disorder characterized by transthyretin (TTR) amyloid deposits and progressive sensorimotor neuropathy. The TTR stabilizer tafamidis was shown to reduce ATTR-PN progression in a Phase III randomized controlled trial (RCT; Fx-005). As no head-to-head trials have directly compared tafamidis to other ATTR-PN therapies, a robust indirect treatment comparison (ITC) would be valuable to decision-makers.

METHODS: A targeted literature review identified three placebo-controlled RCTs of ATTR-PN therapies: tafamidis (Fx-005), patisiran (APOLLO), and inotersen (NEURO-TTR). These RCTs were assessed for inclusion in an ITC by qualitatively comparing study designs, patient populations, baseline patient characteristics, and efficacy and safety outcomes. We assessed the feasibility of conducting ITCs using aggregated data and matching-adjusted indirect comparisons (MAICs) of individual patient data (IPD).

RESULTS: Neurologic impairment was a primary efficacy endpoint in each trial, but could not be compared because trials used different composite scores, for which measurement techniques and scoring varied. Large differences were also observed for key inclusion criteria and patient characteristics, precluding ITCs for other outcomes. For example, Fx-005 included treatment-naïve early-stage patients with Val30Met mutations, whereas >33% of patients in APOLLO and NEURO-TTR had Stage 2 disease, >48% had other TTR mutations, and >53% received prior ATTR-PN therapies. Major differences in mean patient age, sex, and disease duration were also observed between Fx-005 and comparator trials. An IPD MAIC could partially adjust for some of these differences, although considering the degree of heterogeneity, this would reduce effective sample sizes and limit the robustness of analyses.

CONCLUSIONS: The inability to compare neurologic impairment limits the clinical relevance of ITCs comparing Fx-005 to NEURO-TTR or APOLLO. Further, the extent of heterogeneity between populations precluded valid ITC estimates using available RCT data. This conclusion calls into question the robustness of recently published ITCs of these therapies.

References: None.

Keywords: Amyloidosis

Grant Support: Funding for the project was provided by Pfizer Inc.
Poster 138

Small-fibre sensory and sudomotor neuropathy as early and stage-dependent biomarkers of transthyretin-amyloid neuropathy

Chi-Chao Chao, Sung-Tsang Hsieh

Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan

Purpose: Small-fibre symptoms are early presentations of familial amyloid polyneuropathy (FAP) with transthyretin (TTR) mutations. This study aimed to explore early and stage-dependent biomarkers.

Methods: We recruited patients and carriers with TTR-A97S; performed pathological, neurophysiological, and psychophysical tests; and analysed clinical associations with FAP stage score (stage), including (1) skin biopsies to measure intraepidermal nerve fiber (IENF) density, sweat gland innervation index (SGII) of protein gene product 9.5 [SGII(PGP9.5)], and (2) nerve conduction studies (NCS), quantitative sensory testing, and autonomic function tests. Results: There were 66 TTR-A97S subjects (25 carriers and 41 patients). Among the carriers, 15 were asymptomatic (stage 0), and the remaining 10 were symptomatic (stage 1) with carpal tunnel syndrome or autonomic symptoms. There were 21, 15, and 5 patients at stage 2, 3, and 4, respectively. The expression of skin pathologies were distinct according to stage. IENF density were reduced in carriers vs. controls; IENF density showed gradual reductions from stage 0 through 4. In contrast, SGII(PGP9.5) of carriers were similar to those of controls but started to decline in patients from stage 2. In carriers, the IENF density had a higher abnormal rate compared with the abnormal rates of NCS, thermal thresholds and autonomic function tests. In contrast, the abnormal rates of all tests in patients were higher than 75%. The abnormal rates of the IENF density, NCS, and thermal thresholds were similar. When tests of pathology, neurophysiology, and psychophysics were all included, IENF density and SGII(PGP9.5) were still correlated with stage. Conclusion: These observations suggest (1) skin denervation is an earliest biomarker of FAP, and (2) distinct stage-dependent patterns of skin and sudomotor denervation from carriers to advanced stages of FAP.

References: None.

Keywords: Amyloidosis, Small Fibers

Grant Support: None.
A Natural History and Outcome Measure Discovery Study of Charcot-Marie-Tooth 4J

Diana Castro¹, Michael Shy²

¹University of Texas Southwestern, Children’s Health, Dallas, TX, USA, ²University of Iowa, Iowa City, IA, USA

Introduction: Charcot-Marie-Tooth type 4J (CMT4J) is a rare inherited sensorimotor demyelinating peripheral neuropathy caused by FIG4 gene mutations and characterized by childhood-onset gait abnormalities and balance difficulties, with rapid progression to asymmetrical upper and lower extremity muscle weakness and atrophy. Respiratory compromise and premature death may also occur. Currently, there is no available treatment. Animal models demonstrate the possibility of gene transfer therapy via viral vectors. This study aims to characterize the natural history of CMT4J and to determine clinically meaningful outcome measures for use in clinical studies of these therapies. Methods: This multi-center, longitudinal, prospective observational natural history study of patients with clinical and molecularly confirmed diagnosis of CMT4J plans to enroll up to 20 patients from the US and internationally. Those unable to travel to the investigative sites may consent to the study, supply medical records and surveys remotely. Medical records will be reviewed for historical information and patients will undergo a multitude of assessments every 6 or 12 months including: physical and neurological examinations, standard laboratory testing, CMT outcome measurements (CMTPedS, CMTNSv2-R, CMT-FOM, CMTHI), nerve conduction and imaging (MRI calf fat fraction) studies, biochemical assays, and sleep and movement monitoring (wearable device). Pulmonary function test and neuropsychological (Vineland Adaptive Behavior Scales, Pediatric QoL Inventory) testing will be conducted every 12 months. Follow-up is for 5 years. Conclusions: This study hopes to expand our knowledge of the natural history of CMT4J, provide insights on any genotypic and phenotypic correlation, and ultimately identify outcome measures for a planned future interventional clinical trial.

References: None.

Keywords: CMTR

Grant Support: Neurogene
Inherited peripheral neuropathies (IPN) is a group of genetically and clinically heterogeneous disorders, such as Charcot-Marie-Tooth disease (CMT), hereditary neuropathy with liability to pressure palsy (HNPP), distal hereditary motor neuropathy (dHMN), and hereditary sensory autonomous neuropathy (HSAN). We performed genetic screening in the Korean 1,222 IPN families (486 CMT1, 318 CMT2, 106 CMTX, 187 HNPP, and 125 others) by the methods of 17p12 duplication/deletion test, aCGH, WES, and targeted sequencing for ~70 IPN-related genes. This cohort study identified genetic causes from 744 families out of 1,222 families (60.9%). PMP22 duplication and deletion were frequently observed in 25.0% (63.0% of CMT1) and 9.5% (62.0% of HNPP) of total cases, respectively. Subsequently, mutations in GJB1 (7.2%), MFN2 (4.1%), MPZ (2.9%), PMP22 point mutation (1.9%), NEFL (1.2%), HSPB1 (0.6%), GDAP1 (0.5%), BSCL2 (0.5%), GARS (0.4%), EGR2 (0.3%), SH3TC2 (0.3%), DCTN1 (0.3%), KIF5A (0.3%), MARS (0.3%), and MORC2 (0.3%) were observed. Among the genetically diagnosed families, 628 (84.4%) families have dominant mutations. Ethnic-specificity was slightly noticed in several genes. This study will provide useful data for exact molecular diagnosis and treatment for peripheral neuropathies.

References: None.

Keywords: CMTR, Human Genetics

Grant Support: None.
In patients with Charcot-Marie Tooth Disease 1A (CMT1A), peripheral nerves display aberrant myelination during postnatal development, followed by slowly progressive demyelination and axonal loss during adult life. We could show that myelinating Schwann cells in a rat model of CMT1A exhibit a developmental defect that includes the reduced transcription of genes required for myelin lipid biosynthesis. Consequently, lipid incorporation into myelin is reduced, leading to an overall distorted stoichiometry of myelin proteins and lipids with ultrastructural changes of the myelin sheath. Importantly, the substitution of phospholipids in the diet is sufficient to overcome the myelination deficit of affected Schwann cells in vivo, rendering lipid supplementation an easily translatable therapeutic approach in CMT1A.

References: CMT-NET (01GM1511C), BMBF

Keywords: CMTR, Pre-clinical Studies, Schwann Cell

Grant Support: None.
Genetic Heterogeneity of Autosomal Recessive Charcot-Marie-Tooth Disease in a Turkish Cohort

Esra Battaloglu¹, Ayse Candayan¹, Gulshan Yunisova², Arman Cakar², Derek Atkinson³, Hacer Durmus Tekce⁴, Albena Jordanova⁵, Yesim Parman²

¹Bogazici University, Department of Molecular Biology and Genetics, Istanbul, Turkey, ²Istanbul University, Istanbul Medical School, Istanbul, Turkey, ³Antwerp University Center for Molecular Neurology, Max Planck Institute of Immunobiology and Epigenetics, Freiburg, Germany, ⁴Istanbul University Istanbul Medical School, Istanbul, Turkey, ⁵Antwerp University Center for Molecular Neurology, Antwerp, Belgium

Charcot-Marie-Tooth (CMT) disease is a group of generally non-syndromic, peripheral neuropathies that make up an interesting research focus. The clinical and genetic heterogeneity of CMT creates a challenge for diagnosis; although advanced technologies are frequently utilized, only 45-60% of CMT patients receive genetic diagnosis. The genetic diagnosis rate is even lower for autosomal recessive CMT cases.

In order to identify novel genes/alleles causing autosomal recessive CMT and determine the gene/allele frequency for known genes in Turkey, we have analyzed 56 patients diagnosed with CMT in the clinical setting, presenting with early onset polyneuropathy and additional symptoms that increase severity who were all born to consanguineous parents. All the patients were initially screened for mutations in the GDAP1 gene and six patients (10.7%) were found to have recurrent mutations in this gene. Whole exome sequencing was performed for the remaining patients; after a structural filtering and verification of the variants, 15 patients were shown to have recurrent mutations in SH3TC2, MFN2, PRX, EGR2 and GJB1 genes, while 13 patients carried novel variants in GDAP1, HINT1, MME, MPZ, NEFL, NDRG1, SBF2, C12orf65, SACS, SPG7 and FXN genes.

All patients were initially diagnosed with CMT, however the genetic findings indicated other neurological disorders in three patients, suggesting it might not always be sufficient to analyze WES data based on initial clinical diagnosis, especially in neurological disorders with overlapping features. Among the 56 patients included, 34 received genetic diagnosis suggesting a diagnosis rate of 60.7%. Although the genes mentioned here have been known to be disease-causing for a long time, more than one-third of genetically diagnosed patients exhibited novel mutations in these genes. This study can serve as a reference for the development of genetic diagnosis tools specific to the population.

References: None.

Keywords: Human Genetics, CMTR

Grant Support: This study is supported by TUBITAK Project number 215S883 and Bogazici University Research Fond project number 14784.
Myopathies and neuropathies associated with Pro209 mutations in BAG3 have comparable molecular deficits

Elias Adriaenssens¹, Barbara Tedesco², Laura Mediani³, Valeria Crippa⁴, Serena Carra³, Angelo Poletti², Vincent Timmerman¹

¹Peripheral Neuropathy Research Group, Institute Born Bunge, University of Antwerp, Antwerp, Belgium, ²Centro di Eccellenza sulle Malattie Neurodegenerative, Università degli Studi di Milano, Milan, Italy, ³Center for Neuroscience and Neurotechnology, University of Modena and Reggio Emilia, Modena, Italy, ⁴Centro di Eccellenza sulle Malattie Neurodegenerative, Università degli Studi di Milano, Milano, Italy

Three missense mutations targeting the same proline 209 codon in the co-chaperone Bcl2-associated athanogene 3 (BAG3) have been reported to cause distal myopathy, dilated cardiomyopathy or Charcot-Marie-Tooth type 2 neuropathy. The molecular pathology of Pro209 mutations in BAG3, explaining the variable clinical spectrum described in these rare patients, has so far not been investigated. Here we studied the expression profile of the three different Pro209_BAG3 variants, their effect on BAG3 solubility and aggregation properties, and how the mutations affect binding of BAG3 to its molecular partners in the chaperone-assisted selective autophagy (CASA) complex. We found that the molecular consequences of these three mutations are very similar. All BAG3_Pro209 mutants showed decreased solubility and increased aggregation propensity compared to the BAG3 wild type protein. Instead, the solubility of a different BAG3_Glu455Lys mutant, which is linked to dilated cardiomyopathy, was similar to wild type BAG3. Furthermore, all three BAG3_Pro209 mutants had a decreased capacity to clear mutant superoxide dismutase (SOD1_G93A) aggregates, without altering the interaction with the small heat shock protein HSPB8. These experiments suggest that HSPB8-independent functions of BAG3 may contribute to the distinct clinical phenotypes seen in the patients with the Pro209 mutations in BAG3.

References: None.

Keywords: Human Genetics, Axonal Biology

Grant Support: None.
Follow up of hereditary transthyretin neuropathy at early stages: new clinical and electrophysiological scores

Chrystel Chéraud Bonfort¹, Jean Pascal Lefaucheur², Tarik Nordine³, Thierry Gendre⁴, Violaine Planté Bordeneuve⁵

¹Service de Neurologie CHR Metz Thionville, Metz, France, ²Unité de Neurophysiologie Clinique Hôpital Henri Mondor APHP, EA 4391 Faculté de Médecine de Créteil UPEC, Créteil, France, ³Unité de Neurophysiologie Clinique Hôpital Henri Mondor APHP, Créteil, France, ⁴Service de neurologie Hôpital Henri Mondor APHP, Créteil, France, ⁵Service de neurologie Hopital Henri Mondor APHP, GRC Institut de Recherche sur l'Amylose UPEC, Créteil, France
Introduction:

In the context of new therapeutics available in hereditary transthyretin amyloidosis with polyneuropathy (hATTR+PN), the development of reliable markers for an early diagnosis and follow up of the PN is essential. Composite clinical and electrophysiological scores, as NIS+7 and modified NIS+7 (mNIS+7), were developed to assess the progression of the neuropathy.

Aim:

To test the reliability of new clinical and electrophysiological scores to assess hATTR+PN at early stages.

Methods:

This monocentric retrospective study included consecutive hATTR patients with mild to moderate PN (NIS<40) evaluated twice, by the same investigators, at intervals from 1 to 3 years. Clinical evaluations involved the NIS and a new purely sensory clinical score (SCS) ranging from 0 to 100 (thermic, pain and vibration senses). From electrophysiological evaluations, we calculated 4 scores: two corresponding to the electrophysiological component of the NIS+7 and mNIS+7, and two purely sensory electrophysiological scores, based on a sum of sensory nerve action potential amplitudes at the lower limbs (LL-SES) or the 4 limbs (4L-SES).

Results:

The study enrolled 51 subjects (30 men), aged from 25 to 81 years old (mean of 56 years old), with average NIS of 11.4 (0-38) and SCS of 24.8 (0-75). All clinical and electrophysiological scores correlated with each other at baseline (p<0.005). However, the score difference between 2 time points found only one clinico-electrophysiological correlation between the new SCS and the LL-SES (p=0.03). In addition, a tendency towards significant correlation was found between the SCS and the 4L-SES (p=0.06) and the NIS and the LL-SES (p=0.08).

Conclusion:

Two new scores, purely sensory, based on clinical examination (SCS) and standard nerve conduction study (LL-SES), appeared to be the most relevant to follow up hATTR+NP progression at early stages. These scores are easier to perform in daily practice than the NIS+7 or mNIS+7.

References: None.

Keywords: Amyloidosis

Grant Support: None.
A point mutation in the Schwann cell-specific 5' UTR of the GJB1 gene, c.-103C>T [NM_00016.5, chrX:71,223,249 (hg38)] causes CMTX1, whereas the adjacent GJB1 c.-102G>A [NM_00016.5, chrX:71,223,250 (hg38)] is a polymorphism. The pathological mechanisms underlying the c.-103C>T mutation are still unclear. Previous studies have suggested the c.-103C>T change disrupts an internal ribosomal entry site (IRES) and abolishes 5' cap-independent translation (Hudder and Werner, 2000). These experiments were conducted using the rat GJB1 5' UTR sequence, which differs in both sequence and secondary structure when compared to human GJB1 5' UTR (92.52% sequence similarity). Additionally, in silico assessment with Human Splicing Finder 3.1 (Desmet et al., 2009) revealed that the GJB1 c.-103C>T mutation creates an exonic donor splice site and disrupts an exonic splicing enhancer site, and no such changes are caused by the GJB1 c.-102G>A polymorphism. IRES activity is experimentally assessed through a bicistronic assay. This allows for the comparison of 5’ cap-dependent translation and IRES-driven 5’cap-independent translation by analysing the expression of two reporter genes from a single bicistronic mRNA. We have generated a construct where translation of the first reporter gene firefly luciferase (fLuc) is 5’ cap-dependent, and expression of the second reporter gene, NanoLuc luciferase (nLuc) requires the human GJB1 5' UTR to initiate translation through a 5' cap-independent mechanism. This construct was transfected into a rat Schwann cell line (RT4) to model CMT pathology, as it has been shown that IRES function is highly dependent on cell type. Additionally, the impact of the c.-103C>T mutation on GJB1 splicing will be assessed using the pSpliceExpress minigene system (Kishore et al., 2008) to determine changes in sequence and abundance of mature GJB1 mRNA. Investigation to fully resolve the pathogenic mechanism underlying the GJB1 c.-103C>T mutation is warranted to develop the most appropriate approach for therapy.


Keywords: CMTR, Human Genetics, Schwann Cell

Grant Support: None.
Poster 146

Experience with Patisiran in the treatment of hereditary Transthyretin amyloidosis neuropathy

Lucia Galan, Alejandro Horga, Vanesa Pytel, Lorenzo Silva, Rafael Hernandez-Sáez, Antonio Guerrero-Sola

Hospital Clínico San Carlos, Madrid, Spain
introduction Hereditary transthyretin amyloidosis AhTTR is a progressive systemic disease caused by mutations in transthyretin gene. It is potentially mortal in the absence of treatment. Till recently the only treatments approved were Tafamidis and liver transplantation applicable only in early stages. In some cases the disease still progressed. Recently siRNA therapy (Patisiran) has proven to be effective in AhTTR neuropathy. We present our experience with Patisiran in AhTTR neuropathy in real life

Population: Seven patients with AhTTR, ages 57-82, median 70.

3 stage II Coutinho, 4 patients in stage I non responders to Tafamidis.

Mutation: 5 Val30Met, one Glu89Gln, one Ala60Thr. Patisaran and premedication administered as per protocol. One patient missed two consecutive doses. 4 patients missed one or more doses not consecutives.

Number of infusions between 7 and 37, median 14

In two patients dexamethasone dose was reduced to 7.5 and 5 mg

Results

Safety: Infusion was well tolerated. One patient had facial flushing. In the patient who reduced dexamethasone to 5 mg facial flushing appeared.

No severe adverse events considered related to the drug occurred. A patient suffered an arm fracture that premedication may have worsened

Effectivity: 4 patients showed neurological stabilization. Two of them with improvement in dysautonomia. One of them although neurologically stable feel that he was worsening from a cardiological point of view and dropped out

2 patients showed a neurological progression although less than expected from natural history

The other after a first reversal in the PND stage missed two doses then worsen first and stabilized later. She also showed ocular progression

All patients but one showed a block of 80-90% of Transthyretin.

Conclusion Patisiran is a new therapeutic alternative for the treatment of AhTTR. It is safe and effective drug. The correct frequency of its administration may be important for its efficacy

Keywords: Amyloidosis, Other

Grant Support: None.
Transthyretin-induced cytoskeleton remodeling: a double-edged sword

Jessica Eira¹, Nídia Macedo², Francesca Bartolini³, Mónica Sousa², Márcia Liz²

¹ICBAS, IBMC/i3S, University of Porto, Porto, Portugal, Porto, Portugal, ²IBMC/i3S, University of Porto, Porto, Portugal, Porto, Portugal, ³Department of Pathology & Cell Biology, Columbia University, New York, New York, NY, USA

Under physiological conditions, transthyretin (TTR) participates in nerve biology by increasing axonal transport, axon growth and regeneration. When mutated, TTR causes familial amyloid polyneuropathy (FAP), a neurodegenerative disease characterized by the deposition of TTR amyloid fibers, particularly in the peripheral nervous system (PNS), resulting in a dying-back axonopathy that culminates in neuronal death. The cytoskeleton is crucial for neuronal function including axonal transport and growth and, when disrupted, it is associated with neurodegeneration. Here we investigated the hypothesis that soluble WT and aggregated mutant TTR may have a dual role in modulating the neuronal cytoskeleton. Indeed, our results show that while soluble WT TTR enhances microtubule (MT) dynamics, aggregated TTR disrupts actin organization in the growth cone. Using a TTR KO mouse model expressing the MT end-binding protein EB3-YFP in neurons we show that TTR plays a role in regeneration by modulating MT dynamics after sciatic nerve injury. By proteomics, we identified Src kinase as a putative player in the molecular mechanism underlying the effect of WT TTR on MTs. In relation to mutant TTR aggregates, we determined that their effect on the actin cytoskeleton is mediated by the RAGE receptor and activation of RhoA in the growth cone of DRG neurons. Altogether, our data describe the dual activities of WT versus aggregated TTR on the neuronal cytoskeleton, highlighting their pivotal roles in normal nerve biology and in the pathophysiology of FAP. Our findings may contribute in the future to the discovery of new therapeutic strategies for this disorder.

References: None.

Keywords: Amyloidosis, Axonal Biology, Axonal Regeneration, Small Fibers

Grant Support: This work was financed by: FEDER - Fundo Europeu de Desenvolvimento Regional funds through the COMPETE 2020 - Operacional Programme for Competitiveness and Internationalisation (POCI), Portugal 2020, and by Portuguese funds through FCT - Fundacao para a Ciencia e a Tecnologia/Ministerio da Ciencia, Tecnologia e Ensino Superior in the framework of the project POCI-01-0145-FEDER-028336 (PTDC/MED-NEU/28336/2017); project Norte-01-0145-FEDER-000008 - Porto Neurosciences and Neurologic Disease Research Initiative at I3S , supported by Norte Portugal Regional Operational Programme (NORTE 2020), under the PORTUGAL 2020 Partnership Agreement, through FEDER; and Luso-American Development Foundation. J Eira is a FCT fellow (J Eira: SFRH/BD/116343/2016). MA Liz is funded by the FCT investigator programme.
Sleep Disorders in Charcot-Marie-Tooth Disease

Silvia Fenu¹, Giuseppe Didato¹, Daniela Calabrese¹, Giuseppe Vita², Anna Mazzeo², GianMaria Fabrizi³, Angelo Schenone⁴, Tiziana Cavallaro⁵, Marina Grandis⁴, Stefano Previtali³, Isabella Allegri⁶, Luca Padua⁷, Costanza Pazzaglia⁸, Aldo Quattrone⁹, Irene Tramacere¹, Chiara Pisciotta¹, Fiore Manganelli¹⁰, Lucio Santoro¹⁰, Flavio Villani¹¹, Davide Pareyson¹

¹Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, ²University of Messina, Messina, Italy, ³University of Verona, Verona, Italy, ⁴University of Genoa, Genoa, Italy, ⁵Ospedale San Raffaele, Milan, Italy, ⁶UOC Neurologia Azienda Ospedaliera di Parma, Parma, Italy, ⁷IRCCS Fondazione Don Carlo Gnocchi, Catholic University of the Sacred Heart, Rome, Italy, ⁸Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, ⁹Magna Grecia University, Catanzaro, Italy, ¹⁰Federico II University, Naples, Italy

There are a few reports of sleep disorder occurrence in Charcot-Marie-Tooth disease (CMT). We investigated sleep quality and abnormalities in a series of CMT patients and healthy controls employing two scales, the PSQI (Pittsburgh Sleep Quality Index) and ESS (Epworth Sleepiness Scale), both validated in Italian.

Two hundred and sixty-two patients (142 females, aged 20-82 years, mean 47.1) and 58 controls (not affected relatives or friends of patients; 26 females; aged 21-74 years, mean 45.2) answered to the questionnaires.

ESS (range 0-24, 24 worst score, ≥11 abnormal sleepiness): CMT patients had a mean score of 7.3 (SD 4.3, range 0-21) with 60 subjects (23%) reporting scores ≥11 (among whom 33 CMT1A, 6 CMT1X, 5 CMT1B, 3 CMT2I/J). There was no significant difference with controls (6.6 ± 4.3, range 0-18) (p=0.23, Mann-Whitney test); 12 healthy subjects (21%) had scores ≥11. There was no correlation between disease severity and ESS scores.

PSQI (range 0-21, 21 worst score, ≥5 bad sleeper): there was no significant difference in the mean scores between CMT patients (9.1 ± 3.0, range 1-18) and controls (8.7 ± 2.7, range 4-17) (p=0.36, Mann-Whitney test) and the percentage of patients with scores ≥5, indicative of poor sleep quality, was high in both groups (>90%, p>0.7). In the subscores there were no differences between the two groups but for higher scores among CMT subjects for the item "sleep disturbances" (p = 0.0000) and, surprisingly, among controls for “daytime dysfunction” (p = 0.026). Further analyses are ongoing.

In conclusion, we found no clearcut evidence for sleep abnormalities in our CMT population. Both ESS and PSQI mean scores were similar in CMT and controls. There was no correlation between abnormal scores and CMT subtype or disease severity.

References: None.

Keywords: CMTR

Grant Support: Supported by Telethon-UILDM grant GUP09013
Charcot-Marie-Tooth Neuropathy Type 1B with Clinical Response to Immunomodulatory Therapy related to Inflammatory Overlap

Davide Cardellini¹, Tiziana Cavallaro¹, Gian Maria Fabrizi¹, Federica Taioli¹, Sergio Ferrari¹, Giampietro Zanette²

¹Neurology Division, Department of Neuroscienze AOUI Verona, Verona, Italy, Verona, Italy, ²Neurology Division, Pederzoli Hospital, Peschiera del Garda, Verona, Italy, Peschiera del Garda, Verona , Italy

Charcot-Marie-Tooth disease type 1 (CMT1) may converge phenotypically with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP); on the other hand, CMT1 may be complicated by superimposed CIDP. Neuropathological distinction between CIDP and CMT1 results from the different pathological changes (segmental demyelination in CIDP versus dysmyelination in CMT1).

A 33 year-old man, without familial or neurological antecedents, manifested subacute paresthesias of hands and feet, fatigue and cramps in the lower limbs. Examination revealed mild weakness and slight impairment of vibration sense of feet and hands, generalized hypo/areflexia without pes cavus and peroneal atrophy. Motor and sensory Nerve Conduction Velocities were decreased at four limbs (MNCV of ulnar nerve = 31 m/s), conduction blocks (CB) outside compression sites were reported. The CMT neuropathy score was 8. Cerebro-spinal-fluid protein content was normal. High-resolution ultrasound (HRUS) was consistent with CIDP disclosing asymmetrical and focal, moderate, enlargements of cross-sectional area (CSA) at right median nerve at elbow, arm and axilla; left median nerve at axilla; right ulnar nerve at arm; left and right peroneal nerve at fibular head and bilateral hypertrophy of cervical roots. Multiplex Ligation-dependent Probe analysis rule out Copy Number Variations of PMP22, MPZ and GJB1. Sanger sequencing detected a novel pathogenic heterozygous c.204C>T transition on MPZ introducing a premature stop (p.Tyr68Ter). After diagnosing CMT1B plus CIDP, we started a standard IGIV regimen (2gr/kg in 5 days) repeated every 6-8 weeks, according to response wear-off. Evaluation after 1 year revealed an improvement of daily activities and disappearance of positive sensory symptoms (CMTNS = 3). Nerve conduction studies and HRUS revealed no more CB and a reduction of CSA enlargments.

Due to the possible coexistence of CIDP and CMT1 atypical demyelinating neuromuscular diseases may require an extensive diagnostic work up. HRUS may represent an additional tool complementary to routine neurophysiology and CSF investigations.

References: None.

Keywords: CMTR, Inflammatory

Grant Support: None.
Prevalence And Characterization Of Pain In CMT1A Patients.

Helen Azevedo¹, Henrique Costa², Eduardo Davidovich³, Camila Pupe², Osvaldo Nascimento¹

¹Universidade Federal Fluminense, Rio de Janeiro, Brazil, ²Universidade Federal Fluminense, Rio de Janeiro, Brazil, ³Universidade Federal Fluminense, Rio de Janeiro, Brazil

Charcot-Marie-Tooth disease (CMT) is the most common hereditary neuropathy. Although under-diagnosed, pain is a common complaint of these patients. There are, however, few studies evaluating the actual pathophysiology of this symptom. The objective of this study is to assess pain prevalence and characteristics in patients with CMT. Tools used for pain assessment were: Neurological evaluation; LANSS and DN4 scale - for the type of pain; VAS – for pain intensity; pain site according to anamnesis and clinical evaluation; Gravity scale of Charcot-Marie-Tooth disease (CMTNS); SF-36 questionnaire for assessment of quality of life. Furthermore, nerve conduction studies for neurophysiological classification and molecular tests were used to determine the genetic type. A convenience sample of patients was evaluated from September 2018 to February 2019, and others causes of painful neuropathies were ruled out. Results: Twelve CMT1A patients, with median age of 43.5, were evaluated and 9 have pain as a symptom (75%). Neuropathic pain was found in 33.4% of this sample by LANSS scale, and 50% by DN4. There was no association between gender or cavus feet and pain. There was correlation between SF-36 physical functioning domain and intensity of pain in VAS scale and between limitations due to physical health domain and VAS scale (p < 0.01). Conclusion: The prevalence of pain is a relevant symptom for CMT1A patients in this sample. In the analyzed sample the pain is mixed: neuropathic and nociceptive. Furthermore, the results showed that the lower the pain, the greater the functional capacity and less the limitation in the physical aspects. Its correlation with physical limitation suggests that the pain relief could bring quality of life to these individuals. Highlight this treatable symptom that could have a great impact in an untreatable disease so far is our goal to follow this research.


Keywords: CMTR, Pain

Grant Support: None.
**Poster 151**  

**Phosphor proteomic studies in DI-CMTC**  

**Maria-Luise Erfurth**, Eline Celis, Jurgen Van Den Heuvel, Albena Jordanova  

*VIB, University of Antwerp, Antwerp, Belgium*

Aminoacyl-tRNA synthetases (ARS) are the largest family of proteins implicated in Charcot-Marie-Tooth disease (CMT), the most common inherited peripheral neuropathy. ARS are ubiquitous essential enzymes normally required for protein biosynthesis. However, in neurodegeneration a distinct unknown cellular mechanism appears to be at work. We have established *Drosophila* and human cellular models to study the tyrosyl-tRNA synthetases (YARS$^{CMT}$) causing Dominant Intermediate CMT type C (DI-CMTC). Based on data obtained from a genetic modifier screen in *Drosophila* we performed differential phosphor-proteomic analysis of neuroblastoma (SH-SY5Y) cells stably expressing YARS$^{CMT}$. We identified a total of 16 differentially expressed and 54 differentially phosphorylated proteins in the presence of YARS$^{CMT}$ mutations compared to expression of wildtype YARS. The CMT phosphor-signature overlapped with six candidate modifiers already identified in the genetic modifier screen in *Drosophila*. Reactome analysis connects the affected phosphor-proteins to pathways involved in gene expression and diseases of signal transduction while GO-term analysis places them into several neuronal compartments including axon, membrane bound vesicles and cell junctions. Our preliminary findings suggest a putative link between the function of tyrosyl-tRNA synthetase and phosphor-signaling in neurodegeneration, linking DI-CMTC with a novel class of druggable molecular players.

**References:** None.

**Keywords:** Other

**Grant Support:** This study is supported by the Research Foundation Flanders based on a postdoctoral fellowship and a KAN-grant awarded to MLE.
Clinical practice guidelines for children with Charcot-Marie-Tooth disease (CMT) are being developed as part of an international effort to standardise care. The availability and incorporation of guidelines is important for clinical care and clinical trial readiness in this rare disease. The evidence based guideline development process included systematic literature reviews across 10 clinical questions, Delphi methodology to generate consensus where evidence did not exist and application of the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) approach to evaluate the body of literature. Three types of guideline recommendations were generated; evidence based recommendations were generated from the systematic literature reviews of the 10 clinical questions. Most of the remaining recommendations were consensus based. Despite the lack of evidence, a rigorous consensus process and guideline method (GRADE) was utilised. In anticipation of large-scale randomised controlled trials for CMT, these clinical practice guidelines will inform best practice management of children with CMT.

References: None.

Keywords: CMTR

Grant Support: None.
Synovial Sarcoma of the Median Nerve in a Pediatric Patient: A Case Report

Robert Allman, Yifan Guo, Richard Zeri

East Carolina University, Brody School of Medicine; Vidant Medical Center, Greenville, NC, USA

Synovial Sarcomas account for nearly 10% of all soft tissues sarcomas. Extremities are the most common site of origin but these tumors have been known to arise from alternative sites such as the heart, lung, and small intestines. In the rarest of occasions the tumors may arise from peripheral nerves. Rarer still is an intraneural synovial sarcoma seen in the pediatric male population. We describe a case in which a synovial sarcoma was found on the median nerve of the right hand of a 15 year old male. The patient presented to the clinic with an enlargement of a right hand lesion located at the base of the thenar eminence. The patient subsequently underwent a MRI of the hand which showed a median nerve lesion measuring 6 x 4 cm. The patient was then taken for excision of the tumor with the plastic surgery team and it was successfully removed under microscopic magnification. The final pathological report showed a monophasic synovial tumor and FISH positive for SS18 gene rearrangement. Immunohistochemistry was for positive for TLE1 (transducin-like enhancer-1) and focal S100 expression. Given positive margins of the specimen the patient was referred to the medical oncologist for further treatment with chemotherapy and radiation, according to ARST1321, Regimen A. The patient’s follow up MRI 1 year later showed no disease recurrence and he had full motor and sensation function in the effected hand. In conclusion, this case is notable for rarity of disease, anatomical location and patient population. There have only been 23 cases of intraneural synovial tumors and only 5 of those cases involved the median nerve. Of those 5 cases two of the patients were under the age of 18.


Keywords: Human Genetics, Other

Grant Support: None.
Diabetes is a risk of ischemic stroke (IS), ischemic heart disease (IHD) and diabetic foot (DF); however, it is obscure if the diabetic neuropathy (DN) is a risk of eventual death (EV). We then conducted a 5-year prospective study on development of DF, IHD, IS, and EV by using the severity grading system of distal symmetric DN by nerve conduction study (NCS) of the lower limb: sensory NCS of the sural nerve and motor NCS of the tibial nerve. The system is now widely utilized in Japan under the name of Baba’s DN classification (BDC). The BDC has five stages; BDC-0 (normal): no NCS abnormality, BDC-1 (mildly abnormal): presence of any delay in MCV, SCV, F-wave latency, BDC-2 (moderately abnormal): fall in sural SNAP amplitude less than 5µV, BDC-3 (severely abnormal): fall in plantar-CMAP amplitude to 2-5mV, BDC-4 (ultimately abnormal): fall in plantar-CMAP less than 2mV (Jpn J Clin Neurophysiol 2013; 41:143-150). We carried out NCS in 286 patients in between 2007 and 2012, and categorized them by BDC and followed them five years or until premature EV. In results, there was no EV from NSC-0, -1, and -2 groups (n=133), while three from NCS-3 group (n=32) and two from NCS-4 group (n=21) were found dead unexpectedly, or died of sepsis after serious foot infection. Any of EV, DF, IHD and/or IS happened as follows; NCS-0: 0%, NCS-1: 3%, NCS-2: 24%, NCS-3: 53%, NCS-4: 57%. In conclusion, the risk of EV was extremely high in patients with severe somatic DN, and the incidence of DN-related foot and vascular events increased in parallel with the BDC severity. NCS is a useful test to evaluate of the risk of life-threatening events of DN.
Poster 155

A Prospective Study of Neuropathic Symptoms Preceding Clinically Diagnosed Diabetic Polyneuropathy: ADDITION-Denmark

Signe Andersen¹, Laura Määttä², Daniel Witte³, Lasse Bjerg⁴, Marit Jørgensen⁵, Troels Jensen⁶, Morten Charles⁷

¹Danish Pain Research Center, Department of Public Health, Aarhus University, Aarhus, Denmark, ²Danish Pain Research Center, Department of Clinical Medicine, Aarhus University, Aarhus, Denmark, ³Department of Public Health, Aarhus University, Aarhus, Denmark, Danish Diabetes Academy, Odense, Denmark, Aarhus, Denmark, ⁴Department of Public Health, Aarhus University, Aarhus, Denmark, ⁵Steno Diabetes Center Copenhagen, National Institute of Public Health, University of Southern Denmark, Denmark, Copenhagen, Denmark, ⁶Danish Pain Research Center, Department of Neurology, Aarhus University Hospital, Aarhus, Denmark, Aarhus, Denmark, ⁷Department of Public Health, Research Unit of General Practice, Aarhus University, Aarhus, Denmark, Aarhus, Denmark
Introduction

To evaluate prospectively if diabetic polyneuropathy (DPN) follows the prevailing hypothesis for the course of nerve-fiber affections with progression from pure small nerve-fiber- via mixed nerve-fiber- to pure large nerve-fiber affection.

Methods

Repeated assessments of nerve-fiber specific symptoms were obtained in 518 participants of the ADDITION-Denmark study from the time of a diagnosis of type 2 diabetes by screening using specific items of the Michigan Neuropathy Screening Instrument questionnaire. DPN was clinically assessed after 13 years of diabetes fulfilling Toronto criteria for confirmed DPN. The course of symptoms reflecting dysfunction of specific nerve-fibers was evaluated and the association between symptoms and DPN after 13 years was estimated using logistic regression models.

Results

An overall stable, yet heterogeneous course of symptoms was seen during 13 years. According to the hypothesis of symptoms progression, 205 (40,4%) participants remained free of symptoms, 50 (9,9%) had stable symptoms, 124 (24,5%) progressing symptoms and 128 (25,2%) participants improved in symptoms. Cross-sectional estimates showed a higher risk of DPN (ORs between 1.7 and 3.8) for participants with mixed nerve-fiber symptoms compared to participants without symptoms. Moreover, a gradient for higher risk of DPN was seen by progressing symptoms.

Conclusions

No evidence was seen for the hypothesis of the course of nerve-fiber affections in DPN as reflected by specific symptoms from the time of a screening-based diagnosis of type 2 diabetes during 13 years. However, this study provided stronger epidemiological evidence for neuropathic symptoms being prospectively associated with a higher risk of DPN.

References: None.

Keywords: Diabetes

Grant Support: Research reported in this publication is part of the International Diabetic Neuropathy Consortium (IDNC), which is supported by a Novo Nordisk Foundation Challenge Programme (grant number NNF14OC0011633)
Exploratory Study about the Molecular Mechanisms Underlying the Development of Cisplatin-Induced Peripheral Neuropathy

Aina Calls¹, Esther Udina², Roser Velasco³, Xavier Navarro², Jordi Bruna³

¹Intitute of Neurosciences Department of cell Biology Physiology and Immunology Universitat Autònoma de Barcelona, Bellaterra, Spain, ²Institute of Neurosciences Department of Cell Biology Physiology and Immunology Universitat Autònoma Barcelona, Bellaterra, Spain, ³Department of Cell Biology Physiology and Immunology Universitat Autònoma Barcelona, Bellaterra, Spain

Oncologic patients treated with cisplatin often develop a cisplatin-induced peripheral neuropathy (CPIN) that can be treatment limiting. Its pathophyisiology is incompletely understood and the potential role of satellite glial cells (SGC) on its establishment has never been assessed.

In the present study, we perform a single-cell RNA-sequencing (scRNA-seq) of DRG cell populations from CIPN-developing mice to determine which are the main molecular mechanisms involved in the development of this neuropathy.

To induce the neuropathy, cisplatin was intraperitoneally injected once a week at a dose of 7mg/kg until reaching a total cumulative dose of 42mg/kg in 2.5-month-old c-Balb female mice. Nerve conduction studies show a progressive reduction in sensory nerve amplitudes in both digital and caudal nerves along cisplatin treatment, whereas no effects are seen in the motor conductions. On the other hand, cisplatin-treated mice develop mechanical allodynia by means of a progressive decrease in their threshold to mechanical stimuli. Sensory dysfunctions are even worse six weeks after the last cisplatin-administration, fact that suggests a coasting effect, similarly to what is commonly observed in cancer patients treated with platinum drugs. At the end of the treatment, animals receiving cisplatin have similar amount of myelinated nerve fibers in the sciatic nerve and no differences in the density of intraepidermal nerve fibers compared to control animals. In contrast, when analysing DRG neurons by transmission electron microscope, cisplatin-treated mice present large and flat mitochondria, prominent dilatations in their endoplasmic reticulum system, and autophagosome-like vesicles. For the scRNA-seq, DRG from control or cisplatin-treated mice have been isolated. The cell type clusterization has been performed by considering the relative expression of well-known cellular markers. Results of the scRNA-seq are currently under analysis.

References: None.

Keywords: Other

Grant Support: FI-DGR-2016 (AGAUR, Generalitat de Catalunya)
Chemotherapy-induced peripheral neuropathy involves specific cellular targets. The case of Cisplatin, Taxol and Vincristine.

Noelle Callizot, Alexandre Henriques, Clemence Ferrugia, Maud Combes, Philippe Poindron

Neuro-Sys SAS, Gardanne, France

Chemotherapy-induced peripheral neuropathy (CIPN) is the most common side effect caused by the antineoplastic treatment (platinum compounds, vinca alkaloids and taxanes). These side effects (often but not obligatorily irreversible) lead to the reduction, discontinuation or even interruption of the treatment. There are currently no approved treatment or prevention strategies. CIPN preferentially takes place in Dorsal Root Ganglia (DRG), sensory neurons, satellite cells and Schwann cells (SCs). Different underlying mechanisms are proposed to explain CIPN: nuclear DNA damages, altered axonal transport, microtubule changes, ionic channel dysfunctions, modifications of peripheral vascularization, modifications in the Transient Receptors Potentials expression or glutamate signaling, reactive oxygen species production, mitochondrial function impairment, but the primary causes still remain unclear.

Effects of Cisplatin, Vincristine and paclitaxel (Taxol®) compounds were evaluated on rat primary DRG cocultured with SCs. Different culture protocols using a) myelinated sensory neurons (to evaluate the effects on the myelin sheaths) or b) sensory neurons cocultured with non-myelinating SCs (to evaluate the effects on each cell types) were developed. Toxicity of the drugs (applied at different times and doses) was investigated on the neuronal and SC survival, neurite network and myelin sheaths. Using immunostaining method and protein quantification, we showed that each agent displayed a specific neurotoxicity impacting neurite outgrowth (Vincristine and Taxol) or neuronal cell survival (Cisplatin). Specific impairments of SC survival and myelination processes were also observed. Cisplatin first showed a large and massive demyelination followed with neuronal damages; by contrast, Taxol first showed a massive axonal degeneration enhancing a consecutive demyelination whereas a combined effect (myelin/axon) was observed with Vincristine.

Drugs with different chemical structures caused development of peripheral nervous system lesions, which include axonopathy (through dying back axonal damage) and/or neuronopathy (with the involvement of DRG neuronal cell body) associated or not with demyelination.

References: None.

Keywords: Axonal Biology, Schwann Cell, Pre-clinical Studies, Small Fibers, Pain

Grant Support: None.
Should we prevent thrombosis related to Intravenous Immunoglobulin infusions with systematic anticoagulant prophylaxis?

Robin Arcani, Shahram Attarian, Aude-Marie Grapperon, Emilien Delmont

Referral centre for neuromuscular diseases and ALS, hôpital La Timone, Marseille, France

Background: Intravenous immunoglobulins (IVIg) are commonly used for treatment of dysimmunediseases, but they are known to promotethrombotic events. We have compared in this study the thrombosis incidences of patients who received anticoagulant prophylaxis based on personal thrombotic risk and those systematically treated by anticoagulant prophylaxis during IVIg infusions.

Methods: The medical records of patients who received IVIg infusions to treat neuromuscular disorders were retrospectively studied during two periods: the on-demand period (May 2013–January 2015), when patients received anticoagulant prophylaxis based on personal thrombotic risk factors, and the systematic period (May 2015–January 2017), when patients received systematic anticoagulant prophylaxis with low-molecular-weight (LMW) heparin.

Results: Of the 334 total patients included, 19/153 received anticoagulant prophylaxis in the on-demand period, and 181 were treated in the systematic period. In the on-demand period, thrombosis occurred in three patients (3/153, 2%) as one central retinal artery occlusion, one pulmonary embolism, and one brachiocephalic vein thrombosis. In the systematic period, thrombosis occurred in two patients (2/181, 1%), both as pulmonary embolisms. There was no statistical difference in thrombosis incidence between the periods (p = 0.66). The only factor associated with thrombosis was splenectomy (20% versus 0.3% in patients without thrombosis, p = 0.03). There were no adverse events due to thromboprophylaxis by low-molecular-weight heparin in either period.

Conclusion: Systematic thromboprophylaxis with LMW heparin was safe but it did not significantly reduce the incidence of thrombosis versus thromboprophylaxis based on personal thrombotic risk.

Tip: Spaces Around Mathematical Operators: A space is usually inserted on either side of a mathematical operator. This is a stylistic preference followed by many style guides.

References: None.

Keywords: Inflammatory

Grant Support: None.
Poster 159

Contactin-1 connects CIDP and nephrotic syndrome

Janev Fehmi¹, Stephen Keddie², Staffan Persson³, Emilien Delmont⁴, Andrea Cortese⁵, Alexander Davies⁶, Alan Salama⁷, Marilina Marilina Antonelou⁸, Aisling Carr⁹, Lunn Michael⁵, David Bennett⁶, Luis Querol¹⁰, Simon Rinaldi⁸
Introduction

Although rare, the link between demyelinating neuropathies and nephrotic syndrome has been previously reported in a number of case reports. We herein describe a series of 12 patients, who all demonstrate a shared association between CIDP, nephrotic syndrome and contactin-1 (CNTN1) antibodies. We present the key clinical characteristics of this patient cohort, and evaluate the hypothesis that CNTN1 is the common antigenic target in both peripheral nerve and kidney.

Case series

A predominantly male patient cohort present with a subacute onset of proximal and distal sensorimotor symptoms in a non-length dependent pattern. Pain, ataxia and tremor are among the most frequent atypical features observed in individual patients. Two patients experienced abdominal bloating, in one resulting in abdominal weakness, which upon EMG demonstrated considerable spontaneous activity indicating severe active denervation of the rectus abdominis. The remainder of neurophysiological findings were consistent with a demyelinating sensorimotor radiculoneuropathy with early axonal loss.

Serology confirmed high titre antibodies against CNTN1 in all cases. When renal biopsy was performed this invariably demonstrated membranous glomerulonephritis (MGN) as the cause of nephrotic syndrome, with extensive immunoglobulin and complement deposition.

All patients were treated with corticosteroids, with variable response, and most required at least 3 further immuno-suppressive or -modulatory treatments to achieve a good outcome, in both neurological and renal disease.

Discussion

This group of patients add to our existing understanding of the anti-CNTN1 clinical spectrum. Importantly they also provide an opportunity to investigate the common pathophysiological mechanism linking demyelinating neuropathies and nephrotic syndrome. We propose CNTN1 is a shared antigenic target subject to antibody mediated attack in both peripheral nerve and glomerular membranes within the kidney. This has important implications, both in the systemic assessment of patients with demyelinating neuropathies, as well as initiating prompt and appropriate treatment to prevent irreversible nerve and kidney damage.

Keywords: Inflammatory, Node

Grant Support: Guarantors of Brain GBS/CIDP Foundation
Poster 160

Effects of Intravenous Immunoglobulin (IVIG) on Cardiovascular Function, Cytokines and Complement Activation in Cynomolgus Monkeys

Ann Fancher¹, Jessica Whritenour², Allyson McGuinty², William Reagan², Declan Flynn², Jay Janz¹, Joseph Brady², Siddhartha Bhatt²

¹Pfizer Inc, Cambridge, MA, USA, ²Pfizer Inc, Groton, CT, USA

Intravenous immunoglobulin (IVIG) is an effective treatment for inflammatory neuropathies, particularly chronic inflammatory demyelinating polyneuropathy (CIDP). Despite its widespread use, clinical and nonclinical effects of IVIG on important safety endpoints such as cardiovascular function, cytokine production and complement activation are not well described in the literature. Therefore, the current study was conducted to evaluate the potential effects of IVIG on arterial blood pressure; heart rate; electrocardiogram (RR, PR, QRS, QT, and corrected QT (QTc) intervals); body temperature; and physical activity in conscious unrestrained, telemetry-implanted male cynomolgus monkeys. Pharmacokinetics (PK), biomarkers (cytokines and complement activation products), and clinical pathology (hematology, coagulation, and clinical chemistry) were also evaluated. Monkeys (N=4/group) received vehicle or 100, 500, or 1000 mg/kg of IVIG, administered via stepped intravenous infusion. These doses were selected based upon the approved clinical doses and recommended infusion rates of IVIG for the treatment of CIDP. All doses were tolerated and no IVIG-related clinical observations or body weight changes were observed. IVIG-related cardiovascular effects were limited to increased heart rate (+10 to 14 bpm) and corresponding decreases in RR and QT intervals in the 1000 mg/kg dose group. There were no effects on QTc interval. IVIG-related, non-dose-dependent increases in the serum concentrations of IL-1RA, IL-6, IL-10, IL-12/23p40, and IL-13 were observed following administration of doses ≥500 mg/kg. Peak increases (compared with predose values) ranged from 3.3x-46.2x (IL-1RA), 3.1x-41.7x (IL-6), 2.2x-8.5x (IL-10), 7.5x-22.3x (IL-12/23p40), and 2.3x-19.9x (IL-13). No changes in complement activation products (C3a, C4a, Bb, or sC5b9), hematology or coagulation parameters were observed. Systemic exposure increased in an approximately dose-proportional manner and was comparable to published human exposure. In conclusion, IVIG administration at clinically relevant doses produced increases in heart rate and cytokine release.

References: None.

Keywords: Pre-clinical Studies, Inflammatory

Grant Support: None.
Neuromuscular complications following target therapy in cancer patients: beyond Immune Checkpoint Inhibitors.

Chiara Demichelis¹, Caterina Lapucci², Angela Zuppa¹, Stefano Grisanti², Carlo Genova³, Paola Queirolo⁴, Angelo Schenone², Marina Grandis², Luana Benedetti²

¹DINOGMI, University of Genova and Policlinico San Martino, Genova, Italy, ²DINOGMI, University of Genova and Policlinico San Martino, Genova, Italy, ³Lung Cancer Unit, Policlinico San Martino, Genova, Italy, ⁴Oncologia Medica 2, Policlinico San Martino, Genova, Italy

In the last years, many new drugs have been developed targeting different oncology pathways, overall improving both quality of life and survival in several malignancies. However, the increasingly widespread use of these therapies is associated with novel toxicities, mainly immune-related adverse events (irAEs). Different irAEs are now well characterized and, among them, neuromuscular complications following immune checkpoint inhibitor (ICPi) therapy are increasingly studied. However, there are also neurologic complications related to the use of other targeted therapies, less known and probably underestimated. Herein we describe four oncological patients who developed neuromuscular diseases after administration of different targeted therapies, who came to our observation in the last few months. The first two patients were treated with Nivolumab and Ipilimumab, both monoclonal antibodies targeting the immune checkpoint molecules programmed cell death protein-1 (PD1) and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), respectively. The first patient, treated for lung adenocarcinoma, developed myasthenia gravis, with high-titre positivity of AChR-Antibodies; the second one, affected by mesothelioma, developed dysphagia, dysphonia, dysautonomia and progressive respiratory failure. The neurophysiological study was suggestive of Lambert-Eaton Syndrome. The third and the fourth patients were not treated with ICPi, or other monoclonal antibodies. The former, a woman with a melanoma, was treated with the association of Vemurafenib and Cobimetinib, BRAF and MEK inhibitors, respectively. She developed a sub-acute axonal motor neuropathy, with predominant cranial nerve involvement. The latter, a man with a gastrointestinal stromal tumour (GIST), received therapy with Imatinib, tyrosine kinase inhibitor and precursor of the targeted therapy. He developed head drop, dysphagia and respiratory failure. AChR-Antibodies showed high-titre positivity. In conclusion, we strengthen the relevance of neuromuscular complications in patients treated not only with the latest ICPi, but also with “older” and apparently better-known targeted therapies; in both cases consequences can be life-threatening, if not promptly managed.

References: None.

Keywords: Inflammatory

Grant Support: None.
Multicenter Study Investigating the Association of GBS with Flavivirus and other Arbovirus in Asia-organizational challenges.

Sherwin Joy Agustin¹, Umapathi Thirugnanam¹, Ivy Lai Lim Yip¹, Thashi Chang², Ohnmar Ohnmar³, Monica Saini⁴, Lisa Ng⁵, Hugh Willison⁶, Bart Jacon⁷, Neelika Malavige⁸, Terrence Thomas⁹, Surat Tanprawat¹⁰, Sara Khan¹¹, Hoang Nghia¹², Le Trung Hieu Nguyen¹³, Say Saysavath¹⁴, S Somchit Vorachit¹⁵, Moe Moe Zaw¹⁶, Meenakshi Bhattacharya¹⁷, Prafulla Shembalkar¹⁸
Anecdotal reports of doctors working in South and South-East Asia (S SEA) report that diarrhea associated Guillain-Barre Syndrome (GBS) is infrequent and cases increase after rainy season when Arbovirus carrying mosquitoes breed. Zika Virus could also be endemic in this region where it was described first in 1950s. The primary objective is to study if Flavivirus and other Arbovirus are important pathogens in the development of GBS in S SEA. Our secondary aim is to help, through this collaborative work, improve diagnosis and care of GBS patient to international evidence-based standards in under resourced parts of Asia. This is a multicenter study involving hospitals in Singapore, Myanmar, Laos, Vietnam, Thailand, Pakistan, Sri Lanka and India. It has a cooperative affiliation with Zika-IGOS (ZIKA -international Guillain-Barre Syndrome Outcome Study) and funded by International GBS-CIDP foundation and BMRC A*STAR Singapore. Study involves examining GBS patients, hospital and community controls for evidence of recent flavivirus and arbovirus infection using various microbiological assay that account for confounding cross and co-infections. The challenge of obtaining Institutional Review Board approvals and cross border legal contracts from various centres has continued to result in considerable delay. We only started recruitment from December 2017. To date we have a total of 46, 25, 16 patients from Sri Lanka, Singapore and Myanmar respectively. The rest are still struggling with various organizational and logistic obstacles. Another major impediment is inadequate funding. The central fund of USD 50,000 is largely used to facilitate transport and storage of specimens. Each center therefore has to find additional funding to support local work. Working with multiple countries has the advantage of facilitating recruitment of diverse patients relatively quickly but increases administrative complexity exponentially. Ongoing challenges include the maintenance of data accuracy and sustaining the commitment of the collaborators.


Keywords: Inflammatory, Pre-clinical Studies, Clinical Trials

Does F chronodispersion reflect the conduction variability of the motor neurons?

Elisabeth Chroni¹, Alexandros Tzanos², Dimitra Veltsista¹

¹University of Patras, Medical School, Patras, Greece, ²University Hospital of Patras, Medical School, Patras, Greece

Introduction: It is widely accepted that F-waves of shorter latency are generated by large, fast conducting neurons, while those of longer latency by small, slowly conducting neurons. This view has been questioned by researchers, who proposed that the latency range (F chronodispersion) could also be explained by an unequal delay along the distal neural branches, depending on the distance of each motor unit from the recording electrode. To investigate this issue, we recorded F-waves from a distal and a proximal site of the same nerve. The classical view will be justified if F chronodispersion is lower at proximal stimulation, where conduction along shorter distances is estimated. Methods: Ten healthy volunteers (aged 27.6±4.1, 5 females) participated in this study. Forty consecutive stimuli were applied to the ulnar nerve at the wrist and elbow and to the peroneal at the ankle and knee. F-waves minimum and maximum latencies (Flatmin, Flatmax) were measured and corresponding conduction velocities (FCVs) were estimated by the formula: FCVx=(2*Distance/Flatmin-Mlat-1) *[Flatmin/(Flat-x-1)], where x=each F-wave. Results: For the ulnar nerve, F chronodispersion, i.e. Flatmax-Flatmin, was significantly shorter at the elbow (mean±sd 2.5±0.7) as opposed to the wrist (3.8±1.0 paired t-test, p= 0.003); likewise for the peroneal, F chronodispersion was shorter at the knee (3.7±1.7) vs the ankle (5.3±2.2, p=0.05; 38-50m/s). Conclusion: Our findings showed that F chronodispersion values depend on stimulation site, being lower at proximal stimulation. It is a reliable measure of motor neuron conduction properties. Moreover, FCVs where faster along proximal parts a finding similar to M-response CVs.

References: None.

Keywords: Other

Grant Support: N/A
Safety and Tolerability of panzyga® (human normal immunoglobulin - IVIG) in Patients with CIDP

Steven Baker¹, Lidia Cosentino², Elisabeth Clodi³

¹McMaster University, Hamilton, Canada, ²Octapharma Canada Inc, Toronto, Canada, ³Octapharma PPG, Vienna, Austria

IVIG has been a mainstay of therapy for CIDP over the last two decades. IVIG has been shown to be generally well tolerated and easy to administer. Gammatrack, a post-marketing surveillance study was designed to obtain data on long-term safety of IVIG and SCIG products in patients with various indications in routine clinical practice in Canada since their introduction through Canadian Blood Services and Hema Quebec through national tenders. This interim data analysis of the ongoing study describes the safety of panzyga® in CIDP patients at a large, adult, teaching, tertiary referral, neuromuscular center in Canada. As this is a non-interventional study, the dose, frequency and duration of treatment was at the discretion of the treating physician. Patient data, treatment modalities and adverse drug reactions (ADR) were recorded. Disease status was recorded at each visit as either improved, maintained or deteriorated. A total of 11 patients (3 women, 8 men) with a confirmed diagnosis of CIDP were enrolled in the study and were between 47 and 76 years (mean 59.9). The majority (72.7%) of patients had moderate disease. The mean total dose was 0.9 g/kg bodyweight every 4 weeks (median interval). A total of 78 infusions were administered with a mean dose of 87.3 g per infusion. The median maximum infusion rate was 4.8 ml/kg/h, however the reported maximum infusion rate was 10.1 ml/kg/h. Disease status was reported as improved at 10 visits, as maintained in 64 visits and had deteriorated at 3 visits. From the 78 infusions administered, a total of 15 individual case safety reports including 30 ADRs were collected. Headache followed by fatigue were the most commonly reported ADRs. All ADRs were assessed as non-serious. Our findings confirm panzyga® as a safe, well-tolerated and effective therapy for patients with CIDP in routine clinical practice.

References: None.

Keywords: Inflammatory

Grant Support: Gammatrack is an Octapharma sponsored Non-Interventional Study.
Objective: Multifocal motor neuropathy (MMN) is an inflammatory neuropathy, characterized by IgM antibodies directed at the glycolipid GM1 with largely unknown etiology. A previous study showed an association with the DRB1*15:01 allele. We aimed to explore the association between MMN and the HLA-class II DRB1, DQB1 and DQA1 loci in depth.

Methods: We performed high-resolution HLA-class II typing for the DRB1, DQB1 and DQA1 loci in 126 well-characterized MMN patients and assessed disease associations with haplotypes. We used a cohort of 1305 random individuals as a reference for haplotype distribution in the Dutch population. MMN associated haplotypes were correlated to detailed clinical parameters.

Results: The DRB1*15:01-DQB1*06:02 haplotype (probably as an extended haplotype including the HLA-DQA1*01:02 allele) (OR 1.6 (95% CI 1.1-2.2), p <.05) and the DRB1*12:01-DQB1*03:01 haplotype (probably as an extended haplotype including the HLA-DQA1*05:05 allele) (OR 2.7 (95% CI 1.2-5.5), p<.05) were more frequent in patients with MMN. These haplotypes were found in 46% of patients and were not associated with MMN disease course or response to treatment.

Conclusion: Multifocal motor neuropathy is associated with the DRB1*15:01-DQB1*06:02 and DRB1*12:01-DQB1*03:01 haplotypes. These HLA molecules or gene variants in their immediate vicinity may promote inflammation underlying MMN.

References: None.

Keywords: Inflammatory, Human Genetics

Grant Support: None.
Guillain-Barré syndrome (GBS), an immune-mediated polyneuropathy, is the most common cause of acute flaccid paralysis in children. The aim of our study was to identify the clinical, laboratory, imaging, and electrophysiological features of pediatric patients, as well as management and outcomes. This retrospective chart review includes 40 patients with GBS at a tertiary academic children’s hospital from 2012 to 2018. The race/ethnicities represented were Hispanic (55%), Caucasian Non-Hispanic (27.5%), African-American (10%), Indian (5%), and other (2.5%). The most frequent initial presenting complaint was gait change (56%) followed by pain (26%). Initial physical exam findings included hyporeflexia/areflexia (84%), weakness (71%), and inability to ambulate (59%). EMG/NCS was performed for 73% of patients, revealing AIDP in 48% and an axonal variant in 31%. Of those with an axonal variant, 80% were Hispanic compared to 10% Caucasian. Those diagnosed with AIDP were 50% Hispanic and 36% Caucasian. For treatment, 57% of patients received IVIG, 27% plasma exchange (PLEX), and 16% a combination of both. Patients admitted to the PICU or who required mechanical ventilation were more likely to be treated with PLEX or IVIG/PLEX combination as opposed to IVIG (p=0.002 and p=0.037, respectively). The Hughes Functional Grading Scale (HFGS) was used to categorize severity of illness. There was a statistical difference in HFGS score at presentation, nadir of illness, and discharge with regards to treatment, as patients with higher scores were more often treated with IVIG/PLEX combination. After discharge, 63% of patients exhibited a return to baseline strength at follow up in clinic, with no statistical difference in median length of time between groups. However, recovery time was longest for Hispanic patients, those with an axonal variant, and patients treated with IVIG/PLEX combination. These results add to our knowledge and understanding of the pediatric GBS population in a diverse region of the U.S.


Keywords: Inflammatory

Grant Support: None.
**Poster 167**

**Rituximab for treatment of treatment resistant chronic inflammatory demyelinating polyradiculoneuropathy: a retrospective chart review**

Mazen Dimachkie, Matthew Varon, Duaa Jabari, Constantine Farmakidis, Omar Jawdat, Melanie Glenn, Jeffrey Statland, Richard Barohn, Mamatha Pasnoor  

*The University of Kansas Medical Center, Kansas City, KS, USA*

**OBJECTIVE:** To evaluate the therapeutic response to rituximab in patients presenting with treatment-resistant CIDP.

**BACKGROUND:** Several case reports and small observational studies have demonstrated variable efficacy of rituximab for treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

**METHODS:** Retrospective chart review was performed on the patients who presented to the neuromuscular clinics with CIDP and received rituximab for this diagnosis. Demographic and clinical information was obtained. Baseline and post treatment MRC sum score, inflammatory neuropathy cause and treatment (INCAT) disability score, and modified Rankin score (mRS) were retrospectively inferred from data available in the chart.

**RESULTS:** A total of 5 patients (2 males and 3 females; age range 36 to 72) were identified who had received rituximab for treatment of CIDP in our neuromuscular database. These have been previously treated with multiple therapies without adequate clinical response. The median number of prior therapies was three; including corticosteroids, mycophenolate mofetil, IV immune globulin, azathioprine, and plasma exchange. Three patients received rituximab for management of chronic symptoms of CIDP. Two patients received rituximab infusions while admitted for acute symptomatic exacerbation. Three of five patients demonstrated robust improvement in response to rituximab. Average MRC sum score increase was 22 (range 0-60), average decrease in INCAT was 3.2 (range 2-6), and median mRS decreased from 3 to 2 over follow up period of 9 to 24 months.

**CONCLUSIONS:** Rituximab may be a treatment option for patients with CIDP whose symptoms are refractory to more conventional treatments.

**References:** None.

**Keywords:** Inflammatory, Other

**Grant Support:** None.
Poster 168

Nerve Conduction Studies in Patients Included in the International Guillain-Barré Syndrome Outcome Study (IGOS).

Samuel Arends1, Judith Drenthen1, Peter Van den Bergh2, David Cornblath3, Hessel Franssen4, Robert Hadden5, Badrul Islam6, Bart Jacobs1, Satoshi Kuwabara7, Ricardo Reisin8, Nortina Shahrizaila 9

1Erasmus MC University Medical Center, Rotterdam, Netherlands, 2University Hospital St-Luc, Brussels, Belgium, 3John Hopkins University School of Medicine, Baltimore, USA, 4Utrecht University Medical Center, Utrecht, Netherlands, 5King's College Hospital, Maidstone Hospital, London, United Kingdom of Great Britain and Northern Ireland, 6International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh, 7Chiba University Hospital, Chiba, Japan, 8Hospital Britanico, Buenos Aires, Argentina, 9University of Malaya Medical Centre, Kuala Lumpur, Malaysia

Introduction

Nerve conduction studies (NCS) are helpful in diagnosing, subtyping and prediction of outcome of Guillain-Barré syndrome (GBS). Previous studies of NCS in GBS have been of limited value due to small patient numbers, single country studies or absence of long-term clinical follow-up. In IGOS, a large number of NCS data from all over the world is available in combination with clinical and serological data. The aim of this study is to analyze these data in relation to the NCS reference values used and to describe the NCS characteristics and subtypes of GBS.

Methods

In the first 1562 patients included in IGOS, 1035 (66%) underwent at least one NCS. For the current study we selected 955 adult patients. NCS characteristics were analyzed based on published reference values and compared with local reference values. Patients were classified according to Hadden criteria (1998).

Results

Median timing of NCS after onset of disease was 10.0 days (0 - 114). The peroneal nerve was most often tested of all motor nerves (1196 times, 892 patients). Using published reference values, the NCS were classified as axonal in 10.3%, demyelinating in 49.3%, equivocal in 32.7%, inexcitable in 2.7% and normal in 5.0%. With Hadden criteria, a prolonged distal motor latency of the median nerve was the most frequent demyelinating feature (right 40.0%, left 34.9%). When both sural and sensory median nerve were investigated, 18.0% of patients showed a sural sparing pattern. These preliminary results will be compared to GBS classification based on local reference values and will be presented at the conference.

Conclusions

IGOS provides electrophysiological data from a large international cohort of patients that will be used to determine the influence of reference values on the electrodiagnosis of GBS as well as to optimize the utility of NCS in the diagnosis and prognosis of GBS.

References: None.

Keywords: Inflammatory

Grant Support: -
Serbian validation of the I-RODS questionnaire in patients with chronic inflammatory demyelinating polyneuropathy

Ivo Bozovic1, Stojan Perić1, Marielle HJ Pruppers2, Milutin Petrović3, Aleksandar Stojanov4, Gordana Djordjević4, Bogdan Bjelica5, Zorica Stevic1, Ivana Basta6, Catharina G Faber7, Ingemar SJ Merkies8

1Neurology Clinic, Clinical Center of Serbia, Belgrade, Serbia, 2University Medical Center Utrecht, Utrecht, Netherlands, 3Neurology Clinic, Clinical Center of Kragujevac, Kragujevac, Serbia, 4Neurology Clinic, Clinical Center of Nis, Nis, Serbia, 5School of Medicine University of Belgrade, Belgrade, Serbia, 6Neurology Clinic, Clinical Center of Serbia, Beograd, Serbia, 7Maastricht University Medical Centre, Maastricht, Netherlands, 8University Hospital Rotterdam, Rotterdam, Netherlands

Background: I-RODS seems to be a valid activity measure for use in clinical trials in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Our aim was to translate and validate the I-RODS for use in CIDP patients from Serbia.

Patients and Method: Study comprised 83 patients diagnosed with CIDP. I-RODS was translated and cross-culturally validated using standard guidelines. Following scales were also administered: MRC sum score, INCAT sensory and disability scores, Krupp’s Fatigue Severity Scale, Beck Depression Inventory and Visual Analogue Scale for pain.

Results: According to I-RODS, significant proportion of our patients reported that “running” (51%), “dancing” (41%) and “standing for hours” (40%) were impossible tasks to perform, while “teeth brushing” (94%), “eating” (88%) and “reading a newspaper/book” (82%) were noted as the easiest items. Patients with more muscle weakness (lower MRC sum score) and more severe INCAT sensory score had lower I-RODS score (p<0.01). Also, patients with fatigue, depression and pain had lower I-RODS scores (p<0.01). I-RODS score in patients with INCAT disability score ≤1 was 78±19 compared to 51±30 in patients with INCAT >1 (p<0.01). I-RODS score correlated with total SF-36 score (rho=+0.73, p<0.01), as well as with all domain scores.

Conclusion: Serbian version of I-RODS seems to be a valid activity measure for use in CIDP patients. I-RODS was able to assess different levels of disability, it was in association with impairment measures, INCAT disability scale and quality of life.

References: None.

Keywords: Inflammatory, Other

Grant Support: None.
Poster 170

Role of Comorbidities on Clinical Presentation, Treatment Choice, Response to Treatment and Disability in CIDP.
Only few studies investigated the role of comorbidities in CIDP, and little is known on their frequency, impact on treatment choice, disability, quality of life and treatment response. This information could be useful to tailor treatment choice on the individual patient and to better understanding eligibility requirements of clinical trials in CIDP. We used the data from a web-based database of Italian patients with CIDP to determine the frequency of different comorbidities in this condition, their impact on the outcome, treatment choice and treatment response. Using a structured questionnaire we collected information related to demographic and clinical data and comorbidities. By January 2019, 404 patients with a diagnosis of CIDP according to the EFNS/PNS criteria were included. We collected data on co-morbidities from 393 of these patients. One or more co-morbidities were reported by 302 patients (77%) including hypertension (36%), thyroid disorders (16%), other immune diseases (15%), or diabetes (12.5%). One or more co-morbidities influenced the choice of treatment in 48% of the patients. Only diabetes and monoclonal gammopathy somehow influenced the course of CIDP: patients with diabetes had lower MRC sumscore (p=0.0481), higher disability by INCAT (p=0.0046) and I-RODS (p=0.0017), worse QoL (p=0.0029), and lower response rate to treatment (p=0.0022), while patients with IgM but not IgG or IgA monoclonal gammopathy had higher disability by INCAT (p=0.0293). More patients with motor CIDP had IgM monoclonal gammopathy (p=0.0344) compared to patients with typical CIDP. Patients with pure sensory CIDP more frequently had other immune diseases (p=0.0173) compared to patients with typical CIDP. Co-morbidities are frequent in patients with CIDP and in almost 50% of the patients they may influence the choice of treatment. Only diabetes and IgM monoclonal gammopathy appeared to have an impact on disease severity or clinical presentation and diabetes appeared to influence the response to therapy.

References: None.

Keywords: Inflammatory, Diabetes, Other

Grant Support: Regione Lombardia, Italy Kedrion Biopharma (Italy) CSL Behring (Italy) Humanitas Clinical and Research Institute (Milan, Italy) GBS-CIDP Foundation International (USA)
Economic Evaluation Of Subcutaneous Vs Intravenous Immunoglobulin Therapy In Chronic Inflammatory Demyelinating Polyneuropathy: Real Life Study

Bernardo Maria De Martino¹, Francesco Tuccillo¹, Eugenia Piscitelli², Marida Massa², Carmela Simona Serio², Gaspare Guglielmi³, Francesco Habetswallner⁴

¹UOC Neurophysiopathology - AORN A. Cardarelli, Naples, Italy, ²UOC Pharmacy - AORN A. Cardarelli, Naples, Italy, ³Director UOC Pharmacy - AORN A. Cardarelli, Naples, Italy, ⁴Director UOC Neurophysiopathology - AORN A. Cardarelli, Naples, Italy
Background:

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare neurological disorder characterized by progressive weakness, caused by damage to the myelin sheath of the peripheral nerves.

The prevalence of CIDP is estimated to be around 1-8 cases per 100,000 individuals.

Treatment for CIDP includes corticosteroids, plasmapheresis and immunoglobulin (IVIg). IVIg may be used as a first-line therapy and can be very effective but there are drawbacks.

In recent years there has been growing interest in subcutaneous immunoglobulin (SCIG).

Prior researches have suggested that SCIG is equally effective and less expensive than IVIg.

Our department of Neurophysiopathology is recognized by Campania region as a center for the certification and treatment of rare neuromuscular diseases. Our aim is to evaluate cost-efficacy of SCIG VS IVIg in our reality.

Methods

In our study we used:

- AIFA website to examine the prescriptions of IVIG, because in Italy IVIG are intensively monitored by the Italian Medicine Agency using web-based registers.

- SaniArp (the regional health web system) to examine the prescriptions of SCIG.

- So.Re.Sa (the regional purchasing centre) to identify the cost of Immunoglobuline.

- Medical records to know the clinical history of each patient.

- Neurologists’ opinion and hospital statistical sources to identify and quantify the health care and non-health care resources.

Results

13 patients, with CIDP hospital-based IVIG were switched to home-based SCIG.

After one year receiving SCIG, 12 patients reported good outcome. Only one patient after the aggravation of symptoms shifted to IVIG again.

The costs-analysis is based on 1-year time IVIG therapy VS 1-year SCIG.

It includes immunoglobulin, drugs for premedication and complications management, health care services, costs related to self-infusion pump and disposables. Non-health care costs include transport, loss of working days, leisure time for patients and caregivers.

Considering the cost of immunoglobulin, SCIG seems to have the highest economic impact. However, this is offset by the health care and non-health care savings.
References: None.

Keywords: Inflammatory

Grant Support: None.
GD1a/GT1a Ganglioside Complex Antibody in Guillain-Barré Syndrome: Case Report and Studies on the Epitope Formation.

Atsuro Chiba, Takayuki Shiratori, Ayumi Uchibori, Mizuki Ayano, Masanori Nakajima, Chizuko Ooishi, Yaeko Ichikawa
Kyorin University, Tokyo, Japan

[Purpose] Presentation of a case with Guillain-Barré syndrome and a rare anti-ganglioside complex antibody, and a trial study on the mechanism of the epitope formation of the complex antigen. [A case report] A 77-year-old female acutely developed motor weakness with diminished tendon reflexes in her all extremities two weeks after acute pharyngitis with diarrhea. Her cranial nerves, sensory system and respiratory muscles were intact. Nerve conduction studies detected conduction block at first and temporal dispersion in the follow-up. Serum IgG antibody against ganglioside GD1a/GT1a complex was solely positive. She responded to IVIg well, and discharged directly to her home on the 28th hospital day. We assumed that her pathological state was acute motor conduction neuropathy. [Studies on GD1a-GT1a interaction] Idea and methods: In interaction of two molecules, there would be some force between them. In a situation that such two molecules are moving on same medium with respective rates, the interacting force between them would affect the moving rates and mobilities would shift from the intrinsic ones. Based on this idea, we studied interaction between GD1a and GT1a by thin-layer chromatography (TLC). Two gangliosides were applied onto high-performance TLC plates in different points so that one ganglioside which moved faster overtook the other one during development of TLC. After development, the mobilities of the gangliosides were compared between with and without such overtaking. Results: We tried several solvent conditions, but any significant mobility shifts in overtaking condition were observed. However, in TLC-immunostaining with the patient’s serum, positive band was detected in-between point of GD1a and GT1a. Conclusions: Trace of force between the two gangliosides could not be detected in this method, but the formation of complex antigen epitope occurred. As for GD1a/GT1a case, just their presence side-by-side might be enough for the epitope formation, instead of a different structure conformed by interaction.

References: None.

Keywords: Inflammatory

Grant Support: None.
Poster 173

Safety and Tolerability of High Infusion Rates of Intravenous Immunoglobulin in Patients with CIDP

Carolina Barnett¹, Yue Jiang², Hans Katzberg², Christine Heung², Shaber Mannan², Eduardo Ng³, Evelyn Sarpong³, Jafar Shabanpour², Vera Bril²

¹University Health Network, university of Toronto, Toronto, Canada, ²University Health Network, Toronto, Canada, ³University Health Network, Toronto, Canada
Objective: To determine the safety and tolerability of higher infusion rates of Panzyga®, 10% intravenous immunoglobulin (IVIG) in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

Background: IVIG, the first-line treatment for CIDP, is typically infused over 4-5 hours. The long infusion time is inconvenient for patients and increases healthcare costs. Recent studies suggest that rapid infusion can be safe and well tolerated, but there are no prospective data in CIDP.

Design/Method: This is an open-label, prospective study. Patients naïve to IVIG, or those with last infusion over a month before screening, were loaded with 2g/kg IVIG 10% (Panzyga®, Octapharma), over 2 days. All patients received a maintenance dose of 1g/kg every 3 or 4 weeks. In the first 4 infusions, IVIG was infused using standard rates, beginning at 0.01 mL/kg/min up to 0.08mL/kg/min. In patients who tolerated the highest standard rate, infusion rates were increased according to tolerance to 0.10mL/kg/min (infusion 5), 0.12mL/kg/min (infusion 6), and 0.14mL/kg/min (infusions 7-13). We recorded all adverse events during the infusions and during the study period.

Results: We enrolled 25 patients. Up to October 2017, 114 infusions were completed at standard rate, 21 at 0.1 mL/kg/min, 14 at 0.12 mL/kg/min, and 81 at 0.14 mL/kg/min. During the study period, 45 adverse events (non-fatal) occurred in 18 patients. Only 12 adverse events occurred during the infusion: 11 with standard rates and 1 with higher infusion rate. 3 patients withdrew from the study due to adverse events after the loading dose, a fourth due to pneumonia, and a fifth for personal reasons. Complete study data will be analysed and presented at PNS.

Conclusion: Rapid infusion of IVIG (Panzyga®), up to 0.14mL/kg/min, is safe and well tolerated in CIDP subjects. Most adverse events occurred during standard infusion rates, particularly after the

References: None.

Keywords: Inflammatory, Other

Grant Support: Octapharma. clinician-initiated research
Poster 174

Propensity modelling as a means to advance treatment in GBS

Amy Davidson¹, Alex Doet², Christine Verboorn³, Bart Jacobs⁴, Hugh Willison⁵

¹Department of Neurology, Institute of Neurology, Glasgow, United Kingdom of Great Britain and Northern Ireland, ²Department of Neurology, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, Netherlands, ³Department of Neurology, Erasmus MC, University Medical Centre, Rotterdam, Netherlands, ⁴Department of Neurology, Department of Immunology, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, Netherlands, ⁵Institute of Infection immunity and inflammation, University of Glasgow, Glasgow, United Kingdom of Great Britain and Northern Ireland
Introduction

Despite best efforts the treatment of GBS has not evolved in the last 25 years. Attempts at randomised controlled trials are challenging due to the infrequent presentation of patients. Comparative observational studies with patients who have received standard treatment (IVIg or plasma exchange) matched for propensity score could provide first indication for new treatment efficacy. The aim of the study is to build such a propensity model for GBS patients, using recognised prognostic indicators as a basis.

Methods

The International GBS Outcome Study (IGOS) is a prospective observational cohort study designed to collect data on prognostic factors and relevant clinical outcome measures.

Results

Validated data from the first 1300 IGOS patients was selected, with the Bangladeshi cohort excluded currently, due to their marked differences in treatment practice and outcome. Characterisation of cohorts treated with either IVIg (n = 832) or plasma exchange (n=63) has been performed. They have been stratified by GBS disability score at initiation of treatment, modified Erasmus Outcome Score (mEGOS) and Hadden criteria. In the IVIg cohort median disability score was 4, with an mEGOS of 2 and 54% fitted an electrophysiological picture of demyelination. The plasma exchange cohort had a median disability score of 5, with an mEGOS of 9 and 36% demyelination rates. 97% of patients included had treatment started within 7 days. Where repeated treatments were required, repeated IVIg was used most frequently, with plasma exchange rates remaining under 10% even at 3rd round treatment.

Using this information, criteria for propensity scoring have been delineated and we look to report preliminary results at the PNS.

Conclusion

Propensity scoring offers a means to use large observational databases to support therapeutic trials in GBS, and we aim to use the IGOS database and proven outcome criteria to build a model to show this.

References: None.

Keywords: Inflammatory

Grant Support: None.
Introduction

The CIDP spectrum encompasses various different clinical presentations, disease courses, pathophysiological mechanisms and response rates to treatments. To capture the full syndrome, recognize clinically important subgroups and advance to tailored diagnosis and treatment of individual CIDP patients, prospective large cohort studies are needed.

Methods

INCBASE is prospective international web-based modular registry. Newly and previously diagnosed patients with the clinical diagnosis of CIDP will be included.

INCBASE comprises a core module, collecting a minimally required data set of baseline and follow-up data including patient oriented outcome measures. In addition to this core module, individual centers will have the option to include patients in one or more extension modules. Three different extension modules are pre-defined at the start: 1) extensive follow-up module; 2) subcutaneous immunoglobulin module; 3) plasma-exchange/filtration module.

Individual centers will have the option to collect baseline and serial follow-up biomaterials. Data will be entered via a web-based system and (optional) biomaterials will be stored locally. In addition, data from current registries similar to the core module can be deposited in the INCBASE registry. Participating centers will be enabled to export and use their own data, which will aid collaboration between centers. Studies based on the composite data from INCBASE will require approval by the Steering Board.

Future

INCBASE will result in a unique collection of clinical data and biomaterials from a large sample. Expertise centers from various European, American and Asian countries have expressed an interest in participating. The aim of the registry is to optimize the diagnostic criteria, to identify biomarkers of disease activity and treatment response, and to construct prediction models of treatment response and outcome in individual patients. INCBASE will also provide an infrastructure for international and national collaboration in the conduct of therapeutic and other studies in CIDP. First inclusions are expected in July 2019.

References: None.

Keywords: Inflammatory

Grant Support: None.
Multicentre Study Investigating Association of Guillain-Barre Syndrome with Flaviviruses and other Arboviruses in Sri Lanka

Asitha Goonetilleke¹, Thirugnanam Umapathi², Neelika Malavige³, Shashika Dayarathna¹, Laksiri Gomes³, Nicholas Yeo⁴, Jason Kam⁴, Lisa Ng⁴, Thashi Chang⁵

¹Faculty of Medicine, University of Colombo, Sri Lanka, Colombo, Sri Lanka, ²National Neuroscience Institute, Department of Neurology, Singapore, Singapore, Singapore, ³Centre for Dengue Research, University of Sri Jayawardenepura, Sri Lanka, Nugegoda, Sri Lanka, ⁴Singapore Immunology Network, Agency for Science, Technology and Research, Singapore, Singapore, Singapore, ⁵Department of Clinical Medicine, Faculty of Medicine, University of Colombo, Sri Lanka, Colombo, Sri Lanka

The aim of this study is to understand the relationship between Guillain-Barre Syndrome (GBS) and antecedent Flaviviral and other Arboviral infections in South and Southeast Asia. The study involves hospitals in Singapore, Myanmar, Laos, Vietnam, Thailand, Pakistan, Sri Lanka and India. GBS patients, hospital and community controls were examined for recent Dengue (DENV), Zika (ZIKV) and Chikungunya (CHIKV) infections, using various microbiologic assays that account for confounding cross and co-infections. Tests include multiplex real time RT-PCR that differentiates ZIKV, DENV1, DENV2, DENV3, DENV4 and CHIKV; ZCD multiplex that differentiates ZIKV, DENV and CHIKV and single-plex confirmation for ZIKV, DENV and CHIKV. In addition, virion-based ELISA for ZIKV, DENV1, DENV2, DENV3, DENV4, CHIKV and neutralization assays for ZIKV, DENV and CHIKV were done. We present the preliminary data of 32 patients. Three (SL 30, 36, 43) had evidence of recent DENV (DENV 4, 2, 2 respectively) infections by positive PCR tests on sera obtained at 15, 15 and 3 days of GBS onset respectively. SL36 was diagnosed clinically with DENV before developing GBS. SL30 and 36 had raised serum IgM and IgG against DENV (DENV 1, 2, 4). The ZIKV IgM was also positive, likely due to cross-reaction. SL43 only had raised DENV1 IgG only. SL30, 36 and 43 had raised CHIKV IgG but not IgM. SL30 and SL36 showed stronger level of neutralizing activity against DENV then ZIKV. SL43 did not show significant neutralizing activity against DENV and ZIKV. As expected in an endemic region, the cases and controls had evidence of previous exposure to various combinations of ZIKV, DENV and CHIKV. Our preliminary data suggests that DENV may be responsible for only a minority of GBS cases in Sri Lanka. We have yet to find evidence of ZIKV and CHIKV triggering GBS.

References: None.

Keywords: Inflammatory, Schwann Cell, Other

Grant Support: 1) GBS-CIDP foundation 2) Biomedical Research Council (BMRC) 3) BMRC A*STAR-led ZIKA Virus Consortium Fund (Project number: 15/1/82/87/001), Agency for Science And Technology (A*STAR)
Ibrutinib in Neuropathy with Anti-Myelin-Associated Glycoprotein (MAG) Antibody.

Francesca Castellani¹, Andrea Visentin², Marta Ruiz¹, Marta Campagnolo¹, Cinzia Candiotto³, Alessandro Salvalaggio¹, Roberta Bertorelle³, Chiara Brianì¹

¹Department of Neurosciences, University of Padova, Padova, Italy, ²Hematology and Clinical Immunology Unit, Department of Medicine, University of Padova, Padova, Italy, ³Immunology and Molecular Oncology, Veneto Institute of Oncology IOV -IRCCS, Padova, Italy
No adequate immunotherapy has so far been shown to be effective in anti-myelin-associated glycoprotein (MAG) antibody neuropathy.

Recently, the discovery of the mutational profile of the \textit{MYD88} and \textit{CXCR4} genes have radically changed the diagnosis and prognostic evaluation of IgM monoclonal gammapathies.

Namely, \textit{MYD88}^{L265P} has been found to be the most common mutation in Waldenström’s Macroglobulinemia (WM) and IgM-MGUS. Since \textit{MYD88}^{L265P} interacts with nuclear-factor kB (NFkB) signaling, it plays a crucial role in response to ibrutinib, the first-in-class inhibitor of Bruton’s tyrosine kinase. Moreover, WM patients with \textit{MYD88} mutated and \textit{CXCR4} wild-type have been shown to have better and longer response to ibrutinib. Although in anti-MAG neuropathy patients the IgM paraprotein is commonly a MGUS, in a minority of patients it may underscore a lymphoproliferative disorder, mainly WM.

We report on two anti-MAG neuropathy patients treated with ibrutinib.

Patient 1 is a 73-year-old man, with long-history of anti-MAG antibody neuropathy. He had undergone plasma exchange, intravenous immunoglobulins, rituximab with only partial benefits. After symptoms worsening, bone marrow biopsy (BOM) showed WM, with \textit{MYD88}^{L265P} mutated and \textit{CXCR4}^{S338X} wild-type assessed by allele-specific PCR. He started treatment with ibrutinib 420 mg/die. Monoclonal protein and IgM levels decreased from 6.5g/L to 4.0g/L and from 7.2g/L to 5.1g/L, respectively.

Patient 2 was a 80-year-old man, with severe anti-MAG antibody neuropathy. BOM was consistent with WM harbouring \textit{MYD88}^{L265P} and unmutated \textit{CXCR4}. He started treatment with ibrutinib 420 mg/die.

After 4 and 2 weeks of treatment, respectively, patient 1 reported an improvement in sensory symptoms at feet, while patient 2 reported a slight improvement in paresthesia, numbness and also strength improvement at lower limbs. Treatment was well tolerated. These preliminary data point to a possible efficacy of ibrutinib in anti-MAG antibody neuropathy, which is the most common disabling paraproteinemic neuropathy, where active treatment is eagerly needed.


\textbf{Keywords}: Inflammatory

\textbf{Grant Support}: None.
Four-Month Response Rate In Patients With CIDP Treated With intravenous immunoglobulins 5%. The Neurotrack cohort

Jerome FRANQUES¹, Corinne Pottier², Françoise Bouhour³, Vincent Lefebvre⁴, Stephane Beltran⁵, Chafke Belmokhtar⁶, Jean-Charles Crave⁶, Taylor Pindi Sala⁶, Pierre Clerson⁷

¹Private Hospital La CASAMANCE, Aubagne, France, ²Pontoise hospital, Pontoise, France, ³Pierre Wertheimer Hospital, Lyon, France, ⁴Rodez hospital, Rodez, France, ⁵Tours hospital, Tours, France, ⁶Octapharma France, Boulogne-Billancourt, France, ⁷Soladis, Roubaix, France

Purpose

Intravenous immunoglobulins (IgIV) 5% (Octagam® 50 mg/mL) is indicated for the treatment of Chronic inflammatory demyelinating polyradiculoneuropathies (CIDP). The continuation of IgIV treatment is conditioned by the patients response after 4 months. With long-term data being very scarce, NEUROTRACK investigates the efficacy and tolerability of this IVIG in CIDP.

Methods

This prospective, observational, multicenter cohort study plans to enroll 20 adult CIDP patients. Patients with history of immunoglobulin (Ig) therapy could enter the study if the treatment has been stopped for at least 12 weeks. The response was defined by the change in Overall Neuropathy Limitation Scale (ONLS) score ≥ 1 point without concomitant therapy with corticosteroids, other Ig, plasma exchange, rituximab, azathioprine or cyclosporine. The planned follow-up duration is 12 months. Interim results of the first 4 months of IVIg therapy are reported here.

Results

Eighteen patients entered the study so far, of these 15 (mean age 69±13 years, 67% males) have been followed for at least 4 months with response assessment based on ONLS. 11 patients had a typical form of CIDP diagnosed 42±38 months before entry. 5% IVIg was first-line therapy in 4 patients; other patients medical history included treatment with corticosteroids (N=2), plasma exchange (N=2), IgG (N=10, taken for 1.6±2.9 years) or immunosuppressive drugs (N=2). ONLS score was 4.5±2.1 at entry. After 4 months of IVIg treatment at a mean dose of 1.9±0.3 g/kg/every 4.9±1.6 weeks, the response rate (RR) was 60% [95% confidence interval] and ONLS score was 2.9±2.3. Three patients had stopped the treatment for inefficacy (N=2) or poor tolerability (N=1). Adverse events were non-specific and of mild intensity.

Conclusion

In conclusion, treating CIDP patients with a 5% IVIg was well tolerated and associated with a 60% RR 4 months after therapy initiation. Results after 12 months are expected.

References: None.

Keywords: Inflammatory, Clinical Trials, Pain, Schwann Cell, Other

Grant Support: None.
Update of International CIDP Outcome Study (ICOS): a Prospective Study on Predictors of Disease Course

Carina Bunschoten1, Merel Broers1, Bart Jacobs1, Ilse Lucke2, Gwen van Lieverloo2, Sander Bus2, Max Adrichem2, Ludo van der Pol3, Stephan Goedee4, Filip Eftimov2

1Erasmus MC, University Medical Center, Rotterdam, Netherlands, 2Amsterdam University Medical Center, Amsterdam, Netherlands, 3Brain Center Rudolf Magnus, University Medical Center, Utrecht, Netherlands, 4Brain Center Rudolf Magnus, University Medical Center, Utrechts, Netherlands

Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an immune-mediated neuropathy with considerable heterogeneity in clinical presentation, electrodiagnostic features, treatment response and long-term outcome. This heterogeneity may indicate the presence of atypical CIDP variants and CIDP-like disorders with different pathophysiology requiring different treatment strategies, rather than a phenotypical spectrum.

Methods

The International CIDP Outcome Study (ICOS) is a prospective, observational, multicenter study based on the format of the International GBS Outcome Study (IGOS) and currently running in three Dutch academic hospitals. The aim of ICOS is to describe the clinical and electrophysiological variation and to define the clinical and biological determinants of distinct CIDP variants, including disease activity, treatment response and outcome in at least 1000 patients with a minimum follow-up period of 2 years. ICOS also aims to facilitate therapeutic studies and to collaborate with other (international) CIDP registries, including INCbase, and the ICOS protocol has recently been published and available for interested parties. All patients fulfilling the EFNS/PNS 2010 criteria for possible, probable or definite CIDP are eligible for participation in ICOS, independent of age, duration and severity of disease or treatment status. ICOS contains detailed clinical, diagnostic and treatment data, various validated clinical outcome measures and biomaterials (DNA, cerebrospinal fluid and serial serum samples) at standardized time-points.

Results

By February 2019, 179 patients have been included in ICOS (77 incident (43%) and 102 prevalent cases (57%)), with a median age of 60 years at diagnosis (interquartile range (IQR) 51-68 years), and a male predominance (67%). The clinical phenotypes in the ICOS cohort include typical CIDP (70%) and atypical CIDP variants (30%) (asymmetric 20%, predominant motor 5%, sensory 3% or predominant distal involvement 2%). At the conference we will present an update on the ICOS cohort, together with an additional cohort of treatment-naive CIDP patients.


Keywords: Clinical Trials, Inflammatory, Other

Grant Support: None
Poster 180

Phase 3 Study of HyQvia for Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP): ADVANCE CIDP-1 Infusion Protocol

Shabbir Hasan¹, Kim Duff², Andras Nagy³, Leman Yel¹

¹Baxalta US Inc., a Takeda company, Cambridge, MA, USA, ²Baxalta US Inc., a Takeda company, Lexington, MA, USA, ³Baxalta Innovations GmbH, a Takeda company, Vienna, Austria

Introduction: Intravenous immunoglobulin (IVIG), the mainstay of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) treatment, is limited by venous access and increased risk of systemic adverse events, and the volume of subcutaneous immunoglobulin administration is limited by hyaluronan. HYQVIA® (Immune Globulin Infusion [Human] 10% with recombinant human hyaluronidase [rHuPH20]; fSCIG) allows for dispersion and absorption of large-dose subcutaneous immunoglobulin by self-infusion and can be infused at rates and frequencies similar to IVIG, with better systemic tolerability. Therefore, it is being investigated as a novel treatment for CIDP in a phase 3 study.

Objectives: Describe the infusion protocol for fSCIG as maintenance CIDP therapy in ADVANCE CIDP-1 (NCT02549170).

Methods: Planned enrollment in this prospective, global, multicenter study is 174 adults. Patients with CIDP receiving stable IVIG for ≥12 weeks will be randomized equally to fSCIG or placebo (with rHuPH20). The primary outcome is relapse rate (proportion of patients with increase ≥1 point in adjusted Inflammatory Neuropathy Cause and Treatment disability scale score from baseline). Recommended sites for infusion are the upper to middle abdomen and thighs with a 24G needle(s). The number of infusion sites can be 1, 2, or 3, and a needle set can be single, bifurcated, or trifurcated. The maximum infusion volume per infusion site is 600 mL for patients ≥40 kg and 300 mL for patients <40 kg. On a given infusion day, the maximum infusion volume should not exceed 1200 mL for patients ≥40 kg or 600 mL for patients <40 kg. After the initial 2 infusions, infusion rate may be increased up to 300 mL/h/site. Patients receive fSCIG with the same frequency as their prerandomization IGIV treatment.

Results: This study is ongoing and blinded.

Summary/Conclusion: fSCIG, enabling infusion rates and volumes similar to IVIG, is being evaluated as a novel maintenance therapy for CIDP.

References: None.

Keywords: Inflammatory, Clinical Trials

Grant Support: None.
**Poster 181**

Dermal neovascularization as early biomarker in POEMS syndrome: a preliminary case-control study

Camille Guibert¹, Laurent Magy¹, Laurence Richard¹, Stéphanie Durand², Jean-Michel Vallat¹, Mathilde Duchesne¹

¹University Hospital of Limoges, Limoges, France, ²University of Limoges, Limoges, France

**Introduction:** Despite current knowledge, the diagnosis of POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein and Skin changes) syndrome is still challenging. The polyneuropathy involves large as well as small fibers, as shown by skin biopsy. Because of the role of Vascular endothelial growth factor (VEGF) in this disease, we investigated the dermal vascularization, in skin samples from patients with POEMS syndrome and looked for correlations with small nerve fiber involvement in this disorder.

**Methods:** We included patients suffering from POEMS syndrome and control cases (one group of healthy subjects and five groups representing the most common causes of polyneuropathies that could be mistaken for POEMS syndrome: CIDP, monoclonal gammopathy, diabetes, amyloidosis and vasculitis). Each patient (except controls) had both skin and nerve biopsies in the University Hospital of Limoges between 2009 et 2018. The density of vessels in skin and nerve (anti-alpha-smooth muscle actin antibody), and intraepidermal nerve fiber (anti-PGP 9.5 Ab) density was assessed for each case.

**Results:** Six patients with POEMS syndrome were included, and 12 patients per control group. Density of cutaneous vessels was significantly higher in POEMS patients than in all the control groups. IENF density of POEMS patients was significantly lower than in healthy controls, but significantly higher than in all the other groups. Density of nerve vessels just tended to be increased in POEMS patients but was significantly higher in perineurium when compared to normal control group. No correlation was found between vascularization of skin and vascularization of nerve, and intraepidermal nerve fiber density, and VEGF levels in patients with POEMS syndrome.

**Conclusion:** Increased vascularization in skin samples seems to be an interesting biomarker to help distinguishing POEMS syndrome from alternative diagnoses, but the link with the loss of intraepidermal nerve fiber is unclear and needs further investigation.

**References:** None.

**Keywords:** Small Fibers

**Grant Support:** None.
A Scale for Evaluation of Muscle Cramps: Development of the Toronto Cramp Impact Index (TCII)

Hans Katzberg, Vera Bril, Carolina Barnett-Tapia

University Health Network, University of Toronto, Toronto, Canada

Introduction:

Traditional clinical and research efforts aimed at assessing the muscle cramps has focused on evaluating cramp frequency, which may not capture the entire impact of muscle cramps on patient health. We propose the Toronto Cramp Impact Index (TCII), a patient reported assessment tool which aims to capture the complete cramp experience.

Methods:

We conducted semi-structured interviews, organizing data into themes and sub-themes to understand patients’ cramp experiences. We used data-saturation to determine number of interviews. We used the identified themes and a literature review to formulate questions relevant to muscle cramps. A preliminary set of questions and answers was drafted and circulated to neuromuscular and cramp experts worldwide via an online survey. An updated item draft was re-circulated to patients for final wording prior to upcoming validation phase of the study.

Results:

Eleven patients with idiopathic cramps and cramps related to neurological and medical conditions completed the interviews. The following themes were extracted: 1) cramp severity 2) interference with sleep 3) interference with daytime activities 4) effects of cramp on mental health. Taking into account existing published measures of cramp assessment, we developed 15 questions spanning all themes. Thirty-five out of 40 experts including neurologists and measurement experts answered a web-based questionnaire rating the questions and offered modification suggestions. Six patients assessed this modified version through cognitive debriefing and provided further feedback. We used expert and patient input to draft the final measure.

Conclusion:

The proposed pre-validation draft of the TCII will be presented at the PNS which integrates patient input, evidenced-based and expert opinion and offers a simple, efficient and comprehensive tool which can be used to evaluate patients with muscle cramps. The tool will undergo additional reliability and validation assessments prior to final release.

References: None.

Keywords: Pain

Grant Support: University of Toronto, Division of Neurology, New Initiatives Grant
HIV-associated sensory neuropathy (HIV-SN) is a common neurological complication of HIV infection, impacting up to 40% of patients. HIV-SN is predominantly a small fibre neuropathy which occurs in a stocking and glove distribution. Pathological features include reduced intraepidermal nerve fibre density and perineural infiltration of inflammatory cells. We investigated the effect of polymorphisms in three genes, \( P2X7R \), \( P2X4R \) and \( CAMKK2 \), involved in inflammation and neuronal repair, and the expression patterns of the encoded proteins \textit{ex vivo}.

HIV+ Indonesians (n=202) attending clinics in Jakarta were assessed for neuropathy using the Brief Peripheral Neuropathy Screen (a validated diagnostic tool) and genotyped for 48 polymorphisms spanning the three adjacent genes, using OpenArray technology. Haplotypes were derived using fastPHASE and haplotype networks were built using Median-Joining methods. Multivariable models optimally predicting HIV-SN were determined using factors achieving p<0.2 in bivariate analyses. Distal leg skin biopsies were collected from of a subset of HIV patients with (n=3) and without HIV-SN (n=3), and healthy controls (n=3). Biopsies were stained to visualise nerves (PGP9.5), cell nuclei (DAPI) and the expressed proteins (P2X7R, P2X4R and CaMKK2) and imaged with confocal microscopy.

After correcting for a lower CD4 T-cell count and >500 copies of HIV RNA/ml, two haplotypes from both \( P2X7R \) and \( CAMKK2 \) associated with increased risk of HIV-SN (model; \( p=0.0002 \), pseudo \( R^2=0.11 \)) and three polymorphisms in \( CAMKK2 \) associated with reduced risk (model; \( p=0.0002 \), pseudo \( R^2=0.11 \)). A \( CAMKK2 \) haplogroup incorporating these three polymorphisms also associated with reduced risk (\( p=0.02 \), OR=0.43 CI=0.21-0.88). The expression of the encoded protein, CaMKK2, was greater in the epidermis of patients with HIV-SN than patients without or healthy controls.

We have identified polymorphisms in \( CAMKK2 \) which mark risk of HIV-SN and found the expression of CaMKK2 is upregulated in affected tissues. The results implicate CaMKK2 in the pathogenesis of HIV-SN.

References: None.

Keywords: Small Fibers, Human Genetics, Inflammatory

Grant Support: None.
Poster 184

Heme and Sensory Neuropathy: Insights From Novel Mutations in the Heme Exporter FLVCR1

Deborah Chiabrando¹, Francesca Bertino¹, Kyra Firestone², Emanuele Bellacchio³, Kelly Jackson⁴, Alexander Asamoh⁵, Joseph Hersh⁵, Veronica Fiorito⁶, Francesca Destefanis⁶, Rusty Gonser⁷, Megan Tucker², Emanuela Tolosano⁸
Hereditary sensory and autonomic neuropathies (HSANs) are a group of clinically and genetically heterogeneous disorders of the Peripheral Nervous System (PNS) mainly characterized by impaired nociception and autonomic dysfunction. We previously identified heme metabolism as a novel pathway contributing to sensory neurons maintenance and nociception. Indeed, we reported mutations in the Feline Leukemia Virus subgroup C Receptor 1 (FLVCR1) gene in individuals affected by HSAN (1,2). FLVCR1 gene encodes for two heme export proteins, FLVCR1a (plasma membrane) and FLVCR1b (mitochondria), crucially involved in the regulation of cellular heme homeostasis (3-5).

In this work we report on two additional patients carrying novel biallelic mutations in FLVCR1 translation initiation codon (TIC) (c.2T>C; p. (Met1Thr), c.3G>T; p. (Met1Ile)). The aim of this project was to describe the impact of the c.2T>C; p. (Met1Thr) mutation on protein structure and function in comparison with other HSAN-related FLVCR1 mutations.

We generated the FLVCR1 mutant by site-directed mutagenesis and we overexpressed it in HEK293T cells and in HeLa cells. We found that TIC mutations interfere with translation in two different ways: by lowering levels of translation of wild-type protein and by inducing translation initiation from a downstream in frame ATG. We showed that mutant FLVCR1 correctly localizes on the plasma membrane where it retains, at least in part, heme export activity.

The identification of novel FLVCR1 mutations in HSAN reinforces the crucial role of heme in sensory neurons maintenance and pain perception. Moreover, our in vitro findings demonstrate that heme export is not completely lost in HSAN patients and suggest that modulation of FLVCR1 activity may be important for therapeutic purposes.


Keywords: Pain, Human Genetics, Other

Grant Support: None.
Poster 185

Ignoring Clustering Effect in Multi-Site PAIN-CONTRoLS: A Patient-Informed Cryptogenic Polyneuropathy Clinical Trial. Reasonable Assumption?

Alexandra Brown, Richard Meier, Byron Gajewski, Mamatha Pasnoor, Laura Herbelin, Kim Kimminau, Mazen Dimachkie, Richard Barohn

University of Kansas-Medical Center, Kansas City, KS, USA

Background: Cryptogenic sensory polyneuropathy (CSPN) is a common, slowly progressive neuropathy that affects adults and presents with significant neuropathic pain. We presented the primary findings at this meeting in 2018.

Objective: To compare the relative effectiveness of four medications in reducing pain for CSPN patients: nortriptyline, duloxetine, pregabalin, and mexiletine.

Methods: We performed a prospective randomized open labelled comparative effectiveness study of CSPN patients with funding from Patient Centered Outcomes Research Institute (PCORI). The co-primary endpoints are the change in Likert pain scale and quit rates. The primary measure was multinomial, either the participant quit the drug, or experienced a positive or negative response. The primary analysis utilized a Bayesian multinomial model. The outcome was a utility function which was a composite of the efficacy and quit rates. This was a multisite trial but the primary analysis ignored any possible clustering effects of participants recruited from the same site. A Bayesian multinomial model with clustering was fit to determine if the assumption of ignoring the clustering was reasonable.

Results: Across 42 sites, 402 CSPN patients were randomized to nortriptyline (n=134), duloxetine (n=126), pregabalin (n=73), and mexiletine (n=69). Utilizing the Bayesian multinomial model without clustering effects, the utility function of nortriptyline was 0.81 (95% credible interval 0.69-0.93); duloxetine was 0.80 (95% CrI is 0.68-0.92); pregabalin was 0.69 (95% CrI 0.55-0.84), and mexiletine was 0.58 (95% CrI of 0.42-0.75). The utility was similar for the model accounting for the clustering effect of the 42 sites: 0.81 (95% CrI 0.70-0.93); 0.80 (95% CrI is 0.69-0.92); 0.70 (95% CrI 0.55-0.85); 0.59 (95% CrI of 0.43-0.76), respectively.

Conclusion: The Bayesian multinomial model with clustering is an improvement over the primary model without clustering, the inference regarding the best performing drug or drugs did not change. Therefore, the prespecified statistical analysis plan for PAIN-CONTRoLS was reasonable.

References: None.

Keywords: Pain, Clinical Trials

Grant Support: Supported By: University of Kansas Medical Center CER-1306-02496 Clinicaltrial.gov registry identifying number: NCT02260388
Neuropathic pain is a frequent feature of peripheral neuropathy and defined as pain caused by a lesion or disease of the somatosensory nervous system. Small fiber degeneration easily detected by skin biopsy is a typical cause of peripheral neuropathic pain for which multiple etiologies are recognized including the recently discovered mutations in genes that encode voltage-gated sodium channel (VGSC). Some studies suggested that also skin resident cells such as keratinocytes could play a role in nociception because of the expression of pain-related ion channels, including the VGSC subunit Nav1.7. To what extend Nav1.7 expression can vary in painful neuropathies is unknown. Our study investigates its expression in the epidermis and dermal nerves of patients diagnosed with painful small fiber neuropathy (SFN) based on reduced intraepidermal nerve fiber density (IENFD).

We performed quantitative immunofluorescence analysis of skin biopsy sections from SFN patients harboring pathogenic gain-of-function variants in SCN9A and SCN10A and age-matched healthy controls. Patients with SFN caused by mutations in SCN9A and SCN10A showed decreased Nav1.7 signal intensity and different clustering along dermal fibers compared to healthy controls. The analysis of signal intensity in keratinocytes confirmed a similar decrease of Nav1.7 staining. Our preliminary data suggest that changes in the expression of Nav1.7 could be detected in SFN caused by SCN9A and SCN10A, potentially providing a novel cutaneous biomarker of disease.

References: None.

Keywords: Pain

Grant Support: This research study has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No. 721841
<table>
<thead>
<tr>
<th></th>
<th>Title</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Consequences of SAC3/FIG4 deficiency to phosphoinositides in fibroblasts of patients with CMT4J</td>
<td>Jun Li</td>
</tr>
<tr>
<td>2</td>
<td>Schwann Cell Transcript Biomarkers for Hereditary Neuropathy Skin Biopsies</td>
<td>John Svaren</td>
</tr>
<tr>
<td>3</td>
<td>Unravelling hallmarks of axonal degeneration in Charcot-Marie-Tooth type 2 using induced pluripotent stem cells</td>
<td>Jonas Van lent</td>
</tr>
<tr>
<td>4</td>
<td>Adult Polyglucosan Body Disease Presenting With A Peripheral Neuropathy: Broadening The Clinical Spectrum</td>
<td>Jonathan De Winter</td>
</tr>
<tr>
<td>5</td>
<td>A recessive repeat expansion causes CANVAS and is a common cause of Late-Onset Sensory Ataxia</td>
<td>Andrea Cortese</td>
</tr>
<tr>
<td>6</td>
<td>Whole Genome Sequencing in CMT cases from the 100,000 Genome Project</td>
<td>Menelaos Pipis</td>
</tr>
<tr>
<td>7</td>
<td>Epidemiology Of Hereditary Transthyretin (hATTR) Amyloidosis: A Real-World Analysis Of A US Commercially Insured Population</td>
<td>Spencer Guthrie</td>
</tr>
<tr>
<td>8</td>
<td>Mutations in MORC2 cause axonal neuropathy with complex features.</td>
<td>Carolynne Doherty</td>
</tr>
<tr>
<td>9</td>
<td>Fatigability in Children with different CMT subtypes</td>
<td>Rosemary Shy</td>
</tr>
<tr>
<td>10</td>
<td>IN VIVO MAPPING OF CORTICAL MYELINATION IN CMT1A PATIENTS</td>
<td>Stefano Tozza</td>
</tr>
<tr>
<td>12</td>
<td>Molecular and functional characterization of cellular component associated with CMT1A endo- and perineurium</td>
<td>Giovanna Capodiveno</td>
</tr>
<tr>
<td>13</td>
<td>Digitally assessed patient-reported real-world care standards for Charcot-Marie-Tooth disease in the UK and US</td>
<td>Mark Larkin</td>
</tr>
<tr>
<td>14</td>
<td>Two novel mutations in the FAM134B gene: expanding the clinical and genetic spectrum of HSAN</td>
<td>Catarina Falcão de Campos</td>
</tr>
<tr>
<td>15</td>
<td>A fast low-cost protocol to obtain motor neurons from iPSc by Sedimentation Field Flow Fractionation</td>
<td>Federica Miressi</td>
</tr>
<tr>
<td>16</td>
<td>Diagnostic Challenges in HSAN: A Patient with 2 Unreported SCN9A and SCN11A Mutations</td>
<td>Francisco Gondim</td>
</tr>
<tr>
<td>17</td>
<td>Impact of Patisiran, an RNAi Therapeutic, on Diarrhea Symptoms in Patients with Hereditary Transthyretin-Mediated Amyloidosis</td>
<td>Laura Obici</td>
</tr>
<tr>
<td>18</td>
<td>PXT3003 pleotherapy improves neuromuscular dysfunction in Charcot-Marie-Tooth type 1A</td>
<td>Thomas Prukop</td>
</tr>
<tr>
<td>19</td>
<td>Homozygosity for the Glu89Gln mutation in hATTR : first report of an Italian family</td>
<td>Anna Mazzeo</td>
</tr>
<tr>
<td>20</td>
<td>The biological significance of exploring CMT1A hypercellularity in peripheral nerves</td>
<td>Davide Visigalli</td>
</tr>
<tr>
<td>21</td>
<td>Cardiopulmonary Exercise Test Performance and Predictors of Aerobic Capacity in Charcot Marie Tooth Disease 1A</td>
<td>Gita Ramdharay</td>
</tr>
<tr>
<td>22</td>
<td>ESCOR-TTR: A National patient support program to monitor patients treated for hereditary transthyretin-mediated amyloidosis (hATTR)</td>
<td>David ADAMS</td>
</tr>
<tr>
<td>23</td>
<td>Sensitivity of Clinically Assessed Measures of Balance and Computerized Dynamic Posturography in Pediatric CMT</td>
<td>Timothy Estilow</td>
</tr>
<tr>
<td>24</td>
<td>Severe distal motor involvement in a non-compliant adult with biotinidase deficiency</td>
<td>Thierry Kuntzer</td>
</tr>
<tr>
<td>26</td>
<td>Spinal muscular atrophy caused by an original MORC2 mutation</td>
<td>Marion Masingue</td>
</tr>
<tr>
<td>28</td>
<td>Efficacy of a videogame intervention in Charcot- Marie-Tooth on balance and gait training</td>
<td>Prada Valeria</td>
</tr>
<tr>
<td>29</td>
<td>Expanding the clinical manifestations of the DNAJB2 c.352 + 1G&gt;A mutation</td>
<td>Fernanda Figueiredo</td>
</tr>
<tr>
<td>30</td>
<td>Application of unbiased molecular datasets and machine learning for discovery of novel dHMN-associated genes</td>
<td>Matthew Jennnings</td>
</tr>
<tr>
<td>31</td>
<td>A novel mutation c.941A&gt;G in WARS gene was identified in a Chinese dHMN family</td>
<td>Ruxu Zhang</td>
</tr>
<tr>
<td>Page</td>
<td>Title</td>
<td>Author</td>
</tr>
<tr>
<td>------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>32</td>
<td>THE PATH TO DIAGNOSING CHARCOT-MARIE-TOOTH DISEASE: THE PATIENT EXPERIENCE</td>
<td>Allison Moore</td>
</tr>
<tr>
<td>33</td>
<td>Neuropathy-Related Disease Burden in Hereditary Transthyretin Amyloidosis Relative to Diabetic Neuropathy</td>
<td>Michael Pollock</td>
</tr>
<tr>
<td>34</td>
<td>Sensory Neuron-derived IGF-1 Augments Neurite Outgrowth And This Autocrine/paracrine Pathway Is Suppressed in Diabetes</td>
<td>Reza Aghanoori</td>
</tr>
<tr>
<td>35</td>
<td>Distal Symmetric Polyneuropathy is Likely the First Neurologic Complication of Obesity</td>
<td>Ericka Chant</td>
</tr>
<tr>
<td>36</td>
<td>Distribution of obesity is a key differentiator of neuropathy status</td>
<td>Brian Callaghan</td>
</tr>
<tr>
<td>37</td>
<td>Deletion of SARM1 has a Protective Effect for High-fat Diet-induced Peripheral Neuropathy and Glucose Intolerance</td>
<td>Ahmet Hoke</td>
</tr>
<tr>
<td>38</td>
<td>Plasma Deoxydihydroceramides are Elevated in People with Diabetic Neuropathy and Correlate with Neuropathy Severity</td>
<td>Vera Fridman</td>
</tr>
<tr>
<td>39</td>
<td>Early Parallel Progression Of Peripheral And Cardiac Autonomic Nerve Dysfunction In Recent-Onset Type 1 Diabetes</td>
<td>Gidon Bönhof</td>
</tr>
<tr>
<td>40</td>
<td>Oxidative Stress and Human Diabetic Neuropathy: Role of NADPH Oxidase 5</td>
<td>Faye Mendelson</td>
</tr>
<tr>
<td>41</td>
<td>Saturated and Monounsaturated Fatty Acids Differentially Regulate Nerve Function in Murine Models of Obesity</td>
<td>Amy Rumora</td>
</tr>
<tr>
<td>42</td>
<td>Altered Nerve Triglycerides in Mouse Models of Diabetes with Neuropathy.</td>
<td>Phillipe O'Brien</td>
</tr>
<tr>
<td>43</td>
<td>Risk Factors for the Development of Chemotherapy Induced Peripheral Neuropathy: A Retrospective Study</td>
<td>Noah Kolb</td>
</tr>
<tr>
<td>44</td>
<td>Depleted Systemic Markers of Neuroinflammation And Growth Factors In Type 2 Diabetes Patients With Polyneuropathy</td>
<td>Gidon Bönhof</td>
</tr>
<tr>
<td>45</td>
<td>Sensory polyneuropathy associated with vitamin D deficiency</td>
<td>Sa-Yoon Kang</td>
</tr>
<tr>
<td>46</td>
<td>Liability Of The Voltage-Gated Potassium Channel SK3 Repeat Polymorphism To Acute Oxaliplatin-Induced Peripheral Neurotoxicity</td>
<td>Andreas Argyriou</td>
</tr>
<tr>
<td>47</td>
<td>The Relationship Between Changes in Orthostatic Blood Pressure and Symptoms in Patients with Orthostatic Hypotension</td>
<td>Christopher Gibbons</td>
</tr>
<tr>
<td>48</td>
<td>Enhanced Schwann cell and Axonal Regeneration during M. leprae infection following Intracutaneous Axotomy in Armadillos</td>
<td>Gigi Ebenezer</td>
</tr>
<tr>
<td>49</td>
<td>Macrophage And Perisynaptic Schwann Cell Responses To Distal Nerve Injury In An AMAN Mouse Model</td>
<td>Madeleine Cunningham</td>
</tr>
<tr>
<td>50</td>
<td>The Association of Dengue Infection and Guillain-Barré Syndrome in Malaysia: A Case Control Study</td>
<td>Cheng-Yin Tan</td>
</tr>
<tr>
<td>51</td>
<td>Pure Motor Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) in 17 Patients: Clinical Characteristics, Electrophysiological Study</td>
<td>Antoine Pegat</td>
</tr>
<tr>
<td>52</td>
<td>CIDP with antibodies to CNTN1 is associated with HLA-DRB11 haplotype</td>
<td>Cinta Lleixà</td>
</tr>
<tr>
<td>53</td>
<td>Clinical and serological investigations in CIDP patients with antibodies against CNTN1/Caspr1 complex.</td>
<td>Elba Pascual-Goñi</td>
</tr>
<tr>
<td>54</td>
<td>Serum Contactin-1 Levels In Chronic Inflammatory Demyelinating Polyneuropathy – A Pilot Study</td>
<td>Luuk Wieske</td>
</tr>
<tr>
<td>55</td>
<td>Treatment Status Following Corticosteroid And Immunoglobulin Treatment In The International CIDP Outcome Study (ICOS)</td>
<td>Sander Bus</td>
</tr>
<tr>
<td>56</td>
<td>Medical Research Council (MRC) Scores as an Outcome Measure of Strength in Guillain-Barré Syndrome</td>
<td>Melissa Mandarakas</td>
</tr>
<tr>
<td>57</td>
<td>Diagnostic Delay and Work-Up of CIDP in the International CIDP Outcome Study (ICOS) cohort</td>
<td>Carina Bunschoten</td>
</tr>
<tr>
<td>58</td>
<td>Ultrastructural Mechanisms of Macrophage-Induced Demyelination in Guillain-Barré Syndrome</td>
<td>Haruki Koike</td>
</tr>
<tr>
<td>59</td>
<td>Antibody- and macrophage-mediated internodal demyelination in CIDP: clinical, electrophysiological, immunological and pathological correlations</td>
<td>Jean-Michel Vallat</td>
</tr>
<tr>
<td>60</td>
<td>Prognostic features for death and progression in patients with POEMS syndrome</td>
<td>Stephen Keddie</td>
</tr>
<tr>
<td>61</td>
<td>Protective Effects Of Endogenously Expressed Calpain Inhibitor In A Mouse Model Of Guillain-Barré Syndrome.</td>
<td>Rhona McGonigal</td>
</tr>
<tr>
<td>Page</td>
<td>Title</td>
<td>Author/Reference</td>
</tr>
<tr>
<td>-----</td>
<td>----------------------------------------------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>63</td>
<td>Optimizing electrodiagnosis for chronic inflammatory demyelinating polyneuropathy with automated analysis and machine learning</td>
<td>Ilse Lucke</td>
</tr>
<tr>
<td>64</td>
<td>Post Dengue Guillain Barre Syndrome Subtypes: A Case Series</td>
<td>Sathyajith Ambawatte</td>
</tr>
<tr>
<td>65</td>
<td>Types and treatment practices in GBS in a tertiary care center in Sri Lanka</td>
<td>Anomali Vidanagamage</td>
</tr>
<tr>
<td>67</td>
<td>Effectiveness And Tolerance Of Subcutaneous Immunoglobulin In CIDP – A Substudy Of INCbase</td>
<td>Jeffrey Allen</td>
</tr>
<tr>
<td>68</td>
<td>Association Of IgM Antiglycolipid Antibodies With Clinical Features In Fisher Syndrome And Related Disorders.</td>
<td>Kenichi Kaida</td>
</tr>
<tr>
<td>69</td>
<td>Long-term QoL And Treatment Satisfaction Outcomes of Subcutaneous Immunoglobulin IgPro20 in CIDP: PATH Extension Study</td>
<td>Ivo van Schaik</td>
</tr>
<tr>
<td>70</td>
<td>Diagnosis and Management of Guillain-Barré Syndrome in Ten Steps</td>
<td>Sonja Leonhard</td>
</tr>
<tr>
<td>71</td>
<td>Axonal Loss at Time of Diagnosis Predicts Long-Term Disability in Chronic Inflammatory Demyelinating Polyneuropathy</td>
<td>Ali Al-Zuhairy</td>
</tr>
<tr>
<td>72</td>
<td>Diagnose and treatment of chronic inflammatory demyelinating polyneuropathy with IgG4 anti-neurofascin155 antibody : Clinical practice in China</td>
<td>Jie Lin</td>
</tr>
<tr>
<td>73</td>
<td>Increased Effector B cells in Peripheral Blood of Chronic Inflammatory Demyelinating Polyneuropathy Patients</td>
<td>Ayse Nur Ozdag Acarlı</td>
</tr>
<tr>
<td>74</td>
<td>Diagnostic yield and clinical utility of nerve biopsy in evaluation of neuropathy</td>
<td>Cheng-Ying Ho</td>
</tr>
<tr>
<td>75</td>
<td>Characterization of a Relapsing/Remitting, Disease Course for Corticosteroid-Responsive Small-Fiber Neuropathy</td>
<td>Anne Oaklander</td>
</tr>
<tr>
<td>76</td>
<td>Next generation sequencing in idiopathic sensory neuronopathies.</td>
<td>Alberto Martinez</td>
</tr>
<tr>
<td>77</td>
<td>Acute small fibre neuropathy: a neglected condition?</td>
<td>Thierry Gendre</td>
</tr>
<tr>
<td>78</td>
<td>Analysis of 193 whole genome sequencing data to understand neuropathic pain disorders.</td>
<td>Andreas Themistocleous</td>
</tr>
<tr>
<td>79</td>
<td>SCN11A Arg225Cys mutation causes nociceptive pain without detectable peripheral nerve pathology.</td>
<td>Jun Li</td>
</tr>
<tr>
<td>80</td>
<td>Pregabalin for muscle cramps in patients with liver cirrhosis, A randomized, double-blind, placebo-controlled study</td>
<td>So Hyun Ahn</td>
</tr>
<tr>
<td>81</td>
<td>mNIS+7 Components and Lower Limb Function Responsiveness in Inotersen Treatment of Hereditary Transthyretin Amyloidosis Polyneuropathy</td>
<td>P. James Dyck</td>
</tr>
<tr>
<td>82</td>
<td>Patient Assisted Intervention for Neuropathy: Comparison of Treatment in Real Life Situations Quality of Life</td>
<td>Mamatha Pasnoor</td>
</tr>
<tr>
<td>83</td>
<td>SENSORY-MOTOR PACLITAXEL POLYNEUROPATHY CHARACTERIZATION IN A RAT MODEL</td>
<td>PAOLA ALBERTI</td>
</tr>
<tr>
<td>84</td>
<td>Modelling dHMNX and CMTX6 using patient derived iPSC motor neurons.</td>
<td>Gonzalo Perez Siles</td>
</tr>
<tr>
<td>85</td>
<td>Human iPSC-derived motor neuron model of CMT2A from MFN2 mutations</td>
<td>Robert Baloh</td>
</tr>
<tr>
<td>86</td>
<td>The Italian Registry for Charcot-Marie-Tooth disease</td>
<td>Davide Pareyson</td>
</tr>
<tr>
<td>87</td>
<td>Implications of Disease Progression During Childhood and Adolescence on Walking Speed in Charcot-Marie-Tooth Disease</td>
<td>Sylvia Ounpuu</td>
</tr>
<tr>
<td>88</td>
<td>Multicenter Retrospective Study In Patients With CMT1b In France: Genotype-Phenotype Correlations.</td>
<td>Marie SUBREVILLE</td>
</tr>
<tr>
<td>89</td>
<td>Genotype and phenotype in Thai children with Charcot-Marie-Tooth Disease.</td>
<td>Oranee Sanmaneechai</td>
</tr>
<tr>
<td>90</td>
<td>Modeling Axonal Degeneration in CMT2E using Human Motor Neurons</td>
<td>Mario Saporta</td>
</tr>
<tr>
<td>91</td>
<td>Mutation Burden and Oligogenic Inheritance in a large Inherited Axonopathy Cohort</td>
<td>Stephan Zuchner</td>
</tr>
<tr>
<td>92</td>
<td>Hyperglycosylation of Myelin Protein Zero: from pathogenesis to therapeutic options.</td>
<td>Marina Grandis</td>
</tr>
<tr>
<td>93</td>
<td>Neddylation plays a critical role for formation, maturation and maintenance of Schwann cell myelin sheaths</td>
<td>Ashwin Woodhoo</td>
</tr>
<tr>
<td>Page</td>
<td>Title</td>
<td>Author(s)</td>
</tr>
<tr>
<td>------</td>
<td>----------------------------------------------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>94</td>
<td>Cell adhesion and choline-dependent metabolism in PNS myelination</td>
<td>Haesun Kim</td>
</tr>
<tr>
<td>95</td>
<td>The Integrated Stress Response Contributes to Charcot-Marie-Tooth Type 2D Peripheral Neuropathy in Mice</td>
<td>Emily Spaulding</td>
</tr>
<tr>
<td>96</td>
<td>Role of the ER stress transcription factor XBP1 in Charcot-Marie-Tooth disease type 1B</td>
<td>Thierry Touvier</td>
</tr>
<tr>
<td>97</td>
<td>NRG1 type I dependent autoparacrine stimulation of Schwann cells in onion bulbs of peripheral neuropathies</td>
<td>Ruth Stassart</td>
</tr>
<tr>
<td>98</td>
<td>CaMKII Potentiates TRPV4 Mediated Calcium Influx, Resulting in Mitochondrial Axon Transport Disruption and Neurodegeneration</td>
<td>Brian Woolums</td>
</tr>
<tr>
<td>99</td>
<td>Improving Physical Function in Persons with Peripheral Neuropathy Using Sensory Neuromodulation - Clinical Trial Update</td>
<td>Lars Oddsson</td>
</tr>
<tr>
<td>100</td>
<td>Variable Presentation of Hereditary Transthyretin-Mediated (hATTR) Amyloidosis: A Single Center Experience with the Patisiran PAAP</td>
<td>Yessar Hussain</td>
</tr>
<tr>
<td>101</td>
<td>A complex inherited sensory neuropathy related to compound heterozygous mutation in the FN gene</td>
<td>Matilde Laura</td>
</tr>
<tr>
<td>102</td>
<td>The longitudinal change in nerve cross-sectional area of Charcot-Marie-Tooth disease type 1A</td>
<td>Yu-ichi Noto</td>
</tr>
<tr>
<td>103</td>
<td>Systematic Survey of Electrophysiological Findings in Myotonic Dystrophy Type 1 (DM1)</td>
<td>Nina Khizanishvili</td>
</tr>
<tr>
<td>104</td>
<td>Dysregulated Adhesion in CMT1A Patient Fibroblasts and iPSC-derived Schwann Cells.</td>
<td>Kathryn Moss</td>
</tr>
<tr>
<td>105</td>
<td>Two Independent Cases of de novo GARS(p.Gly327Arg) Mutation that Causes a Predominantly Motor Axonal Neuropathy</td>
<td>Diana Lee</td>
</tr>
<tr>
<td>106</td>
<td>Resolving a multi-generational neuromuscular mystery</td>
<td>Nivedita Jerath</td>
</tr>
<tr>
<td>107</td>
<td>TTR Knockdown Therapy in Patients with hATTR Amyloidosis Who Have Disease Progression despite Liver Transplant</td>
<td>Orly Moshe-Liie</td>
</tr>
<tr>
<td>108</td>
<td>A Novel Pathogenic Variant of NEFL responsible for Deafness associated with Peripheral Neuropathy</td>
<td>Anne-Sophie LIA</td>
</tr>
<tr>
<td>109</td>
<td>Electrophysiological features of hereditary ATTR amyloidosis misinterpreted as chronic inflammatory demyelinating polyneuropathy</td>
<td>Nobuhiko Ohashi</td>
</tr>
<tr>
<td>110</td>
<td>A novel HINT1 mutation identified in two Norwegian patients with peripheral neuropathy</td>
<td>Helle Høyer</td>
</tr>
<tr>
<td>111</td>
<td>Compound Heterozygous Mutations of SH3TC2 in Charcot-Marie-Tooth Disease Type 4C Patients</td>
<td>Ah Jin Lee</td>
</tr>
<tr>
<td>112</td>
<td>Examining Mutation-Specific Impact on the Long, Distal Motor Axon in ALS using iPSC-derived Motor Neurons</td>
<td>Katie Marshall</td>
</tr>
<tr>
<td>113</td>
<td>Characterising Neurophysiological Findings in Charcot-Marie-Tooth Disease caused by Frameshift Mutations in NEFH</td>
<td>Arjuna Nagendran</td>
</tr>
<tr>
<td>114</td>
<td>Phrenic Neuropathy in Trembler J Neuropathic Mice</td>
<td>Lucia Notterpek</td>
</tr>
<tr>
<td>115</td>
<td>Use of GAITRite system to investigate walking ability in Charcot Marie Tooth patients</td>
<td>Laura Mori</td>
</tr>
<tr>
<td>116</td>
<td>Efficacy of Patisiran in Patients with hATTR Amyloidosis and Prior Tafamidis Use: Analysis of APOLLO</td>
<td>Hollis Lin</td>
</tr>
<tr>
<td>117</td>
<td>Charcot-Marie-Tooth disease type 2N Patients with AARS Mutations</td>
<td>Ah Jin Lee</td>
</tr>
<tr>
<td>118</td>
<td>Greater auricular nerve amyloidoma as a presenting manifestation of AL amyloidosis with underlying lymphoplasmacytic lymphoma</td>
<td>Chinar Osman</td>
</tr>
<tr>
<td>119</td>
<td>PREGNANCY IN CHARCOT-MARIE-TOOTH DISEASE: DATA FROM THE ITALIAN CMT NATIONAL REGISTRY</td>
<td>Chiara Pisciotta</td>
</tr>
<tr>
<td>120</td>
<td>The nerve echogenicity assessment in Charcot-Marie-Tooth disease type 1A</td>
<td>Yuta Kojima</td>
</tr>
<tr>
<td>121</td>
<td>OPA3-related autosomal dominant optic atrophy and cataract (ADOAC) plus syndrome.</td>
<td>Alejandro Horga</td>
</tr>
<tr>
<td>122</td>
<td>Neuropathic Pain and Clinical Characteristics in Charcot-Marie-Tooth Disease Subtypes</td>
<td>Elina Millere</td>
</tr>
<tr>
<td>123</td>
<td>Neuropathy-causing mutations in TRPV4 disrupt TRPV4-RhoA interaction and cytoskeletal modulation</td>
<td>Brett McCray</td>
</tr>
<tr>
<td>Page</td>
<td>Title</td>
<td>Authors</td>
</tr>
<tr>
<td>------</td>
<td>----------------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>126</td>
<td>Functional Characterization of Human iPSC-derived Motor Neurons with Loss of Neurofilament Light</td>
<td>Svetlana Molchanova</td>
</tr>
<tr>
<td>127</td>
<td>Serum neurofilament light chain is a sensitive biomarker for degeneration of immature SMA motor axons</td>
<td>Lingling Kong</td>
</tr>
<tr>
<td>128</td>
<td>Small Fibers impairment In Charcot-Marie-Tooth Disease: The Role Of Laser Evoked Potentials.</td>
<td>Alessia Peretti</td>
</tr>
<tr>
<td>129</td>
<td>Using C. Elegans to model X-linked Charcot-Marie-Tooth (CMTX6) disease.</td>
<td>Ramesh Narayanan</td>
</tr>
<tr>
<td>130</td>
<td>Assessment of neuropathic pain in patients with Charcot-Marie-Tooth disease type 1A</td>
<td>Stojan Peric</td>
</tr>
<tr>
<td>131</td>
<td>Two families with Charcot-Marie-Tooth-4H due to mutations in FGD4: Broadening the phenotype</td>
<td>Tara Jones</td>
</tr>
<tr>
<td>132</td>
<td>Childhood Onset Charcot-Marie-Tooth Disease</td>
<td>Isabella Moroni</td>
</tr>
<tr>
<td>133</td>
<td>Molecular analysis and clinical diversity of hereditary motor neuropathy</td>
<td>Xiaoxuan Liu</td>
</tr>
<tr>
<td>134</td>
<td>Generation of interchangeable disease models for Charcot-Marie-Tooth involving tRNA-synthetases: in search for common toxic pathways</td>
<td>Laura Morant</td>
</tr>
<tr>
<td>135</td>
<td>Acupuncture Management for Diabetic Neuropathy: A case report</td>
<td>Yun Jin Kim</td>
</tr>
<tr>
<td>136</td>
<td>Multimodal Assessment Of Intensive Care Unit-Acquired Weakness (ICU-AW) In Severe Acute Stroke Patients</td>
<td>Berin İnan</td>
</tr>
<tr>
<td>137</td>
<td>Dose-dependent Chemotherapy-induced peripheral autonomic neuropathy: acute injury and slow recovery</td>
<td>Ying Liu</td>
</tr>
<tr>
<td>138</td>
<td>Quantitative gait analysis in patients with diabetic polyneuropathy</td>
<td>Dongah Lee</td>
</tr>
<tr>
<td>139</td>
<td>Oncomodulin is Required for the Conditioning Lesion Response in Dorsal Root Ganglion Neurons In Vivo</td>
<td>Jon Niemi</td>
</tr>
<tr>
<td>140</td>
<td>Aberrant DEGS1 activity alters sphingolipid metabolism and causes leukodystrophy and axonal degeneration</td>
<td>Thorsten Hornemann</td>
</tr>
<tr>
<td>141</td>
<td>Sensory nerve conduction studies in ALS patients: a retrospective study</td>
<td>Aikaterini Papagianni</td>
</tr>
<tr>
<td>142</td>
<td>Electrophysiological Findings in Critical Illness Neuropathy</td>
<td>Giuseppe Piscosquito</td>
</tr>
<tr>
<td>143</td>
<td>Ischiofemoral impingement syndrome provoked by childbirth: an unusual case of a severe sciatic mononeuropathy</td>
<td>Elie Naddaf</td>
</tr>
<tr>
<td>144</td>
<td>Autophagy inhibition affects from the spinal cord level which induces symptom change in PIPN mouse</td>
<td>Ji Hyun Lee</td>
</tr>
<tr>
<td>145</td>
<td>Evidence of Altered Peripheral Nerve Function in a Rodent Model of Pre-diabetes</td>
<td>Md Jakir Hossain</td>
</tr>
<tr>
<td>146</td>
<td>Caloric Restriction Improves Peripheral Nerve Function and Glucose Tolerance in Diet-Induced Obese Mice</td>
<td>Shayna Mason</td>
</tr>
<tr>
<td>147</td>
<td>Bilateral abducens palsy associated with anti-GQ1b antibody: A single center experience</td>
<td>Kee Hong Park</td>
</tr>
<tr>
<td>148</td>
<td>Reliability of Resynthesis technique to identify proximal conduction block: A series of 20 cases.</td>
<td>Roberto Pontes</td>
</tr>
<tr>
<td>149</td>
<td>Clinical Subtypes And Anti-Glycolipid Antibodies In Chronic Inflammatory Demyelinating Polyneuropathy</td>
<td>Motoi Kuwahara</td>
</tr>
<tr>
<td>150</td>
<td>Usefulness of subperineurial edema and C5b9 deposition in sural nerves for predicting treatment response</td>
<td>Wei Ping Kay Ng</td>
</tr>
<tr>
<td>151</td>
<td>MR neurography in differential diagnosis of CIDP, MMN and CMT</td>
<td>Masaki Kobayashi</td>
</tr>
<tr>
<td>152</td>
<td>A case of Lewis-Sumner syndrome mimicking vasculitic neuropathy</td>
<td>Jin-Ah Kim</td>
</tr>
<tr>
<td>153</td>
<td>GBS- Getting Better Slowly and Growing Back Slowly: Do Not Give Up too Early!</td>
<td>Wee Lin</td>
</tr>
<tr>
<td>154</td>
<td>Factors Associated with Residual Fatigue in Guillain-Barré Syndrome: Focus on Low-Income Countries</td>
<td>Nowshin Papri</td>
</tr>
<tr>
<td>155</td>
<td>A Case Of Guillain-Barré Syndrome With Treatment-Related Fluctuation</td>
<td>Nghia Hoang</td>
</tr>
<tr>
<td>Page</td>
<td>Title</td>
<td>Authors</td>
</tr>
<tr>
<td>------</td>
<td>-----------------------------------------------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>156</td>
<td>Multicentre Study Investigating the Association of Guillain-Barre Syndrome with Flaviviruses and other Arboviruses in Singapore.</td>
<td>Christen Sheng Jie Lim</td>
</tr>
<tr>
<td>157</td>
<td>Serial Studies Reveal &quot;Covert&quot; Sural-sparing Pattern in Guillain-Barre Syndrome</td>
<td>Jasmine Shimin Koh</td>
</tr>
<tr>
<td>158</td>
<td>Pharmacokinetic Modelling and Simulation of Flexible Dosing Regimens of Subcutaneous Immunoglobulin (IgPro20) in CIDP Patients</td>
<td>Xuewen Ma</td>
</tr>
<tr>
<td>159</td>
<td>CSF neurofilmament heavy chain: A possible biomarker of Guillain-Barré syndrome</td>
<td>Jee-Eun Kim</td>
</tr>
<tr>
<td>160</td>
<td>Human Leukocyte Antigen (HLA)-DQB1 Polymorphisms and Their Haplotype Patterns in Patients with Guillain-Barré syndrome</td>
<td>Zhahirul Islam</td>
</tr>
<tr>
<td>161</td>
<td>Temporal Profile of Anti-Ganglioside Antibodies in Recurrent Guillain-Barre Syndrome</td>
<td>Takamasa Kitaoji</td>
</tr>
<tr>
<td>162</td>
<td>Experimental autoimmune neuritis (EAN): Morphological evidence for mitochondrial damage</td>
<td>Ines Muke</td>
</tr>
<tr>
<td>163</td>
<td>Predominantly Abnormal Sensory Responses at Disease Onset and Electrophysiological Characteristics of Anti-Neurofascin 155 Neuropathy</td>
<td>Stefanie Kar Yan Hung</td>
</tr>
<tr>
<td>164</td>
<td>Detection of IgG and IgM antibodies against nodo-paranodal proteins in CMT and CIDP</td>
<td>Lorena Martín-Aguilar</td>
</tr>
<tr>
<td>165</td>
<td>Disability, Fatigue and Treatment Safety During Long-Term Intravenous Immunoglobulin (Gamunex® 10%) Therapy in CIDP Patients</td>
<td>Juliane Klehmet</td>
</tr>
<tr>
<td>166</td>
<td>Time to Relapse After IVIG Withdrawal Predicts Relapse of Placebo-Treated CIDP Subjects in PATH Study</td>
<td>Richard Lewis</td>
</tr>
<tr>
<td>167</td>
<td>Medical Research Council Grading System Revisited in CIDP Through Rasch Analyses: The PATH Study</td>
<td>Ingemar Merkies</td>
</tr>
<tr>
<td>168</td>
<td>Impact of Diagnosis Delay in Chronic Inflammatory Demyelinating Polyneuropathy: Results from a Global Patient Survey</td>
<td>Rajiv Mallick</td>
</tr>
<tr>
<td>169</td>
<td>Epitope Mapping for Anti-FGFR3 Autoantibodies in Sensory Neuropathy</td>
<td>Christian Moritz</td>
</tr>
<tr>
<td>170</td>
<td>Multicentre Study Investigating the Association of Guillain-Barre Syndrome with Flaviviruses and other Arboviruses in Myanmar</td>
<td>Kyaw Hlaing</td>
</tr>
<tr>
<td>171</td>
<td>Patient Demographics and Clinical Features of Typical and Atypical CIDP–A Single-Center Experience from Turkey</td>
<td>Yesim Parman</td>
</tr>
<tr>
<td>172</td>
<td>IVlg treatment in chronic inflammatory neuropathies – experience of single neuromuscular centre.</td>
<td>Marta Lipowska</td>
</tr>
<tr>
<td>173</td>
<td>MUNIX: A Potential New Monitoring Tool of Treatment Response in Chronic Inflammatory Demyelinating Polyneuropathy</td>
<td>Andrew Lawley</td>
</tr>
<tr>
<td>174</td>
<td>Small volume plasma exchange (SVPE) kit</td>
<td>Saysavath Keosodsay</td>
</tr>
<tr>
<td>175</td>
<td>Clinical spectrum of stiff person syndrome associated with glutamic acid decarboxylase antibodies</td>
<td>Anza Memon</td>
</tr>
<tr>
<td>176</td>
<td>Peripheral neuropathy associated with neuralgial antibodies: clinical, electrodiagnostic and histopathological characteristics</td>
<td>Pritikanta Paul</td>
</tr>
<tr>
<td>177</td>
<td>Subcutaneous immunoglobulin administration via manual push technique in chronic inflammatory demyelinating polyradiculoneuropathy patients</td>
<td>Erdira Peci</td>
</tr>
<tr>
<td>178</td>
<td>Characteristics and management of peripheral nervous system adverse events induced by anti-PD-1 or anti-PD-L1 immunotherapy</td>
<td>Léo Plaçais</td>
</tr>
<tr>
<td>179</td>
<td>Spontaneous Secretion Of Anti-GM1 Antibodies By Peripheral Blood Plasmablasts In A Patient With Guillain-Barré Syndrome</td>
<td>Ruth Huizinga</td>
</tr>
<tr>
<td>180</td>
<td>Assessment of paranodal region in skin of Chronic Inflammatory Demyelinating Polyradiculoneuropathy patients</td>
<td>Raffaella Lombardi</td>
</tr>
<tr>
<td>181</td>
<td>MULTIFOCAL MOTOR NEUROPATHY (MMN) IN A 33 YEAR OLD feMALE</td>
<td>Elene Nebadze</td>
</tr>
<tr>
<td>182</td>
<td>Intravenous Immunoglobulin (IVIG) Therapy in Idiopathic lumbosacral plexopathy: Report of two cases</td>
<td>Demet Ilhan Algin</td>
</tr>
<tr>
<td>183</td>
<td>Characteristics of Late-Onset Val30Met Transthyretin Amyloidosis with Polyneuropathy from the Transthyretin Amyloidosis Outcomes Survey</td>
<td>Marcia Waddington-Cruz</td>
</tr>
<tr>
<td>184</td>
<td>SCN9A Channelopathy Of Extremes: From Hyperexcitability, Hyperalgesia and Hypertension To Hypoplastic Limbs, Hyponatremia And Hypomineralization.</td>
<td>Isis Joosten</td>
</tr>
<tr>
<td>185</td>
<td>A Comparative Study of Human Hairy and Glabrous Skins</td>
<td>Baohan Pan</td>
</tr>
<tr>
<td>Page</td>
<td>Title</td>
<td>Author</td>
</tr>
<tr>
<td>------</td>
<td>----------------------------------------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>186</td>
<td>Diagnostic Performance of Sudoscan in Young Patients Evaluated For Small-Fiber Neuropathy and Healthy Controls</td>
<td>Max Klein</td>
</tr>
<tr>
<td>187</td>
<td>Dynamic Sweat Test (DST) in Small Fiber Neuropathies</td>
<td>Maria Nolano</td>
</tr>
<tr>
<td>188</td>
<td>Mutations in Cell Adhesion Molecules Belonging to the CADM Family Cause Charcot-Marie-Tooth Disease</td>
<td>Adriana Rebelo</td>
</tr>
</tbody>
</table>
Consequences of SAC3/FIG4 deficiency to phosphoinositides in fibroblasts of patients with CMT4J

Jun Li, Assia Shisheva, Diego Sbrissa, Bo Hu

Wayne State University School of Medicine, Detroit, MI, USA

Introduction: Charcot-Marie-Tooth disease type-4J (CMT4J) is autosomal recessively inherited peripheral neuropathy caused by compound heterozygous mutations in FIG4 (also known as SAC3) gene, to result in severe loss/absence of the SAC3/FIG4 protein, which triggers neuronal degeneration, segmental demyelination, sensory disorder and limb muscle weakness. In mouse fibroblasts, the absence of the phosphatidylinositol (PtdIns) 3,5P2 5-phosphatase SAC3/FIG4 leads to reduced PtdIns(3,5)P2 due to disassembly of PtdIns(3,5)P2-metabolizing machinery, composed of the PIKfyve kinase, the ArPIKfyve scaffold and the SAC3/FIG4 phosphatase. Decreases of PtdIns(3,5)P2 over 70% is incompatible with life as shown in genetically modified mouse models deficient in either of the three genes. However, phosphoinositides (PIs) in humans with loss-of-function CMT4J mutations have never been evaluated. How changes in PIs relate to lysosomal phenotypes is also unclear. Methods: De-identified fibroblasts were obtained as previously described (Hu et al, 2016). Fibroblasts were labeled with myo-[2-3H] inositol to equilibrium. Extracted PIs were quantified by HPLC. Results: Compared to fibroblasts from normal human controls (n=9), both PtdIns(3,5)P2 and PtdIns5P levels were significantly decreased in CMT4J fibroblasts (n=13) by 36.4±3.6% and 43.1±4.4%, respectively (mean±SEM; p<0.0001). Whereas mean values for PtdIns3P levels remained unchanged vs. controls, there were high variations in PtdIns3P among individual patients. Morphological alterations in the form of multiple endolysosomal vacuoles, typically seen under PtdIns(3,5)P2 reduction, were apparent but not in fibroblasts from all CMT4J patients. Patients who failed to display aberrant cytoplasmic vacuolation exhibited significantly low levels of PtdIns3P vs. controls. Conclusions: 1). Our study assesses for the first time the PI profiles in humans with CMT4J. 2). The phenotypes in CMT4J patients may not be solely due to reduction of PtdIns(3,5)P2, but also to that of PtdIns5P, known to be involved in non-canonical autophagy. 3). Lack of vacuoles in fibroblasts from some CMT4J patients may be related to low PtdIns3P levels.

References: None.

Keywords: CMTR, Human Genetics

Grant Support: U.S. Department of Veterans Affairs (IBX003385A)
Charcot-Marie-Tooth disease (CMT) is most commonly caused by duplication of a chromosomal segment surrounding Peripheral Myelin Protein 22, or PMP22, gene, which is classified as CMT1A. Several candidate therapies reduce Pmp22 levels in CMT1A rodent models, but development of biomarkers for clinical trials in CMT1A is a challenge given its slow progression and the difficulty in obtaining nerve samples. Quantitative PCR measurements of PMP22 in dermal nerves have been performed using skin biopsies in human clinical trials for CMT1A, but this approach does not show increased PMP22 mRNA in CMT1A patients compared to controls. One complicating factor is the variable amounts of Schwann cells (SC) in skin. The objective of the study was to develop a novel method for precise evaluation of PMP22 levels in skin biopsies that can discriminate CMT1A patients from controls. To accomplish this, we have developed methods to normalize PMP22 transcript levels to SC-specific genes that are not altered by CMT1A status. Several CMT1A-associated genes were assembled into a custom Nanostring panel to enable precise transcript measurements that can be normalized to variable Schwann cell content. Nanostring technology enables direct detection of transcripts without cDNA synthesis and amplification. The digital expression data from Nanostring analysis showed reproducible elevation of PMP22 levels in CMT1A vs. control skin biopsies, particularly after normalization to SC-specific genes. This platform should be useful in clinical trials for CMT1A as a measure of target engagement that can be used to optimize dosing, and the same normalization framework is applicable to other types of CMT.

References: None.

Keywords: CMTR, Schwann Cell, Other

Grant Support: This work was supported by U54NS065712 provided by NINDS/NCATS-ORD, a core grant to the Waisman Center from NICHD (U54 HD090256), and by a grant from the Charcot-Marie-Tooth Association.
Unravelling hallmarks of axonal degeneration in Charcot-Marie-Tooth type 2 using induced pluripotent stem cells

Jonas Van lent¹, Manisha Juneja¹, Peter Verstraelen¹, Lotte Conings¹, Bob Asselbergh², Vicky De Winter¹, Winnok De Vos¹, Vincent Timmerman¹

¹University of Antwerp, Antwerp, Belgium, ²University of Antwerp, VIB, Antwerp, Belgium

Introduction: Our knowledge in the disease mechanisms of Charcot-Marie-Tooth (CMT) has significantly increased due to the successful generation of transgenic mouse models recapitulating the neuropathy phenotype. The human induced pluripotent stem cell (hiPSC) technology seems promising to substitute animal models of disease and may facilitate the identification and validation of reliable molecular therapies. We aimed to obtain an in vitro cellular model to study the hallmarks of axonal degeneration among different CMT2 subtypes. Methods: We reprogrammed fibroblasts derived from five CMT2 patients with different causal mutations in the MFN2, NEFL, HSPB8 and HSPB1 genes using Sendai-virus transductions. We differentiated these hiPSC lines, along with healthy controls, into spinal motor neurons using an established protocol [1]. We investigated: 1. signs of neurodegeneration using high content phenotypic screening, 2. cytoskeletal abnormalities disturbing axonal transport, 3. axonal transport deficits in mitochondria and 4. abnormalities in neuronal excitability using calcium imaging. Results: We successfully generated spinal motor neurons from hiPSCs with an efficiency of almost 95% from both patients and controls. A decrease in neurite area, length and branching for the MFN2, NEFL and HSPB1 patient lines indicated an altered neurite network. Deficits in mitochondrial trafficking and morphology were found in neurons from MFN2 and NEFL patient iPSC lines. Preliminary data revealed electrophysiological abnormalities based on calcium imaging, such as a shorter recovery time after stimulation in motor neurons derived from patients. Conclusions: Our findings provide insights into the molecular and cellular phenotypes of hiPSC-derived models for axonal CMT neuropathies.


Keywords: Axonal Biology

Grant Support: None.
Adult Polyglucosan Body Disease Presenting With A Peripheral Neuropathy: Broadening The Clinical Spectrum

Jonathan De Winter¹, Willem De Ridder², Tine Deconinck³, Danique Beijer³, Martin Lammens¹, Jonathan Baets²

¹Antwerp University Hospital, Edegem, Belgium, ²Antwerp University Hospital, University of Antwerp, Edegem, Belgium, ³University of Antwerp, Edegem, Belgium

The purpose is twofold. First, to present a rare cause of a polyneuropathy with leukodystrophy as an initial presentation of a multisystemic polyglucosan body disease. Second, to expand the current knowledge concerning adult-onset GBE-deficiency phenotypes. A 49-year old man presented at our neuromuscular department with a two-year history of gait difficulties and distal sensory abnormalities. Distal weakness was noted as well as pedes cavi. Clinical examination was in keeping with a motor predominant peripheral neuropathy and mild pyramidal features. Nerve conduction studies showed a predominantly motor mixed axonal-demyelinating neuropathy. MR-imaging revealed confluent white matter lesions in both hemispheres. Family history revealed a younger brother with a similar albeit milder clinical phenotype. After five years of follow-up the patient had developed a progressively severe spasmodic gait with wheelchair use, neurogenic bladder dysfunction, discrete cerebellar ataxia and cognitive and behavioral changes. Progressive leukodystrophy and myelopathy were evident from serial MRIs. Distal weakness preceded proximal weakness in the lower limbs, analogous to a more pronounced motoric predominant neuropathy. Although mildly elevated serum CK levels (500-600U/L) were observed, muscle biopsy did not show primary myopathic abnormalities. Due to liver enzyme abnormalities, a liver biopsy was performed and showed a micro-macrovesicular steatosis. Whole exome sequencing showed compound heterozygous mutations (p.Thr254Ala and Ile694Asn) in Glycogen Branching Enzyme 1 (GBE1) and segregation in the family was confirmed. In conclusion, we report a case of an adult polyglucosan body disease (APBD) with a peripheral nerve system impairment dominating the initial presentation. We broaden the current knowledge of GBE1-related disorders by representing a combination of the two allelic forms of GBE1 deficiency, namely GSD-IV (glycogen storage disease type 4) and APBD. The first is associated with involvement of the liver and skeletal muscles in childhood, the second with peripheral neuropathy and central nervous system involvement in adults.

References: None.

Keywords: Human Genetics

Grant Support: None.
Poster 5

A recessive repeat expansion causes CANVAS and is a common cause of Late-Onset Sensory Ataxia

Andrea Cortese¹, Roberto Simone², Roisin Sullivan², Jana Vandrovcova², Huma Tariq², Yau Wai Yan², Jack Humphrey², Zane Jaunmuktane², Prasanth Sivakumar², Muhammad Ilyas³, James Polke², Eloise Tribollet², Pedro Tomaselli⁴, Grazia Devigili⁵, Ilaria Callegari⁶, Maurizio Versino⁷, Vincenzo Salpietro², Stephanie Efthymiou², Diego Kaski⁸, Nick Wood², Nadja Andrade⁹, Elena Buglo¹⁰, Adriana Rebelo¹⁰, Alexander Rossor², Adolfo Bronstein¹¹, Pietro Fratta², Wilson Marques⁴, Sarah Beecroft¹², Gianina Ravenscroft¹², Nigel Laing¹², Richard Roxburgh¹³, Tanya Stojkovic¹⁴, Alexandra Durr¹⁵, Vincent Huin¹⁵, Rita Horvath¹⁶, Charlotte Sumner¹⁷, Stephan Zuchner¹⁰, Henry Houlden², Mary Reilly²
Late-onset ataxia is a common reason for neurological consultation, but its cause often remains idiopathic. Cerebellar dysfunction, but also proprioceptive or vestibular impairment, can lead to ataxia. When in combination, this more severe type of ataxia is termed cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS). Both sporadic and familial cases of CANVAS have been reported, suggesting the possibility of a recessive transmission of the disease. The aim of this study was to identify the genetic cause of CANVAS. We performed non-parametric linkage analysis and genome sequencing. We identified an intronic recessive pentanucleotide repeat expansion in RF gene as the cause of CANVAS and a common cause of late-onset sensory ataxia. The presence of the repeat expansion was confirmed by repeat-primed PCR, long-range PCR and southern blot. Functional studies were performed to assess the effect of the repeat expansion on the expression of the repeat-hosting gene. The recessive repeat expansion, ranging in patients from 400 to several thousand repeats, showed full segregation in 23 cases from 11 families. Additionally, 33 (22%) out of 150 sporadic cases with late-onset ataxia from a single-centre carried the recessive repeat expansion. The percentage raised to 62% in patients with sensory neuronopathy and cerebellar involvement and 92% in full-blown CANVAS disease. Screening of additional cases with late-onset ataxia or CANVAS from Australia, New Zealand and France identified another 18 positive cases from seven unrelated families. Notably, the pentanucleotide repeat expansion does not affect expression of the repeat-hosting gene at mRNA and protein levels in patient fibroblasts. These data, together with the observation of an allelic carrier frequency of the expanded repeat of 0.7% in the European population, suggests that this biallelic pentanucleotide repeat expansion represents a frequent cause of late-onset ataxia and identifies an unconventional disease-causing mechanism in this late-onset recessive disorder.

References: None.

Keywords: CMTR, Human Genetics

Grant Support: A.C. is funded by the inherited neuropathy consortium, which is a part of the NIH Rare Diseases Clinical Research Network (RDCRN) (U54NS065712) and Wellcome Trust (204841/Z/16/Z). A.M.R. is funded by a Wellcome Trust Postdoctoral Fellowship for Clinicians (110043/Z/15/Z). H.H. is also supported by Rosetrees Trust, Ataxia UK, The MSA Trust, Brain Research UK, MDUK, The Muscular Dystrophy Association (MDA), Higher Education Commission (HEC) of Pakistan and The Wellcome Trust (Synaptopathies Strategic Award). The INC (U54NS065712) is a part of the NCATS Rare Diseases Clinical Research Network (RDCRN). RDCRN is an initiative of the Office of Rare Diseases Research (ORDR), NCATS, funded through a collaboration between NCATS and the NINDS. S.Z. thanks the National Institute of Health (4R01NS075764) for its support.
Poster 6

Whole Genome Sequencing in CMT cases from the 100,000 Genome Project

Menelaos Pipis¹, James Polke², Mariola Skorupinska¹, Jana Vandrovcova³, Carolynne Doherty¹, Matilde Laura³, Henry Houlden⁴, Alexander Rossor¹, Mary Reilly³

¹MRC Centre for Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, United Kingdom of Great Britain and Northern Ireland, ²Neurogenetics Unit, UCL Queen Square Institute of Neurology, London, United Kingdom of Great Britain and Northern Ireland, ³MRC Centre for Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, United Kingdom of Great Britain and Northern Ireland, ⁴MRC Centre for Neuromuscular Diseases, Neurogenetics Unit, UCL Queen Square Institute of Neurology, London, United Kingdom of Great Britain and Northern Ireland

Whole genome sequencing (WGS) as a single molecular genetic test is very appealing with the ability to simultaneously sequence both nuclear and mitochondrial genomes. It can reliably detect coding, splice-site and non-coding single nucleotide variants (SNV) as well as large balanced and unbalanced structural variants. As part of the 100,000 Genome Project which was launched in 2012, we have recruited 290 pedigrees for WGS, who had genetically undiagnosed CMT despite gene panel and other molecular genetic testing.

We present the phenotypic and initial WGS analysis of our first 40 CMT cases, with a provisional genetic diagnosis achieved in 10 pedigrees (25%) to date. Analysis of SNV and small insertions/deletions (indels) in all genes known to cause monogenic Mendelian disease (mini-exome) has been carried out and we identified variants in MORC2, HINT1, MT-ATP6, IGHMBP2, POLG, VRK1, MME and WARS. The avalanche of sequence data that accompanies WGS necessitates effective filtering of variants and this can be aided by setting a maximum credible population allele frequency for pathogenic variants in dominant and recessive CMT genes. As illustrated by some of our cases, the inclusion of trio-based WGS studies (affected proband and unaffected parents) allows the identification of de novo variants and the determination of variant phase in cases of compound heterozygosity. Furthermore, in more complex pedigrees, the recruitment of multiple affected and unaffected individuals from the same pedigree allows linkage through genome-wide genotyping of a large number of single nucleotide polymorphisms.

Incorporating WGS as a first-line test in CMT clinical practice will be normal practice in the future. Our caseload illustrates the multiple advantages of this approach as current gene panel-based and other molecular genetic testing does not achieve a diagnosis in 40% of our CMT cases.

References: None.

Keywords: CMTR, Human Genetics

Grant Support: This research was made possible through access to the data and findings generated by the 100,000 Genomes Project.
Epidemiology Of Hereditary Transthyretin (hATTR) Amyloidosis: A Real-World Analysis Of A US Commercially Insured Population

Spencer Guthrie1, Sheila Reddy2, Eunice Chang2, Ryan Tieu2, Marian Tarbox2, Michael Pollock1

1Akcea Therapeutics, Cambridge, MA, USA, 2Partnership for Health Analytic Research, LLC, Beverly Hills, CA, USA

Introduction: This study’s objective was to generate a recent US estimate of incidence of hATTR amyloidosis, a rare genetic, progressive, and fatal disease caused by build-up of misfolded transthyretin protein (amyloid) in organs and tissues; focusing on patients with hATTR-associated polyneuropathy and/or mixed phenotype.

Methods: We identified patients ≥18 years diagnosed with hATTR amyloidosis in Truven Health Analytics MarketScan® Commercial and Medicare Supplemental data, using a claims-based algorithm due to lack of specific medical coding. Diagnosis required ≥1 medical claim with a relevant diagnosis code for amyloidosis (ICD-10-CM: E85.0-4, E85.89, E85.9; excludes light chain and wild type) in the calendar year (CY) of 2016 and ≥1 occurrence of qualifying criteria for hATTR any time during study (2013-2017): ≥15 days diflunisal use without >30-day gap, liver transplant, or claim with code E85.1 or E85.2. All disease-free enrollees (continuously enrolled and without a diagnosis code of amyloidosis in CY2015) were included. Annual incidence was calculated as the number of new cases of hATTR patients divided by total at-risk patient years from January 1st to diagnosis (cases) or enrollment end (non-cases) in CY 2016 and reported per million person years (PMPY). Enrollment was continuous during at-risk period.

Results: Annual incidence of hATTR in 2016 was 9.0 patients PMPY. Incident cases were concentrated in older age groups (65+ years: 23.3, 55-64 years: 14.6, 35-54 years: 5.8, 18-34 years: 2.2 PMPY) and slightly more common among females than males (9.6 vs. 8.3 PMPY). Estimates in 2017 followed mostly similar patterns but were truncated due to data censoring.

Conclusions: The epidemiology of hATTR amyloidosis is not well understood or quantified. This study reveals a small but meaningful number of new patients diagnosed with hATTR in the US in 2016. Consistent with previous studies, new cases are predominately of advanced age. Future estimation of prevalence is planned.

References: None.

Keywords: Amyloidosis

Grant Support: None.
Mutations in MORC2 cause axonal neuropathy with complex features.

Carolynne Doherty¹, Menelaos Pipis¹, Andrea Cortese¹, Alexander Rossor¹, Adnan Manzur², Francesco Muntoni², Mary Reilly¹

¹MRC Centre for Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, United Kingdom of Great Britain and Northern Ireland, ²Dubowitz Neuromuscular Centre, UCL Great Ormond Street Institute of Child Health, London, United Kingdom of Great Britain and Northern Ireland

Introduction: MORC2 is a DNA dependent ATPase which relaxes chromatin to facilitate repair of damaged DNA. Mutations in this gene cause axonal CMT, first described in 2016.(1) We have identified three families who carry these mutations.

Case presentations: A 25-year-old male presented with painful distal tingling and hand “locking” and cramping. He first walked at 18 months. On examination there was retinal pigmentary change, pyramidal and subtle cerebellar signs and neuropsychometry demonstrated an IQ of 80. Neurophysiology confirmed an axonal motor and sensory neuropathy with severe denervation on EMG. Extensive diagnostic evaluation included targeted genetic testing and the CMT2/intermediate panels and metabolic evaluation but did not yield the diagnosis. Ultimately a p.R252W mutation was identified in MORC2 following whole exome sequencing. The proband’s 5-year-old child was found to have delayed motor and language skills, labile behaviour and axonal neuropathy. Subsequently a 27-year-old female was found to have the same mutation, with delayed motor milestones, intellectual disability, toe walking, and hearing impairment. A wheelchair is needed for mobility since age 22. A third patient (29-year-old woman) has been found to have the p.E236G mutation and has required a wheelchair since age 27, with a history or delayed motor milestones, early foot deformity, scoliosis and patchy upper limb symptoms. Her 4-year-old child is also affected with speech and language delay, an abnormal gait at 15 months and brisk lower limb reflexes, weakness of ankle dorsiflexion and marked asymmetrical varus deformity.

Discussion: A phenotypic spectrum of axonal neuropathy with associated features such as hearing impairment, retinal dystrophy, pyramidal features and neurodevelopmental abnormalities has been reported associated with MORC2 mutations. We describe the clinical features in three families identified through whole exome or mini exome sequencing and discuss the literature.


Keywords: CMTR, Human Genetics

Grant Support: Dr Carolynne Doherty and Professor Mary Reilly are grateful to the Muscular Dystrophy Association for their grant support.
Poster 9

Fatigability in Children with different CMT subtypes

Rosemary Shy¹, D Mnatsakonova², R Zuccharino³, C Pisciotta², C Bacon³, ME Shy⁴

¹Carver College of Medicine, Department of Neurology, University of Iowa, Iowa City, IA, USA, ²University of Iowa, Iowa City, IA, USA, ³University of Iowa, Carver College of Medicine, Iowa City, IA, USA, ⁴University of Iowa, Carver College of Medicine, Iowa City, IA, USA

OBJECTIVE: We hypothesis that severely affected children with different types of CMT will fatigue in the last minute of the 6minute walk test used in CMTPedS. BACKGROUND: Prior studies demonstrated that children with SMA walk shorter distances in the last minute of the 6MWT, and that this may also be true in CMT. Prior studies with a smaller group of children with CMT1A did not demonstrate fatigability

METHODS: 180 children with CMT underwent the 6MWT test at the University of Iowa CMT clinic between 2013-2018. These included 78 subjects with CMT1A, 20 with CMT2A, 11 with CMT1E, 7 with CMT4C and 7 other rare types each containing only 1-3 individuals. Patients unable to ambulate or adequately follow directions were excluded. Participants were all in barefoot. Walking times were recorded for each minute of the 6MWT and z score results 1-4 were also compared to the overall CMTPedS Scores (0-44). RESULTS: No patient with CMT1A demonstrated significant reduction in the distance walked during the 6th minute compared to the first minute of the study, consistent with our prior data. Subjects with CMT2A, CMT1B, CMT4C and most other subtypes typically had higher CMTPedS scores and walked shorter distances overall than children with CMT1A. However, these children also did not demonstrate fatigability in the 6th minute of their walk. Children evaluated over several years did not develop fatigability in follow up studies. Rare individuals with distal HMN did fatigue during the last minute; these individuals were not genetically diagnosed. CONCLUSIONS: Ambulatory children with different subtypes of CMT did not fatigue during the last minute of the 6MWT even if their CMT was severe as defined by higher CMTPedS scales. The 6 minute walk is therefore not able to routinely demonstrate fatigability in most ambulatory children with CMT.


Keywords: CMTR, Clinical Trials

Grant Support: NCATS/NINDS, Muscular Dystrophy Association, Charcot Marie Tooth Association
IN VIVO MAPPING OF CORTICAL MYELINATION IN CMT1A PATIENTS

Stefano Tozza¹, Raffaele Dubbioso¹, Sirio Cocozza², Maria Nolano¹, Daniele Severi¹, Giuseppe Pontillo², Lucio Santoro¹, Fiore Manganelli¹

¹Department of Neuroscience, Reproductive Sciences and Odontostomatology, University of Naples “Federico II”, Naples, Italy, ²Department of Advanced Biomedical Sciences, University of Naples “Federico II”, Naples, Italy

A single previous paper has demonstrated, using brain magnetic resonance imaging (MRI), diffuse subcortical white matter (WM) abnormalities in patients with Charcot-Marie-Tooth type 1A (CMT1A) disease. Moreover, pathological examination of the brain of a patient with PMP22 gene duplication showed diffuse hypomyelination sparing the U fibres.

A novel neuroimaging method based on the ratio of T1/T2-weighted magnetic resonance images, offers a non-invasive estimate of myelin content in the cerebral cortex. Therefore, to test whether also cortical myelination was reduced in CMT1A disease we applied this technique to a cohort of patients with PMP22 duplication.

Ten CMT1A patients (5 females, age: 30.20 ± 9.40 y) and 20 healthy controls (11 females, age: 30.25 ± 10.85 y) were investigated. All patients underwent clinical assessment and brain MRI. The myelin content in the cerebral cortex was studied using the MRI analysis technique based on the ratio of T1- and T2-weighted signal intensities.

Patients showed lower T1/T2-weighted ratio values in parietal and temporal areas. The two most significant clusters appeared in the postcentral gyrus, mainly peaking in the primary somatosensory cortex, and in the superior and inferior temporal lobes.

Our study demonstrates that myelin content in the cerebral cortex is reduced in CMT1A patients. The most involved cortical areas are those that are typically more myelinated in humans.

The mechanism of CNS myelin involvement in CMT1A is not clear as well it remains to establish if the reduced myelin content in the cerebral cortex may be a primary process or secondary to cortical remodeling due to peripheral axonal loss.

References: None.

Keywords: CMTR, Clinical Trials

Grant Support: None.
CMT1A is a congenital dysmyelinating disorder of the PNS characterised by ultrastructural abnormalities of the myelinated fibers which account for defective neuropathology and neurophysiology. In previous studies we demonstrated the critical contribution of lipids to the abnormal CMT1A myelin that is incorrectly formed and organised since the very early stages of development. Here, MALDI-IMS analysis performed for the first time in CMT1A neuropathy, displayed an impairment of lipid architecture both in myelinated fibers and connective tissue. Indeed, the spatial resolution applied to analyse in situ the distribution of lipid species demonstrated substantial differences in the organization of CMT1A rat sciatic nerve endonevrium and perinevrium compared to age- and gender-matched controls. These chemical and structural differences were corroborated by histological studies performed on experimental and human CMT1A. To further unravel the biological rationale underlying this issue, we isolated and investigated from the molecular and functional standpoint purified Schwann cells, endoneurial fibroblasts and perineurial cells from CMT1A rats and control littermates. Overall, we found significant differences between the two genotypes for each of the analysed condition to sustain a congenital mala organization of CMT1A peripheral nerves. Since we support the need to retrieve important biological features as critical targets for CMT1A, it is our opinion that these studies will allow a better comprehension of the molecular mechanisms undelying CMT1A neuropathy, fundamental to identify effective therapeutic strategies.

References: None.

Keywords: Schwann Cell, CMTR, Metabolic

Grant Support: None.
Digitally assessed patient-reported real-world care standards for Charcot-Marie-Tooth disease in the UK and US

Mark Larkin¹, Tjalf Ziemssen², Shahram Attarian³, Florian Thomas⁴, Allison Moore⁵, Daniel Tanesse⁶, Xavier Paoli⁷, Viviane Bertrand⁷, Youcef Boutalbi⁷, Emma Bagshaw¹, Hara Kousoulakou¹

¹Vitaccess Ltd., Oxford, United Kingdom of Great Britain and Northern Ireland, ²Universitätsklinikum Carl Gustav Carus an der Technischen Universität, Dresden, Germany, ³Assistance Publique - Hopitaux de Marseille, Marseille, France, ⁴Hackensack University Medical Center, Hackensack, USA, ⁵Hereditary Neuropathy Foundation, New York, USA, ⁶CMT France CMT France CMT France, Fougères Cedex, France, ⁷Pharnext SA, Issy-les-Moulineaux, France
Introduction:

The objective of this analysis was to examine self-reported standards of care received by people with Charcot-Marie-Tooth disease (CMT) in UK and US real-world practice.

Methods:

Adults with CMT were recruited to a two-year international observational study exploring the real-world impact of the disease. Data were collected via CMT&Me, a bespoke ‘bring your own device’ app, through which participants were asked questions about demographic, CMT-management-related and quality-of-life variables. This interim analysis examined standards of CMT management reported by UK and US participants, including promptness of diagnosis and access to appropriate healthcare professionals. Outcomes were compared against clinical guidelines.

Results:

Diagnosis and care standards were generally aligned with guidelines. Around half of study participants received their CMT diagnosis within a year of first seeking medical care; however, substantial minorities reported experiencing diagnostic delays of several years and/or did not know their CMT subtype at the time of study participation.

The majority of participants had at least yearly access to several members of a multidisciplinary care team, including family doctors, neurologists, physical/physiotherapists, orthotists, and occupational therapists, among others. However, the type and number of healthcare professionals visited varied considerably between participants. Most people visited a neurologist – the professional recommended to coordinate CMT care – at least once a year; however, a sizable minority did not. A physical/physiotherapist, another important professional with the CMT care team, was seen at least annually by only around half of participants. The majority of people visited their family doctor at least once a year for problems with their CMT.

Conclusions:

CMT care standards in the UK and US are broadly in alignment with guidelines; however, there is scope to improve time-to-diagnosis and access to appropriate healthcare professionals. This ongoing registry will provide further real-world insights into areas for the development of CMT care.

References: None.

Keywords: Other

Grant Support: None.
Two novel mutations in the FAM134B gene: expanding the clinical and genetic spectrum of HSAN

Catarina Falcão de Campos¹, Marie Vidailhet², Alix de Becdelièvre³, Benoît Funalot⁴, Nathalie Bonello-Palot⁵, Tanya Stojkovic⁶

¹Department of Neurology, Hospital de Santa Maria, Centro Hospitalar Lisboa Norte, Lisbon, Portugal, ²Department of Neurology, APHP, GH-Pitié-Salpêtrière; ICM and Sorbonne University, Paris, France, ³Department of Genetic, APHP, GHU Henri Mondor Hospital; INSERM U955, Equipe 5, Créteil, France, ⁴Department of Genetic, APHP, GHU Henri Mondor Hospital; INSERM U955, Equipe 10, Créteil, France, ⁵Department of Medical Genetics, APHM, Timone enfants Hospital, Marseille, France, ⁶Myology Institut, APHP, GH-Pitié-Salpêtrière, Paris, France

Hereditary sensory autonomic neuropathy (HSAN) type II is a rare, autosomal recessive, early onset sensory neuropathy, characterized by severe and progressive sensation impairment, leading to ulcero-mutilating complications. Although sensory symptoms predominate, motor involvement can also occur. FAM134B gene mutations have been recently reported to be associated to HSAN2B. We report the clinical and neurophysiological findings of two non-related families with HSAN2B, carrying two novel mutations in FAM134B gene.

Family-I: Three sisters from a consanguineous Turkish family presented HSAN type II phenotype with variable severity. The clinical manifestations started during early-childhood with difficulty in running and jumping, feet deformities and scoliosis. At 12 years of age, ulcero-mutilating complications appeared. The oldest sister presented a more severe phenotype with right foot amputation. Neurological examination displayed thermo-algic and vibratory hypoesthesia with glove and stock distribution; no motor weakness. Remarkably, brisk deep tendon reflexes associated to Babinski sign were noticed. Mild dysautonomic features, such as lipohymia, were present. Nerve conduction studies (NCS) showed an axonal sensorimotor polyneuropathy. A novel homozygous mutation c.896_897delAA (p.Lys299Argfs*6) was found in the FAM134B gene.

Family-II: A Portuguese female patient with no known family history and no obvious consanguinity was submitted to corrective surgery of hallux valgus at the age of 13. This surgery was complicated by rejection reaction of the osteosynthesis material. During follow-up, she presented recurrent plantar ulcerations complicated with osteomyelitis. Neurological examination revealed decreased thermoalgetic and vibratory sensation in the lower and upper limbs. Slight distal motor weakness in lower limbs and absent deep tendon reflexes were also observed. There was no dysautonomia. NCS showed an axonal sensory-motor polyneuropathy with marked sensory impairment. A novel homozygous mutation c.1426del (p.Gln476Argfs*57) was found in the FAM134B gene.

In conclusion, this report expands the clinical and genetic spectrum of HSAN2B and emphasizes the phenotype variability even within the same family.

References: None.

Keywords: CMTR

Grant Support: None.
A fast low-cost protocol to obtain motor neurons from iPSc by Sedimentation Field Flow Fractionation

Federica Miressi1, Serge Battu2, Nicolas Vedrenne1, Marion Rassat1, Laurence Richard3, Sylvie Bourthoumieu4, Frédéric Favreau5, Franck Sturtz6, Anne-Sophie Lia6, Pierre-Antoine Faye6

1University of Limoges, MMNP, EA 6309, F-87000 Limoges, France, Limoges, France, 2University of Limoges, HCP, EA 3842, F-87000 Limoges, France, Limoges, France, 3CHU Limoges, Service de Neurologie, F-87000 Limoges France, Limoges, France, 4University of Limoges, MMNP, EA 6309, CHU Limoges, Service de Cytogénétique F-87000 Limoges, France, Limoges, France, 5University of Limoges, MMNP, EA 6309, CHU Limoges, Service Biochimie Génétique Moléculaire, F-87000 Limoges France, Limoges, France, 6University of Limoges, MMNP, EA 6309, CHU Limoges, Service Biochimie Génétique Moléculaire, F-87000 Limoges France, Limoges, France

Human induced pluripotent stem cells (hiPSc), generated for the first time in 2007, show the same properties as embryonic stem cells, with the advantage that they can be obtained from any differentiated cell types. Thanks to this feature, iPSc are widely used to create cellular lines that can not be directly taken from living patients, like motor neurons. Several protocols have been developed to differentiate iPSc into motor neurons: most of them are long and costly, requiring specific growth factors and cell culture media. We have already described a new method to obtain neural progenitors from iPSc using the Sedimentation Field Flow Fractionation (SdFFF)(1). This strategy of cell sorting enables to separate the neural fraction only on the basis of physical criteria, like size, density, or shape, avoiding labeling cells with antibodies or using expensive culture media. Furthermore, this approach helps to decrease the culture time so that we were able to obtain a cellular population enriched in neural progenitors in only 10 days. Here we report our last studies about the potential application of the method. After obtaining neural progenitors by SdFFF, we verified if they are capable to finalize the differentiation process up to motor neurons stage. SdFFF is a versatile, low-cost and noninvasive technique of cell sorting. Motor neurons derived from iPS cells and enriched by SdFFF could represent a good and easy to obtain cellular model for the study of peripheral neuropathies.


Keywords: CMTR

Grant Support: Région Nouvelle Aquitaine, University of Limoges
Diagnostic Challenges in HSAN: A Patient with 2 Unreported SCN9A and SCN11A Mutations

Francisco Gondim, Cláudia Schiavon, Gabriela Ejima Basso

Universidade Federal do Ceará, Fortaleza, Brazil

Hereditary Sensory Autonomic Neuropathy (HSAN) is a rare group of inherited peripheral neuropathies caused by at least 15 different types of mutations and characterized by disproportional sensory impairment with different degrees of autonomic and motor involvement. A 68-year-old man reported a history of simultaneous onset of numbness in the feet and hands in his 40s (denied any symptoms during childhood or adolescence), gradual loss of fingerprints, followed by mutilations/deformities in his hands and feet due to multiple injuries, such as burning (see attached photo). He gave written consent for this report. He also complained of burning feet and cold intolerance, generalized itching, arthritis and decreased hearing. He denied taste or olfactory impairment. He also reported that his father died at age 86, had worse deformities than him and had been diagnosed with leprosy. His neurological exam revealed absent ankle jerks and generalized hyporeflexia, high sock pain and vibration loss and decreased vibration in the hands. His EMG revealed a demyelinating sensorimotor neuropathy and work-up for acquired causes of neuropathy was negative, including a negative nerve biopsy to rule out leprosy. Genetic testing revealed 2 unreported mutations: C>A chr3:38,926,843 heterozygous for gene SCN11A and C>T chr2:167,133,677 heterozygous for gene SCN9A. No knock-out mice or gene function study was conducted to evaluate the mutations. In summary, this is a novel, predominantly severe sensory neuropathy phenotype (HSAN) resulting from an yet unidentified altered function of SCN9A and/or SCN11A genes. Further studies are necessary to evaluate the clinical phenotype in the relatives and evaluate the mutation effect in animal models of the disease to further understand the neurobiology of the new mutations observed.


Keywords: Human Genetics, Axonal Biology, Small Fibers, CMTR, Pain

Grant Support: CNPq
Impact of Patisiran, an RNAi Therapeutic, on Diarrhea Symptoms in Patients with Hereditary Transthyretin-Mediated Amyloidosis

Laura Obici1, Alejandra González-Duarte2, Mária Waddington-Cruz3, Quinn Dinh4, Hollis Lin4, Madeline Merkel4, Yue Wang4, Mitsuharu Ueda5

1Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, 2Instituto Nacional de Ciencias Médicas y Nutrición, Salvador Zubirán, Mexico City, Mexico, 3Hospital Universitario Clementino Fraga Filho, Rio de Janeiro, Brazil, 4Alnylam Pharmaceuticals, Cambridge, MA, USA, 5Kumamoto University Hospital, Kumamoto, Japan

Introduction: hATTR amyloidosis is a rapidly progressive disease often resulting in wasting, weight loss, and reduced quality of life. This is due in part to debilitating diarrhea caused by amyloid deposition in the gastrointestinal tract and autonomic nerves. Inanition associated with progressive peripheral or autonomic neuropathy is a leading cause of death among these patients. In the Phase 3 APOLLO study, patisiran demonstrated improvements on dysautonomia as measured by COMPASS-31 and Norfolk QOL-DN. This analysis further evaluates the impact of patisiran on diarrhea.

Methods: APOLLO was an international, randomized (2:1), double-blinded, placebo-controlled study of patisiran 0.3mg/kg or placebo IV q3W in patients with hATTR amyloidosis with polyneuropathy (NCT01960348). Change in presence and severity of diarrhea symptoms was evaluated descriptively using question-level analyses from COMPASS-31 and Norfolk QOL-DN.

Results: APOLLO enrolled 225 patients: median age 62 years, 74% male, 43% V30M, FAP Stage 1 (46%) and 2 (53%). At baseline, two-thirds reported mild to severe bouts of diarrhea in the prior year on COMPASS-31. After 18 months, patisiran treated patients were 3.5-fold more likely to report improvement in diarrhea compared to placebo patients (18% vs 5%, respectively). Patients treated with patisiran were also more likely to remain stable in their diarrhea severity than those receiving placebo (54% vs 42%, respectively). On Norfolk QOL-DN, more placebo-treated patients progressed to moderate or severe diarrhea and/or loss of bowel control at 18 months vs baseline (43% vs 33%, respectively); fewer patisiran-treated patients had moderate or severe symptoms at 18 months vs baseline (27% vs 34%, respectively).

Conclusions: Following 18 months, patisiran was more likely to improve or stabilize diarrhea at a lower-grade severity than placebo based on question-level analyses of patient-reported questionnaires. These data reinforce the clinical benefit of patisiran in addressing the debilitating autonomic symptoms of hATTR amyloidosis.


Keywords: Amyloidosis

Grant Support: None.
PXT3003 pleotherapy improves neuromuscular dysfunction in Charcot-Marie-Tooth type 1A

Thomas Prukop¹, Stephanie Wernick², Lydie Boussicault³, David Ewers², Karoline Jäger⁴, Lisa Linhoff², Julia Adam², Michael Bartl¹, Dirk Czesnik⁴, Jana Zschüntzsch⁴, Jens Schmidt⁴, Julien Laffaire³, Philippe Rinaudo³, Nathalie Cholet³, Anthony Brureau³, Serguei Nabirotchkin³, Klaus-Armin Nave², Rodolphe Haji³, Daniel Cohen³, Michael Sereda¹

¹Max-Planck-Institute of Experimental Medicine, University Medical Center, Goettingen, Germany, ²Max-Planck-Institute of Experimental Medicine, Goettingen, Germany, ³Pharnext, Issy-Les-Moulineaux, France, ⁴University Medical Center, Goettingen, Germany

The most common type of Charcot-Marie-Tooth disease (CMT1A) is caused by a duplication of PMP22, leading to dysmyelination, axonal loss and progressive muscle weakness. No therapy is currently available. PXT3003, a low-dose combination of baclofen, naltrexone and sorbitol, is a novel polytherapeutic approach reported to slow disease progression in the Pmp22 transgenic rat model of CMT1A. This effect was even more striking after early postnatal short-term administration that improved PI3K-AKT/MEK-ERK signaling dysbalance, axonal diameter distribution and partially prevented disease manifestation in CMT1A rats. Distal motor latencies (DML) correlated with the clinical improvement of CMT1A rats (Prukop et al., 2019). However, the synergistic effect of the single components of PXT3003 remained elusive. Thus, using a DRG co-culture system derived from transgenic rats we first found that PXT3003 exhibited a superior activity on myelination when compared to its single and dual components. We then applied a clinically relevant study design with late-onset therapy start in phenotypically affected CMT1A rats at multiple PXT3003 dosages and dual components for 3 months. In line with the in vitro data, PXT3003 treated animals exhibited a superior performance in contrast to single components when examining clinical endpoints. In order to address the effect of PXT3003 on the motor unit-beyond Schwann cell pathology, we then examined the neuromuscular junctions (NMJ) and muscle pathology in treated CMT rats. PXT3003 protected the number of functional NMJs in CMT1A rats. Moreover, in isolated muscles of CMT1A rats, we observed a shift in favor of fast contracting fibers after PXT3003 treatment. We thus conclude that baclofen, naltrexone and sorbitol contribute to the effect of PXT3003. We hypothesize that PXT3003 supports axonal function, improves the function of NMJs and consecutive muscle innervation which may contribute to the improved motor function observed in CMT1A rats.


Keywords: Pre-clinical Studies, Schwann Cell, Axonal Biology

Grant Support: This trial was supported by Pharnext.
Homozygosity for the Glu89Gln mutation in hATTR: first report of an Italian family

Anna Mazzeo, Federica Taioli, GianMaria Fabrizi, Luca Gentile, Claudia Stancanelli, M'hamed Aguennoz, Massimo Russo, Giuseppe Vita

1Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy, Messina, Italy, 2Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy, Verona, GA, Italy, 3Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy, Verona, Italy

Introduction. Hereditary transthyretin amyloidosis (hATTR) is related to different point mutations in the 127-amino acid TTR gene. In most of these, inheritance is autosomal dominant; homozygosity has been reported in V30M and V122I mutations. Patients homozygous for the V30M mutation do not appear to suffer from more severe disease (Holmgren et al., 1992), and asymptomatic homozygous V30M gene carriers have been described (Ikeda et al., 1992). A more recent study reported the largest homozygous V122I cohort, demonstrating an association with earlier onset. We describe the first case of ATTR homozygous for the amyloidogenic Glu89Gln mutation with an early onset and rapid course of disease.

Patient and Results. A 39-year-old man had a 2-year history of dyspnea and hypertrophic cardiomyopathy with diffuse left ventricular wall thickening. Because of cardiac worsening, he underwent cardiac transplantation. 2 years later he complained mainly of impotence. He then manifested others features of progressive and severe autonomic involvement (orthostatic hypotension, constipation alternating with diarrhea). He sudden died at 48 years. Family history was positive for heart failure: the mother and three of her brothers. 2/4 died at 53 to 63 years of age, and onset of symptoms had been at 45 to 56 years of age. The other two are heterozygous. His father died at 84 years. Conclusions. In our single-center experience in Sicily, Glu89Gln mutation is characterised by 5th - 6th decade onset, neuropathy as presenting symptoms with heart dysfunction. Homozygosity for the Glu89Gln mutation is associated with an earlier onset and rapid course of disease with severe cardiac and autonomic disturbances. Transthyretin analysis should be considered in young patients with heart disease mainly in presence of autonomic features such as impotence, hypotension and gastrointestinal dysmotility.

References: None.

Keywords: Amyloidosis

Grant Support: None.
The biological significance of exploring CMT1A hypercellularity in peripheral nerves

Davide Visigalli¹, Giovanna Capodivento¹, Daniela Marubbi², Angelo Schenone³, Lucilla Nobbio¹

¹DINOGMI University of Genoa, IRCCS San Martino Hospital, Genoa, Italy, ²DIMES University of Genoa, IRCCS San Martino Hospital, Genoa, Italy

The prevalent feature of CMT1A neuropathy is dysmyelination associated with an abnormal remodelling of the whole peripheral nerve. Although the number of myelinated axons is reduced in CMT1A due to an impasse of Schwann cells (SC) differentiation program, abnormal proliferation is also a well-known aspect of pathological nerves both in animal models and human patients. Several cell types other than SC have been proposed to mediate this process in CMT1A. However, the role of most of these cells is still unclear.

In an experimental model of CMT1A, we confirmed a remarkable increase of cell nuclei and DNA, by immunofluorescence and Sybr-Green assays, either in motor and sensitive peripheral nerves. Interestingly, this increase was evident starting from 30 days after birth and deeply grew over time. Since we aimed at identifying a molecular determinant paralleling this progressive increase of cells, we performed real time qPCR starting from a transcriptome profiling already performed in our lab. We found a significant overexpression of genes still underexplored in CMT1A but whose role is well known in cell proliferation, glial differentiation, tissue remodelling and monocyte differentiation. Interestingly, these genes are strongly and early modulated following crush injury to suggest a role in peripheral nerve plasticity. In our opinion, in peripheral nerves it is present a not well defined cellular type with specific undescribed function that is overexpressed in CMT1A and participate in the development of neuropathological abnormalities specific of this neuropathy.

References: None.

Keywords: CMTR, Schwann Cell

Grant Support: None.
Poster 21

Cardiopulmonary Exercise Test Performance and Predictors of Aerobic Capacity in Charcot Marie Tooth Disease 1A

Gita Ramdharry1, Amanda Wallace1, Philip Hennis2, Aleksandra Pietrusz2, Magdalena Dudziec3, Katherine Jones4, Matilde Laura1, Michael Hanna2, Mary Reilly2

1University College Hospitals NHS Foundation Trust, University College London, London, United Kingdom of Great Britain and Northern Ireland, 2University College London, London, United Kingdom of Great Britain and Northern Ireland, 3Kingston University, University College London, London, United Kingdom of Great Britain and Northern Ireland, 4University College London NHS Foundation Trust, London, United Kingdom of Great Britain and Northern Ireland
**Background:** Investigations of people with Charcot-Marie-Tooth disease (CMT) found reduced activity than the general population (1–3) and de-conditioning, as measured by exercise testing in seven participants (4). The objective of this study was to report in detail the cardiopulmonary response during maximal cycling exercise in a larger cohort of patients with CMT 1A. A second objective was to explore potential predictors of aerobic capacity with measures of physical impairment and functional performance.

**Methods:** Twenty-two people with CMT1A were recruited. Participants underwent maximal cardiopulmonary exercise testing (CPET) using a semi-recumbent cycle ergometer. During the test, on-line gas exchange was measured. Data were analysed to determine the peak O2 consumption (VO2 peak), anaerobic threshold (AT), maximum heart rate (MHR), ventilatory equivalent for CO2 slope (VE/VCO2) and Respiratory Exchange Ratio (RER). Impairment, functional and patient reported measures were also recorded. Predicted CPET variables were calculated based on published normative data for age, gender and weight (5,6).

**Results:** There was a significant difference in VO2 peak compared to predicted values (CMT: 21.6 ±4.6 ml/kg/min, predicted: 28.0 ±5.2 ml/kg/min; p<0.01), AT (CMT: 12.1 ±2.1, predicted: 15.4 ±2.2; p<0.01) and MHR (CMT: 134.2 ±17.7, predicted: 176.2 ±14.5; p<0.05). There was no difference in ventilatory efficiency (VE/VCO2) and RER was 1.10 indicating that participants were working maximally. Linear regression analysis demonstrated that VO2 peak is related to body fat percentage (R²=0.37, p<0.01) and six minute times walk distance (R²=0.34, p<0.01).

**Conclusion:** Lower than predicted CPET variables were observed that were not explained by cardiopulmonary limitations or reduced effort. This indicates that peripheral factors maybe limiting the exercise bike task, e.g. quadriceps strength. The regression analysis implied prediction of VO2 peak by body fat percentage and 6 minute walking distance, but may not be causative. Six minute walk distance could be a potential proxy measure of cardiopulmonary fitness.

**References:**

**Keywords:** CMTR, Clinical Trials

**Grant Support:** This work was funded by an NIHR Research for Patient Benefit Award PB-PG-0711-25151 (Chief Investigator: G.M.R.). This is a summary of independent research funded by the National Institute for Health Research (NIHR)’s Research for Patient Benefit Program. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health. The Queen Square MRC Centre for Neuromuscular Diseases is supported by a Medical Research Council grant (MR/K000608/1) (M.G.H., M.M.R., G.M.R.). M.M.R. received support from Medical Research Council (MRC), MRC Centre grant (G0601943), and the National Institutes of Neurological Diseases and Stroke and office of Rare Diseases (U54NS065712). This research was also supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre.
Poster 23

ESCOR-TTR: A National patient support program to monitor patients treated for hereditary transthyretin-mediated amyloidosis (hATTR)

David ADAMS¹, Shahram ATTARIAN², Pascal CINTAS³, Laurent MAGY⁴, Yann PEREON⁵, Philippe PETIOT⁶, Jean Philippe CAMDESSANCHE⁷, FILNEMUS FILNEMUS⁸, Francoise PELCOT⁹

¹Univ Paris Sud, APHP, Le Kremlin Bicêtre, France, ²Hôpital de la Timone, Marseille, France, ³Hôpital Pierre Paul Riquet, Toulouse, France, ⁴Centre Hospitalier Universitaire Dupuytren, Limoges, France, ⁵CHU de Nantes, Nantes, France, ⁶Hôpital la croix Rousse, Lyon, France, ⁷CHU St Etienne, Saint Etienne, France, ⁸Filière nationale des maladies neuro musculaires, Marseille, France, ⁹Association Française contre l’Amylose, Marseille, France
**Introduction**

hATTR amyloidosis is a progressive, life-threatening disease caused by a mutation in the TTR gene where amyloid fibrils accumulate in multiple tissues, including nerves and the heart. Due to its rapid progression, patients require close follow-up. Our objective was to create a patient program, ESCOR-TTR, to support both patients and their treating physicians in French centers.

**Methods:**

A group of French hATTR experts (neurologists and cardiologists) and patient representatives gathered to define the best approach to monitor hATTR symptoms between two routine consultations, including patients’ and experts’ needs. The workshop was facilitated by an independent observer and followed up by several expert meetings.

**Results:**

The ESCOR-TTR program was initiated in February 2019 and is expected to run for a minimum of 1 year. Nurses were trained to identify disease progression according to criteria established by the experts. All patients receiving treatment for hATTR are eligible to enroll in the program which consists of an inclusion call and four follow-up calls (months 3, 6, 9 and 12) conducted by a trained nurse. The nurse monitors the course of the patient’s disease and helps the patient to prepare visits with the neurologist at 6 and 12 months and to complete self-assessment questionnaires. In the case of rapid disease progression, she may send an alert to the neurologist. Call content and questionnaires are securely logged and forwarded to the referring neurologist. A nurse helpline is also available for patients who wish to call spontaneously with basic questions.

**Conclusion:**

ESCOR-TTR first global program designed to answer the unmet need of the follow-up of the patients between their visits. The program combines distance monitoring provided by nurses ensuring a closer follow-up of the disease course and standardized national face to face evaluation by physicians. The program has been endorsed by NNEPf, Fibnamus, and Amyloidosis Patient Association.

**References:** None.

**Keywords:** Amyloidosis, Other

**Grant Support:** ALNYLAM PHARMACEUTICAL
Sensitivity of Clinically Assessed Measures of Balance and Computerized Dynamic Posturography in Pediatric CMT

Timothy Estilow¹, Allan Glanzman¹, Megan Beam¹, Michelle Nardone¹, Sabrina Yum²

¹The Children's Hospital of Philadelphia, Philadelphia, PA, USA, ²The Children's Hospital of Philadelphia, Perelman School of Medicine University of Pennsylvania, Philadelphia, PA, USA

We aimed to identify sensitive clinical outcome assessments (COA) and adaptive strategies used to maintain balance in pediatric CMT. Eight participants (11.1±3.3 y/o) (4 male) with CMT 1A completed CMT Pediatric Scale (CMTPedS), Y-Balance test, and computerized dynamic posturography (CDP) Sensory Organization Test (SOT), evaluated utilization of visual/vestibular/somatosensory feedback for postural control, and Motor control tests (MCT), evaluated motor response time. Data was converted to z-scores. Impairment was described as z-score ≥ 2 s.d. below mean, and CMTPedS was used to classify disease severity. CMTPedS score was (12.75±5.92), five participants mild and three moderate disease severity. Dorsiflexion strength (2.59±0.95), sensation (4/8 participants decreased pinprick/vibratory sensation), and BOT-2 Balance subtest (-3.52±3.88) were impaired. Y-balance (0.60±0.89) and CDP composite SOT (-0.17±1.11) didn’t detect impairment; however progressive decrement was observed in conditions with <3 systems available. Participants performed best in static condition with all systems available (0.57). Conflicting visual stimuli negatively impacted performance (-0.14), and performance was the worst (-0.51) with vision occlusion, conflicting somatosensory stimuli, and only vestibular input available. MCT showed increased latency times (176.5ms ±19.27; normal latency < 150-160ms) for motor response. Anterior (COG) was present in 6/8 participants, consistent with limited dorsiflexion range. Increased forward latency responses were evident over backwards translations. Participants with CMT1A demonstrated ability to compensate for decreased somatosensory input and distal weakness on both the Y-Balance and SOT tests with visual compensation and adaptive postural strategies. Anterior COG allowed utilization of strong plantar flexors for support during static and dynamic-static tasks; however they were unable to utilize their weak dorsiflexors to recover from perturbations pushing them backwards. The BOT-2 balance subtest was the most sensitive balance assessment and should be used in assessment of patients with CMT1A as its items provide dynamic movement challenges, visual occlusion, and varied stances that decrease base of support.

References: None.

Keywords: CMTR

Grant Support: None.
Severe distal motor involvement in a non-compliant adult with biotinidase deficiency

Thierry Kuntzer¹, Géraldine Van Winckel², Diana Ballhausen³, Christel Tran³

¹Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland, ²Division of Genetic Medicine, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland, ³Division of Genetic Medicine, Lausanne University Hospital (CHUV), Lausanne, Switzerland

Biotinidase deficiency (BD) is an autosomal recessive disorder in which affected neonates are unable to recycle biotin and present hypotonia, seizures, ataxia, developmental delay or sensorineural hearing loss. When diagnosed by screening and treated by biotin supplementation outcome is excellent.

We report a young adult BD patient diagnosed by newborn screening who was asymptomatic while on therapy. Six months after voluntary interruption of biotin, he developed a progressive bilateral drop foot and inability to put on tiptoe suggestive of distal motor neuropathy. His biotinidase leukocyte residual activity was found to be null. Molecular analysis of the BTD gene showed a newly homozygous insertion c.1372_1373insT, p.C458Lfs*26. Despite biotin reintroduction, muscle weakness did not improve.

Transition to adulthood may be associated with non-compliance with therapy. The neurological findings in this adult are similar to those of other adults with biotinidase deficiency ascertained in adolescence and adulthood. Prognosis in these symptomatic older individuals may be dependent on the delay in biotin treatment.

References: None.

Keywords: Human Genetics, Metabolic

Grant Support: None.
Spinal muscular atrophy caused by an original MORC2 mutation

Marion Masingue¹, Philippe Latour², Tanya Stojkovic¹

¹Centre de Référence de pathologie neuromusculaire Paris-Est, Institut de Myologie, GHU Pitié-Salpêtrière, Paris, France, ²Département de Neurobiologie, Centre de Biologie Est, Hospices Civils de Lyon, Bron, France

Spinal muscular atrophy (SMA) and distal muscular atrophy (dSMA) are genetic disorders caused by the degeneration and loss of anterior horn cells in the spinal cord. The main gene involved in SMA is SMN1, and to date at least 20 genes have been identified in dSMA. However numerous cases remain unexplained genetically.

So far MORC2 has been described as causing axonal Charcot Marie Tooth disease type 2Z. We report the case of a patient presenting with a MORC2 mutation leading to AMS. The patient, a female of 43 years old, displayed cramps and muscular weakness since age 30. There was no familial history. Clinical examination revealed distal weakness in the upper limbs and a proximal deficit in the lower limbs, with pes cavus. Electroneuromyography (ENMG) showed neurogenic features in all four limbs, with normal motor and sensory conduction. ENMG was normal for her sister.

Screening of the SMN1 gene was normal, and no mutation was found in the dSMA genes. However, exome sequencing allowed us to identify a new original mutation in the MORC2 gene. This mutation c.1152C>A (p.His384Gln) is localized in the functional highly preserved domain S5 of the gene, where five pathogenic mutations have been previously described. It is predicted as pathogenic itself.

Sequencing of the MORC2 gene of her mother and sister (both asymptomatic) was normal. Her father was deceased hence no DNA was available. This observation broadens the genotypic spectrum of SMA, and is the first to report an original MORC2 mutation in such a phenotype.

References: None.

Keywords: CMTR, Human Genetics

Grant Support: None.
Poster 28

Efficacy of a videogame intervention in Charcot-Marie-Tooth on balance and gait training

Prada Valeria¹, hamedani Mehrnaz², Mennella Giulia², Polimone Alberto², Mori laura², Grandis Marina ², Gemelli Chiara², Schenone Angelo²

¹DINO GMI, University of Genova, Genova, Italy, ²DINO GMI, genova, Italy

Charcot-Marie-Tooth disease (CMT) is the most common neuromuscular disease. Patients with CMT neuropathy have often weakness and loss of sensitivity to lower limbs. The feet dysfunction and deformities strongly influence the disability and the quality of life of patients with CMT and, to date, there is not an effective pharmacological therapy to ameliorate the symptoms or to slow the progression of neuropathy. The aim of this project is to further evaluate the efficacy of different rehabilitative protocols and to demonstrate the safety and the efficacy of a rehabilitative protocol with a play station that is easy to transport at home, thinking about an “at home rehabilitation” with an easy to use and cheap instrument, available on the market.

We are recruiting 30 patients with diagnosis of CMT and we are performing the following evaluation with a blind operator before the treatment: strength (MRC), equilibrium (Berg's balance scale), walk (10 meters walk test and 6 meters walk test) and gait analyses. Patients have been invited to fill a questionnaire about the limitations perceived (walk-12).

We then randomized the patients in 3 groups: Stretching and proprioceptive exercises (previously, we have demonstrated the efficacy of this protocol), Nintendo Wii with balance board and a sham-group (massage). Every physiotherapist had to strictly follow the times and the sequences of the exercises of the protocol. They have been blindly re-evaluated at the end of rehabilitation.

Currently, we have the final data of 8 patients. As expected, we found that performances of CMT patients at the balance board are lower compared to normal controls. Spe and Wii treatments showed an better improvement comparing to massage in all evaluations, particularly Spe improves the quality of gait, Wii seems to improve the balance. More data are needed to complete the statistical analyses (at the end of the treatments).

References: None.

Keywords: Other

Grant Support: None.
Expanding the clinical manifestations of the DNAJB2 c.352 + 1G>A mutation

Fernanda Figueiredo, Pedro Tomaselli, Silmara Gouvea, Wilson Junior

University of São Paulo, Ribeirão Preto, Brazil

Background: DNAJB2 gene is almost exclusively expressed in neuronal cells and has been associated to several types of hereditary neuropathies. The homozygous DNAJB2 c.352 + 1G>A mutation seems to be associated not only to dHMN and CMT2 but also to Parkinson’s disease and cerebellar ataxia.

Aim: To present a Brazilian patient with the DNAJB2 c.352 + 1G>A mutation in homozygosis presenting a complex clinical phenotype.

Case report: In a screening study using NGS, we identified the c.352 + 1G>A mutation in homozygosity in a patient followed in our outpatient clinic. He was first seen at the age of 18 years complaining of weakness and walking problems since he was 15. There was no sensory manifestation. He was the only affected member of his family. There was no consanguinity. On examination there was distal weakness and decreased ankle and wrist reflexes. Sensory examination, coordination, cranial nerves and speech were normal. His disease progressed, and on his last evaluation at the age of 29 his weakness and atrophy worsened significantly. He needs support to walk, has severe proximal weakness, vibration is decreased distally, his tendon jerks are absent but on plantar stimulation toes go up and there is triple flexion. EMG shows now a motor and sensory axonal neuropathy (CMAP: R-Peroneal = 0.13 mV, 32.9 m/s; R-Posterior tibial = 0.14 mV, 32.2 m/s; SNAP: R-sural 2.78 uV, 43.8 m/s).

Discussion/Conclusion: This presentation seems to indicate that the DNAJB2 c.352 + 1G>A mutation may also involve the corticospinal tract.


Keywords: Human Genetics, Other, Other, Other, Other

Grant Support: CAPES; PRONAS; INCT Translational Medicine and FAPESP and FAEPA.
Application of unbiased molecular datasets and machine learning for discovery of novel dHMN-associated genes

Matthew Jennings¹, Alexander Smith², Rita Horvath¹, Alan Robinson²

¹Department of Clinical Neurosciences, University of Cambridge, Cambridge, United Kingdom of Great Britain and Northern Ireland, ²MRC Mitochondrial Biology Unit, University of Cambridge, Cambridge, United Kingdom of Great Britain and Northern Ireland

A single causative disease gene cannot be identified for many distal hereditary motor neuropathy (dHMN) patients, despite advances in genomic technology. The use of combined annotation datasets to predict pathogenic variants has been shown using the mitochondrial proteome prediction tool, MitoMiner. This approach is hindered for dHMN, however, by a lack of unbiased datasets relating to the peripheral nerve. Therefore we used experimental datasets to train a predictive model to identify novel dHMN-causing genes and variants.

dHMN-causative variants were compiled by using ClinVar alongside control variants generated from ExAC. These variants were annotated using variant-level annotations, such as protein pathogenicity scores, alongside gene-level annotations, including values from experimental datasets. These annotated files were used as positive and negative training sets to train a random forest machine-learning model. This model was optimized and tested against exome data from patients with known mutations causing dHMN and can effectively distinguish disease-causing variants from a large proportion of other mutations. We used the model to make predictions of pathogenic variants for a cohort of unsolved neuropathy cases.

We have found the use of experimental datasets—especially those relating to the axonal transcriptome—effective in identifying dHMN genes. We see unexpected features being used by the model, such as minimal levels of gene expression in non-neural tissues. The model's accuracy can be improved by adding more non-biased datasets relating to the peripheral motor neuron, and the generation of these data should be encouraged. Our bioinformatic tool applies a systematic non-biased approach to identifying novel dHMN variants appropriate for the next generation sequencing era.

References: None.

Keywords: Axonal Biology, Human Genetics, Other

Grant Support: None.
A novel mutation c.941AG in WARS gene was identified in a Chinese dHMN family

Ruxu Zhang¹, Binghao Wang², Qi Niu³, Beisha Tang⁴, Stephan Zuchner⁵

¹the Third Xiangya Hospital, Central South University, Changsha, Hunan, China, ²Third Xiangya Hospital, Central South University, Changsha, Hunan, China, ³The First Affiliated Hospital of Nanjing Medical University, Nanjing, China, ⁴Xiangya Hospital, Central South University, Changsha, Hunan, China, ⁵John P. Hussman Institute for Human Genomics, University of Miami Miller School of Medicine, Miami, FL, USA

Distal hereditary motor neuropathy (dHMN) is a clinically and genetically heterogeneous group of inherited neuropathies that share the common feature of progressive distal muscle weakness and wasting without sensory abnormalities. To investigate the clinical and genetic features of dHMN caused by WARS mutations in mainland China, we performed Sanger sequencing of the coding regions of WARS in 160 unresolved CMT patients. We detected a rare heterozygous WARS variant, c.941A>G (D314G), in the proband of an autosomal dominant dHMN family. This variant segregated with the phenotype in 5 affected family members in 3 generations. The clinical features included adolescence to adulthood onset (15~23y), mild to moderate distal weakness and muscle wasting, and minimal sensory findings. Nerve electrophysiological studies indicated motor axonal degeneration. D314G was not present in gnomAD and 250 healthy controls from China. The variant was predicted to be ‘damaging’ or ‘probably damaging’ by in silico prediction tools and as ‘likely pathogenic’ according to the ACMG guidelines. Although this variant is located at the second nucleotide of exon 8, RNA analysis ruled out altered splicing. Structural analysis showed that the p.D314G substitution is located in a deep ‘Trp- and ATP-binding’ pocket, and might have an influence on the recognition, binding and activation of Trp. Our report expands the clinical and mutational spectrum of WARS to a mild and later onset phenotype.

References: None.

Keywords: Human Genetics

Grant Support: the National Natural Science Foundation of China (81771366), the Hunan Provincial Natural Science Foundation (2017JJ2365), the Science Foundation of Health and Family Planning Commission of Hunan Province (A2017001)
THE PATH TO DIAGNOSING CHARCOT-MARIE-TOOTH DISEASE: THE PATIENT EXPERIENCE

Allison Moore¹, Robert Moore¹, Courtney Hollet², Joy Aldrich³

¹Hereditary Neuropathy Foundation, New York, USA, ²Hereditary Neuropathy Foundation, Chesterfield, USA, ³Hereditary Neuropathy Foundation, Seattle, USA

OBJECTIVES: Charcot-Marie-Tooth (CMT) patients cite a long path to obtaining an accurate diagnosis of their disease, even with a family history of CMT. This study assessed the path to diagnosis experienced by CMT patients, considering family history of disease, initial presentation of symptoms, and length of time to obtain a diagnosis.

METHODS: Hereditary Neuropathy Foundation, in association with Hannah’s Hope Fund, created the Global Registry for Inherited Neuropathy (GRIN), to capture detailed Inherited Neuropathy (IN) patient history via an online, IRB approved patient survey from 2013Q1-2019Q1. IN patients (N=2,195) engaged in an eight question survey regarding family history of CMT and diagnosis.

RESULTS: 76% of CMT patients have a history of the disease in their family. Overall, 59% of patients take over one year to get an accurate diagnosis of CMT, with 23% of patients taking five years or more to get diagnosed. 42% present symptoms of age 15 years or younger, with 26% of patients being 30 years or older. 30% of patients were the first to notice their CMT symptoms, while 27% of patients were first identified by a healthcare practitioner (HCP). Neurologists were overwhelming identified at the HCP who first diagnosed CMT at 33%; other practitioners were noted with de minimis results. Genetic testing was the leading method for obtaining an accurate diagnosis at 24%, with electrodiagnostic studies (EDX) next at 15%

CONCLUSIONS: CMT patients can present symptoms early in life, yet it can still take several years to obtain a definitive diagnosis, even with a family history of the disease. While HCP’s early identification of patient symptoms is sizably represented, given the large cohort of youthful manifestation of the disease coupled with the length of time it takes to obtain a definitive diagnosis, increase symptom awareness across the spectrum of HCP’s is indicated.

References: None.

Keywords: Other

Grant Support: None.
Neuropathy-Related Disease Burden in Hereditary Transthyretin Amyloidosis Relative to Diabetic Neuropathy

Michael Pollock¹, Aaron Yarlas², Andrew Lovley², Spencer Guthrie¹, Asia Sikora Kessler², Michelle White²

¹Akcea Therapeutics, Boston, MA, USA, ²Optum, Johnston, RI, USA

Introduction: Hereditary transthyretin amyloidosis (hATTR) is a rare and fatal disease resulting in progressive polyneuropathy and cardiomyopathy. Polyneuropathy symptoms and outcomes associated with hATTR amyloidosis resemble those of diabetic neuropathy (DN). An instrument designed to capture multiple dimensions of quality of life (QOL) in patients with DN – the Norfolk QOL-DN – has been validated with patients with hATTR amyloidosis. It is possible to examine the relative QOL burden of hATTR amyloidosis by comparing Norfolk QOL-DN scores from this population with scores observed for patients with DN.

Methods: The Norfolk QOL-DN captures QOL in patients who suffer from neuropathy with scores ranging from -4 to 136 (higher scores represent lower QOL). In addition to a total score, five domains can be assessed: physical functioning/large-fiber neuropathy (PF/LPN; range -4-56 points), symptoms (0-32), activities of daily living (ADL; 0-20), autonomic neuropathy (0-12), and small-fiber neuropathy (SFN; 0-16). Norfolk QOL-DN scores observed across three published studies of hATTR patients¹,²,³ were compared to scores observed in a cross-sectional survey⁴ of 25,000 patients with diabetes, with or without DN, and with or without ulceration, gangrene or amputation.

Results: Patients with hATTR amyloidosis reported Norfolk QOL-DN total scores of approximately 50 points, with scores at about 25 points for PF/LPN, 10 for symptoms, 7 for ADL, 6 for SFN, and 3 for autonomic neuropathy. These scores are roughly 40% higher than patients who self-reported diabetes with DN; however, they closely match scores from patients who self-reported diabetes with DN accompanied by at least one episode of ulceration, gangrene, or amputation.

Conclusions: The QOL burden of patients with hATTR amyloidosis exceeds that for patients with DN and no complications, but closely matches that of patients with DN accompanied by ulceration, gangrene, or amputation.


Keywords: Amyloidosis, Clinical Trials

Grant Support: None.
Sensory Neuron-derived IGF-1 Augments Neurite Outgrowth And This Autocrine/paracrine Pathway Is Suppressed in Diabetes

Reza Aghanoori¹, Mohamad-Reza Aghanoori¹, Darrell Smith², Prasoon Agarwal¹, Vernon Dolinsky¹, Vinith Yathindranath¹, Donald Miller¹, Paul Fernyhough¹

¹University of Manitoba, Winnipeg, Canada, ²St. Boniface Hospital Albrechtsen Research Centre, Winnipeg, Canada

The level of insulin-like growth factor 1 (IGF-1) in serum of diabetic patients and animal models with type 1 and 2 diabetes declines significantly as the disease progresses. Recently, IGF-1 has been used for treatment of neurodegenerative disorders including Alzheimer’s disease and amyotrophic lateral sclerosis. We hypothesized that impaired autocrine/paracrine IGF-1 in dorsal root ganglia (DRG) was a contributing factor to progressive neurodegeneration and impaired nerve regeneration in diabetic sensory neuropathy. DRG neuron cultures and tissues from age-matched control or streptozotocin (STZ)-induced type 1 diabetic rats were used for in vitro and in vivo studies. Despite no difference in IGF-1 receptor level, IGF-1 protein and mRNA levels in liver and DRG tissues were significantly (P<0.05) lower in type 1 diabetic rats vs age-matched control rats. DRG neurons derived from control rats secreted a higher amount of IGF-1 into the culture media compared to cultures from diabetic rats (P<0.05). IGF-1 mRNA was expressed in neurons of the DRG and brain rather than in glial cells or sciatic nerve tissue as determined by RNA-FISH and Northern blot analysis. The hyperglycemic state suppressed IGF-1 mRNA expression in DRG neurons after 2 days which was relieved by treatment with (10nM) IGF-1 or an aldose reductase inhibitor, Sorbinil (blocks polyol pathway activity under high glucose). Bioinformatic screening and chromatin immunoprecipitation assay revealed NFAT1 and CEBP-β functional binding sites on the IGF-1 gene promoter in rat DRG neurons. In growth factor-free media, either IGF-1 neutralizing antibody or two IGF-1-targeting encapsulated siRNAs (in cationic nanoparticles) downregulated IGF-1 receptor and Akt S473 phosphorylation, and lowered background neurite outgrowth in cultured DRG neurons. In conclusion, downregulation of endogenous IGF-1 in DRG neurons in diabetes may contribute to pathogenesis of progressive distal dying-back neurodegeneration and up-regulation of neuronal IGF-1 at the mRNA level may be a promising target for therapy.

References: None.

Keywords: Axonal Biology, Axonal Regeneration, Other

Grant Support: Funded by CIHR grant # MOP-130282
Previous studies suggest that the metabolic syndrome (MetS) is associated with distal symmetrical polyneuropathy (DSP), and that diabetes and obesity are the main metabolic drivers. The aim of this study is to investigate the association of MetS components with retinal and cognitive function in a bariatric surgery cohort prior to surgery. Patients were recruited from the Bariatric Surgery Clinic at the University of Michigan and lean controls from a research website (no MetS components based on NCEP/ATPIII definition). Participants underwent extensive metabolic phenotyping including a glucose tolerance test and fasting lipid profile. DSP was defined using the Toronto consensus definition of probable clinical neuropathy. Retinal function was measured with frequency doubling technology perimetry (mean deviation), and cognitive function with the NIH Toolbox (composite score). Multivariable linear regression models were used to evaluate the association between MetS components and retinal/cognitive function. We recruited 138 bariatric surgery participants and 46 lean controls. The DSP prevalence was 2.2% in lean controls, 12.1% in normoglycemic, 7.1% in pre-diabetic, and 40.8% in diabetic bariatric participants (p<0.01 for trend). Retinal function was -0.4 (2.8), -0.4 (2.7), -2.1 (4.02), and -1.4 (4.4) (p=0.04 for trend), and cognitive function was 116.9 (13.7), 105.0 (17.4), 105.1 (17.8), 101.6 (18.7) (p<0.01 for trend) for these same groups. Pre-diabetes (-1.8, 95%CI: -3.6,0.0) was the only MetS component associated with retinal function. Systolic blood pressure (2.2, 95%CI: 0.1, 4.3) and waist circumference (-1.4, 95%CI -2.3,-0.5) were associated with cognitive function. Obesity alone may be sufficient to cause DSP and cognitive decline. Similar to previous data for DSP, pre-diabetes and obesity are associated with retinal and cognitive function respectively. Interestingly, while clinical DSP is common in this population, clinical retinopathy and dementia are not, indicating that DSP may be the first metabolic complication in the morbidly obese.

References: None.

Keywords: Metabolic, Diabetes

Grant Support: The project described was supported by Grant Number P30DK020572 (MDRC) from the National Institute of Diabetes and Digestive and Kidney Diseases.
While much is known about diabetes and neuropathy, much less is known about the relationship between obesity and neuropathy. Therefore, we aimed to determine the prevalence of neuropathy stratified by glycemic status to evaluate whether obesity alone is a potential cause of neuropathy. We also aimed to determine the association between the distribution of obesity, using extensive anthropometric measurements, and neuropathy. We performed a cross sectional, observational study in patients attending a bariatric surgery clinic prior to intervention. We also recruited lean controls from a research website. Neuropathy was defined by the Toronto consensus definition of probable neuropathy. Diabetes and pre-diabetes were defined according to the Expert Committee on the diagnosis and classification of diabetes mellitus, and the metabolic syndrome by NCEP/ATPIII criteria. We compared nine anthropometric measurements between obese participants with and without neuropathy. We used multivariable logistic regression to explore associations between these measures, and other metabolic risk factors, and neuropathy. We recruited 138 obese individuals and 46 lean controls. The mean age (SD) was 45.1 (11.3) in the obese population (76% female) and 43.8 (12.1) in the lean controls (82% female). The prevalence of neuropathy was 2.2% in lean controls, 12.1% in obese participants with normoglycemia, 7.1% in pre-diabetes, and 40.8% in diabetes (p=<0.01). Waist circumference was the only anthropometric measure that was larger in those with neuropathy (139.3 cm vs. 129.1 cm, p=0.01). Hip-thigh (71.1 cm vs. 76.6 cm, p<0.01) and mid-thigh (62.2 cm vs. 66.3 cm, p=0.03) circumferences were smaller in those with neuropathy (139.3 cm vs. 129.1 cm, p=0.01). Hip-thigh (71.1 cm vs. 76.6 cm, p<0.01) and mid-thigh (62.2 cm vs. 66.3 cm, p=0.03) circumferences were smaller in those with neuropathy. Waist circumference (OR=1.07, 95%CI 1.02-1.12), systolic blood pressure (OR=2.89, 95%CI 1.49-5.61), and triglycerides (OR=1.31, 95%CI 1.00-1.70) were significantly associated with neuropathy. Normoglycemic obese patients have a high prevalence of neuropathy indicating that obesity alone may be sufficient to cause neuropathy. Central obesity, but not general obesity, is significantly associated with neuropathy.

References: None.

Keywords: Metabolic, Diabetes

Grant Support: The project described was supported by Grant Number P30DK020572 (MDRC) from the National Institute of Diabetes and Digestive and Kidney Diseases.
Poster 37

Deletion of SARM1 has a Protective Effect for High-fat Diet-induced Peripheral Neuropathy and Glucose Intolerance

Ahmet Hoke, Junsoon Kim, Aysel Fisgin

Johns Hopkins University, Baltimore, MD, USA

Introduction: Recently, SARM1 has been highlighted as a critical factor causing axon degeneration both in acute neuronal injury and subacute/chronic conditions such as chemotherapy-induced peripheral neuropathy. Here, we evaluated the effect of SARM1 deletion for the development of distal neuropathy and glucose intolerance after the high-fat diet (HFD).

Methods: SARM1 knockout (KO) mice and wild-type (WT) littermates were fed with normal diet or HFD for 12 weeks. Analysis of thermal test, sensory nerve conduction study (NCS) and intra-epidermal nerve fiber density (IEND) at the hind paws were carried out after diet for the assessment of distal neuropathy. We also measured fasting blood glucose level every week and performed glucose tolerance test, insulin tolerance test, insulin secretion test and innervation of pancreas at the end-point for evaluation of glucose/insulin homeostasis.

Results: WT mice with HFD developed thermal hypoalgesia and significant loss of IEND compared to WT with the normal diet. However, in SARM1 KO mice with HFD, the development of thermal hypoalgesia and the loss of IEND were prevented. There were no significant differences for sensory NCS between groups. Although both SARM1 KO mice and WT littermates showed increased fasting blood glucose level when fed HFD, SARM1 KO mice had significantly lower fasting blood glucose level than WT at the end of the study. Moreover, SARM1 KO mice fed HFD showed less insulin resistance compared to WT on the insulin secretion test and had preserved innervation of the pancreatic islet cells.

Conclusions: This study reveals SARM1 as a potent regulator of distal axonal degeneration and dysfunctional glucose/insulin metabolism induced by HFD. The further research uncovering precise molecular mechanisms will be needed.

References: None.

Keywords: Pre-clinical Studies, Axonal Biology

Grant Support: This study was supported by AMRF and Korean Neurological Association.
Plasma Deoxydihydroceramides are Elevated in People with Diabetic Neuropathy and Correlate with Neuropathy Severity

Vera Fridman, Simona Zarini, Stefan Sillau, Bryan Bergman, Eva Feldman, Brian Callaghan, Jane Reusch

1University of Colorado Anschutz Medical Campus Department of Neurology, Aurora, CO, USA, 2University of Colorado Anschutz Medical Campus Division of Endocrinology, Metabolism, and Diabetes, Aurora, CO, USA, 3University of Michigan Department of Neurology, Ann Arbor, MI, USA

Diabetic neuropathy (DN) is a debilitating condition that affects up to 50% of people with diabetes. Altered sphingolipid metabolism in diabetes may lead to an accumulation of atypical, neurotoxic deoxysphingolipids (dSLs) associated with neuropathy. dSLs can arise from reduced availability of the amino acid L-serine and/or the presence of excessive L-alanine. Studies have not investigated which dSL molecules are relevant to DN. We hypothesized that dSLs are elevated with DN. We examined dSL species using LC/MS/MS in plasma samples from a university based weight management program from age and HbA1C matched subjects with obesity (0, n=19), obesity with Type 2 Diabetes (T2D) (OD, n=18), obesity with T2D and DN (ODN, n=19), and lean controls (LC n=19). Sample means for the majority of deoxydihydroceramides (1-deoxyDHCer) for the four groups followed the same order from lowest to highest: LC, O, OD, ODN. Adjusting for pair-wise comparisons, mean levels of most 1-deoxyDHCer species were higher in the ODN as compared to the LC groups (0.527 vs. 0.226 pmol/100 µl for C16 1-deoxyDHCer, p=0.0021; 1.129 vs. 0.385 pmol/100 µl for C18 1-deoxyDHCer, p=0.0002; 1.136 vs. 0.492 pmol/100 µl for C20 1-deoxyDHCer, p<0.0001; 2.461 vs 1.585 for C22 1-deoxyDHCer, p=0.0496; 0.181 vs. 0.932 pmol/100 µl for C24:1 1-deoxyDHCer, p=0.0073). Mean levels of C20 1-deoxyDHCer were higher in the ODN group than the O group (1.136 vs. 0.733 pmol/100 µl, p=0.0350). No significant difference was observed between OD and ODN groups. Further analysis demonstrated that L-alanine was higher and L-serine lower in ODN versus LC (326.2 vs. 248.0, p=0.0086 and 70.2 vs. 89.8, p=0.0110), consistent with a causal contribution to the observed dSL profiles. 1-deoxyDHCer correlated inversely with nerve fiber density across all groups. These novel findings indicate that 1-deoxyDHCer are elevated in individuals T2D and DN and may be important biomarkers and/or mediators of DN.

References: None.

Keywords: Diabetes, Metabolic

Grant Support: Supported by NIH/NCATS Colorado CTSA Grant Number UL1 TR002535. Contents are the authors’ sole responsibility and do not necessarily represent official NIH views.
Poster 39

Early Parallel Progression Of Peripheral And Cardiac Autonomic Nerve Dysfunction In Recent-Onset Type 1 Diabetes

Gidon Bönhof1, Alexander Strom2, Karsten Müssig3, Oana-Patricia Zaharia2, Julia Szendroedi3, Michael Roden3, Dan Ziegler3

1German Diabetes Center, Division of Endocrinology and Diabetology at HHU, Düsseldorf, Germany, 2 German Diabetes Center, German Center for Diabetes Research (DZD), Düsseldorf, Germany, 3 German Diabetes Center, German Center for Diabetes Research (DZD), Division of Endocrinology and Diabetology at HHU, Düsseldorf, Germany

Purpose: We previously demonstrated an early parallel involvement of small and large fibers in recent-onset type 2 diabetes. Here we hypothesized that this pattern may also be pertinent to type 1 diabetes (T1D).

Methods: Motor and sensory nerve conduction velocity (MNCV, SNCV), vibration perception thresholds (VPT), thermal detection thresholds (TDT), intraepidermal nerve fiber density (IENFD), and heart rate variability (HRV) were assessed in participants with T1D from the German Diabetes Study (GDS) at baseline (diabetes duration £1 year) and in glucose-tolerant controls: CON/T1D-B: n=96/360; age [median (1st; 3rd quartile)]: 34.5 (26.0; 46.8)/34.6 (26.5; 45.3) years; male: 72/58%; BMI: 25.0 (22.9; 28.3)/24.0 (22.0 (22.0; 27.0) kg/m²; diabetes duration: -/173 (114; 173) days; HbA1c: 5.1 (5.0; 5.3)/6.4 (5.9; 7.2)%; M-value (hyperinsulinemic-euglycemic clamp): 11.6 (9.1; 13.6)/8.2 (6.5; 10.4) mg*kg⁻¹*min⁻¹.

Results: T1D-B showed lower peroneal MNCV ([mean±SEM]: 45.8±0.2 vs 47.0±0.3 m/s), median MNCV (55.1±0.2 vs 56.0±0.7 m/s), and IENFD (10.0±0.5 vs 11.2±0.5 fibers/mm) than CON (P<0.05). In T1D, a deterioration from baseline to 5 years (n=151) was noted for ulnar and median MNCVs and SNCVs (e.g. ulnar MNCV: 57.4±0.4 vs 56.3±0.3 m/s), malleolar VPT (0.76±0.07 vs 1.12±0.12 µm), and HRV indices (e.g. standard deviation of normal RR intervals (SDNN): 69.3±2.4 vs 62.0±2.1 ms; root mean square of successive differences (RMSSD): 42.8±2.3 vs 34.7±2.0 ms) (all P<0.05). Peroneal MNCV, sural SNCV, and TDT remained unchanged. The decline in MNCV was associated with an increase in HbA1c (e.g. median nerve: β=-0.316, P=0.004) and the deterioration in HRV with decreasing M-value (e.g. SDNN: β=0.246, P=0.041).

Conclusions: Within the first 5-6 years of type 1 diabetes despite good glycemic control, the deterioration in median and ulnar MNCV was related to worsening HbA1c levels, while cardiac autonomic dysfunction progressed in relation to increasing insulin resistance.

References: None.

Keywords: Small Fibers

Grant Support: This work was supported by the Ministry of Culture and Science of the State of North Rhine-Westphalia and the German Federal Ministry of Health. This study was supported in part by a grant from the German Federal Ministry of Education and Research to the German Center for Diabetes Research (DZD).
Oxidative Stress and Human Diabetic Neuropathy: Role of NADPH Oxidase 5

Faye Mendelson¹, Stephanie Eid², John Hayes², Kai Guo³, Crystal Pacut², Junguk Hur³, Eva Feldman ²

¹University of Michigan, Ann Arbor, MI, USA, ²University of Michigan, Ann Arbor, USA, ³University of North Dakota School of Medicine and Health Sciences, Grand Forks, USA

Diabetic Neuropathy (DN) is a common complication of diabetes. The underlying pathophysiological mechanisms of DN are not clear. However, reactive oxygen species (ROS) appear to play a key role in the cellular and molecular injury observed in DN. NADPH oxidase (NOX) enzymes generate ROS and of the 5 isoforms of NOX (1-5), NOX5 is present only in man. The aim of this study was to investigate a role for NOX5 in DN in cutaneous nerve fibers and sural nerve biopsies of subjects with DN.

Cellular localization of NOX5, myelin basic protein (MBP) and protein gene product (PGP) 9.5 were determined in cutaneous nerve fibers of non-diabetic controls and subjects with DN. NOX5 methylation status, gene expression and protein levels were assessed in subjects with DN that were divided into two groups based on changes in sural nerve myelinated fiber density: regenerators (showing significant nerve regeneration) and degenerators (showing significant nerve degeneration).

Our preliminary findings show that NOX5 is present in diabetic myelinated cutaneous nerve fibers, but absent in control fibers. Genome-wide DNA methylation analysis revealed that the NOX5 promoter, enriched with CpG sites, is hypomethylated in sural nerve biopsies of the degenerator cohort compared to the regenerator. Focused qPCR array revealed alteration of gene profiles in the oxidative and antioxidative pathways of the degenerator sural nerves compared to regenerators. In particular, NOX5 was increased at both the mRNA and protein levels in the degenerator cohort. The increase in NOX5 protein expression in degenerator sural nerves was accompanied with a decrease in MBP levels relative to the regenerator group.

Overall, our results point to a potential epigenetic and mechanistic role for NOX5 in DN, although further mechanistic studies are needed to provide more insight into the contribution of NOX5 to DN pathogenesis.

References: None.

Keywords: Diabetes

Grant Support: None.
Neuropathy is the most prevalent complication of type 2 diabetes (T2D) and prediabetes. The progression of neuropathy in prediabetic and T2D patients correlates with dyslipidemia characterized by elevated levels of circulating saturated fatty acids (SFAs). Recent studies indicate that dietary replacement of SFAs with monounsaturated fatty acids (MUFAs) improves the metabolic health of prediabetic and T2D patients; however, the differential effect of dietary SFAs and MUFAs on neuropathy is unknown. This study examined the impact of SFAs and MUFAs on nerve function.

Three groups of mice were fed diets with varying fatty acid composition from 6 to 24 weeks including a standard diet (SD), a SFA-rich high fat diet (HFD), and a SFA-rich HFD until 16 weeks followed by a MUFA-rich HFD (HFD-MUFA) until 24 weeks. At 24 weeks, both HFD and HFD-MUFA groups exhibited impaired glucose tolerance, increased body weight, and higher body fat mass compared to the SD group. Despite equivalent metabolic dysfunction in HFD and HFD-MUFA groups, the HFD-MUFA mice exhibited a complete restoration in sural and sciatic nerve conduction velocity. In parallel, intraepidermal nerve fiber density was significantly increased in HFD-MUFA mice compared to HFD mice.

To identify molecular changes underlying the restoration of sensory function in HFD-MUFA mice, we next evaluated the effect of SFA palmitate and MUFA oleate on mitochondrial dynamics in cultured dorsal root ganglion (DRG) sensory neurons. Diabetic concentrations of palmitate impaired mitochondrial transport and function in DRG axons. Supplementation of palmitate treatments with oleate prevented the impairment of axonal mitochondrial transport and restored mitochondrial membrane potential and ATP production in DRG neurons.

Together, these results support the contention that the development of neuropathy in prediabetes is related to mitochondrial dysfunction induced by SFAs, and that MUFAs reverse the progression of neuropathy by protecting mitochondrial function and dynamics in DRG neurons.

References: None.

Keywords: Metabolic, Diabetes, Axonal Biology

Grant Support: This study was supported by U.S. National Institutes of Health (NIH) National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Grants R24 DK082841 and R01 DK107956 (to E.L.F.) and F32 1F32DK112642 and T32 1T32DK101357 (to A.E.R.); the NIDDK DiaComp Award DK076169 (to E.L.F.); Novo Nordisk Foundation Grant NNF14OC0011633 (to E.L.F.); the Milstein, Nathan and Rose Research Fund; the American Diabetes Association, the Program for Neurology Research and Discovery; and the A. Alfred Taubman Medical Research Institute. Confocal microscopy and image analysis were completed at the Michigan Diabetes Research Center’s Microscopy and Image Analysis Core, supported by NIH NIDDK Grant P60DK020572.
Lifestyle changes, including dietary reversal (DR), can ameliorate peripheral neuropathy (PN) in patients with prediabetes and type 2 diabetes (T2D) however the mechanisms remain unclear. Our objective was to identify the contributions of altered nerve lipid profiles in PN development using mouse models of diabetes that underwent DR. 5wk old mice were fed a standard (10% kcal fat; SD) or high fat diet (60% kcal fat; HF) and at 12wk, a subset of HF mice were injected with STZ to induce a more diabetic-like phenotype. To simulate DR, subsets of HF and HF-STZ mice were placed on the SD from 16-24wk. At study conclusion, untargeted and targeted lipidomic profiling, complemented with RNAseq gene expression analysis, was performed on sciatic nerve (SCN) tissue. Compared to HF and HF-STZ mice, PN was corrected in HF-DR and HF-STZ-DR animals. Untargeted lipidomics revealed that triglycerides were increased in HF and HF-STZ SCN tissue but decreased in SD and DR groups. Quantitative targeted lipidomics validated these findings with an increase in triglycerides containing saturated fatty acids being observed in HF mice. Gene expression analysis revealed numerous differentially expressed genes that were dysregulated in HF and HF-STZ SCN but reversed by DR while KEGG enrichment indicated that lipid metabolism pathways were enriched. The lipidome and transcriptome datasets were integrated and identified a biologically relevant correlation between lipid levels and genes involved in triglyceride regulation. In parallel, DGAT2 expression, the enzyme required for triglyceride synthesis, was increased in sural nerve biopsies from hyperlipidemic diabetic patients with PN. We demonstrate that DR in HF and HF-STZ mice can restore PN that coincides with restoration of nerve lipid homeostasis. Collectively, these findings strengthen the hypothesis that abnormal nerve-lipid signaling is a key player in peripheral nerve dysfunction and suggest that lipid centric therapeutic interventions are needed for PN.

References: None.

Keywords: Diabetes, Pre-clinical Studies, Metabolic, Other, Other

Grant Support: This work was supported by the National Institutes of Health (1DP3DK094292, 1R24082841 to E.L.F.); Novo Nordisk Foundation Center for Basic Metabolic Research (NNF14° C0011633 to E.L.F.); Nathan and Rose Milstein Research Fund; Sinai Medical Staff Foundation Neuroscience Scholar Fund 2; Robert C Graham Fund; Walbridge Aldinger Graduate Fellowship Fund (Post-doctoral Fellowship to P.D.O.); American Diabetes Association (7-12-BS-045); Program for Neurology Research & Discovery; and the A. Alfred Taubman Medical Research Institute; the University of North Dakota Post-Doc Pilot Grant (to K.G.). Research reported in this publication was also supported by Core Services supported by the National Institute of Diabetes and Digestive Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) under award number U2CDK110768 (MMPC). Plasma insulin measurements were performed at The Vanderbilt MMPC (supported by NIH grants DK059637 and DK020593) and lipid measurements were performed by the Cincinnati MMPC (supported by NIH grant DK059630).
Poster 43

Risk Factors for the Development of Chemotherapy Induced Peripheral Neuropathy: A Retrospective Study

Noah Kolb¹, John Singleton², Joan Skelly³, Summer Karafaith², Alpert Smith⁴
Introduction: The objective of this study was to assess frequency, severity and risk factors for chemotherapy induced peripheral neuropathy associated (CIPN) with paclitaxel treatment.

Methods:

A natural language processing tool was utilized to perform retrospective chart review on paclitaxel treated breast cancer patients at the University of Utah between 1999 and 2015. CIPN risk factors were determined via time stamped ICD9/10 records while progress notes were reviewed for CIPN diagnosis and NCI CTCAE severity. Stepwise logistic modeling was used to determine the significant risk factors for the development of CIPN.

Results:

The mean age of the 549 patients was 52±12 with 99.6% female, and 57.9% weekly and 42.1% dose dense paclitaxel. Mean total paclitaxel dose (mg/m2) of those with vs. those without CIPN was 754±231 vs. 738±256 p=0.49.

At the conclusion of chemotherapy: 74% had CIPN: 32% grade 1, 35% grade 2, 4% grade 3, <1% grade 4 or 5 neuropathy. At 2 years after chemotherapy: 36% had CIPN: 20% grade 1, 15% grade 2, <1% grade 3, 4 or 5, 14% CIPN still present but unable to determine severity. There was no significant difference in the percent with CIPN between dose dense and weekly dosing (75.5% vs 71.9%, p=0.31).

Result of stepwise regression modeling:

Significant risk factors for the development of CIPN: pre-existing non-diabetic/non- hereditary neuropathy (OR=12.0 (95%CI: 5.72-25.28)) and hyperlipidemia (OR=1.91 (1.13-3.21)). Risk factors for persistent CIPN at 2 years: Non-diabetic/non-hereditary neuropathy (OR=4.42 (2.94-6.63)), diabetic polyneuropathy (OR=3.46 (1.11-10.79)) and hypertension (OR=1.95 (1.33-2.86)).

Conclusions:

Approximately 75% of breast cancer patients treated with paclitaxel develop CIPN and it frequently persists 2 years later. Regression modeling demonstrates that pre-existant neuropathy, hyperlipidemia and hypertension may represent important risk factors for CIPN development and persistence.

References: None.

Keywords: Other

Grant Support: None.
Depleted Systemic Markers of Neuroinflammation And Growth Factors In Type 2 Diabetes Patients With Polyneuropathy

Gidon Bönhof¹, Alexander Strom², Julia Kannenberg², Margit Heier³, Wolfgang Rathmann², Annette Peters⁴, Christa Meisinger⁵, Michael Roden⁶, Barbara Thorand⁴, Christian Herder⁶, Dan Ziegler⁶

¹German Diabetes Center, Division of Endocrinology and Diabetology at HHU, Düsseldorf, Germany, ²German Diabetes Center, German Center for Diabetes Research (DZD), Düsseldorf, Germany, ³Helmholtz Zentrum München, Munich, Germany, ⁴Helmholtz Zentrum München, German Center for Diabetes Research (DZD), Munich, Germany, ⁵Helmholtz Zentrum München, German Center for Diabetes Research (DZD), München, Germany, ⁶German Diabetes Center, German Center for Diabetes Research (DZD), Division of Endocrinology and Diabetology at HHU, Düsseldorf, Germany

Purpose: The determinants and mechanisms contributing to diabetic sensorimotor polyneuropathy (DSPN) remain unclear. Since inflammation and altered nerve regeneration have been implicated in the pathogenesis of both DSPN and neuropathic pain, we hypothesized that the corresponding biomarkers could be associated with DSPN and may have the potential to discriminate between the painful and painless DSPN entities.

Methods: We measured 92 serum biomarkers including pro- and anti-inflammatory cytokines, chemokines, and growth factors (GF) using the Proseek Multiplex INF I assay (OLINK Proteomics) in 304 individuals with type 2 diabetes and polyneuropathy (DSPN+), defined by the Toronto Consensus Criteria (2011), as well as in 158 individuals with type 2 diabetes without DSPN (DSPN-) and 354 individuals with normal glucose tolerance and without DSPN (NGT) ([mean±SD]: age: 68±9/71±6/69±5 years; male: 76/59/41%; BMI: 30.8±5.3/30.8±4.4/26.9±3.7 kg/m²; diabetes duration: 13.5±9.6/7.6±5.8/– years; HbA1c: 7.4±1.3/6.6±1.0/5.5±0.3%). Within DSPN+, 161 participants suffered from neuropathic pain.

Results: After adjustment for multiple testing and sex, age, BMI, HbA1c, and smoking, the serum levels [normalized protein expression values] of 17 biomarkers including four cytokines (e.g. tumor necrosis factor ligand superfamily-12 (TNFSF12): 9.06±0.35 vs 9.30±0.32 and 9.45±0.29), five chemokines (e.g. C-C motif ligand-4 (CCL4): 7.93±0.68 vs 8.36±0.64 and 8.18±0.57), and four growth factors (e.g. Neurotrophin-3: 0.87±0.40 vs 1.00±0.33 and 1.03±0.34) were lower, while the level of one chemokine was higher in DSPN+ (CCL20: 5.79±1.23 vs 5.24±1.11 and 4.91±1.18) compared to DSPN- and NGT (P<0.05). No differences in biomarker levels were found in DSPN+ individuals with or without neuropathic pain. In diabetes, six biomarkers were associated with measures of peripheral nerve function (e.g. TNFSF12 with sural sensory nerve conduction velocity: r=0.259, P<0.0001).

Conclusions: Deficits in systemic cytokines, chemokines, and growth factors promoting nerve regeneration in type 2 diabetes are linked to polyneuropathy in general but not specifically to the painful or painless entity.

References: None.

Keywords: Inflammatory, Pain
Grant Support: The study was funded in part by grants from the European Union Seventh Framework Programme FP7/2007-2013 (PROPANE consortium; grant no. 602273), the German Center for Diabetes Research, and from the German Diabetes Association (Deutsche Diabetes-Gesellschaft, DDG). This work was also supported by the Ministry of Culture and Science of the State of North Rhine-Westphalia and the German Federal Ministry of Health. This study was supported in part by a grant from the German Federal Ministry of Education and Research to the German Center for Diabetes Research (DZD). Helmholtz Zentrum München – German Research Center for Environmental Health is funded by the German Federal Ministry of Education and Research and by the State of Bavaria. Research was supported within the Munich Center of Health Sciences (MC-Health), Ludwig-Maximilians-Universität, as part of LMUinnovativ.
Poster 46

Sensory polyneuropathy associated with vitamin D deficiency

Sa-Yoon Kang

Jeju National University School of Medicine, Jeju, Korea (Republic of)

Introduction: Vitamin D deficiency is closely related with diabetic polyneuropathy. However, there is no report of peripheral neuropathy associated with vitamin D deficiency in non-diabetic patient. Methods: We describe a 55-year-old woman with vitamin D deficiency presenting with progressive gait ataxia and paresthesia. Results: Neurological examination showed hypoactive deep tendon reflexes and proprioceptive sense impairment. Nerve conduction studies revealed sensory polyneuropathy. Serum 25(OH)D3 and 1,25(OH)2D3 levels were 1.9 ng/mL (normal range; 9.5~55.5) and 1.4 pg/mL (19.6~54.3), respectively. Serum total calcium and vitamin B12 values were 5.5 mg/dL (8.6~10.0) and 185.9 pg/mL, respectively. Serial nerve conduction studies were performed for 1 year, while she received treatment for vitamin D deficiency. There was progressive clinical improvement, but electrophysiological findings were not improved. Conclusion: To my knowledge, this is the first report of sensory polyneuropathy associated with vitamin D deficiency state was developed in non-diabetic patient.

References: None.

Keywords: Metabolic

Grant Support: None.
Liability Of The Voltage-Gated Potassium Channel SK3 Repeat Polymorphism To Acute Oxaliplatin-Induced Peripheral Neurotoxicity

Andreas Argyriou¹, Anna Antonacopoulou², Paola Alberti³, Jordi Bruna⁴, Chiara Briani⁵, Roser Velasco⁴, Guido Cavaletti³, Haralabos Kalofonos²

¹Department of Neurology, “Saint Andrew’s” State General Hospital of Patras, Patras, Greece, ²Department of Medicine-Division of Clinical Oncology; Clinical and Molecular Oncology Laboratory, Rion-Patras, Greece, ³Experimental Neurology Unit, University of Milano-Bicocca, Monza, Italy, ⁴Unit of Neuro-Oncology, Hospital Universitari de Bellvitge-ICO L’Hospitalet-IDIBELL, Barcelona, Spain, ⁵Department of Neurosciences, University of Padova, Padova, Italy

Aim: Thus far, there are conflicting results on the causal role of potassium channels in the pathogenesis of acute Oxaliplatin-Induced Peripheral Neurotoxicity (OXAIPN). As such, we tested the hypothesis that the voltage-gated potassium channel SK3 repeat polymorphism confers liability to acute OXAIPN.

Methods: DNA from 151 Oxaliplatin-treated patients for colorectal cancer was extracted. Genotyping was performed with DNA fragment analysis by capillary electrophoresis of PCR products. The frequency of the 11 most common hyperexcitability symptoms associated with the acute OXAIPN was assessed by a descriptive questionnaire (yes/no response format), while the severity of acute OXLIPN was scored basing on the number of symptoms reported by the patients at each clinical assessment. The increased number of acute symptoms was considered as being suggestive of an increased severity of acute OXAIPN.

Results: A total of 130/151 (86.1%) patients developed any grade of acute OXAIPN. Grade I neurotoxicity was revealed in 43 (28.5%) patients; grade II in 34 (22.5%) and grade III in 53 (53.1%) patients. Genotyping revealed alleles carrying 11 to 20 CAG repeats. The majority of patients was heterozygous (131; 89.4%). The most common numbers of CAG repeats were 15 (n=46), 16 (n=53) and 17 (n=89). Patients carrying alleles with either 15-17 CAG repeats (p=0.601) or 17 repeats (p=0.161) did not experience a higher incidence of grade III (treatment-emergent) acute OXAIPN. Likewise, no increased incidence of acute treatment-emergent OXAIPN was noted in heterozygous patients carrying either two short alleles (< 19 CAG repeats) or one short and one long (≥ 19 CAG repeats) allele (p=0.701).

Conclusion: Our study failed to provide evidence to support a causal relationship between the SK3 repeat polymorphism and acute OXAIPN.

References: None.

Keywords: Other

Grant Support: None.
Poster 48

The Relationship Between Changes in Orthostatic Blood Pressure and Symptoms in Patients with Orthostatic Hypotension

Christopher Gibbons¹, Ben Illigens¹, Razvan Lapusca¹, Marta Campagnolo¹, Ahmad Abuzinadah², Istvan Bonyhay¹, Dong-In Sinn³, Roy Freeman¹
Background: Orthostatic hypotension (OH) is a cardinal feature of the autonomic peripheral neuropathy. Patients with OH can present with a wide range of symptoms, although often without clear link to blood pressure (BP).

Objective: To define the relationship between changes in BP on orthostatic symptom development in patients with OH.

Methods: In this retrospective study we reviewed 1037 charts of patients for autonomic testing from January 2016 to March 2018. Systolic, diastolic and mean arterial pressures were recorded continuously and each minute of testing. Change in blood pressures was compared to baseline values after supine rest, prior to testing. BP measures included the lowest BP in the first 3 minutes of tilt, the absolute BP value on tilt vs the lowest and the orthostatic BP-drop. Subjects were questioned about symptoms of orthostatic intolerance at baseline and two times during the first ten minutes of tilt.

Results: Eighty-nine patients (57% male, mean age 69 years) with OH were included in the final analysis. All patients completed the symptom questionnaires during tilt table testing. Supine hypertension was present in 59%. The majority (78/89) of patients had OH related to neurodegenerative disease or peripheral neuropathy, with lightheadedness and dizziness the most common symptoms. There was no relationship between magnitude of blood pressure fall and maximum symptoms ($R^2=0.0$, $P=NS$) or total symptoms ($R^2=0.04$, $P=NS$). There was no relationship between absolute lowest blood pressure and maximum symptoms ($R^2=0.02$, $P=NS$) or total symptoms ($R^2=0.05$, $P=NS$).

Conclusions: These results suggest a poor relationship between the magnitude of the orthostatic blood pressure fall, the absolute orthostatic blood pressure and symptoms. Many patients are asymptomatic despite substantial BP falls and low orthostatic blood pressures. These findings have implications for clinical care of patients with OH and clinical trials to treat patients with OH.

References: None.

Keywords: Small Fibers, Other

Grant Support: None.
Poster 49
Enhanced Schwann cell and Axonal Regeneration during M. leprae infection following Intracutaneous Axotomy in Armadillos

Gigi Ebenezer\textsuperscript{1}, Maria Pena\textsuperscript{2}, Richard Truman\textsuperscript{3}, Linda Adams\textsuperscript{2}, Kelly Wagner\textsuperscript{1}, Michael Polydefkis\textsuperscript{1}
Nine–banded armadillos develop peripheral neuropathy after experimental *M. leprae* infection that closely recapitulates human lepromatous leprosy neuritis. We used the armadillo model to determine whether *M. leprae* infection alters cutaneous nerve regeneration following intracutaneous axotomy to further understand the pathogenesis of *M. leprae* associated peripheral neuropathy.

15 naïve and 18 *M. leprae*-infected armadillos underwent 3mm excisional skin punches in abdominal skin at 12, 13 and 14 months post-*M. leprae* inoculation. 4mm concentric punches, overlapping the previous 3mm excision punch sites yielded samples that were 30, 60 and 90 days post-axotomy. 3mm skin punches were obtained at the distal leg at 16 months. 50µm sections were immunostained with the panaxonal marker PGP9.5, and anti-p75, the Remak Schwann cell marker. Axonal and Schwann cell growth rates were assessed by measuring changes in epidermal innervation over time, expressed as mean±SE.

Both collateral sprouting and vertical regenerative axon regrowth from the deeper dermis led to complete reinnervation of the epidermis at the axotomy site by 60 days post axotomy. The axonal growth rate was significantly (*p*=0.01) higher in infected animals ( naïve: 21.9+2.5, *M. leprae*: 30.6+2.8 mm/day) at the early 30 day post axotomy time point. Later timepoints had similar growth rates. There was a similar trend towards increased Schwann cell nuclear proliferation (cells/day, naïve: 118+14, *M. leprae*: 137+13) at 30 days. At the distal leg, epidermal nerve fiber density was reduced in infected animals compared to controls (14.3+2.8 vs. 9.5+1.2 fibers/mm, *p*=0.04) while Schwann cell number remained elevated in infected animals (*p*=0.02).

These results suggest that *M. leprae* infection leads to increased and persistent Schwann cell proliferation in response to injury. This is initially associated with enhanced axonal regeneration that slows over time and is ultimately associated with distal axon loss.

**References:**

**Keywords:** Axonal Regeneration, Schwann Cell, Small Fibers

**Grant Support:** Health Resources and Services Administration (HRSA), National Hansen’s Disease Programs
Macrophage And Perisynaptic Schwann Cell Responses To Distal Nerve Injury In An AMAN Mouse Model

Madeleine Cunningham, Gavin Meehan, Sophie Robinson, Rhona McGonigal, Hugh Willison

University of Glasgow, Glasgow, United Kingdom of Great Britain and Northern Ireland

In the acute motor axonal neuropathy (AMAN) variant of Guillain-Barré syndrome (GBS), autoantibodies against gangliosides damage peripheral nerve axons by activating the classical complement cascade. In mouse models, anti-ganglioside antibodies (AGAbs) plus a complement source are used to target the distal motor nerve terminal (mNT), outwith the blood-nerve barrier. In large nerve bundles (spinal roots, nerve trunks), macrophage infiltration into the periaxonal space is a key early feature of AMAN, potentially acting as both executors of axonal injury and assisting in essential debris clearance. At the presynaptic mNT, perisynaptic Schwann cells (pSCs) overlying the terminal axonal membranes respond rapidly to mNT injury, and have been implicated in debris clearance. In this study, we have evaluated the relative responses of macrophages and pSCs to distal nerve injury in our AMAN model.

Three days after AGAb and complement-mediated injury, injured and control diaphragms from MacGreen mice (expressing EGFP in monocytes and macrophages) were analysed for macrophage content and activation state. In parallel, ex vivo nerve-muscle preparations were used to investigate the role of pSCs in mNT injury. In vivo, we show macrophage numbers are not elevated in the diaphragm, nor do they shift to pro- or anti-inflammatory phenotype. However, there is a redistribution of macrophages towards the vicinity of the mNT, indicating that tissue-resident macrophages are attracted to the injury. As the mNT regenerates rapidly, these macrophages are unlikely involved in continued nerve damage. We are currently investigating whether they are critical for debris clearance to allow regeneration. In contrast, observations from ex vivo mNT injury studies demonstrate pSCs do rapidly become phagocytic and engulf axonal debris from the injured mNT.

In conclusion, pSCs are important for clearance of debris and subsequent axonal regeneration. Tissue-resident macrophages are also attracted towards the mNT after localised injury, and their role is being investigated.

References: None.

Keywords: Axonal Biology, Axonal Regeneration, Inflammatory, Schwann Cell

Grant Support: Wellcome Trust
Introduction: In Guillain-Barré syndrome (GBS), two thirds of patients are reported to have antecedent infections up to four weeks prior to the onset of weakness. The profiles of antecedent infections vary geographically. In Southeast Asia, arthropod-borne viruses are common and dengue, specifically, is hyperendemic. In this case-control study, we aim to determine the association of a recent dengue infection and GBS in a Malaysian population. Methods: Consecutive patients presenting with features supportive of GBS were recruited between 2010 and 2018. The frequency of dengue virus infections was determined by dengue IgM antibodies. The sera of neurological controls with a similar distribution in age, gender, and period of sampling were obtained. Sera from patients with GBS were obtained before treatment. Results: A total of 95 patients with GBS were recruited. Evidence of recent dengue infection was present in 20.0% of GBS patients compared to 7.4% of neurological controls (19/95 vs 5/68, OR 3.2, 95% CI 1.1-8.9, p = 0.025). On univariate analysis, GBS patients with dengue IgM were associated with diarrheal symptoms (p = 0.027), severe disease at nadir (Medical Research Council sum score: p = 0.009; GBS disability score: p = 0.018), need for ventilation (p = 0.002), facial palsy (p = 0.004), absence of anti-ganglioside antibody (p = 0.022) and acute inflammatory demyelinating polyneuropathy (AIDP) subtype on electrodiagnosis (p < 0.001). AIDP subtype (p = 0.008) was the only independent associated factor on multivariate analysis. The presence of dengue IgM antibodies in patients with GBS was not associated with age, gender, disease progression, sensory deficits, cerebrospinal fluid albuminocytological dissociation or clinical outcome at 6 months. Conclusions: A recent dengue infection is significantly associated with GBS in Malaysia. Dengue-associated GBS patients were more likely to have AIDP on electrophysiology.


Keywords: Inflammatory

Grant Support: Dr. CY Tan receives research grant from the University of Malaya (BK074-2017).
Introduction: Pure motor Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) is a rare and poorly described form of CIDP.

Methods: Patients with definite or probable CIDP with pure motor clinical form, in a polyneuropathic distribution with abnormalities in sensory conductions studies in electrodiagnostic (EDX) studies (Pure Clinical Motor CIDP, PCM-CIDP) or without (Pure Motor CIPD, PM-CIDP) were included.

Results: 17 patients (prevalence of 2%) were included, with male predominance (71%), and a median age at onset of 48 years. At peak of severity, patients had upper and lower limb weakness (94%), with distal and proximal weakness in four limbs in 8 patients (53%). Clinical course was progressive in 12 patients. 6 patients had an associated disease including 3 patients with paraneoplastic CIDP (B-cell lymphoma, lung cancer and palate cancer), one patient with HIV, one patient with HCV and Sjögren syndrome and one patient with Inflammatory bowel disease. 12/16 and 4/5 patients had response to intravenous immunoglobulin (IVIg) and corticosteroids respectively. In EDX study, conduction block (CB) (82% of patients) and F abnormalities (88%) were frequent. Antiganglioside antibodies were positive in 3 patients (20%) including 2 patients with GM1+. The CSF protein was mildly elevated (>50mg/dl) in 11 patients (79%). During the follow-up, 4 of 10 patients in PCM-CIDP developed mild sensory symptoms, none in PM-CIPD group. Patients with PM-CIDP seem to have poorer outcome at the last follow up (median ONLS 4 versus 2, p = 0.03).

Conclusion: Beyond the previously reported features of pure motor CIDP including the low prevalence, response to IVIg, frequent CBs and F waves abnormalities in EDX study; our study revealed progressive clinical course in majority of patients, frequent associated paraneoplastic disorders and sensibility to corticosteroid therapy. In contrast to PCM-CIDP patients, PM-CIDP patients seem to have poorer outcome and did not develop sensory symptoms during follow-up.

References: None.

Keywords: Inflammatory

Grant Support: None.
CIDP with antibodies to CNTN1 is associated with HLA-DRB11 haplotype

Cinta Lleixà¹, Cinta Lleixà¹, Laura Martínez-Martínez¹, Gemma Boera-Carnicero¹, Elba Pascual-Goñi¹, Lorena Martín-Aguilar¹, Claudia Gianotta², Ilaria Callegari³, Simon Rinaldi⁴, Nicolau Ortiz⁵, Emilien Delmont⁶, Julia Wanschitz⁷, Romana Höftberger⁸, Marteen Titulaer⁹, Bart Jacobs⁹, Eduardo Nobile-Orazio¹⁰, Andrea Cortese¹¹, Thais Armangué¹², Claudia Sommer¹³, Kathrin Doppler¹³, Ruth Huizinga⁹, Óscar De la Calle-Martín¹, Cándido Juárez¹, Luis Querol¹
Introduction: CIDP is a heterogeneous autoimmune disease affecting the peripheral nerves. IgG4 antibodies to contactin-1 (CNTN1) are associated with a specific CIDP subtype. Risk factors associated with the appearance of these antibodies have not been described. HLA class II haplotypes strongly associate with several IgG4-mediated diseases, including anti-NF155-associated CIDP. This study describes the human leukocyte antigen (HLA) class II allele frequencies in chronic anti-CNTN1 positive patients.

Methods: 15 anti-CNTN1 positive and 51 anti-CNTN1 negative CIDP patients were included in the study. The frequencies of the HLA-DRB1 and HLA-DQ alleles were analyzed in all patients and compared with the allele frequencies of the general population obtained from the Allele frequencies database. In silico HLA-peptide binding and CNTN1 antigenicity predictions were performed to analyze overlap between presented peptides and antigenic regions.

Results: When comparing anti-CNTN1+ patients with the normal population: DRB1*11:01 alleles were present in 5 of the 15 anti-CNTN1+ (33.3 vs 14.6%; OR = 3.8, CI = 1.26 to 11.47), DRB1*11:02 alleles were founded in 2 anti-CNTN1+ (13.3 vs 2.84%; OR = 5.87, CI = 1.27 to 27.02) and 1 anti-CNTN1+ patient had the DRB1*11:03 allele (6.67 vs 1.97%; OR = 6.7, CI = 0.82 to 53.63); in contrast, none of the anti-CNTN1+ patients presented the DRB1*11:04 allele (0 vs 9.4%; OR = 1.2, CI = 0.07 to 20.98).

Overall, DRB1*11 alleles appeared in significantly higher proportions in anti-CNTN1+ patients than in normal population (53.33 vs 28.8%; OD = 3.3, CI = 1.14 to 9.56); even though the DRB1*11:04 is more frequently expressed in the general population. DRB1*11 alleles were predicted to present the same peptides and can be considered functionally homologous.

There were no statistically significant differences between the HLA II alleles in anti-CNTN1+ patients and seronegative CIDP patients.

Conclusion: HLA-DRB11 alleles are associated with CNTN1-antibodies in CIDP patients.

References: None.

Keywords: Human Genetics

Grant Support: None.
Poster 54

Clinical and serological investigations in CIDP patients with antibodies against CNTN1/Caspr1 complex.
Introduction:

Autoantibodies against paranodal proteins are useful biomarkers for diagnosis and treatment decision-making in patients with CIDP. Among them, antibodies against contactin-1 (CNTN1) and against contactin-associated protein-1 (Caspr1) were described in small subsets of patients with CIDP. Also, antibodies targeting the paranodal CNTN1/Caspr1 complex (but not CNTN1 alone) were described in one patient with an aggressive CIDP. However, the clinical-immunological features associated with antibodies against the CNTN1/Caspr1 complex have never been described.

Methods:

Eight CIDP patients with antibodies against CNTN1/Caspr1 complex were enrolled for characterization. Antibodies were tested by cell-based assays using HEK293 cells cotransfected with CNTN1 and Caspr1, or transfected with CNTN1 alone. We collected clinical, neurophysiological, laboratory and treatment response data.

Results:

We identified eight patients (5M, 3F) aged between 40 and 75. Patients’ sera showed reactivity only when CNTN1 and Caspr1 were cotransfected, but not when CNTN1 was transfected alone. All patients fulfilled EFNS/PNS definite diagnostic criteria for CIDP. They presented with an aggressive CIDP, with predominantly motor involvement. Half of them were initially diagnosed of Guillain-Barré syndrome due to a subacute onset. Neurophysiological studies showed findings of acquired demyelination in all patients, and acute denervation in at least two of them. Complete response to IVIg or steroids was not observed in any patient, while the response to rituximab in four treated patients was excellent.

Conclusion:

Antibodies against CNTN1/Caspr1 complex are present in a subset of patients with aggressive CIDP with poor response to first line treatments. We recommend screening antibodies against the CNTN1/Caspr1 complex as they will help guide the management. Experiments to elucidate the specific target of the autoantibodies of these patients are undergoing.

Keywords: Inflammatory, Node

Grant Support: None.
Poster 55

Serum Contactin-1 Levels In Chronic Inflammatory Demyelinating Polyneuropathy – A Pilot Study

Luuk Wieske¹, Gwen van Lieverloo¹, Camiel Verhamme¹, Marleen Koel-Simmelink², Ivo van Schaik¹, Filip Eftimov¹, Charlotte Teunissen³

¹Department of Neurology, Amsterdam Neuroscience, Amsterdam UMC, Amsterdam, Netherlands, ²department of Clinical Chemistry, Amsterdam Neuroscience, Amsterdam UMC, Amsterdam, Netherlands, ³department of Clinical Chemistry, Amsterdam Neuroscience, Amsterdam UMC, Amsterdam, Netherlands
Purpose:

Biomarkers assessing disease activity in CIDP are needed to make informed treatment decisions in everyday care. Contactin-1 (CNTN1) is a paranodal axonal adhesion protein. Paranodal and juxtaparanodal proteins, including CNTN1, are targets for autoimmunity in subsets of CIDP patients. We hypothesized that serum CNTN1 levels reflect disease activity in CIDP.

Methods:

Three prospective cohorts of CIDP patients were studied: 1) patients starting induction treatment (IT cohort, N:27) measured at baseline and six months after starting treatment; 2) patients on maintenance treatment starting IVIg withdrawal (MT cohort, N:24) measured at baseline and six months after IVIg withdrawal or at time of relapse and 3) patients in long-term remission without treatment (N:26). Serum CNTN1 was measured using Luminex® assay. Age matched healthy controls (N:33) were used for comparison. Treatment response was defined as improvement by at least the minimal clinical important difference (MCID) on the I-RODS; and/or an increase of ≥8 kPa on grip strength. Relapse was defined as any deterioration requiring retreatment.

Results:

CNTN1 levels were lower in the IT cohort (median 10.2 ng/ml; IQR 8.9-12.5) compared to the MT cohort (12.0; IQR 10.4-15.0), patients in remission (14.2; IQR 11.3-17.7) and healthy controls (13.0; IQR 11.2-14.9; p<0.01 overall). After induction treatment, 2/8 (25%; follow-up sample missing for 1 patient) of the non-responders showed an increase in CNTN1 compared to 12/18 (67%) of the responders (p:0.09). After treatment withdrawal, 5/15 (33%) of patients with a relapse showed a decrease in CNTN1 compared to 7/9 (78%) of the patients without relapse (p:0.09).

Conclusion:

In this pilot study, CNTN1 levels in untreated CIDP patients with active disease were lower compared to patients stable on maintenance treatment, patients in remission and healthy controls. Changes in CNTN1 levels in relation to treatment response should be investigated in a larger cohort.

References: None.

Keywords: Inflammatory

Grant Support: None.
Treatment Status Following Corticosteroid And Immunoglobulin Treatment In The International CIDP Outcome Study (ICOS)

Sander Bus¹, Merel Broers², Carina Bunschoten², Ilse Lucke¹, Gwen van Lieverloo¹, Max Adrichem¹, Stephan Goedee³, Ludo van der Pol³, Bart Jacobs², Filip Eftimov¹

¹Amsterdam UMC, University of Amsterdam, Department of Neurology, Amsterdam Neuroscience, Amsterdam, Netherlands, ²Erasmus MC, University Medical Center, Department of Neurology, Rotterdam, Netherlands, ³University Medical Center Utrecht, Department of Neurology, Brain Center Rudolf Magnus, Utrecht, Netherlands

Background: Treatment in chronic inflammatory demyelinating polyneuropathy (CIDP) mainly consists of corticosteroids or intravenous immunoglobulins (IVIg). Remission is an important long term outcome. Corticosteroid therapy possibly increases the chance of long term remission. We aim to assess duration of treatment and compare remission rates following treatment with corticosteroids (monotherapy or in combination with IVIg) and IVIg.

Methods: Patients fulfilling the EFNS/PNS 2010 criteria for CIDP were prospectively enrolled in the ICOS and treatment data were systematically collected. A preliminary analysis was conducted in treatment naive incident cases from two tertiary centers with a follow-up period of at least one year. For comparison, we grouped patients based on treatment type: corticosteroids (monotherapy or with IVIg) or IVIg monotherapy. We assessed treatment persistence at one year. In addition we assessed remission rates, defined as sustained improvement after discontinuation of treatment.

Results: 31 patients were included of which 22 (71%) received corticosteroids and nine (29%) IVIg monotherapy at baseline. In the corticosteroid group, six received pulsed high-dosed dexamethasone (during six months) and 16 received a combination of IVIg and methylprednisolone (every three weeks during four months). At one year nine (41%) patients in the corticosteroid group were still treated and five (56%) in the IVIg group. In the IVIg group, withdrawal was attempted in seven patients. Remission at one year was achieved in 13 patients (59%) patients treated with corticosteroids compared to four (44%) patients treated with IVIg.

Conclusion: overall about half of patients were treated at one year. Based on this preliminary data, 59% of patients who received corticosteroid monotherapy or the combination therapy were in remission at one year compared to 44% of patients receiving IVIg. At the conference we will present the treatment results of all incident cases in ICOS, including a cohort of patients from a third tertiary center.

References: None.

Keywords: Inflammatory

Grant Support: None.
INTRODUCTION. The Medical Research Council (MRC) scale is an outcome measure of strength, routinely used in neurological examinations. Previous research reported limitations of the MRC scoring system, proposing a collapsed 0-to-3-point scale. We aimed to assess the clinimetric properties of the original 0-to-5-point MRC scoring system and its sensitivity for GBS patients, using data from the International GBS Outcome Study (IGOS)-1300 cohort. METHODS. MRC scores were assessed at entry bilaterally for: shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension and foot dorsiflexion. Rasch analysis was conducted to assess the suitability of the MRC 0-to-5-option response format, individual item fit, local dependency and dimensionality. Discriminative ability was determined by comparing scores to disability level [GBS Disability Score (GBS-DS)]. RESULTS. Data were available from 1099 patients (mean age 49±19 years, 40% female). The cohort comprised 76% (n=838) severely affected patients (GBS-DS≥3). No disordered thresholds were observed, supporting use of the 0-to-5 point response format. It was necessary to combine bilateral measurements to overcome local dependency caused by high inter-item correlations (>0.8). The foot dorsiflexion item required removal from the sum-score to achieve fit to the Rasch model. Rasch-derived MRC sum-scores (0-100, higher values indicate increasing strength) were generated for patients (mean 56.7±25.5). Sum-scores differentiated between patients with mild (mean score 79.3±17.3) versus severe (mean score 49.8±23.6, p<0.001) disability levels. Foot dorsiflexion raw scores (bilateral measures, out-of-10) independently discriminated between disease severity (mild: mean score 8.8±1.5 vs. severe: 5.7±3.4). CONCLUSION. For clinical use, MRC scores in their original format require no adjustment for GBS patients. For research purposes, Rasch-derived MRC sum-scores should be generated, and bilateral measurements combined to account for the symmetrical nature of GBS. Further, we recommend to assess foot dorsiflexion separately, as it may be an important individual indicator of disease severity that cannot be summarized by sum-scores.

References: None.

Keywords: Inflammatory

Grant Support: None.
Diagnostic Delay and Work-Up of CIDP in the International CIDP Outcome Study (ICOS) cohort

Carina Bunschoten\textsuperscript{1}, Ilse Lucke\textsuperscript{2}, Merel Broers\textsuperscript{1}, Bart Jacobs\textsuperscript{1}, Gwen van Lieverloo\textsuperscript{2}, Max Adrichem\textsuperscript{2}, Ludo van der Pol\textsuperscript{3}, Stephan Goedee\textsuperscript{3}, Sander Bus\textsuperscript{2}, Filip Eftimov\textsuperscript{2}

\textsuperscript{1}Erasmus MC, University Medical Center, Rotterdam, Netherlands, \textsuperscript{2}Amsterdam University Medical Center, Amsterdam, Netherlands, \textsuperscript{3}Brain Center Rudolf Magnus, University Medical Center, Utrecht, Netherlands

Introduction

The diagnostic challenges in the spectrum of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) are related to the variation in clinical presentation, electrophysiology, treatment response, and differential diagnosis of CIDP. CIDP is a treatable disorder and an early and correct diagnosis is essential to prevent secondary axonal damage and improve clinical outcome. We aim to describe the diagnostic work-up, identify factors related to diagnostic delay, and investigate the impact on clinical outcome in CIDP.

Methods

A preliminary analysis was conducted in 179 patients included in the International CIDP Outcome Study (ICOS).\textsuperscript{1} For comparisons the median duration to CIDP diagnosis was used to separate patients in an ‘early’ and a ‘late’ diagnosis group.

Results

The time from onset of first symptoms until CIDP diagnosis was median 9 months (interquartile range 4-24, range 1-233 months) and more than 12 months in 70 patients (41%). The diagnostic work-up included nerve conduction studies (100%), lumbar puncture (82%), nerve biopsy (3%), nerve ultrasound (30%), magnetic resonance imaging (33%) and somato-sensory evoked potential (1%). Patients with a late compared to an early diagnosis more frequently had asymmetric CIDP variants (26% vs 8%) and nerve ultrasound examinations (39% vs 19%). Patients with an early diagnosis more frequently had cerebrospinal fluid examinations (94% vs 74%) and more often had elevated CSF protein levels (92% vs 75%).

Conclusions

Based on preliminary analysis, this study confirms the presence of diagnostic delay in CIDP and the first possible related clinical and diagnostic factors have been identified. At the conference, ICOS will be expanded by an additional cohort of treatment naïve CIDP patients and results of the full CIDP cohort regarding diagnostic delay in CIDP, including data on (initial) misdiagnosis, EFNS/PNS classification and possible related impact on clinical outcome.


Keywords: Clinical Trials, Inflammatory

Grant Support: None
Poster 59

Ultrastructural Mechanisms of Macrophage-Induced Demyelination in Guillain-Barré Syndrome

Haruki Koike, Yuki Fukami, Ryoji Nishi, Yuchi Kawagashira, Masahiro Iijima, Masahisa Katsuno, Gen Sobue

Nagoya University Graduate School of Medicine, Nagoya, Japan

Introduction: Although recent advances in the identification of anti-ganglioside antibodies have significantly contributed to clarifying the pathogenesis of Guillain-Barré syndrome, particularly acute motor axonal neuropathy, the mechanism of classical macrophage-induced demyelination in acute inflammatory demyelinating polyneuropathy (AIDP) remains unclear.

Methods: Longitudinal sections of sural nerve biopsy specimens from 11 patients with AIDP exhibiting macrophage-associated demyelinating lesions were examined using electron microscopy. A total of 1205 nodes of Ranvier, with middle sections that were cut perpendicularly, were examined to determine the relationship of the macrophage-associated demyelinating lesions with the nodal regions.

Results: Overall, 252 macrophage-associated demyelinating lesions were identified in the longitudinal sections. Of these, 40 lesions exhibited complete demyelination with no association with the lamellar structures of myelin. In 183 lesions, the macrophage cytoplasm was located at the internodes without association with the nodes of Ranvier or paranodes. In particular, these internodal lesions were more frequent in one patient (152 lesions). Focal unraveling of the myelin layers apposed to the macrophage cytoplasm was frequently seen at the Schmidt-Lanterman incisures, where uncompaction of the myelin lamellae is observed under normal conditions as well. In the remaining 29 lesions, the involvement of nodal regions was obvious. Invasion of the macrophage cytoplasmic processes into the space between the paranodal myelin terminal loops and axolemma from the node of Ranvier was observed in three patients. Immunohistochemistry suggested complement C3d deposition in the areas with initial macrophage-associated demyelinating lesions in patients who underwent biopsy during early disease phase.

Conclusions: The initial macrophage-associated demyelinating lesions were located not only at the internodes but also at the paranodes. The sites at which the macrophages initiated phagocytosis of myelin might be associated with the location of complement deposition in certain patients with AIDP.

References: None.

Keywords: Inflammatory, Node, Schwann Cell

Grant Support: None.
Antibody- and macrophage-mediated internodal demyelination in CIDP: clinical, electrophysiological, immunological and pathological correlations

Jean-Michel Vallat¹, Stéphane Mathis², Elisa Vegezzi³, Mathilde Duchesne¹, Laurence Richard¹, Laurent Magy¹, Antonino Uncini⁴, Jérôme Devaux⁵

¹National reference center for rare peripheral neuropathies and Department of Neurology, Limoges, France, ²Department of Neurology (Nerve-Muscle Unit), CHU Bordeaux, Bordeaux, France, ³C. Mondino National Neurological Institute, Pavia, Italy, ⁴Department of Neurosciences, Imaging and Clinical Sciences University G. d’Annunzio, Chieti-Pescara, Italy, ⁵Institute for Neurosciences of Montpellier, INSERM U1051, Montpellier, France

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a heterogeneous disorder considered an auto-immune disease involving both cellular and humoral immunity. IgG fixation on the outer surface of the Schwann cell has been described in patients’ nerve biopsies, suggesting that autoantibodies may be implicated in the demyelination process, and antibodies against specific nodal and paranodal junction components have been recently identified. In a cohort of 178 french CIDP patients we found that 31% of patients’ sera presented an IgG reactivity toward the node and paranode of mouse sciatic nerve. Interestingly, 18% of the patients presented a strong IgG or IgM reactivity against the internodal compact myelin. We report here the clinical, electrophysiological, immunological, and microscopic features of six of these CIDP patients in whom sural nerve biopsies were available. Five over six patients fulfilled the EFNS/PNS electrophysiological criteria for definite CIDP. These five patients showed increased (1.6 to 5.1 times) duration of proximal compound muscle action potential in at least two nerves. Electron microscopy of sural nerve biopsies showed normal paranodes and nodes, but demonstrated the presence of macrophage-mediated demyelination restricted to the internode. Immunolabeling for Nav channels, MPZ, and neurofilament-H confirmed the presence of segmental demyelination and remyelination. However, the nodal region appeared unaffected in these patients. Altogether these results indicate that CIDP patients with antibodies to internodal myelin or nodal/paranodal components show differential morphological features and pathogenic mechanisms.

References: None.

Keywords: Schwann Cell, Inflammatory, Other, Other, Other

Grant Support: Grant support from the Agence Nationale pour la Recherche (ACAMIN project) under the frame of E-Rare-2, the ERA-Net for Research on Rare Diseases, the Association Française contre les Myopathies (grant #21532) and the GBS-CIDP Foundation International.
Poster 61

Prognostic features for death and progression in patients with POEMS syndrome

Stephen Keddie¹, Janev Fehmi², Mahima Kapoor¹, David Foldes³, Aisling Carr¹, Mary Reilly¹, Shirley D'sa³, Simon Rinaldi², Michael Lunn¹

¹MRC Centre for Neuromuscular DiseasesNational Hospital for Neurology and Neurosurgery, London, United Kingdom of Great Britain and Northern Ireland, ²Nuffield department of Clinical Neurosciences, Oxford, United Kingdom of Great Britain and Northern Ireland, ³Cancer Division, Department of HaematologyUniversity College London Hospitals NHS Foundation Trust, London, United Kingdom of Great Britain and Northern Ireland
Background

POEMS syndrome is a rare multisystem disorder with favourable long term prognosis if appropriately treated. A proportion of patients appear resistant to treatment, some relapse and few die. Ascertaining prognostic factors will assist with identifying high risk patients likely to require more frequent monitoring or more aggressive or alternative therapeutics.

Aim

To evaluate individual risk factors and produce a predictive model for risk of progression or death in POEMS syndrome.

Methods

We retrospectively analysed 100 patients with newly diagnosed POEMS syndrome at our institute from 1998 to present day. We performed univariate and multivariate regression analysis to identify statistically significant risk factors leading to poor outcome.

Results

A binomial logistic regression was performed which ascertained the effect of Haematological non-response (hNR), VEGF non-response (vNR), low glomerular filtration rate (GFR), low albumin at presentation and treatment with autologous stem cell therapy (vs other forms of treatment) on the likelihood of progression or death. The regression model was statistically significant, $X^2 = 50.117$ ($p<0.005$). The model explained 54% (Nagelkerke $R^2$) of the variance in progression or death and correctly classified 87% of cases. Sensitivity was 70%, specificity 95%, positive predictive value was 88% and negative predictive value 86%.

Conclusion

Haematological non-response (hNR), VEGF non-response (vNR), low glomerular filtration rate (GFR), low albumin at presentation and treatment with autologous stem cell therapy (vs other forms of treatment) are significant risk factors in outcome (progression or death) in POEMS syndrome.

References: None.

Keywords: Inflammatory

Grant Support: Dr Keddie is funded by ABN and Guarantors of Brain
Axon degeneration accounts for poor recovery in patients with Guillain-Barré syndrome (GBS), but there are no first-line treatments to target this key stage in pathogenesis. Animal models of the acute motor axonal neuropathy (AMAN) variant have demonstrated that injury to the nerve is caused by autoantibodies to axonal antigens activating the complement cascade, culminating in the formation of a pore. Uncontrolled influx of water and ions, including calcium, through the pore results in conduction block and structural disruption through activation of the calcium-dependent cleavage enzyme calpain. We assessed the potential of calpain inhibition as an axon protective therapy using transgenic mice that over-express the endogenous calpain inhibitor calpastatin (hCAST). Axonal integrity was compared between wild type (WT) and hCAST mice (n=4/group) in our established ex vivo and in vivo injury models of AMAN. Immune-mediated injury was induced at distal axons by administering monoclonal anti-ganglioside antibodies and complement. Neurofilament, a known calpain substrate, was used as a marker of axonal structural integrity. As the diaphragm is the target in our in vivo model, respiratory function was measured by whole-body plethysmography as a functional output. Axon integrity (neurofilament immunolabeling) is significantly protected in ex vivo injury preparations from hCAST compared to WT mice, while nodal integrity is partially protected. In vivo, both WT and hCAST mice acutely develop weakness, and respiratory dysfunction. Distal axonal neurofilament immunolabeling was significantly reduced in WT mice, and in contrast was protected in hCAST mice. In summary, calpain inhibition can protect the axonal integrity of the nerve in an in vivo injury paradigm, but not the acute loss of function, as expected from the effects of uncontrolled ion flux. These studies provide proof of principle that calpain inhibition can protect axons in vivo and lays the foundation for further animal and clinical study using exogenous calpain inhibitors.

References: None.

Keywords: Axonal Biology, Node Biology, Pre-clinical Studies, Inflammatory

Grant Support: Wellcome Trust
Optimizing electrodiagnosis for chronic inflammatory demyelinating polyneuropathy with automated analysis and machine learning

Ilse Lucke, Wouter Potters, Mireille Kamminga, Ivo van Schaik, Filip Eftimov, Camiel Verhamme

Amsterdam UMC - University of Amsterdam, Amsterdam, Netherlands

Background: Diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) is based on consensus guidelines in which interpretations of nerve conduction studies (NCS) have a major role. Automated analysis could improve interpretation of findings to fit into the current electrodiagnostic criteria, which could lead to better diagnostic accuracy. In addition, machine learning is able to detect complex relationships in datasets, which are not visible to the human eye or simple statistical models.

Objectives: to evaluate the diagnostic accuracy of the current EFNS/PNS electrodiagnostic criteria with (out) adaptations and to explore the diagnostic accuracy of machine learning algorithms.

Methods and results: NCS data from patients suspected of subacute or chronic immune mediated neuropathies were extracted from our NCS database in the period between 2009 and 2018. Automating the electrodiagnostic criteria (EFNS/PNS 2010) (85 CIDP patients and 180 patient controls) showed a relatively high sensitivity and moderate specificity. Adaptations to the electrodiagnostic criteria were implemented to explore changes in diagnostic accuracy, such as: exclusion of known pressure segments, the allowed amount of temporal dispersion in the leg nerves, the implementation of CMAP area instead of amplitude, and defining minimal distal CMAP amplitude to allow the criteria to be valid. Especially exclusion of the distal CMAP duration criterion led to an improved specificity. Subsequently, we explored a machine learning model: a Random Forest Classifier algorithm. This algorithm uses the input parameters to create random dichotomous decision trees and then averages the outcomes, thereby creating a robust model for classification. Preliminary results showed that the performance of this random forest classifier was higher than the current EFNS/PNS electrodiagnostic criteria.

Conclusions: Implementing adaptations of the current consensus-based electrodiagnostic guidelines for CIDP improve the diagnostic accuracy in our hospital. A data-driven approach using machine learning algorithms may further improve diagnostic performance.

References: None.

Keywords: Inflammatory

Grant Support: None.
Dengue, a Mosquito-borne Flavivirus infection is endemic in Sri Lanka, with a cumulative reported cases of over 180,000 during the past two years [1]. Neurological complications of dengue occur as a result of metabolic disturbance, viral invasion or immune reaction [2]. Guillain-Barré syndrome (GBS) is a rare post infectious immune mediated complication. We report a case series of GBS subtypes following dengue hemorrhagic fever (DHF). The first case is a 24 year old man, who had acute ascending flaccid paralysis with global areflexia and bifacial palsy for four days after 10 days of dengue critical phase. Clinical diagnosis of GBS was made and started on intravenous immunoglobulin (IVIg). Nerve conduction showed acute inflammatory demyelinating polyradiculoneuropathy (AIDP) subtype. The patient fully recovered in 14 days. The second case is a 17 year old woman, who presented with back pain, acute flaccid paralysis and worsening lower limb pain with areflexia for 5 days after 12 days of dengue critical phase. She later developed respiratory paralysis. Her nerve conduction showed acute motor-sensory axonal neuropathy (AMSAN) subtype. She was treated with IVIg. She was extubated in 7 days and fully recovered in 6 weeks. The third case is a 19 year old man, who had ascending acute flaccid paralysis with areflexia for 6 days after 9 days of dengue critical phase. His nerve conduction showed acute motor axonal neuropathy (AMAN) subtype. He was treated with IVIg and he improved rapidly. All 3 cases were diagnosed as DHF with a positive nonstructural protein 1 antigen and Dengue IgM antibodies. Day 10 Cerebrospinal fluid examination revealed albuminocytologic dissociation in all patients. This case series highlights that post dengue infection GBS can exhibit either demyelinating or axonal forms. High degree of clinical suspicion and timely management is crucial. Duration of recovery may vary according to the subtype.


Keywords: Inflammatory, Other

Grant Support: None.
Poster 65

Types and treatment practices in GBS in a tertiary care center in Sri Lanka

Anomali Vidanagamage¹, Dinusha Dharmaratne², Lakmal Samarasinghe², Kamal Gunaratne³, Arjuna Fernando³

¹National Hospital, Sri Lanka, Colombo, Sri Lanka, ²National Hospital Sri Lanka, Colombo, Sri Lanka, ³National Hospital, Colombo, Sri Lanka
Introduction

The recommended mode of treatment in Guillain-barre (GBS) is either intravenous immunoglobulin (IV IG) or therapeutic plasma exchange (PEX). However, in the presence of delayed recovery, repeated cycles of IV IG and PEX is a practice under debate.

This study aimed at evaluation of types of GBS and modes of therapy used upon Sri Lankan patients. The number of patients encountered was 25, with an age distribution from 17 to 86 years with 13 males and 12 females.

On initial nerve conduction, 13 were of AIDP, 4 were AMAN and rest had nonspecific F wave abnormalities. All the patients were treated with either IV IG or PEX. The 8 patients who showed delayed recovery indicated by a persistent GBS disability score (DS) of 4 or 5 at 2 weeks were given a second course of therapy.

Out of the 25 patients, 8 patients received more than one cycle of treatment and 1 received 3 cycles and 1 received 4 cycles. (IV IG + IVIG - 4, IV IG + PEX - 2, IV IG + TPE + TPE - 1, IV IG + IV IG + TPE + TPE - 1) The mean duration of onset of the second cycle of therapy is 15.7 days and the third cycle is 26 days. The mode of the second cycle was decided depending on the facilities available and clinicians preference. Among the 6 patients who received 2 cycles only, improvement by at least 1 DS had occurred within 18 to 30 days.

The patient who received 3 cycles, improved up to DS 2, within 36 days.

The patient who received 4 cycles didn’t show major improvement.

Conclusion

In the presence of delayed recovery, repeating the second cycle of IVIG or PEX seems to give favorable outcomes which need further studies.

References: None.

Keywords: Inflammatory, Clinical Trials

Grant Support: None.
Effectiveness And Tolerance Of Subcutaneous Immunoglobulin In CIDP – A Substudy Of INCbase

Jeffrey Allen

department of Neurology, University of Minnesota, Minneapolis, USA

Introduction

Subcutaneous immunoglobulin (SCIG) has recently been shown to be an efficacious maintenance therapy for chronic inflammatory demyelinating polyneuropathy (CIDP). Questions remain however concerning long-term effectiveness, tolerability and the optimal switching regimen from intravenous immunoglobulin (IVIg) to SCIG. A specific module will be incorporated within INCbase, a prospective international registry, to provide real-life answers to these questions.

Methods

CIDP patients fulfilling the definite or probable CIDP criteria who are currently stable on treatment with IVIg or SCIG and new patients starting on SCIG (Hizentra; CSL Behring, King of Prussia, PA, USA) will be included in a multicenter study. Standardized data that includes outcome measures and treatment data will be collected at baseline and every 6 months for 2 years. In the event of deterioration unplanned study visits will be conducted to capture interval outcomes and treatment data. The primary outcome is the proportion of patients who are persistent with SCIG treatment after a 1-year follow-up. Persistence is defined as the absence of (a) discontinuation of or (b) switch from initial SCIG treatment. Main secondary outcomes include relapses (both attributed and not attributed to tapering/withdrawal of treatment), treatment withdrawal not attributed to relapse, changes in disability, impairment and quality of life between the start of treatment and after 1 and 2 years of follow-up, proportion of patients tapered off SCIG and adverse events. In an exploratory analysis, we will assess the impact of different SCIG switching regimes. In addition, we will collect data on reasons for switching from IVIg to SCIG and vice versa, and the rationale for the choice of the initial dose and titration schedule will be determined. We will include at least 150 patients on SCIG treatment and 150 patients on IVIg treatment. First results are expected in June 2023.

References: None.

Keywords: Inflammatory

Grant Support: This INCBase substudy is supported by CSL Behring.
Association Of IgM Antiglycolipid Antibodies With Clinical Features In Fisher Syndrome And Related Disorders.

Kenichi Kaida¹, Masato Kadoya¹, Motoi Kuwahara², Hiroshi Takazaki¹, Keishi Yamazaki¹, Yukari Komuta¹, Susumu Kusunoki², Kyoichi Nomura³, Katsunori Ikewaki¹

¹Department of Neurology, National Defense Medical College, Tokorozawa, Japan, ²Department of Neurology, Kindai University Faculty of Medicine, Osaka-Sayama, Japan, ³Department of Neurology, Saitama Medical Center, Saitama Medical University, Kawagoe, Japan

In Guillain-Barré syndrome (GBS) and Fisher syndrome (FS), molecular mimicry is a main mechanism of antiglycolipid antibody generation. However, the pattern of IgG antibodies (IgG-abs) is often different from that of IgM antibodies (IgM-abs), even in anti-GQ1b-associated FS that shows homogeneous features. The discordance between IgG and IgM antibody patterns is not fully explained by molecular mimicry or class-switching. Objective: To clarify characteristics of patients with FS or its related disorders who show the discordance between IgG and IgM antibody patterns. Methods: Sera from 61 patients with FS, 14 with Bickerstaff brainstem encephalitis (BBE), and 12 with FS-GBS overlap (FGO) were used for antiglycolipid antibody screening. Antibody pattern and clinical findings of patients with the discordance between IgG and IgM antibodies were compared with those of patients with only IgG-abs. Results: Seventy-two patients had some IgG-abs, 47 (FS31, BBE10, FGO6) of whom had IgG-abs to GQ1b and/or GT1a without IgM-abs (G group), 12 (FS7, BBE2, FGO3) had IgG and IgM antibodies to GQ1b and/or GT1a and IgM-abs to other glycolipids (partial discordance, M1 group), and 13 (FS9, BBE1, FGO3) had IgG-abs to GQ1b and/or GT1a and IgM-abs to other glycolipids (partial discordance, M2 group). Mean age at onset was 49.6 years old in a group G, 38.1 in M1 and 32.8 in M2. Antecedent respiratory infection was 83% in G, while gastrointestinal infection was 42% in M1 and 54% in M2. Mean Hughes grade was 3.1 in G, 2.7 in M1 and 1.8 in M2. Class-switching of IgM-abs to GalNAc-GD1a, GM2, or GM1 seldom occurred. Conclusion: Patients in groups M1 and M2 were characterized by younger onset, antecedent gastrointestinal infection, and milder disability, with statistical significance. Antecedent infection may regulate production of IgM antiglycolipid antibodies, while class-switching may be influenced by the type of antiglycolipid antibodies or age of onset.

References: None.

Keywords: Inflammatory

Grant Support: None.
Introduction: Little is known about the long-term health-related quality of life (HRQoL) outcomes of chronic inflammatory demyelinating polyneuropathy (CIDP) patients treated with subcutaneous immunoglobulin (SCIG). Long-term HRQoL data from patients treated with SCIG IgPro20 (Hizentra®, CSL Behring, King of Prussia, PA, USA) in the 48-week open-label PATH extension study are presented.

Methods: Subjects started with 0.4 g/kg IgPro20 weekly and switched to 0.2 g/kg weekly after 24 weeks. In case of CIDP relapse, 0.4 g/kg was re-initiated. After a study amendment, subjects started on 0.2 g/kg weekly with dose increase at CIDP relapse. General QoL (EQ-5D), treatment satisfaction (TSQM) and work productivity (WPAI-GH) were assessed at Baseline, Week 25 and study completion.

Results: Relapse rates by INCAT (Inflammatory Neuropathy Cause and Treatment) score were 10% (during treatment with 0.4 g/kg, n=72) and 48% (during treatment with 0.2 g/kg [n=73]; 89% of whom recovered within 4 weeks upon switching to 0.4 g/kg). Across all EQ-5D domains, the health status in non-relapsers was more likely to be maintained or improved than in relapsers. This was most notable for ‘usual activities’ (92% vs 75%, respectively). Maintenance/improvement rate in non-relapsers was ≥90% for all domains in both doses; for relapsers this was 60–80% for 0.2 g/kg and 75–88% for 0.4 g/kg depending on the domain. Most TSQM assessments remained stable (except in ‘convenience’ which improved regardless of relapse and ‘side effects’ which improved in non-relapsers). WPAI-GH remained stable apart from ‘work productivity loss’ and ‘absenteeism’, both of which got better in relapsers.

Discussion: HRQoL, treatment satisfaction and work productivity were generally maintained or improved in CIDP patients treated with SCIG for up to 72 weeks. Relapse had limited impact, possibly

References: None.

Keywords: Inflammatory

Grant Support: This study was supported by CSL Behring.
Diagnosis and Management of Guillain-Barré Syndrome in Ten Steps

Sonja Leonhard¹, Melissa Mandarakas¹, Francisco de Assis Aquino Gondim², Kathleen Bateman³, Maria Brito Ferreira⁴, David Cornblath⁵, Pieter van Doorn¹, Mario Dourado⁶, Richard Hughes⁷, Badrul Islam⁸, Susumu Kusunoki⁹, Carlos Pardo¹⁰, Ricardo Reisin¹¹, James Sejvar¹², Nortina Shahrizaila¹³, Cristiane Soares¹⁴, Thirugnanam Umapathi¹⁵, Yuzhong Wang¹⁶, Eppie Yiu¹⁷, Hugh Willison¹⁸, Bart Jacobs¹

¹Erasmus University Medical Center, Rotterdam, Netherlands, ²Hospital Universitário Walter Cantidio, Fortaleza, Brazil, ³University of Cape Town, Cape Town, South Africa, ⁴Hospital da Restauração, Recife, Brazil, ⁵Johns Hopkins University School of Medicine, Baltimore, MD, Netherlands, ⁶Hospital Universitário Onofre Lopes, Natal, Brazil, ⁷UCL Queen Square Institute of Neurology, London, United Kingdom of Great Britain and Northern Ireland, ⁸International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), Dhaka, Bangladesh, ⁹Kindai University Faculty of Medicine, Osaka, Japan, ¹⁰Johns Hopkins University School of Medicine, Baltimore, MD, USA, ¹¹Hospital Británico, Buenos Aires, Argentina, ¹²Centers for Disease Control and Prevention, Atlanta, GA, USA, ¹³University of Malaya, Malaysia, ¹⁴Hospital Federal dos Servidores do Estado, Rio de Janeiro, Brazil, ¹⁵National Neuroscience Institute, Singapore, Singapore, ¹⁶Affiliated Hospital of Jining Medical University, Jining, China, ¹⁷The Royal Children's Hospital Melbourne, Murdoch Children's Research Institute, The University of Melbourne, Melbourne, Australia, ¹⁸University of Glasgow, Glasgow, United Kingdom of Great Britain and Northern Ireland

The Guillain-Barré syndrome (GBS) is a rare, but potentially fatal, immune-mediated disease of peripheral nerves and nerve roots that is usually triggered by infections. GBS can be a complex disorder to manage, as clinical presentation is heterogeneous and prognosis varies widely between patients. Managing GBS can be especially challenging in outbreak periods, as was most recently seen during the Zika virus epidemic in French Polynesia and Latin America. In absence of an international clinical guideline for GBS, we developed a consensus guideline for the diagnosis and management of GBS. This guideline aimed for general applicability in all clinical environments, irrespective of specialist capabilities or availability of resources, and was developed by an international team of neurologists with support from representatives of the GBS-CIDP Foundation International. The guideline is based on current literature and expert consensus and has a 10-step approach to facilitate its use in clinical practice. These steps cover: early recognition, diagnosis, intensive care unit admission, treatment indication and selection, monitoring and treatment of disease progression, prediction of clinical course, and long-term management. To make sure this guideline remains clinically applicable, we will continue to actively seek feedback and make updates based on results from ongoing and future research. This consensus guideline will also form the basis for the development of online information resources and teaching courses to further improve the world-wide management of GBS. These resources will be directed towards clinical neurologists, other healthcare workers, and patients with GBS and their relatives.

This consensus guideline can help improve the management of GBS world-wide, and is the first step towards the development of up-to-date, consensus-based information and training material for GBS.

References: None.

Keywords: Inflammatory

Grant Support: Horizon 2020, ZikaPLAN Grant Agreement No. 734584
Axonal Loss at Time of Diagnosis Predicts Long-Term Disability in Chronic Inflammatory Demyelinating Polyneuropathy

Ali Al-Zuhairy\textsuperscript{1}, Johannes Jakobsen\textsuperscript{1}, Christian Krarup\textsuperscript{2}

\textsuperscript{1}Department of Neurology, Neuroscience Center, Copenhagen University Hospital (Rigshospitalet), Copenhagen, Denmark, \textsuperscript{2}Department of Clinical Neurophysiology, Neuroscience Center, Copenhagen University Hospital (Rigshospitalet), Copenhagen, Denmark

Purpose: To evaluate the predictive power of electrophysiological measures of axonal loss for the clinical long-term outcome in patients treated for chronic inflammatory demyelinating polyneuropathy (CIDP).

Methods: A hospital-based long-term electrophysiological follow-up study was conducted in 2018 in patients studied for the first time between 1985 and 2006. The clinical status in 2018 was evaluated using the Inflammatory Rasch-built Overall Disability Scale (I-RODS). Motor and sensory nerve conduction studies were carried out in nerves in the arm and leg.

Results: Fourteen CIDP patients were included, five of whom were in remission. The median time since onset of CIDP was 17.5 years (range 12.0 – 30.0) and the median time elapsed between the initial and the follow-up electrophysiological studies was 14.2 years (range 11.4 – 24.2). Twelve patients walked independently, one needed ambulatory support and one had no walking function. The I-RODS was 74.5 (range 28.0 – 100.0) at follow-up. The median combined electrophysiological z-score of motor and sensory action potential amplitudes was -4.7 (range -11.5 – -1.6) at time of diagnosis and -3.4 (range -12.6 – -0.3) at follow-up (p=0.08, not significant). There was a significant association between initial and current axonal loss following univariate regression analysis, the p-value and coefficient of determination (R\textsuperscript{2}) being 0.01 and 0.42 respectively. Univariate regression analysis also revealed a highly significant association between initial axonal loss and current I-RODS, the p-value and R\textsuperscript{2} being <0.0001 and 0.73 respectively. There was a significant reduction in current demyelination compared to initial demyelination (p=0.03) as indicated by the change in conduction velocity z-scores.

Conclusion: The axonal loss at the initial diagnostic electrophysiological examination was predictive for the long-term disability and for the axonal loss at follow-up. In addition, the axonal loss did not worsen throughout the disease course.

References: None.

Keywords: Inflammatory

Grant Support: None.
Poster 72

Diagnose and treatment of chronic inflammatory demyelinating polyneuropathy with IgG4 anti-neurofascin155 antibody: Clinical practice in China

Jie Lin

Fudan University, Huashan Hospital, Shanghai, China

Objective: To describe the diagnose and the treatment in patients with chronic inflammatory demyelinating polyneuropathy who harbored antibodies against NF155.

Methods: Sera from 32 CIDP patients, 29 with other neuropathies in our clinical were collected for anti-NF155 antibody measurement by Cell-based assay (CBA). To characterize the clinical features, nine additional CIDP outpatients presented with tremor and distal acquired demyelinating symmetric phenotype were included. Clinical information, electrophysiology and response to treatment were obtained in patients with anti-NF155 immunoglobulinG4 (IgG4) antibody positive CIDP.

Results: 6 patients (18.75%) with IgG4 autoantibodies against NF155 from 32 CIDP patients, no patients with other neurologic disorders were positive. 4 patients (44.4%) with IgG4 autoantibodies against NF155 from 9 additional CIDP outpatients presented with tremor and distal acquired demyelinating symmetric phenotype. Anti-NF155 antibody positive CIDP were associated with younger onset age, tremor, distal limb weakness and high frequency of gait disturbance, deep and superficial disturbance. Higher cerebrospinal fluid protein levels and longer F-wave latencies than anti-NF155 antibody negative patients. Treatment with rituximab were added in 2 patients, they all improved dramatically. Plasma exchange were given in 2 patients, rapid and effective improvement were observed.

Conclusion: Anti-NF155 antibody positive CIDP patients occur in a special subgroup of CIDP patients with younger onset age, tremor, distal acquired demyelinating symmetric phenotype, higher cerebrospinal fluid protein levels and longer F-wave latencies. Plasma exchange and rituximab were effective for patients with anti-NF155 IgG4 antibody-positive CIDP.

References: None.

Keywords: Inflammatory, Other

Grant Support: None.
Increased Effector B cells in Peripheral Blood of Chronic Inflammatory Demyelinating Polyneuropathy Patients

Ayse Nur Ozdag Acarli1, Vuslat Yilmaz2, Nermin Gorkem Sirin Inan1, Aysun Soysal3, Fikret Aysal3, Hacer Durmus Tekce1, Erdem Tuzun4, Yesim Parman1

1Istanbul University, Istanbul Medical Faculty, Istanbul, Turkey, 2Istanbul University, Institute of Experimental Medicine, Istanbul, Turkey, 3Bakirkoy Mazhar Osman Mental Health and Neurological Diseases Education and Research Hospital, Istanbul, Turkey, 4Istanbul University, Institute of Experimental Medicine, Istanbul, Turkey

OBJECTIVE: Although autoantibodies that target node/paranode of Ranvier proteins were identified in a small subset of CIDP patients, disease-specific autoantibodies linked to CIDP remain unknown in most patients. This study aimed to analyse peripheral B-cell homeostasis, and investigate the differences of B-cell phenotypes among patients with typical, and atypical CIDP, also investigate its value as a biomarker.

METHODS: The study included 25 typical CIDP (15 male, 10 female, 34.3±16.9), 18 MADSAM (12 male, 6 female, 27.8±11.6), 7 DADS (2 male, 5 female, 32.6±17.1) patients who fulfilled the 2010 EFNS/PNS diagnostic criteria for definite (n=49) or probable (n=1) CIDP. Twenty-five age-matched healthy donors (HC) (13 male, 12 female, 33.0±8.0), 19 patients with multiple sclerosis (MS) (11 male, 8 female, 34.9±6.9), and 13 patients with CMT1A (7 male, 6 female, 38.9±13.3) served as disease controls.

Peripheral blood mononuclear cells (PBMCs) were isolated through ficoll density gradient centrifugation, and were stained with anti-human monoclonal CD3-FITC, CD16/CD56-PE, CD45-PerCP, CD19-APC, CD27-FITC, IgD-APC/Cy7, CD138-PE, CD24-PerCP, and CD38-Alexa fluor 700 conjugates (BD FACS AriaII). Acquired T, NK, B-cells, and subgroups of B-cells (immature, naive, memory, regulatory B-cells, plasmablasts, and plasma cells) were analyzed using FlowJo software.

RESULTS: No differences were found in B-cells, T-cells, and natural killer cells percentage in groups of typical, and atypical CIDP, MS, CMT 1A, and HC. However, we detected significant reduction in naive B-cells (CD19+IgD+CD27−) (p<0.01), B10 cells (CD19+CD27+CD24++) (p<0.05), and an elevation in switched memory B-cells (CD19+IgD−CD27+) (p<0.01) in CIDP patients compared to HC. Also CIDP group had significantly higher naïve (p<0.001), and switched memory B-cells (p<0.01) than MS group. Plasmablasts (CD19+CD38++CD138−) were reduced in CIDP patients (p<0.05), and showed a tendency to decrease compared to MS.

DISCUSSION: Decreased plasmablasts, and fully developed nonproliferating plasma cells were thought to be the result of immunomodulating treatment as reported in previous studies. Also, elevated numbers of antibody secreting cells in peripheral blood indicate an overactive humoral immune system, and represent a typical signature in both typical, and atypical CIDP, which is down-scaled after clinically successful IVlg administration. According to our results, increase in frequency of memory B-cells in peripheral blood with a reciprocal decrease of still-dividing precursor cells (naive B-cells) give an impression of a chronic antigen exposure, and overactive humoral immune system.

References: None.

Keywords: Inflammatory, Other

Grant Support: None.
Diagnostic yield and clinical utility of nerve biopsy in evaluation of neuropathy

Cheng-Ying Ho¹, Alexandru Olaru²

¹University of Maryland School of Medicine, Baltimore, MD, USA, ²University of Maryland Medical Center, Baltimore, MD, USA

Background: Nerve biopsy is a diagnostic test used in selected cases for evaluation of acquired neuropathy. The pathologic findings may confirm or change the clinical diagnosis, and help guide treatment. However, it is an invasive procedure with known side effects. To prove its diagnostic value, studies evaluating the diagnostic yield and clinical utility are needed.

Methods: We performed a retrospective review of the clinical information, laboratory data, electrodiagnostic studies, and pathology report of 115 nerve biopsy cases from a single institution. Four categories were defined: 1) Definite diagnosis reached and concordant with the clinical diagnosis; 2) Definite pathologic diagnosis reached but discordant with the clinical diagnosis; 3) Nonspecific (e.g. perineurial chronic inflammation) or unremarkable pathologic findings concordant with the clinical diagnosis, and 4) Nonspecific or unremarkable findings discordant with the clinical diagnosis.

Results: Among the 115 cases of nerve biopsies, 90 cases (78.3%) had a concurrent muscle biopsy. The pathologic findings were abnormal in 81.7% of the cases. A specific diagnosis was established in 27.0% of the cases. Of note, a specific diagnosis was made in 9 additional cases as a result of the muscle biopsy (7.8%). 27.0% of the cases had a definite pathologic diagnosis concordant with the clinical diagnosis, whereas 6.1% had a definite pathologic diagnosis discordant with the clinical diagnosis. 52.2% demonstrated nonspecific pathologic findings but they were concordant with the clinical diagnosis. 14.8% had nonspecific pathologic findings which were discordant with the clinical diagnosis. Overall, the concordance rate between the clinical impression and pathologic findings was 79.1%.

Conclusions: Biopsy altered the diagnosis in more than 20% of the suspected neuropathy cases, and therefore its diagnostic utility should not be overlooked. A concurrent muscle biopsy is strongly encouraged, given our finding that approximately 8% of the cases had unexpected myopathy.

References: None.

Keywords: Inflammatory, Other

Grant Support: NIH K08NS102468 Passano Foundation
Poster 75

Characterization of a Relapsing/Remitting, Disease Course for Corticosteroid-Responsive Small-Fiber Neuropathy

Anne Oaklander¹, Julia Spoendlin², Blake Roschach³, Martin Landolt⁴
Introduction: Small-fiber polyneuropathy (SFN) is an often-painful axonopathy of small-diameter nerve-fibers. There is increasing evidence that disordered inflammation/immunity underlies some acute monophasic and chronic cases initially thought idiopathic.1-3

Methods: With IRB-approval, we collected Small-Fiber Symptom Survey (SSS) data throughout 2017-2019 and reviewed medical records.4

Results: 14 days after upper-respiratory infection (URI), an otherwise-healthy 30-year-old rapidly developed first-ever erythromelalgia comprising heat-induced paroxysms of paresthesias, itch, reddening, and 6-8/10 pain in her feet and hands, worsening with heat or exercise, with minor nose symptoms. Medical history revealed only mild scalp psoriasis and CIDP in a cousin. Examination identified minimal toe and finger weakness. Nerve-conduction, electromyography, and lumbar puncture were normal; autonomic function testing (AFT) was borderline with reduced right-foot sweating. Oral prednisone 60 mg initiated 3 months post-onset gave rapid improvement and was tapered off during 3 months. Remission lasted 3.5 years during which the patient noted only small patches of reduced sensation in fingers and toes in the cold. Then, symptoms returned 10 days post-URI and 4 days after influenza immunization. On day 2, prednisone 80 mg gave major improvement during rapid then slow taper with SSS scores decreased from 27/136 on d6 to 7 on d45. First 0/10 pain was d73; first 0/136 SSS was d208. On d21 lower-leg PGP9.5-immunolabeled skin biopsy was borderline (191 neurites/mm2 skin surface area, at 10.7 centile of predicted). Day-26 examination documented tachycardia, toe-erythema and mild finger-abduction weakness; d30 AFT was normal. Day-26 complement C3 and C4 were normal.5 She remained symptom-free for 6 months until 2 weeks post-URI when symptoms returned (d2SSS 16/136). Prednisone 50 mg was immediately resumed while planning transition to immunoglobulin treatment.

Conclusions: We document a case of relapsing/remitting, corticosteroid-responsive SFN distinct from previously reported monophasic and chronic courses. The temporal link to URIs suggests molecular mimicry may be triggering recrudescences.


Keywords: Inflammatory, Pain, Small Fibers

Grant Support: Supported in part by the National Institutes of Health (R01NS093653, K24NS059892) and the Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Advancing Translational Sciences, National Institutes of Health Award UL 1TR002541) and financial contributions from Harvard University and its affiliated academic healthcare centers.
Next generation sequencing in idiopathic sensory neuronopathies.


University of Campinas, Campinas, Brazil

Introduction: Sensory neuronopathies (SN) are characterized by asymmetric sensory deficits and sensory ataxia. This distinctive pattern emerges from the dorsal root ganglia damage. Its recognition represents a window of opportunity to the investigation of associated diseases. Nonetheless, even with an extensive workup nearly half of the SN patients remain labeled as idiopathic (iSN). NS-like pattern in a broader neurological phenotype is present in several inherited conditions. However, iSN as an isolated manifestation has not been addressed yet through next generation sequencing technics (NGS).

Objective: To investigate possible genetic etiology for iSN.

Methods: We enrolled consecutively all patients with iSN followed in a neuromuscular clinic. Patients were diagnosed following the criteria proposed by Camdessanche and cols in 2009. Patients were labeled as iSN after an extensive workup resulted negative. Peripheral blood samples were used to obtain leukocyte DNA that had the exoma sequenced through NGS. The identified variants were then filtered by the terms: "sensory ataxic neuropathy", "distal peripheral sensory neuropathy", "sensory neuropathy" and “peripheral neuropathy”. The resulting variants were then classified according to the ACMG criteria and those “likely pathogenic” or “pathogenic” were reviewed.

Results: Twenty-two iSN patients were enrolled. Male/female proportion was 9:13 with a mean age of 9.5±7.5 years. None of these iNS patients had a family history of peripheral neuropathy. Most patients had asymmetric sensory deficits and a SN evolving in a chronic fashion (77% and 54% respectively). None of the iSN had definite genetic diagnose identifiable by NGS. Four patients had heterozygote variants in suspected genes (CUBN; POLG; FXN and FLVCR1).

Conclusion: Despite that NGS was not able to identify a monogenetic cause for the iSN patients of this cohort, some hypothesis regarding the disease pathology may be raised: NGS may be not able to identify them or alternatively iSN may behave as complex neurological disease.

References: None.

Keywords: Human Genetics, Inflammatory, Other

Grant Support: FAPESP: Grant # 2013/26410-0.
Poster 77

Acute small fibre neuropathy: a neglected condition?

Thierry Gendre¹, Abir Wahab¹, Julie Bismuth², Jean-Pascal Lefaucheur², Alain Créange¹

¹Department of Neurology, Hôpital Henri Mondor, AP-HP, Université Paris-Est, Créteil, France, ²Department of Neurophysiology, Hôpital Henri Mondor, AP-HP, Université Paris-Est, Créteil, France

**Background:** Small fibre neuropathies (SFN) constitute a disorder involving thinly myelinated Aδ-fibres and unmyelinated C-fibres. Causes are various and often remain unknown. SFN are typically chronic length-dependent polyneuropathies. However, some patients report an acute onset.

**Aim:** To describe a series of patients with an acute small fibre neuropathy (ASFN).

**Methods:** To be included, patients must present with sensory manifestations involving at least two limbs, an exclusive impairment of pain and/or heat sensation on clinical examination and neurophysiological investigation, and a progression phase of less than 4 weeks. Patients with associated large fibre involvement were excluded. We collected their clinical, neurophysiological, and biological data.

**Results:** From November 2017 to February 2019, we prospectively included 11 patients with ASFN (7F:4M, median age: 43.7 [23.5-59.2]). Ten patients reported neuropathic pains. Nine patients presented a non-length-dependent profile. Orthostatic hypotension was present in 3 patients. Ten patients had at least abnormal results of laser-evoked potentials, warm detection thresholds or electrochemical skin conductance. Standard immunological blood tests were normal. AntiFGFR-3 antibodies were positive in 3 patients (6 tested). Cerebrospinal fluid was normal in 4 patients. A precipitating potential event was present in 7 patients: 3 infections, 2 vaccinations, and 2 treatment intolerances. Disease course was characterized by a complete remission in 2 cases, recurrent episodes in 5 cases, and chronicity in 4 patients.

**Discussion:** Few cases of ASFN have been reported, usually with a favourable prognosis. However, the present series shows a variable disease course. The evidence of a precipitating factor in two-thirds of cases and the presence of antiFGFR-3 antibodies support an immune dysfunction, as it was previously suggested with the transient detection of antibodies directed against small fibres. Early immunomodulating treatment is worth to be discussed.

**Conclusion:** ASFN appears as a potential inflammatory neuropathy with an important clinical impact and a variable disease course.


**Keywords:** Small Fibers, Inflammatory, Pain

**Grant Support:** None in relation to this work.
Analysis of 193 whole genome sequencing data to understand neuropathic pain disorders.

Andreas Themistocleous¹, Karyn Megy², Rutendo Mapeta², Sri Deevi², Iulia Blesneac¹, Tom Vale¹, Natalie van Zuydam¹, David Bennett¹

¹University of Oxford, Oxford, United Kingdom of Great Britain and Northern Ireland, ²University of Cambridge, Cambridge, United Kingdom of Great Britain and Northern Ireland

Extreme pain phenotypes, such as erythromelalgia and insensitivity to pain, caused by rare high impact genetic variants, offer us insight into mechanisms that may apply to more common causes of neuropathic pain. The aim of our study was to identify singleton patients and families with extreme pain phenotypes to determine whether variants/mutations were present in genes known to cause neuropathic pain. We included participants with: congenital insensitivity to pain; painless sensory neuropathy; chronic pain caused by erythromelalgia, small fibre neuropathy, and sensory neuropathy. NeuPSIG grading criteria for neuropathic pain were used to stratify the cohort. A total of 219 participants were recruited from secondary care clinics across the UK. Neuropathic pain was classified as: not present (n=9, 4.1%), definite (n=125, 57.1%), probable (n=62, 28.3%), possible (n=12, 5.5%) or unlikely (n=1, 0.5%). Ten participants were unaffected family members. Whole genome sequencing data, acquired using next generation sequencing technology, were available for 193 participants. Previously characterised pathogenic variants in SCN9A, the gene encoding the sodium channel (Nav) 1.7, were identified in 11 participants. For example, the SCN9A pathogenic variant, c.2543T>C (p.Ile848Thr), was identified in a pair of sisters diagnosed with erythromelalgia. Novel uncharacterised variants, predicted through in silico analysis to be pathogenic and confirmed in multi-disciplinary team meetings, were identified in SCN9A, SCN10A, SCN11A and SPTLC1 genes. We have demonstrated that a meticulous phenotyping approach combined with next generation sequencing provides a powerful platform to explore pathophysiological mechanisms of chronic neuropathic pain.

References: None.

Keywords: Pain, Human Genetics, Small Fibers

Grant Support: NIHR Bioresource Wellcome Trust
SCN11A Arg225Cys mutation causes nociceptive pain without detectable peripheral nerve pathology.

Jun Li¹, Ryan Castoro², Christopher Lee³, Megan simmons³, Lan Zhou⁴

¹Wayne State University School of Medicine, Detroit Medical center, Detroit, USA, ²Vanderbilt University Medical Center, Nashville, TN, USA, ³Vanderbilt University Medical Center, Nashville, TN, USA, ⁴University of Texas Southwestern, Dallas, TX, USA

OBJECTIVE: The SCN11A gene encodes the NaV1.9 sodium channel found exclusively in peripheral nociceptive neurons.

METHODS: All enrolled participants were evaluated clinically by electrophysiologic studies, DNA sequencing, and punch skin biopsies.

RESULTS: All affected family members are afflicted by episodes of pain. Pain was predominantly nociceptive, but not neuropathic in nature, which led to diagnosis of fibromyalgia in some patients. All patients had normal findings in nerve conduction studies for detecting large nerve fiber neuropathies and skin biopsies for detecting small nerve fiber pathology.

CONCLUSIONS: Unlike those patients with missense mutations in SCN11A, small fiber sensory neuropathy, and neuropathic pain, the Arg225Cys SCN11A in the present study causes predominantly nociceptive pain with minimal features of neuropathic pain and undetectable pathophysiological changes of peripheral neuropathy. This finding is consistent with dysfunction of nociceptive neurons. In addition, since nociceptive pain in patients has led to the diagnosis of fibromyalgia, this justifies a future search of mutations of SCN11A in patients with additional pain phenotypes such as fibromyalgia to expand the clinical spectrum beyond painful small fiber sensory neuropathy.

References: None.

Keywords: Human Genetics, Pain, Small Fibers

Grant Support: None.
Poster 80

Pregabalin for muscle cramps in patients with liver cirrhosis, A randomized, double-blind, placebo-controlled study

So Hyun Ahn¹, Yoon-Ho Hong², Jin-Ah Kim¹, Jung-Joon Sung¹, Ah Won Kim¹, Min Ju Cha¹, Je-Young Shin¹, Young Nam Kwon¹, Hyun Seok Baek¹

¹Seoul National University Hospital, Seoul, Korea (Republic of), ²Seoul Metropolitan Government Boramae Medical Center, Seoul National University College of Medicine, Seoul, Korea (Republic of)

To assess the efficacy and safety of pregabalin in the treatment of muscle cramps, we performed a randomized, double-blind, placebo-controlled study with 60 patients with frequent muscle cramps (>2 cramps/week) with liver cirrhosis of under 75 years of age. Patients who received pregabalin had a significantly greater reduction in cramp frequency. After the 4-week standard dose period, the mean change from baseline to treatment phase in cramp frequency was 33.3% for the pregabalin group, and 0% for the placebo group (p=0.015). The 50% responder rate was significantly higher in the pregabalin group compared to placebo (68.8% vs. 31.2%). There were no significant differences in the mean changes of pain intensity and number of cramps during sleep between the pregabalin and placebo groups. The scores for all SF-36 domains were higher in the pregabalin group than in the placebo group after the 5-week treatment period. There was significant difference in the “role limitations due to physical health” domain score between the pregabalin and placebo groups (p=0.023). The scores for all LDQOL domains, except the “loneliness” domains, were higher in the pregabalin group than in the placebo group after the 5-week treatment period. Additionally, we evaluated the afterdischarge (duration ≥ 2 sec, end of afterdischarge: pause ≥ 80msec) threshold as a tool of neurophysiological outcome measure before and after pregabalin treatment in 30 patients. The threshold of afterdischarge was higher in the pregabalin group than placebo group. Our clinical and neurophysiologic experience suggests that pregabalin would be helpful in the treatment of muscular cramps in patients with liver cirrhosis.

References: None.

Keywords: Clinical Trials, Pain, Metabolic, Other, Inflammatory

Grant Support: None.
The modified Neuropathy Impairment Score +7 (mNIS+7) was developed from the NIS+7 to better represent neuropathic impairments in transthyretin amyloidosis polyneuropathy. In the 15-month phase 3 trial (NEURO-TTR; NCT01737398), inotersen, an antisense oligonucleotide inhibitor of transthyretin production, demonstrated a significant beneficial effect compared with placebo in the 2 primary outcomes of mNIS+7 and Norfolk Quality of Life—Diabetic Neuropathy questionnaire scores in patients with hereditary transthyretin amyloidosis (hATTR). The NIS is comprised of 3 major components (NIS-weakness, NIS-reflexes, and NIS-sensation loss), and the mNIS+7 is comprised of the 5 attributes of nerve conduction, somatotopic quantitative sensation testing of touch pressure and heat pain, and heart rate response to deep breathing (HRDB). In NEURO-TTR, 5 of the 7 main components of mNIS+7 showed statistically significant benefit by 15 months in patients receiving inotersen versus placebo. HRDB and touch pressure did not reach statistical significance; however, HRDB cannot be assessed in patients with active pacing or atrial fibrillation, which are common in patients with hATTR. In this analysis, we assessed the performance of the components of mNIS+7 by anatomic location (upper and lower limb) as well as the Lower Limb Function (LLF) test. The LLF test assesses 3 functional abilities: a patient’s ability to ambulate on toes, to ambulate on heels, and to arise from a kneeled position. All mNIS+7 components assessed by upper and lower limbs showed a statistically significant benefit in patients receiving inotersen versus placebo except NIS-reflexes (upper limb) and touch pressure (upper and lower limbs). Overall LLF score and each individual LLF test score showed statistically significant benefit by 15 months in patients receiving inotersen compared with placebo. These data support the beneficial effects of inotersen on muscle weakness, muscle stretch reflexes, sensation, attributes of nerve conduction of limb nerves, and lower limb function.

References: None.

Keywords: Amyloidosis, Axonal Biology, Clinical Trials, Human Genetics

Grant Support: Akcea Therapeutics
Poster 82

Patient Assisted Intervention for Neuropathy: Comparison of Treatment in Real Life Situations
Quality of Life

Mamatha Pasnoor1, Byron Gajewski1, Lexie Brown1, Laura Herbelin1, Kim Kimminau1, Chad Parks1, Pam Schlemon2, Mazen Dimachkie1, Richard Barohn1, the PAIN-CONTRoLS Study Team1

1The University of Kansas Medical Center, Kansas City, KS, USA, 2Foundation of Peripheral Neuropathy, Chicago, USA

Background: Cryptogenic sensory polyneuropathy (CSPN) affects adults, causing pain, resulting in poor quality of life (QOL). The primary outcome from the PAIN-CONTRoLS study was presented at this meeting in 2018. We are now presenting the secondary outcomes.

Objective: To compare the effect of four pain medications: nortriptyline, duloxetine, pregabalin and mexiletine on QOL.

Methods: We conducted a comparative effectiveness study of 4 neuropathic pain medications in reducing CSPN pain. In this PCORI funded trial, patient advisors assisted in identifying important outcomes related to QOL. The SF-12 and the PROMIS® pain interference, fatigue, and sleep disturbance scales were used to assess QOL. Participants completed the SF-12 and PROMIS scales at baseline and weeks 4, 8 and 12. Mean T-scores were calculated for each specific medication group and the probability best for each medication was calculated.

Results: 402 patients with CSPN were enrolled in the study (nortriptyline 134, duloxetine 126, pregabalin 73, mexiletine 69 respectively). The mean T-scores for the PROMIS® pain interference is 63.1±7.0, 62.4±6.8, 63.3±5.5, 60.9±7.9; fatigue 59.6±3.4, 59.7±3.3, 59.1±53.7, 59.7±3.2; sleep disturbance is 59.1±9.8; 60.6±8.3, 59.8±8.7, 57.0±11.4. The mean T-scores of the SF-12 physical component is 38.0±10.4; 46.7±10.1, 46.8±11.3, 47.2±11.1. A substantial number of patients quit in the mexiletine group. The probability best for patients who stayed in the study at week 12 for PROMIS® fatigue scores was 0.05, 0.05, 0.05, 0.93; pain interference 0.02, 0.07, 0.00, 0.91. For sleep disturbance and SF-12, there was no statistical clear separation among the drugs in the probability best at 12 weeks.

Conclusion: Overall, there is no significant difference on pain or QOL. However, patients on mexiletine, that could stay in the study for 12 weeks, had a better outcome in pain interference and fatigue scales.

References: None.

Keywords: Pain, Clinical Trials, Small Fibers

Grant Support: PCORI AWARD: University of Kansas Medical Center CER-1306-02496
Poster 83

SENSORY-MOTOR PACLITAXEL POLYNEUROPATHY CHARACTERIZATION IN A RAT MODEL

PAOLA ALBERTI, ANNALISA CANTA, ALESSIA CHIORAZZI, LAURA MONZA, GIULIA FUMAGALLI, ELEONORA POZZI, CRISTINA MEREGLI, NORBERTO OGGIONI, PAOLA MARMIRI, GUIDO CAVALETI

UNIVERSITY OF MILANO-BICOCCA, MONZA, Italy

PURPOSE. Paclitaxel-Induced Peripheral Neurotoxicity (PIPN) is a detrimental condition that affects cancer survivors. It is a mainly sensory, axonal, length-dependent polyneuropathy. There is no treatment for this side effect. A reason for this lack is the absence on definite data on PIPN pathogenesis. Thus, a bench-side approach is warranted to test potential neuroprotectant agents. We characterized a rat model with advanced and standard neurophysiology, as well as with behavioral tests and neuropathology in order to standardize our setting to promptly translate data in clinical trials.

METHODS. Twenty-four female Wistar rats were used. They were divided in control (CTRL) and paclitaxel (PTX, 10mg/Kg, iv, 1qw4ws) groups. Animals were tested with standard neurophysiology (sensory and motor recordings) and dynamic test at base-line and at end of treatment. Nerve Excitability Testing (NET) was assessed at 24, 48, 72 hours after the 1st administration and at end of treatment to characterize axonal properties. At end of treatment, harvesting of caudal and sciatic nerves, DRG and skin biopsy was also performed.

RESULTS. NET monitoring after the 1st administration showed in PTX group: no changes at 24 hours and minor alterations in current/threshold properties and in threshold electrotonus. At end of treatment, standard neurophysiology showed statistically significant changes compatible with a sensory-motor polyneuropathy; dynamic test was also significant for a painful behavior in PTX animals. NET monitoring at the end of treatment showed alterations mainly in threshold electrotonus.

CONCLUSION. We characterized an animal model with a multimodal assessment able to reproduce clinical evidence. We also performed NET monitoring showing early axonal dysfunction. This set of outcome measures will be the core for our future neuroprotection experiments.

References: None.

Keywords: Pain, Pre-clinical Studies, Other

Grant Support: None.
Modelling dHMNX and CMTX6 using patient derived iPSC motor neurons.

Gonzalo Perez Siles¹, Anthony Cutrupi², Jakob Kuriakose³, Rebecca Screnci³, Melina Ellis⁴, Garth Nicholson¹, Marina Kennerson¹

¹Northcott Neuroscience Laboratory (ANZAC Research Institute), Sydney Medical School (University of Sydney), Sydney, Australia, ²Northcott Neuroscience Laboratory (ANZAC Research Institute), Sydney Medical School (University of Sydney), Sydney, Australia, ³School of Life Sciences (University of Technology Sydney), Sydney, Australia, ⁴Northcott Neuroscience Laboratory (ANZAC Research Institute), Sydney, Australia

INTRODUCTION Mutations in the copper (Cu) transporter ATP7A and in the pyruvate dehydrogenase kinase 3 (PDK3) genes cause X-linked hereditary distal motor neuropathy (dHMNX) and X-linked Charcot-Marie-Tooth type 6 neuropathy (CMTX6), respectively. Our investigations using dHMNX and CMTX6 patient fibroblasts have shed light on the pathomechanisms underlying these diseases:
- Fibroblasts harbouring the p.T994I ATP7A mutation show defective retrograde trafficking of mutant ATP7A leading to intracellular Cu dysregulation which has been reproduced in embryonic fibroblasts of a conditional knock in Atp7a mouse model for dHMNX. - CMTX6 patient fibroblasts with the p.R158H mutation show hyperactivity of PDK3 and hyperphosphorylation of the E1 subunit of the pyruvate dehydrogenase complex, a critical regulator of the energy producing Krebs cycle, leading to mitochondrial abnormalities, lactate acidosis and reduced ATP production.

METHODS To investigate how defective ATP7A trafficking and PDK3 kinase hyperactivity leads to axonal degeneration we have established two lines of induced pluripotent stem cells by re-programming fibroblasts from a dHMNX patient with the ATP7A p.T994I mutation (iPSC_dHMNX) and a CMTX6 patient harbouring the PDK3 p.R158H substitution (iPSC_CMTX6).

RESULTS Our data demonstrates the iPSC_dHMNX and the iPSC_CMTX6 lines retain pathogenic molecular phenotypes found in the dHMNX and CMTX6 patient fibroblasts, respectively. iPSC_dHMNX cells show altered ATP7A intracellular distribution. iPSC_CMTX6 cells maintain the E1-hyperphosphorylation signature and treating the patient cells with the PDK inhibitor dichloroacetate reduces the levels of phosphorylation, suggesting PDK3 is an ideal pharmacological target for the development of treatment therapies. We have successfully differentiated spinal cord motor neurons from the iPSC_dHMNX and the iPSC_CMTX6 lines and shown the patient derived motor neurons (MN_dHMNX and MN_CMTX6) display disease specific pathological features.

CONCLUSIONS Patient MN_dHMNX and MN_CMTX6 motor neurons are an ideal neuronal system to model axonal degeneration in dHMNX, CMTX6 and other neurodegenerative diseases in which Cu dysregulation and mitochondrial abnormalities occur.


Keywords: Axonal Biology, Human Genetics, CMTR, Metabolic

Grant Support: None.
Mutations in MFN2 are the most commonly identified genetic cause of Charcot-Marie-Tooth disease type 2A. While long sensory and motor peripheral nerves are the most susceptible structures to MFN2 mutations, a variety of additional phenotypes have been reported including optic atrophy, spastic paraparesis, developmental delay, myopathy, and lipodystrophy. MFN2 is an outer mitochondrial membrane protein that regulates a variety of functions including mitochondrial fusion, transport, ER interactions, and mitophagy. However, the mechanism by which the primarily dominantly inherited point mutations in MFN2 promote mitochondrial and axonal injury remains unknown. We generated induced pluripotent stem cells from two patients with CMT2A (T105M, H361Y). Additionally, we used CRISPR/Cas9 combined with single stranded oligonucleotide donors to generate isogenic control lines using homologous recombination for the T105M and H361Y lines. Subsequently we differentiated CMT2A patient iPSCs into motor neurons using established protocols, fluorescently labeled mitochondria, and used live cell imaging to examine mitochondrial dynamics in axons. Mitochondrial size was found to be smaller in iPSC-MNs from CMT2A patients compared to normal and isogenic controls. Mitochondrial also spent a greater percentage of time paused, and displayed less anterograde movement in CMT2A iPSC-MNs compared to normal or isogenic controls. Ongoing work focuses on examining diverse MFN2 functions in these models, and whether MFN1 augmentation can mitigate phenotypes observed.

References: None.

Keywords: Axonal Biology

Grant Support: None.
The Italian Registry for Charcot-Marie-Tooth disease

Davide Pareyson¹, Daniela Calabrese¹, Giuseppe Vita², Anna Mazzeo², GianMaria Fabrizi³, Angelo Schenone⁴, Tiziana Cavallaro¹, Marina Grandì⁵, Stefano Previtali⁵, Isabella Allegri⁵, Luca Padua⁷, Costanza Pazzaglia⁶, Aldo Quattrone⁶, Isabella Moroni¹, Stefano Tozza¹⁰, Fiore Manganelli¹⁰, Chiara Pisciotto¹, Lucio Santoro¹⁰

¹Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, ²University of Messina, Messina, Italy, ³University of Verona, Verona, Italy, ⁴University of Genoa, Genoa, Italy, ⁵Ospedale San Raffaele, Vita Salute San Raffaele University, Department of Neurology and INSPE, Milan, Italy, ⁶UOC Neurologia Azienda Ospedaliera di Parma, Parma, Italy, ⁷IRCCS Fondazione Don Carlo Gnocchi, Catholic University of the Sacred Heart, Rome, Italy, ⁸Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, ⁹Magna Graecia University, Catanzaro, Italy, ¹⁰Federico II University, Naples, Italy

The Italian Charcot-Marie-Tooth disease (CMT) Registry is fully operative at the https://www.registronmd.it website. It is a dual registry where the patient registers herself/himself, chooses a reference centres among nine spread all over Italy, where the attending clinician, in an ad hoc visit, collects a minimal dataset of information and administers the CMT Examination/Neuropathy Score, CMTES/CMTNSv2, for adults, or the CMT Pediatric Scale, CMTPeds, for children; data are entered in the Registry and encrypted.

796 CMT patients have registered thus far and have chosen one of the 9 reference centers; information has been entered in the Registry for 649 of them (337 females; mean age 47.1, range 7-89). Diagnoses are the following: 407 CMT1, 95 CMT2, 21 CMT4, 8 dHMN, 32 HNPP, 1 HSAN, 85 still unclassified. Genetic diagnosis, achieved in 556 cases, show that the most frequently mutated genes are: PMP22 (295 CMT1A, 32 HNPP, 3 CMT1E), GJB1 (66 CMTX1, 30 females), MPZ (33 CMT1B, 32 CMT2I/J), GDAP1 (7 dominant and 8 recessive cases), MFN2 (17 CMT2A), NEFL (12 cases), and SH3TC2 (12 CMT4C). Clinical score are the following: CMTES (n = 633) mean 8.4 +/- 5.2, range 0-27; CMTNS (n = 190) mean 12.5 +/- 6.5, range 0-31. Ninety-four subjects have at least one follow-up visit; 472 complain of gait difficulties, 294 use orthotics aids, 70 need support for walking (44 unilateral, 26 bilateral) or use a wheelchair (23); 123 patients have scoliosis (9 requiring surgery, 39 bracing), 11 hip dysplasia, 5 optic atrophy and 2 profound hearing loss.

Conclusions: analyses of data from the Italian CMT Registry are giving results which are important for: a) epidemiology of CMT across Italy, b) assessing disease burden to develop standards of care, c) recruiting patients in forthcoming clinical trials. The Registry will be linked to the CMT International Database.

References: None.

Keywords: CMTR

Grant Support: Supported by Telethon-UILDM grant GUP13006.
Implications of Disease Progression During Childhood and Adolescence on Walking Speed in Charcot-Marie-Tooth Disease

Sylvia Ounpuu¹, Gyula Acsadi¹, Kristan Pierz¹, Kelly Pogemiller², Tishya Wren³

¹Connecticut Children's Medical Center, University of Connecticut School of Medicine, Farmington, CT, USA, ²Connecticut Children's Medical Center, University of Hartford, Farmington, CT, USA, ³Children's Hospital of Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, CA, USA

The purpose of this study was to examine differences in preferred walking speed as a function of development and CMT type in youth with CMT. The preferred walking speed of 22 youth with CMT1 (12.2 ± 3.1 years), 12 youth with CMT2 (9.8 ± 4.6 years), and 54 age matched typically developing (TD) peers (9.6 ± 3.4 years) was measured using gait analysis. Some patients were tested more than once resulting in 29 total CMT1 and 22 total CMT2 observations. Changes in walking speed with age were compared among groups using linear mixed effect models including a random intercept term to model the repeated measures for some participants. Walking speed increased with age in controls (2.2 cm/sec/year; 95% CI: 0.7 to 3.6; p=0.004), however, changed at a significantly lower rate and tended to decrease with age in CMT1 (-2.2 cm/sec/year; 95% CI: -4.9 to 0.4; p=0.097) and CMT2 (-2.4 cm/sec/year; 95% CI: -5.0 to 0.3; p=0.085). The differences in walking speed among groups were primarily due to stride length which increased with age in TD peers (4.4 cm per year; 95% CI: 3.5 to 5.4; p<0.001) but decreased with age in CMT1 (-2.1 cm/year; 95% CI: -3.8 to -0.3; p=0.02) and CMT2 (-1.8 cm/year; 95% CI: -3.4 to -0.1, p=0.38). Youth with CMT show a decline in walking speed with age compared to TD peers. This appears to be more severe and starts earlier for those with CMT2 vs. CMT1. The decline in walking speed resulted from reduced stride length, which is likely caused by reduced plantar flexor strength and increased ankle instability. Treatments that increase step length such as plantar flexor strengthening and bracing, which can also improve ankle stability in stance, are likely to improve walking speed and associated function such as keeping up with peers.

References: None.

Keywords: Other, Other, Other, Other, Other

Grant Support: Harold and Rebecca Gross Foundation
Multicenter Retrospective Study In Patients With CMT1b In France: Genotype-Phenotype Correlations.

Marie SUBREVILLE1, Douniazed YAHIAOUI1, Guilhem SOLE2, Sarah LEONARD-LOUIS3, Julien CASSEREAU4, Yann PEREON5, Andoni ECHANIZ-LAGUNA6, Marie-Hélène VIOLEAU2, Sabrina SACCONI7, Juliette ROPARS8, Jean-Baptiste NOURY9, Jean-Baptiste CHANSON9, David ADAMS6, Raul JUNTAS MORALES10, Tanya STOJKOVIC3, Shahram ATTARIAN1

1CHU La Timone, Marseille, France, 2CHU Bordeaux, Bordeaux, France, 3CHU Pitié Salpêtrière, Paris, France, 4CHU Angers, Angers, France, 5CHU Nantes, Nantes, France, 6CHU Kremlin Bicêtre, Paris, France, 7CHU Nice, Nice, France, 8CHU Brest, Brest, France, 9CHU Strasbourg, Strasbourg, France, 10CHU Montpellier, Montpellier, France

Charcot-Marie-Tooth diseases (CMT) are a heterogeneous group of hereditary genetic neuropathies. CMT1b is a rare form of CMT caused by mutations in the myelin protein zero (MPZ) gene. Phenotype is variable and heterogeneous as is the age of onset. Our purpose is to characterize genotype–phenotype correlations and establish baseline clinical data for peripheral neuropathies caused by mutations in the MPZ gene in France. It is important to make clinical trials for patients with MPZ mutations a realistic possibility, in order to reduce misdiagnosis.

We present retrospective data to define the phenotypic spectrum and clinical baseline of patients with these mutations. A cohort of patients with MPZ gene mutations was identified in 11 French reference centers for neuromuscular diseases. Patient phenotypes were quantified by the Charcot–Marie–Tooth disease examination score (CMTES). Genetic testing was performed in all patients to document mutation in MPZ gene indicating diagnosis of CMT1B. There were 80 patients with 44 different MPZ mutations with a mean age of 56 years (range 20–86 years). Childhood onset represented 7%.

Twenty patients wore orthoses, twenty-six required walking assistance or support, and six required wheelchairs. There was hearing loss in seven patients, scoliosis in sixteen patients, optic atrophy in twelve patients and five patients presented with respiratory failure. Hip dysplasia was noted in one patient.

Preliminary data didn’t reveal any significant correlation between CMTES and age of onset, nor between CMTES and age.

These results demonstrate that MPZ mutations can be associated with heterogeneous phenotypes, which is consistent with previous studies. Adult forms appear to be moderately severe with an average onset age of 32 and an average CMTES of 9.

Data obtained from the French cohort is useful as a baseline for future clinical trials of patients with CMT1b.

References: Sanmaneechai et al, Genotype-phenotype characteristics and baseline natural history of heritable neuropathies caused by mutations in the MPZ gene, Brain, 2015

Keywords: CMTR, Human Genetics

Grant Support: None.
Poster 89

Genotype and phenotype in Thai children with Charcot-Marie-Tooth Disease.

Oranee Sanmaneechai¹, Theeraphong Pho-iam¹, Chanin Limwongse¹, Byung-Ok Choi², Ki Wha Chung³

¹Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand, ²Samsung Medical Center, Seoul, Korea (Republic of), ³Kongju National University, Gongju, Korea (Republic of)

Introduction

Charcot-Marie-Tooth disease (CMT) is a group of genetically heterogeneous, despite the clinical similarities. So far, more than 100 gene mutations have been reported to be associated with different types of CMT. However, with the limitation of next generation sequencing in our country, very few studies have been done for genetic identification in CMT patients. The aim of this study is to investigate the CMT genotype and phenotype in Thai children.

Methods

We prospectively evaluate children with the clinical and neurophysiological diagnosis of CMT from January 2017 to October 2018. Clinical presentation, CMTNS or CMTPedS and neurophysiologic studies were documented. DNA samples were sent to Samsung Medical Center and Kongju National University in South Korea for genetic identification with next generation sequencing (NGS) technique.

Results

A total of 25 patients, 19 have axonal CMT and 6 have demyelinating CMT. Mutation analysis by whole exome sequencing (WES) was performed in 25 cases from 24 families. The result of WES revealed genetically confirmed in 21 patients. Patients have mutation in MFN2 (5 patients), PMP22 (3 patients), NEFL (3 patients), GDAP (3 patients), SETX (2 patients), MPZ (1 patients), GJB1 (1 patients), IGHMBP2 (1 patients), EGR2 (1 patients), HK (1 patients). For the pathogenic or likely pathogenic mutations, the mutations were confirmed by Sanger’s sequencing method.

Conclusion

Whole exome sequencing give a higher yield to identify genetic mutation in CMT, especially in pediatric population with higher percentage of axonal subtype CMT and also for the resource-limited country. Future collaboration is crucial for genetic function testing. Further prognosis and genetic counseling can be done after genetic abnormalities had been identified.


Keywords: CMTR

Grant Support: None
Modeling Axonal Degeneration in CMT2E using Human Motor Neurons

Mario Saporta, Renata Maciel, Renata Correa, Juliana Taniguchi, Igor Araujo

University of Miami Miller School of Medicine, Miami, FL, USA

Mutations in neurofilament light chain (NEFL) cause autosomal dominant, axonal Charcot-Marie-Tooth disease (CMT2E). Despite advances in understanding its pathophysiology, there is no disease-modifying therapy for CMT2E. This is partially due to lack of translational models suitable for drug discovery. Our previous work using iPSC-derived motor neurospheres have identified neurofilament deposits in the axons of motor neurons from three N98S CMT2E patients, similar to what has been shown in neflN98S knock in mice. We have also identified two kinase inhibitors that promoted 50% reduction in the number and area of NEFL deposits. The aim of this study was to determine whether evidence of axonal degeneration could be found in N98S CMT2E motor neurons in order to further validate this platform as a reliable disease model and to identify potential in vitro biomarkers of axonal degeneration for use in drug discovery.

Morphological analysis of axons and measurement of neurofilament light chain protein (NEFL) in the culture supernatant of control and N98S CMT2E motor neuron cultures were performed at baseline conditions and after ascending doses of a known axonotoxic compound (Vincristine) in doses ranging from 1 to 10 nM. Despite normal axonal morphology at baseline, N98S CMT2E demonstrated increased levels of NEFL in culture supernatant when compared to controls. Furthermore, N98S CMT2E motor neurons were more susceptible to vincristine-induced axonal degeneration, as demonstrated by both increased supernatant NEFL levels as well as increased axonal beading and breakdown when compared to controls. Taken together, these findings demonstrate that iPSC-derived N98S CMT2E motor neurons are more susceptible to axonal degeneration both at baseline conditions and in response to exposure to vincristine, suggesting that this platform can reliably model CMT-associated axonal degeneration in vitro and could be used to identify modulators of axonal degeneration with therapeutic potential for CMT2E and other axonopathies.

References: None.

Keywords: CMTR, Axonal Biology, Human Genetics, Pre-clinical Studies

Grant Support: Charcot-Marie-Tooth Association National Institutes of Health
Mutation Burden and Oligogenic Inheritance in a large Inherited Axonopathy Cohort

Stephan Zuchner1, Dana Bis-Brewer1, Feifei Tao2, Ziv Gan-Or3, Lisa Abreu2, Patrick Sleiman4, Hakonarson4, Guy Rouleau3

1University of Miami Miller School of Medicine, Miami, FL, USA, 2University of Miami Miller School of Medicine, Miami, USA, 3McGill University, Montreal, Canada, 4Children’s Hospital of Philadelphia, Philadelphia, USA.

Inherited axonopathies include the clinically distinct phenotypes, Charcot-Marie-Tooth (CMT) and Hereditary Spastic Paraplegia (HSP), which both cause slowly-progressing, length-dependent axonal degeneration. Both phenotypes are genetically and phenotypically diverse with close to 100 Mendelian genes involved for each thus far. Whole-exome sequencing of axonopathy patients may identify more than one rare variant within known disease genes. Occurrence of additional rare variation, also referred to as a ‘mutation burden’, has been reported in two independent CMT cohorts (n ≤40) supported by functional zebrafish assays. The data indicate that mutation burden may influence clinical heterogeneity and severity of disease. We sought to replicate a mutation burden across inherited axonopathies in a WES cohort 10-fold larger than the original observations (CMT cases = 357, HSP cases = 515, controls = 931). We tested the mutation burden in cases compared to controls for both non-synonymous and loss-of-function variants at ExAC MAF ≤0.1% and 1%. For each tested variant set, cases harbored a higher average number of qualifying variants (Mann-Whitney, p-value ≤0.05). The significance of this difference was further evaluated by permuting case/control status over 10,000 iterations (p-value ≤0.05). Next, we evaluated the possibility of di- and oligogenic inheritance within each cohort. Cases carrying a qualifying variant in ≥2 genes were classified as di/oligogenic and in ≥3 genes as oligogenic. We observed a difference in the proportion of cases and controls carrying variants for both di/oligogenic and oligogenic inheritance for non-synonymous variation (Chi-squared, p-value ≤0.05). Neither HSP nor CMT showed evidence of oligogenic inheritance for loss-of-function variation; however, HSP cases were enriched for digenic inheritance (Chi-squared, p-value ≤0.05). In this study, we provide further evidence of a mutation burden in CMT cases, demonstrate a mutation burden in HSP cases, and explore potential oligogenic inheritance patterns in a large cohort.

References: None.

Keywords: CMTR, Human Genetics

Grant Support: None.
Hyperglycosylation of Myelin Protein Zero: from pathogenesis to therapeutic options.

Marina Grandis¹, Francesca Veneri², Valeria Prada², Rosa Mastrangelo³, Cinzia Ferri³, Alessandro Geroldi¹, Francesca Bianchi³, Ubaldo Del Carro³, Angelo Schenone¹, Maurizio D'Antonio³

¹University of Genova, Genova, Italy, Genova, Italy, ²University of Genova, Genova, Italy, Genova, Italy, ³San Raffaele Scientific Institute, Milano, Italy, Milano, Italy

Introduction: mutations in the Myelin Protein Zero gene (MPZ), encoding P0, the major structural glycoprotein of peripheral nerve myelin, are found in 5% of Charcot-Marie-Tooth (CMT) patients. P0 variants may cause different gain of function including misglycosylation (either gain-of-glycosylation or loss-of-glycosylation), a novel pathomechanism encompassing several genetic disorders. We decided to establish a mouse model carrying the D61N mutation, a MPZ variant causing hyperglycosylation of P0 (1). Methods: the knock-in mouse model was generated using the Crispr/Cas9 system. The phenotype was characterized by behavioral, electrophysiological and neuropathological tests, at different time points. We evaluated the presence of tremor, the motor capacity, the sciatic motor nerve conduction velocity and cMAP. We performed light microscopy morphological observations, analyzing sciatic nerve semithin sections. We also decided to establish myelinating DRG cultures from wild type (WT) and Mpz D61N/+ embryos. Results: at one and three months of age, all evaluations, showed significant differences in Mpz D61N/+ mice compared with WT animals. Tremor was evident in all Mpz D61N/+ mice and correlated with a significant motor impairment on the accelerating Rotarod where mutant mice showed a reduced average latency to fall. Electrophysiological parameters also differed between the two groups: at one month of age, the average MCV was 11,8m/s ±1,2 in Mpz D61N/+ as compared with 32,88m/s ±1,3 in controls. The pathological analysis confirmed a demyelinating phenotype with a significant increase of the G-ratio in Mpz D61N/+ animals. In myelinating DRG cultures we detected fewer internodes carrying remarkable myelin abnormalities; when DRGs were treated with NB-DNJ, an imno-sugar potentially able to reverse hyperglycosylation, the myelin defects seemed to decrease. Conclusions: we obtained an animal model expressing the P0D61N variant, a mutation causing gain-of-glycosylation in P0 which recapitulates the human phenotype of this variant and we are testing possible therapeutic strategies.


Keywords: CMTR, Schwann Cell, Human Genetics

Grant Support: AFM-Telethon (20572) to Marina Grandis and Maurizio D'Antonio.
**Poster 93**

**Neddylation plays a critical role for formation, maturation and maintenance of Schwann cell myelin sheaths**

Ashwin Woodhoo\(^1\), Miguel Tamayo\(^2\), Marta Palomo–Irigoyen\(^2\), Encarnacion Perez-Andres\(^2\), Marta Varela-rey\(^3\)

\(^1\)CIC bioGUNE, Ikerbasque Research Foundation, Derio, Spain, \(^2\)CIC bioGUNE, Derio, Spain, \(^3\)CIC bioGUNE, Ciberehd, Derio, Spain

Myelinating Schwann cells play a critical role for neuronal function and health. Defective myelination is responsible for the morbidity of a number of peripheral neuropathies, including Charcot-Marie-Tooth disease and diabetic neuropathy. Decades of research has uncovered a complex transcriptional and post-transcriptional program that drives the formation and maintenance of the myelin sheath. In contrast, much less is known about the functional role of post-translational modification (PTM) of proteins in this remarkable biogenic process.

Neddylation, a PTM that involves the conjugation of the ubiquitin-like protein Nedd8 to protein targets, has recently emerged as a central and versatile regulator of many cellular processes, including ubiquitination, protein transcription and signalling transduction. In Schwann cells, a functional role for neddylation has so far not been defined.

In this study, using various models of genetic and pharmacological inhibition of neddylation in vivo, we show that this PTM has complex and extensive regulatory functions in Schwann cells. For instance, genetic inactivation of NAE1, the enzyme that catalyses neddylation reactions, specifically in developing Schwann cells, leads to striking nerve defects that exhibit all the hallmarks of a severe neuropathy, including gait abnormalities, muscle weakness, and hindlimb clasping. Strikingly, NAE1-deficient mice lack peripheral myelin and exhibit active myelin breakdown of the few formed myelin sheaths. Mechanistically, this severe block of myelination is due to a deficiency in the ubiquitin-mediated degradation of negative regulators of myelination in perinatal nerves, which remain artificially elevated, thus blocking myelination. Notably, we also found an important function of neddylation in maturation and maintenance of myelin sheaths, and in the Schwann cell responses to nerve injury.

In summary, our study reveals that PTMs can play a central role in nerve development, and identifies neddylation as a tractable target for the development of new therapies in demyelinating disorders and for nerve regeneration.

**References:** None.

**Keywords:** Schwann Cell, Axonal Regeneration, Other

**Grant Support:** This work was funded by grants to A.W. from: Ministerio de Economia y Competitividad–Plan Nacional de I+D+I (MINECO) (Subprograma Ramon y Cajal RYC2010-06901; Proyectos Retos Investigacion SAF2015- 65360-R; Proyectos Explora Ciencia SAF2015-72416-EXP; Proyectos Europa Excelencia SAF2015-62588-ERC), Spanish Association Against Cancer (AECC; JP Vizcaya), the BBVA foundation, Basque Government Department of Education (PI2013-46), Fundación Vasca de Innovación e Investigación Sanitarias EITB Maratoia (BIO13/CI/015). M.V.R. is grateful for the support of a 2017 Leonardo Grant for Researchers and Cultural Creators, BBVA Foundation. CIBERehd is funded by the Instituto de Salud Carlos III. We thank MINECO for the Severo Ochoa Excellence Accreditation (SEV-2016-0644).
Cell adhesion and choline-dependent metabolism in PNS myelination

Haesun Kim¹, Corey Heffernan¹, Edward Bonder², Jorge Golowasch³, Patrice Maurel¹

¹Rutgers University, Newark, USA, ²Rutgers University, Newark, USA, ³New Jersey Institute of Technology, Newark, USA

During myelination, Schwann cells up-regulate lipid biosynthesis to supply the lipid-rich (70 - 85%) mature myelin sheath. Several of these lipids are directly derived from choline-dependent metabolism, whereas the synthesis pathways of others intersect with choline derivatives. Choline-derived lipids are important both as structural components and as reservoirs of signaling molecules that have a direct implication on the initiation of myelination, the compaction and the maintenance of the myelin sheath. Little is known about the molecular mechanisms that regulate the lipid synthesis during Schwann cell myelination. It is likely, however, that axo-glial interactions are involved. Recently we identified in Schwann cells a protein complex that incorporates cell adhesion molecule Nectin-like 4 (Necl4) and Choline Transporter-Like protein 1 (CTL1). We have shown that intracellular choline homeostasis, as well as choline-dependent lipid biogenesis of phosphatidylcholine and phosphatidylinositol are disrupted in Necl4-deficient Schwann cells. To expand our in vitro data to an in vivo system, we generated a Schwann cell-specific CTL1 knockout mouse (dhhCre;CTL1fl/fl). EM analyses of developing sciatic nerves reveals PN myelination defects including delayed myelination, thinner myelin sheaths as well as myelin in-folding and out-folding. The mice also exhibit impaired motor behavioral performance and reduced nerve conduction thresholds. While choline is a vital nutrient that must be acquired though the diet, cells do have the ability to produce choline de novo through the PEMT pathway. Thought to have little to none biological role in non-hepatic tissues, we show that the PEMT enzymes are strongly expressed in developing sciatic nerves at the onset of myelination. Similar to the CTL1 knockout mice, PEMT knockout mice present numerous myelin abnormalities in the PNS. These results suggest that the regulation of choline metabolism through CTL1 and PEMT pathways is an important parameter to myelin formation.

References: None.

Keywords: Schwann Cell, CMTR

Grant Support: NIH NS065218 and NS090305 to PM
The Integrated Stress Response Contributes to Charcot-Marie-Tooth Type 2D Peripheral Neuropathy in Mice

Emily Spaulding, Robert Burgess

The Jackson Laboratory, The University of Maine, Bar Harbor, ME, USA

Dominant mutations in glycyl-tRNA synthetase (GARS) cause CMT type 2D (CMT2D). How mutations in GARS cause neurodegeneration is unclear, but impaired translation has emerged as a potential toxic gain-of-function mechanism based on work with Drosophila. To test this mechanism in mice, we have profiled translation in motor neurons of mice with mutations in Gars that are validated as CMT2D models. In vivo, cell type-specific, fluorescent non-canonical amino acid-tagging (FUNCAT) has revealed reduced translation in motor neuron cell bodies of mutant Gars mice. To complement the protein analysis, in vivo ribosome-tagging from mutant Gars motor neuron cell bodies was used to identify mRNAs undergoing translation. This revealed an upregulation of transcripts associated with the integrated stress response, including ATF4 and several of its gene targets. Using RNAscope in situ hybridization, we show that (1) activation of the stress response occurs in approximately 70% of mutant motor neurons, (2) most gamma motor neurons do not show this response, (3) a subset of sensory neurons in dorsal root ganglia also upregulate the stress response, and (4) no other cell types in the spinal cord or dorsal root ganglia activate this response. We also find evidence of stress response activation in the spinal cords of mutant Yars-E196K mice, a model of dominant intermediate CMT type C. Genetic experiments reveal that removing GCN2, a kinase that activates the stress response, from mutant Gars mice prevents expression of the most highly upregulated ATF4 gene targets. Removing GCN2 also significantly alleviates neuropathy, resulting in increased body weight, improved grip strength, less denervation at the neuromuscular junction, increased nerve conduction velocity, and less motor axon loss. Because chronic stress response activation is detrimental to motor neurons in this disease context, inhibiting GCN2 in human patients with mutations in tRNA synthetase genes may be

References: None.

Keywords: CMTR, Axonal Biology

Grant Support: Ruth L. Kirschstein NRSA Individual Predoctoral Fellowship F31NS100328 to ELS and RO1 NS054154 to RWB.
Poster 96

Role of the ER stress transcription factor XBP1 in Charcot-Marie-Tooth disease type 1B

Thierry Touvier¹, Rosa Mastrangelo¹, Francesca Veneri¹, Cinzia Ferri¹, Francesca Bianchi², Ubaldo Del Carro², Laurie Glimcher³, Christina E. Barkauskas⁴, Lawrence Wrabetz⁵, Maurizio D'Antonio¹

¹Division of Genetics and Cell Biology San Raffaele Scientific Institute, Milan, Italy, ²Division of Neuroscience San Raffaele Scientific Institute, Milan, Italy, ³Dana-Farber Cancer Institute, Harvard Medical School and Brigham and Women’s Hospital, Boston, USA, ⁴Duke University Medical Center, Durham, USA, ⁵HJKRI-University of Buffalo, Buffalo, USA

Myelin protein zero (Mpz) protein is the most abundant protein in the myelin of peripheral nerves. The mutant MpzS63del causes Charcot-Marie-Tooth (CMT) 1B disease in humans and a similar demyelinating neuropathy in transgenic mice. MpzS63del protein provokes an endoplasmic reticulum (ER) stress in myelinating Schwann cells, resulting in an unfolded protein response (UPR) characterized by activation of PERK, ATF6 and XBP1 pathways. We have previously reported that activation of CHOP and GADD34, two mediators downstream of PERK, is pathogenetic in MpzS63del mice, but the role of the other UPR branches remains to be investigated.

To unravel the role of the XBP1 pathway in CMT1B, we generated new models of CMT1 mice in which XBP1 gene is deleted or overexpressed specifically in Schwann cells and, in parallel, we exploited MpzS63del dorsal root ganglia (DRG) explant cultures in which XBP1 signaling is modulated by gain/loss of function approaches.

We have observed that the absence of XBP1 dramatically worsens hypomyelination and electrophysiological/locomotor parameters in young and adult S63del neuropathic animals. Interestingly, we observed strong upregulation of PERK and IRE1-mediated RIDD signalings in neuropathic animals lacking XBP1. This suggests that the activation of XBP1 targets plays a critical role in limiting MpzS63del toxicity, which cannot be compensated by other stress responses. In addition, we demonstrated in S63del DRG cultures that inhibition of XBP1 pathway impairs myelination while activation of XBP1 signaling ameliorates myelination.

Overall, these data demonstrate that the XBP1 pathway has a essential adaptive role in MpzS63del neuropathy and suggest that activation of this pathway is beneficial for CMT1B and possibly for other neuropathies characterized by UPR activation.

References: None.

Keywords: Schwann Cell

Grant Support: Telethon GGP14147
NRG1 type I dependent autocrine stimulation of Schwann cells in onion bulbs of peripheral neuropathies

Ruth Stassart¹, Robert Fledrich², Dagmar Akkermann³, Vlad Schütza⁴, Tamer Abdelaal⁵, Doris Hermes⁶, Maria Soto-Bernardini⁷, Tilmann Götze⁶, Theresa Kungl⁶, Michael Sereda⁶, Markus Schwab⁸, Klaus-Armin Nave⁶

¹Department of Neuropathology University Clinic Leipzig, Department of Neurogenetics MPI of Experimental Medicine, Leipzig, Germany, ²Institute of Anatomy, University of Leipzig, Leipzig, Germany, ³Deparment of Neuropathology, Leipzig, Germany, ⁴Department of Neuropathology, University Clinic Leipzig, Leipzig, Germany, ⁵Department of Neurogenetics, Max-Planck-Institute of Experimental Medicine, Göttingen, Germany, ⁶Department of Neurogenetics, Max-Planck-Institute of Experimental Medicine, Göttingen, Germany, ⁷Deparment of Neurogenetics, Max-Planck-Institute of Experimental Medicine, Göttingen, Germany, ⁸Hanover Medical School, Hanover, Germany

In contrast to acute peripheral nerve injury, the molecular response of Schwann cells in chronic neuropathies remains poorly understood. Onion bulb structures are a pathological hallmark of demyelinating neuropathies, but the nature of these formations is unknown. Here, we show that Schwann cells induce the expression of Neuregulin-1 type I (NRG1-I), a paracrine growth factor, in various chronic demyelinating diseases. Genetic disruption of Schwann cell-derived NRG1 signalling in a mouse model of Charcot-Marie-Tooth Disease 1A (CMT1A), suppresses hypermyelination and the formation of onion bulbs. Transgenic overexpression of NRG1-I in Schwann cells on a wildtype background is sufficient to mediate an interaction between Schwann cells via an ErbB2 receptor- MEK/ERK signaling axis, which causes onion bulb formations and results in a peripheral neuropathy reminiscent of CMT1A. We suggest that diseased Schwann cells mount a regeneration program that is beneficial in acute nerve injury, but that overstimulation of Schwann cells in chronic neuropathies is detrimental.

References: None.

Keywords: CMTR, Schwann Cell

Grant Support: This work was funded by the ERA-NET for Research Programs on Rare Diseases E-RARE-3 (01GM1605)
Finely tuned calcium dynamics are essential for normal neuronal function, and excessive calcium flux has been repeatedly implicated in the pathogenesis of neurodegenerative diseases. The mechanisms that lead to neuronal dysfunction and degeneration downstream of calcium entry remain poorly defined. Mutations in the non-selective cation channel TRPV4 cause motor predominant peripheral neuropathies, including Charcot Marie Tooth disease subtype 2C (CMT2C). To investigate the role of calcium in neurodegeneration and pathological mechanisms involved in CMT2C, we explored the consequences of CMT2C-causing mutant TRPV4 expression in primary mammalian neurons and in *Drosophila*. Expression of mutant TRPV4 causes neuronal dysfunction and axonal and dendritic degeneration that can be prevented by genetically or pharmacologically inactivating the TRPV4 ion channel pore. While activation of both wild-type and mutant TRPV4 increases intraneuronal calcium, we demonstrate that mutant TRPV4 is more sensitive to stimulation than wild-type TRPV4 in neurons. Additionally, mutant TRPV4 causes neuronal dysfunction manifested as hyperexcitability and impaired mitochondrial transport in the absence of TRPV4 stimulation. Interestingly, acute pharmacologic activation of wild-type TRPV4 also disrupted mitochondrial transport, suggesting mitochondrial transport is regulated by TRPV4 mediated calcium influx. To investigate signaling mechanisms involved in mutant TRPV4 mediated toxicity, we performed a genetic modifier screen in the fly and identified CaMKII as a potent genetic modifier of mutant TRPV4. RNAi silencing of CaMKII prevents neuronal dysfunction and neurodegeneration. Remarkably, pharmacologic inhibition of CaMKII substantially suppresses TRPV4 mediated calcium influx, suggesting CaMKII potentiates TRPV4 activity and operates at the level of calcium entry in our models. Our data suggest that neuropathy-causing mutants sensitize the TRPV4 ion channel, resulting in CaMKII dependent calcium influx and subsequent calcium-dependent disruption of mitochondrial transport and neurodegeneration. Furthermore, they suggest that TRPV4 selective antagonists warrant further investigation as potential therapeutics for TRPV4-mediated peripheral neuropathies.

**References:** None.

**Keywords:** CMTR, Axonal Biology

**Grant Support:** None.
Improving Physical Function in Persons with Peripheral Neuropathy Using Sensory Neuromodulation - Clinical Trial Update

Lars Oddsson¹, Teresa Bisson², Helen Cohen³, Sara Koehler-McNicholas⁴, Doris Kung³, Diane Wrisley⁵

¹RxFunction Inc. Eden Prairie, MN, USA, University of Minnesota, MN, USA; Ben-Gurion University of the Negev, Israel, Eden Prairie, MN, USA, ²University of Minnesota, Medical School, Division of Physical Therapy, Minneapolis, MN, USA, ³Baylor College of Medicine, Houston, TX, USA, ⁴Minneapolis Department of Veterans Affairs Health Care System, Minneapolis, MN, USA, ⁵Department of Physical Therapy, Wingate University, Wingate, NC, USA

Problems with gait and balance in persons with sensory peripheral neuropathy are well documented. A new wearable device, a lower limb sensory neuroprosthesis to substitute for lost plantar sensation, is currently used in a multi-site clinical trial (NCT #03538756). The technology is intended for individuals with sensory peripheral neuropathy associated with balance problems. The device provides gentle directional tactile cues around the lower leg reflecting changes in foot pressure distribution measured with an instrumented foot pad in the shoe. Patients react to these new sensory cues and incorporate them to improve gait and balance. The trial investigates long-term chronic use effects (52 weeks) on clinical and patient-reported outcomes of balance and gait function, quality of life, physical activity/participation and pain. The study will enroll 100 patients across multiple sites 2018-2020. Clinical outcomes include Functional Gait Assessment (FGA), Gait Speed, Timed Up&Go, Four-Stage Balance Test, Vestibular Activities of Daily Living and Activities-Specific Balance Confidence Scales. Fall-rates are monitored and compared to pre-study data. Patients for the study are diagnosed with sensory peripheral neuropathy, a loss of plantar sensation and have associated gait and balance problems. Tactile vibratory sense around the ankle where the leg unit of the device is placed is required and is tested prior to use. FGA score should be below 23, the cut-off for high fall-risk in community dwelling elderly individuals, and the test should be performed without the use of an assistive device as an indication of sufficient motor function to act on new sensory information provided by the device. This presentation will share early observations from the trial and discuss their translation into clinical practice. Results from the study will help refine prescription criteria for the device and further determine whether a short-term in-clinic response is indicative of long-term improvements.

References: None.

Keywords: Clinical Trials, Diabetes, Pain, Other

Grant Support: National Institute on Aging R44AG040865
Variable Presentation of Hereditary Transthyretin-Mediated (hATTR) Amyloidosis: A Single Center Experience with the Patisiran PAAP

Yessar Hussain¹, Jennifer Luth², Richard Hurd²

¹Austin Neuromuscular Center, Austin, TX, USA, ²Alnylam Pharmaceuticals, Cambridge, MA, USA

Introduction: Hereditary transthyretin-mediated (hATTR) amyloidosis is a multisystem disease that can lead to a mixed presentation. Because of this variable presentation, accurate diagnosis and treatment can be delayed.

Methods: This case series evaluates 8 patients at a single center between 2016 – 2018 who were ultimately diagnosed with hATTR amyloidosis. Three enrolled into the patisiran Pre-Approval Access Program (PAAP), were dosed, and had at least a 6-month assessment. The patisiran PAAP is an open-label, multicenter program, consisting of the Expanded Access Protocol (EAP) in the US (NCT02939820; now closed) and Compassionate Use in the EU. The PAAP provides access to patisiran for adults with genotype-confirmed hATTR amyloidosis and symptomatic polyneuropathy who meet eligibility criteria.

Results: We share a series of cases in patients ages 48-79-years who presented with a variety of symptoms, including ascending paresthesias, orthostatic hypotension, heart failure, constipation, and dyspnea. Several of these cases were initially misdiagnosed which prolonged time to correct diagnosis up to 10 years. Diagnosis of hATTR amyloidosis was definitively established after a series of multisystem exams and genetic testing. Of the 3 patients in the PAAP, 1 remained stable at 12 months (PND IIIb), 1 progressed at 6 months (PND IIIb to IV), and 1 improved at 6 months (PND II to I). Patisiran was well tolerated in these 3 patients; all AEs were mild-moderate except one severe AE that was deemed not related to patisiran.

Conclusions: As seen in this case series of a single center, the variable presentation and mixed nature of hATTR amyloidosis makes it a difficult disease to diagnose if there is a lack of clinical suspicion. Upon recognizing the symptoms and considering hATTR amyloidosis as a differential diagnosis, it is possible to diagnose patients earlier and provide treatment for the polyneuropathy manifestations of the disease.

References: None.

Keywords: Amyloidosis

Grant Support: None.
A complex inherited sensory neuropathy related to compound heterozygous mutation in the FXN gene

Matilde Laura¹, Menelaos Papis¹, Michael Lunn¹, Gita Ramdharry¹, Santiago Catania², Dimitri Kullmann³, Kevin Stopps⁴, James Polke⁴, Mary Reilly¹

¹MRC Centre for Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, United Kingdom of Great Britain and Northern Ireland, ²Department of Clinical Neurophysiology, National Hospital for Neurology and Neurosurgery, London, United Kingdom of Great Britain and Northern Ireland, ³Department of Clinical and Experimental Epilepsy, UCL Queen Square Institute of Neurology, London, United Kingdom of Great Britain and Northern Ireland, ⁴Department of Neurogenetics, National Hospital for Neurology and Neurosurgery, London, United Kingdom of Great Britain and Northern Ireland

Friedreich Ataxia (FRDA) is an autosomal recessive hereditary ataxia, caused by a biallelic GAA-trinucleotide-repeat expansion in FXN gene. Neuropathy is a common feature. Compound heterozygosity for an expansion and a sequence mutation are rare and can cause an atypical phenotype with later age onset and slower disease progression. We describe an 80 year old patient who developed unsteadiness and difficulties walking in his 30s. He was diagnosed with Charcot Marie Tooth (CMT) disease at 40. His mobility gradually declined over the years and he has been using a wheelchair for the last 15 years. His younger brother had a similar phenotype but earlier onset. Neurological examination showed normal cranial nerves, normal tone and coordination in the upper limbs. He had distal wasting and mild weakness in the upper limbs. In the lower limbs he had distal weakness and non-length dependent proximal weakness which had a pyramidal distribution. He was areflexic. Sensory examination showed severe loss of vibration sense and proprioception in the upper and lower limbs. Nerve conduction studies were compatible with predominant axonal sensory neuropathy. Because of the unusual features he had spinal cord MRI which revealed an intramedullary lesion in the thoracic cord at T7 vertebral level probably related to a dorsal arachnoid cyst. Next generation sequencing (NGS) CMT2 and HSN panel were negative. Further NGS identified heterozygous Gly130Val pathogenic mutation in FXN and one FXN GAA repeat expansion of approximately 350 GAA repeats in the pathogenic range on the other allele. The G130V is the most frequent missense mutation in FRDA and might account for the production of a partially functional protein and milder phenotype. This interesting case expands the phenotypic variability of FRDA due to compound heterozygous mutations and highlights the importance of considering genetic testing for FRDA in cases of complex inherited sensory neuropathy.


Keywords: CMTR

Grant Support: None.
The longitudinal change in nerve cross-sectional area of Charcot-Marie-Tooth disease type 1A

Yu-ichi Noto1, Yukiko Tsuji1, Fukiko Kitani-Morii1, Yu-ta Kojima1, Kensuke Shiga2, Toshiki Mizuno1, Masanori Nakagawa3

1Department of Neurology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, 2Department of Neurology, Matsushita Memorial Hospital, Osaka, Japan, 3Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

Introduction: The lack of sensitive biomarkers is thought to be one of the factors that led to failures of clinical trials in Charcot-Marie-Tooth disease (CMT). Recently, muscle MRI and neurofilament light were identified as potential sensitive biomarkers of disease progression. It would be beneficial for CMT patients to demonstrate that parameters obtained by non-invasive methods could be sensitive biomarkers. In CMT type 1A (CMT1A), 2-fold to 3-fold increases in nerve cross-sectional area (CSA) is observed by using nerve ultrasound. As such, the aim of this study is to determine the longitudinal change in nerve CSA in adult CMT patients. Methods: This study included 15 patients with CMT1A patients (M:F = 10:5, mean age: 55.1 years old). The measurement of the median and sural nerve CSAs using nerve ultrasound was done 4 times (at baseline, 1, 3, and 5 years after the baseline.) by one examiner. CMT neuropathy score (CMTNS) and CMT examination score (CMTE) were also measured at each visit. Comparison of each parameter between at the baseline and 5 years after the baseline was performed. Results: Regarding nerve CSAs, there was not significant 5-year change in the median (at the wrist, forearm, and upper arm) and sural nerves, although there was a tendency that sural nerve CSA was decreasing with time (p =0.07). Mean CMTNS and CMTE significantly increased linearly over 5 years (from 15.8 to 18.9 point (p <0.01) and from 10.9 to 14.0 point (p <0.01), respectively). Conclusions: Nerve ultrasound method could not detect a 5–year change in nerve CSAs. The longitudinal change in other nerve ultrasound parameters including echogenicity should be explored in the future.


Keywords: CMTR

Grant Support: AMED under Grant Number 18ck0109271h0002
Systematic Survey of Electrophysiological Findings in Myotonic Dystrophy Type 1 (DM1)

Nina Khizanishvili¹, Kristina Stahl², Federica Montagnese², Stephan Wenninger², Nato Bokuchava³, Nana Kvirkvelia⁴, Benedikt Schoser²

¹Friedrich-Baur Institut, Clinic of the University of Munich, Munich, Germany, ²Friedrich-Baur Institut, Clinic of the University of Munich, Munich, Germany, ³Saint Michael Archangel multiprofile clinical Hospital, Tbilisi, Georgia, ⁴Petre Sarajishvili Institute of Neurology, Tbilisi, Georgia

Background: DM1 is an inherited muscular dystrophy with myotonic and myopathic changes in the muscles. We reviewed the literature of electrophysiological findings of DM1 patients to reveal preference of electrophysiological changes.

Methods: all English, German and Russian articles from PubMed and EMBASE about electrophysiological findings in genetically confirmed DM1 patients were reviewed. Articles of case reports of 1 or 2 patients were excluded. Results: A data set of 363 DM1 (175 females) patients was collected. Mean age were 41 years. EMG from 229 DM1 patients showed myotonic discharges in 182 (79.5%) and myopathic changes in 128 (55.9%). From 362 DM1 patients the nerve conduction velocity studies showed neuropathic changes in 79 (21.8%). Out of 41 DM1 patients in 28 (68.3%) a demyelinating neuropathy was found. Axonal neuropathy was evident in 6 (14.6%) and mixed neuropathy in 7 (17.1%). Motor conduction block or a significant temporal dispersion was not reported.

Discussion and conclusion: Our study for the first time summarizes the electrophysiological findings in adults with DM1. Beyond well-known EMG findings, about 20% of DM patients show neurographic alterations. This should prime us to include neurography as a standard element in the work-up of all DM patients.

References: None.

Keywords: Other

Grant Support: None.
Charcot-Marie-Tooth disease, Type 1A (CMT1A) is one of the most common inherited peripheral neuropathies; a demyelinating disorder caused by an additional copy of the PMP22 gene. The PMP22 gene encodes a transmembrane glycoprotein that is enriched in compact myelin but little is known about the endogenous function of PMP22. Previous work in rodents suggests that PMP22 gene dosage may affect stoichiometry of compact myelin structural components, PMP22 degradation and the expression of important myelination genes. These potential models reveal interesting candidate pathways that may be modified in CMT1A rodent models but cannot fully explain the endogenous function of PMP22 or how copy number variation of this gene leads to dysregulated myelination. We are utilizing CMT1A patient fibroblasts and iPSC-derived Schwann cells in order to study PMP22 gene dosage in the genetic background of actual patients. Our recent findings revealed increased substrate adhesion in CMT1A patient fibroblasts as compared to healthy controls. Interestingly, the increased adhesion is correlated with increased cell surface PMP22 protein levels but not total PMP22 protein levels. Additionally, gene ontology analysis of RNA sequencing on both patient fibroblasts and iPSC-derived Schwann cells revealed cell adhesion as a highly significant biological process, which included genes from multiple adhesion families. These findings suggest that PMP22 copy number variation affects adhesion directly through PMP22 surface expression and indirectly by altering expression of additional adhesion genes. Current studies are focused characterizing adhesion phenotypes in iPSC-derived Schwann cells and identifying dysregulated genes in both cell types that contribute to the dysfunctional adhesion by performing rescue experiments. Results from these studies will significantly advance our understanding of PMP22 function, help uncover CMT1A pathomechanisms and reveal targets for novel therapeutics.

References: None.

Keywords: CMTR, Schwann Cell

Grant Support: The Foundation for Peripheral Neuropathy and the Johns Hopkins University Provost’s Postdoctoral Diversity Fellowship
Two Independent Cases of de novo GARS(p.Gly327Arg) Mutation that Causes a Predominantly Motor Axonal Neuropathy

Diana Lee1, Rebecca Meyer-Schuman2, Lois Dankwa1, Chelsea Bacon3, Anthony Antonellis2, Mike Shy3, Steven Scherer1

1University of Pennsylvania, Philadelphia, PA, USA, 2University of Michigan Medical School, Ann Arbor, MI, USA, 3University of Iowa Hospitals & Clinics, Iowa City, IA, USA

Proband 1 is an 18-year-old woman who developed pain while walking and weakness in her hands at age 10. When examined at age 14, she had diminished strength in the distal muscles of her legs and arms, pinprick loss below the ankles, and normal vibration. Her CMT Examination Score (CMTES) was 10 (out of 28). Proband 2 is a 22-year-old woman who developed weakness in her hands and feet around age 13. Her initial exam at age 22 showed weakness in the distal muscles of her legs and arms, as well as normal pinprick and vibration sensation. Her CMT Neuropathy Score was 10 (out of 36). Clinical neurophysiology showed a predominately (proband 1; age 12) or exclusively (proband 2; age 22) motor neuropathy. A clinical gene panel on DNA isolated from proband 1 identified a previously unreported variant in GARS (c.979G>A/p.Gly327Arg). This is a de novo variant as it was absent in both parents. Whole-exome sequencing of proband 2 identified the same GARS mutation, which was not present in the proband’s mother or sister. Through the GENESIS platform, the clinicians who evaluated the two probands became aware of each other’s findings. To determine the functional consequences of the p.Gly327Arg GARS mutation, yeast complementation assays were performed by modeling the variant in both the yeast and human GARS genes. In both cases, the p.Gly327Arg mutation failed to rescue yeast growth, showing that it is a loss-of-function mutation. Based on these results, the finding of a previously unreported GARS variant that is likely de novo in two, unrelated families, and the results of the yeast complementation assay, we believe the p.Gly327Arg GARS mutation is the underlying cause of the neuropathy in these two individuals, both of whom have a motor > sensory neuropathy; which is typical for GARS mutations.

References: None.

Keywords: CMTR, Human Genetics

Grant Support: None.
Poster 107

Resolving a multi-generational neuromuscular mystery

Nivedita Jerath

University of Iowa, Gainesville, FL, USA

Introduction: Valosin containing protein (VCP) mutations have been reported to present with a high degree of variability and can be present in patients even if they may have an initial normal work up. Methods: A middle aged proband was labeled as "normal" and "pain medication seeking" after an unrevealing work up of clinical, laboratory, electrodiagnostic, radiographic, pathologic, and genetic testing. Repeat work up and further genetic testing revealed a pathogenic VCP mutation. Results: The proband presented with chronic neck pain, but had variable features of scapuloperoneal atrophy, which was also seen in her family. The patient and her family were found to have a known pathogenic c.464G>A, p.Arg155His (R155H) mutation in the VCP gene. Conclusion: Despite traditional thinking of attempting to localize neurological syndromes, VCP mutations are difficult to localize as they can present with significant clinical heterogeneity including a scapuloperoneal syndrome with variable neuropathic and myopathic features.

References: None.

Keywords: Human Genetics, Pain

Grant Support: None.
Objective: To report our experience with transthyretin (TTR) knockdown therapy in patients with hereditary TTR amyloidosis (hATTR) who failed liver transplantation. Background: Patients with hATTR amyloidosis, especially those with non V30M mutations, can continue to have disease progression and reduced survival despite early liver transplant. This is thought to be related to wild type ATTR deposition (wtATTR). Newly approved TTR knockdown therapies (Patisiran and Inotersen), significantly suppress the production of both mutated ATTR (mATTR) and wtATTR. Methods: Two patients with hATTR amyloidosis who continued to have disease progression despite liver transplantation were started on Inotersen. Results: The first patient is a 49 year-old man with TTR-Arg50 mutation and the second patient is 64 year-old man with T32C TTR mutation. Both patients underwent liver transplantation 2 years after symptoms onset and both had symptomatic improvement which lasted for 2 years before their disease progressing again. Both patients were started on Inotersen. The first patient was treated for 5 months and stopped because of thrombocytopenia. During treatment, his Neuropathy Impairment Score (NIS) remained stable (124 to 121.5). After stopping treatment, patient’s NIS increased to 140 and he started using a scooter. The second patient has been on the drug for 6 months, and his NIS improved from 124 to 98.5 with no significant side effects. Conclusion: Progression of disease following liver transplant in patients with hATTR amyloidosis is difficult to manage and is probably related to wtTTR. TTR knockdown therapy which suppresses the progression of both mTTR and wtTTR could be a promising treatment for patients with hATTR amyloidosis who continue to have disease progression despite liver transplantation.

References: None.

Keywords: Amyloidosis, Human Genetics

Grant Support: None.
Poster 109

A Novel Pathogenic Variant of NEFL responsible for Deafness associated with Peripheral Neuropathy

Anne-Sophie LIA¹, Justine LERAT², Corinne MAGDELAINE², Hélène BEAUVAIS-DZUGAN², Caroline ESPIL³, Karima GHORAB², Paco DEROUAULT², Philippe LATOUR⁴, Franck STURTZ²

¹Univ Limoges, CHU limoges, Limoges, France, ²Univ. Limoges, CHU Limoges, Limoges, France, ³CHU Bordeaux, BORDEAUX, France, ⁴CHU Lyon, Lyon, France

Neurofilaments are neuron-specific intermediate filaments essential for the radial growth of axons during development and the maintenance of axonal diameter. Pathogenic variants of NEFL are associated with CMT1F, CMT2E, and CMTDIG and have been observed in less than 1% of CMT cases, resulting in the reporting of 35 variants in 173 CMT patients to date. However, only six variants have been reported in 17 patients with impaired hearing. No genotype-phenotype correlations have yet been established. Here, we report an additional case: a 69-year-old female, who originally presented with axonal sensory and motor neuropathy at the age of 45, associated with moderate sensorineural hearing loss, with a slight slope at high frequencies. NGS identified a novel pathogenic variant: c.269A>G, p.(Glu90Gly). Hearing impairment is often linked to CMT due to pathogenic variants of NEFL, especially p.(Glu90Lys) and p.(Asn98Ser), and in our case p.(Glu90Gly). These pathogenic variants are all located at hot spots, in the head domain and the two ends of the rod domain of the protein.

References: None.

Keywords: Human Genetics

Grant Support: None.
Electrophysiological features of hereditary ATTR amyloidosis misinterpreted as chronic inflammatory demyelinating polyneuropathy

Nobuhiko Ohashi1, Minori Kodaira1, Hiroshi Morita2, Yoshiki Sekijima3

1Shinshu University School of Medicine, Matsumoto, Japan, 2Shinshu University, Shinshu University School of Medicine, Matsumoto, Japan, 3Shinshu University, Shinshu University School of Medicine, Matsumoto, Japan

Purpose: To clarify the electrophysiological demyelinating features in patients with hereditary ATTR amyloidosis that may cause a misdiagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP).

Methods: We retrospectively reviewed records of 102 patients with hereditary ATTR amyloidosis (85 Val30Met and 17 non-Val30Met; 37 and 65 from endemic and non-endemic areas) and investigated results of motor nerve conduction studies (MNCSs) with a 2-Hz low-cut filter in the unilateral ulnar and tibial nerves. MNCS parameters were evaluated whether they fulfilled the demyelinating values in the European Federation of Neurological Societies/Peripheral Nerve Society electrodiagnostic (EFNS/PNS EDX) criteria for CIDP. Distal compound muscle action potential (DCMAP) duration is influenced by low-cut filter settings. Therefore, DCMAP duration was analyzed using not only EFNS/PNS EDX criteria but also the cut-off value from the 2-Hz low-cut filter proposed by Mitsuma et al. (2015).

Results: Thirteen of 102 patients (13%) satisfied the definite EFNS/PNS EDX criteria for CIDP with low compound muscle action potential (CMAP) amplitude in the tibial nerve (0.7 ± 0.7 mV) and prolonged DCMAP duration in the ulnar nerve. There were no significant differences in clinical backgrounds between patients with and without the definite EFNS/PNS EDX criteria. Abnormal temporal dispersion and prolongation of distal latency in the tibial nerve were observed in 5 of 13 patients. Only one of 13 patients presented with reduction of motor conduction velocity in each nerve. No patient exhibited conduction block in any nerve. When using the upper value proposed by Mitsuma et al, 10 of 13 patients with definite CIDP criteria were downgraded as those with possible CIDP.

Conclusion: Severe axonal degeneration causes electrophysiological demyelinating features without conduction block in patients with hereditary ATTR amyloidosis. Analysis of DCMAP duration considering low-cut filter settings would be needed to minimize misinterpreting hereditary ATTR amyloidosis as

References: None.

Keywords: Amyloidosis

Grant Support: None.
A novel HINT1 mutation identified in two Norwegian patients with peripheral neuropathy

Helle Høyer¹, Silvia Amor-Barris², Lin Brauteset³, Linda Strand¹, Eline Celis², Johan Helle¹, Albena Jordanova², Geir Braathen¹, Kristien Peeters⁴

¹Department of Medical Genetics, Telemark Hospital Trust, Skien, Norway, ²Molecular Neurogenomics Group, VIB-UAntwerp Center for Molecular Neurology, University of Antwerp, Antwerp, Belgium, ³Department of Children and Youth, Innlandet Hospital Trust, Division Elverum-Hamar, Elverum, Norway, ⁴Molecular Neurogenomics Group, VIB-UAntwerp Center for Molecular Neurology, University of Antwerp, Antwerp, Belgium
Introduction

Recessive mutations in the histidine triad nucleotide binding protein 1 (HINT1) are known to cause axonal CMT neuropathy mostly presenting with neuromyotonia. To date 16 disease causing mutations have been published. To our knowledge, no Norwegian individuals with HINT1-neuropathy have been described previously.

Methods

A panel of 99 peripheral neuropathy genes including HINT1 was examined by next-generation sequencing. Parental samples, available for the 12-year old boy, were examined by Sanger sequencing. Knock-out HeLa cells expressing the p.(Arg95Gln) allele were examined by western blotting. The growth of Hnt1 deficient yeast expressing the HINT1 orthologue carrying the same mutation was monitored in a complementation assay under restrictive conditions (39C, galactose-containing medium).

Results

A 12-year old boy and a 33-year old male were independently referred for genetic analysis of peripheral neuropathies. Genetic testing revealed in both of them two identical heterozygous mutations in the HINT1 gene, NM_005340.6:c.110G>C p.(Arg37Pro) and NM_005340.6:c.284G>A p.(Arg95Gln). Parental testing in the 12-year boy showed that his variants were situated in trans. The p.(Arg37Pro) variant is a known pathogenic founder mutation in Europe. The p.(Arg95Gln) variant has not previously been reported, but it was predicted pathogenic and targeted an amino acid residue at the dimer interface. The novel HINT1 substitution was further modelled in HINT1 knockout HeLa cells and HNT1 knockout yeast. Functional studies showed that the p.(Arg95Gln) mutant did not cause protein degradation in both HeLa and yeast cells. However, the p.(Arg95Gln) mutant was unable to rescue the growth deficiency of a Hnt1-KO strain in yeast complementation assays.

Conclusion

This study reports a novel HINT1 variant identified in two Norwegian patients. These are the first reported Norwegian individuals diagnosed with HINT1-neuropathy. p.(Arg95Gln) is the second pathogenic HINT1 mutation demonstrated to not cause protein degradation but still resulting in a loss of function phenotype.

References: None.

Keywords: Human Genetics

Grant Support: None.
Compound Heterozygous Mutations of SH3TC2 in Charcot-Marie-Tooth Disease Type 4C Patients

Ah Jin Lee¹, Yu Jin Choi¹, Kyung Suk Lee², Byung-Ok Choi³, Ki Wha Chung²

¹Kongju National University, Gongju, Korea (Republic of), ²Kongju National University, Kongju, Korea (Republic of), ³Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea (Republic of)

SH3TC2 mutations cause autosomal recessive Charcot-Marie-Tooth disease type 4C (CMT4C), characterized by spine deformities and cranial nerve involvement. This study identified four CMT4C families in 504 Korean demyelinating and intermediate CMT patients with compound heterozygous SH3TC2 mutations: p.G310E and p.E944G in FC523 and FC657 families and p.G310E and p.G1091V in FC703 and FC1080 families. The mutations were located at the highly conserved regions and several in silico analyses suggested pathogenic prediction of the mutations. The CMT4C frequencies were calculated to 0.33% in total Korean CMT cohort (n = 1,222), and 0.79% in demyelinating and intermediate patients (n = 504). The frequency in the Korean cohort study was relatively lower than other ethnic groups: 0.8% in a large USA CMT cohort, 1.7% in Germany, and 0.47% in Japan. Moreover, no homozygous mutation was found in the Korean patients. The reasons for low CMT4C frequency and no patients with homozygous mutation may be partly due to a strict legal prohibition of consanguineous marriage. Clinically, our patients showed less severe symptoms with no spine deformities, compared with other CMT4C patients. This study will be the first report of Korean CMT4C families with SH3TC2 mutations.

References: None.

Keywords: CMTR, Human Genetics

Grant Support: None.
Examining Mutation-Specific Impact on the Long, Distal Motor Axon in ALS using iPSC-derived Motor Neurons

Katie Marshall, Katherine Marshall, Labchan Rajbhandari, Arun Venkatesan, Nicholas Maragakis, Mohamed Farah

Johns Hopkins University School of Medicine, Baltimore, MD, USA

Amyotrophic Lateral Sclerosis (ALS) is a devastating motor neuron disease that is characterized by progressive dying back of motor axons and death of motor neurons that eventually leads to muscle wasting and death. Distal axon degeneration, dying-back, is a hallmark of motor neuron diseases that precedes symptom onset and motor neuron death both in human patients and animal models.1–4 There is no generally accepted explanation for the selective vulnerability of motor neurons in ALS. The longest axons tend to be the most susceptible to degeneration; therefore, the pathobiology of the long, distal motor axon in motor neuron disease is an area that must be explored thoroughly in order to understand ALS pathology and discover potential novel interventions for patients.

While motor neurons derived from human iPSCs (hMNs) hold promise for advancing ALS research,5–7 the length of axons, regenerative capacity, and mutant-specific innervation of neuromuscular junctions (NMJs) by these human neurons is not characterized. hMNs cluster into circular groups as they grow, and extend axons to other clusters, confounding quantification of axon outgrowth from individual hMNs. To address this, we have cultured hMNs from ALS patients and controls in custom microfluidic devices, and sequestered neuronal cell bodies in the main channel that extended processes through microgrooves into adjacent axonal compartments. We determined that dual-chamber devices with ample room in the axonal compartment are appropriate for examining axonal outgrowth, and allow for individual tracing of axons that are millimeters in length. This system lays the groundwork for introducing relevant cell types and gathering electrophysiological data from myocytes innervated by hMNs. We are now exploring the introduction of relevant cell types, such as myelinating Schwann cells and myocytes, into the axonal compartment in order to study ALS mutation-specific effects on structural and functional innervation of NMJs.


Keywords: Axonal Regeneration, Axonal Biology, Pre-clinical Studies

Grant Support: Muscular Dystrophy Association, MDA 416750: Mechanisms of neuromuscular synapse plasticity induced by BACE1 inhibition (Farah, PI) 2R56NS079339-06: BACE1 inhibition in injured peripheral nerve (Farah, PI)
Characterising Neurophysiological Findings in Charcot-Marie-Tooth Disease caused by Frameshift Mutations in NEFH

Aruna Nagendran¹, Menelaos Pipis², Andrea Cortese², James Polke², Matilde Laura², Julian Blake², Alexander Rossor², Mary Reilly²

¹Department of Clinical Neurophysiology, National Hospital of Neurology and Neurosurgery, Queen Square, London, United Kingdom of Great Britain and Northern Ireland, ²MRC Centre for Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, United Kingdom of Great Britain and Northern Ireland

Neurofilaments form an important part of the axonal cytoskeleton in both the central and peripheral nervous system. They are categorised into light (NEFL), medium (NEFM) and heavy (NEFH) chains and are essential in maintaining neuronal structure. Frameshift mutations in the NEFH gene have been associated with dominantly inherited CMT2, with translation of an abnormally elongated, amyloidogenic amino acid sequence. Clinically, patients typically present with motor-predominant symptoms between the 2nd and 5th decade with early falls and walking difficulties, but known associated features can include relatively early proximal muscle wasting, early ankle plantar-flexion weakness and pyramidal signs. Neurophysiology has been reported to show a motor and sensory axonal neuropathy largely affecting lower limbs, with EMG demonstrating non-length dependent neurogenic changes. We analysed neurophysiology obtained from 6 patients of 4 unrelated families seen at our centre, all of whom had frameshift NEFH mutations. 15 separate studies were performed on these patients. In the context of clinical information on these patients, we aim to further characterise the spectrum of neurophysiological features that can be seen in these patients. Analysis of nerve conduction studies demonstrated broadly symmetrical and length-dependent attenuation of sensory and motor amplitudes. There was isolated attenuation of only two motor responses as exceptions to this pattern. Additional features included consistent Tibial more than Peroneal muscle involvement, as well as mild Median forearm conduction slowing (42-47m/s) in the context of normal Median-APB amplitudes. EMG showed chronic or active neurogenic changes, which were often not clearly length-dependent. In summary, neurophysiology of 6 patients with frameshift NEFH mutations predominantly showed a length-dependent, axonal, sensory and motor neuropathy on NCS, but EMG shows disproportionate proximal muscle involvement. Preferential Tibial muscle involvement and mild slowing of the Median motor forearm segment were also frequently associated features.

References: None.

Keywords: CMTR

Grant Support: None.
Phrenic Neuropathy in Trembler J Neuropathic Mice

Lucia Notterpek¹, Hannah Bazick², Jonathan Larochelle³, malavika nair⁴, Alexa Mealy², Ethan Benevides⁵, Michael Sunshine⁶, Daniel Grey⁵, Darin Falk⁵, David Fuller⁵

¹University of Florida, Gainesville, FL, USA, ²University of Florida, Gainesville, USA, ³University of Florida, Gainesville, USA, ⁴University of Florida, Gainesville, USA, ⁵UF, Gainesville, USA, ⁶UF, Gainesville, USA

Peripheral neuropathies are typically characterized by weakness of the extremities; however respiratory complications have also been documented in Charcot-Marie-Tooth disease type 1A (CMT1A) and Dejerine-Sottas disease (DSS) patients. Trembler J (TrJ) mice carry a point mutation in peripheral myelin protein 22 (PMP22) and serve as a model of DSS. Studies of the neuromuscular junction (NMJ) between the phrenic nerve and diaphragm of homozygous TrJ mice suggest that neuromuscular deficits contribute to respiratory complications in neuropathic patients. We hypothesized that phrenic nerve degeneration leads to destabilization of the NMJ and contributes to respiratory dysfunction. Quantifying multiple morphological parameters from the phrenic nerve of wild type (Wt) and heterozygous TrJ mice revealed highly significant (p<0.0001) demyelination and axonal atrophy in affected samples. Analyses of muscle atrophy gene transcript levels, including Atrogin-1 and MuRF-1, detected a significant down-regulation in affected animals by ~27.7% and 37.9%, respectively. However, protein levels for the same muscle atrophy markers remained stable, suggesting impaired protein turnover. Indeed, diaphragms from TrJ mice showed upregulation of the ubiquitin-proteasome and autophagy pathways compared to Wt, paralleling a phenotype seen in Schwann cells of neuropathic mice. Unexpectedly, we identified significant enlargement of myofiber cross-sectional area in the diaphragm from TrJ vs. Wt mice (974.8 µm² vs. 717.8 µm²). Our findings suggest that severe phrenic nerve neuropathy contributes to NMJ degradation in neuropathic animals, causing detectable, possibly compensatory changes in myofibers of the diaphragm. We also examined breathing patterns using whole body plethysmography, and the results suggest possible changes in the control of breathing in TrJ mice. Specifically, the rate of breathing in TrJ mice is significantly impaired (p=0.0138 vs. WT) when exposed to an acute hypercapnic/hypoxic respiratory challenge. Further elucidating the mechanisms contributing to respiratory dysfunction in neuropathic models will identify appropriate tissue targets for treatments to improve patient quality of life.

References: None.

Keywords: Schwann Cell, Axonal Biology, CMTR, Human Genetics, Axonal Regeneration

Grant Support: None.
Use of GAITRite system to investigate walking ability in Charcot Marie Tooth patients

Laura Mori¹, Cecilia Contenti², Chiara Avanti², Valeria Prada², Angelo Schenone², Carlo Trompetto²

¹University of Genoa - DINOGMI, Genoa, Italy, ²University of Genoa, Genoa, Italy

Here we present the results of the GAITRite system assessment, used in a multicenter randomized, single blind, controlled study to investigate the possible improvements on gait ability in 24 CMT subjects that underwent a rehabilitation treatment.

All subjects were evaluated with clinical scales investigating walking and balance abilities, and an instrumental gait assessment by means of the GAITRite system, an electronic portable walkway able to measure the temporal and spatial gait parameters. Subjects were asked to walk on the carpet for one minute at normal speed (NW), at fast speed (FW), during a cognitive dual task (DT) and overcoming obstacles in height or length (OB). The clinical measures were compared between T0 and T1 using unpaired t-test. Pearson’s correlation coefficients were calculated between all continuous characteristics, Spearman’s correlation coefficient for ordinal outcomes.

We compared both instrumental and clinical data with a control group of healthy age-matched subjects, finding significant differences in both spatial and temporal parameters. Also comparing the NW and FW gait, we found significant differences in both spatial and temporal gait parameters; analyzing DT data, no significant differences were found, hence confirming that in these patients the cognitive performance has no repercussions on the gait. At the OB task temporal and spatial parameters were significant worse respect to NW.

Moreover, we investigate the possible correlations between the clinical assessment and the instrumental data at the NW, finding a strong negative correlation between speed and 10MWT and CMTES and a strong positive correlation between speed and balance tests and with 6MWT.

The present data allow us to suggest the use of the GAITRite system as a useful and rapid tool in the walking evaluation of CMT subjects.


Keywords: CMTR, Clinical Trials

Grant Support: None.
Efficacy of Patisiran in Patients with hATTR Amyloidosis and Prior Tafamidis Use: Analysis of APOLLO

Hollis Lin¹, Laura Obici², Violaine Planté-Bordeneuve³, Matthew White¹, Richard Riese¹, Ole Suhr⁴

¹Alnylam Pharmaceuticals, Cambridge, MA, USA, ²Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, ³Henri Mondor Hospital-Assistance Publique-East Paris- Créteil Université, Créteil, France, ⁴Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden

Introduction: hATTR amyloidosis is a multisystem, life-threatening disease. Patisiran, a RNAi therapeutic, and tafamidis, a TTR tetramer stabilizer, are approved treatments for certain patients with hATTR amyloidosis with polyneuropathy. In the Phase 3 APOLLO study, patisiran demonstrated significant improvement in polyneuropathy and quality of life (QOL) from baseline to 18-months compared to placebo. The impact of patisiran on patients with previous tafamidis treatment prior to enrolling in APOLLO was evaluated.

Methods: APOLLO was a randomized, placebo-controlled study of patisiran in patients with hATTR amyloidosis with polyneuropathy (NCT01960348). Tafamidis-treated patients who entered APOLLO were required to discontinue tafamidis ≥14 days before study entry; discontinuation reason was recorded. Post-hoc analyses evaluated results for mNIS+7, a composite measure of neuropathy, and Norfolk QOL- DN, a measure of QOL, in patients who had received prior tafamidis treatment.

Results: APOLLO enrolled 225 patients of which 74 (32.9%) reported prior tafamidis use. Average (SD) length of time on tafamidis was 17.4 (16.1) months; 25 (33.8%) of these patients discontinued tafamidis due to disease progression and 46 (62.2%) discontinued to participate in APOLLO. Patients with prior tafamidis use who received patisiran demonstrated significant improvement in mNIS+7 and Norfolk QOL-DN from baseline to 18-months (n=45 for both endpoints) compared with placebo (n=15 for mNIS+7 and n=14 for Norfolk QOL-DN) (mNIS+7 LS mean change (SEM): -6.2 (2.4) vs. 20.8 (3.8); Norfolk QOL-DN LS mean change (SEM): -0.8 (2.8) vs 15.1 (4.4), respectively).

Conclusions: Approximately one-third of patients enrolled in the randomized, placebo-controlled APOLLO study were previously treated with tafamidis. These patients who received patisiran treatment for 18 months experienced a significant improvement from baseline in their neuropathy and QOL, compared to placebo, similar to that experienced by the overall patisiran-treated population.


Keywords: Amyloidosis

Grant Support: None.
Charcot-Marie-Tooth disease type 2N Patients with AARS Mutations

Ah Jin Lee¹, Hye Ri Park², Yu Jin Choi², Byung-Ok Choi³, Ki Wha Chung²

¹Kongju National University, Gongju, Korea (Republic of), ²Kongju National University, Gongju, Korea (Republic of), ³Samsung Medical Center & Sungkyunkwan University School of Medicine, Seoul, Korea (Republic of)

Alanyl-tRNA synthetase (AARS) gene encodes a ubiquitously expressed class II enzyme which catalyzes the attachment of alanine to the cognate tRNA. It is known that AARS mutations are usually responsible for autosomal dominant Charcot-Marie-Tooth disease type 2N (CMT2 N). The AARS gene encodes alanyl-tRNA synthetase. Each of the amino acid synthetases catalyzes the attachment of their respective amino acids to the appropriate tRNA. The AARS gene encodes alanyl-tRNA synthetase. Each of the amino acid synthetases catalyzes the attachment of their respective amino acids to the appropriate tRNA. This study identified two CMT2N families in 318 axonal CMT patients with heterozygote AARS mutation: p.Q855R in FC612 family and p.R329H in FC1065 family. The mutations were located at the highly conserved regions and several in silico analyses suggested pathogenic prediction of the mutations. The p.R329H was previously reported as the pathogenic mutation of CMT2N, whereas the likely-pathogenic p.Q855R was unreported novel mutation. The FC1065 patient with p.R329H was clinically and electrophysiologically similar to previously reported patients, but onset age was somewhat different (7 yrs : 25 yrs). The CMT2N frequencies were calculated to 0.19% in total Korean CMT cohort (n = 1,035), and 0.63% in axonal CMT patients.

References: None.

Keywords: CMTR, Human Genetics

Grant Support: None.
Poster 119

Greater auricular nerve amyloidoma as a presenting manifestation of AL amyloidosis with underlying lymphoplasmacytic lymphoma

Chinar Osman¹, Matthew Jenner², Mark Walker², Ashwin Pinto¹, Mike Lunn³, Haider Katifi¹

¹Wessex Neurological Centre, Southampton, United Kingdom of Great Britain and Northern Ireland, ²Southampton General Hospital, Southampton, United Kingdom of Great Britain and Northern Ireland, ³National Hospital for Neurology and Neurosurgery, London, United Kingdom of Great Britain and Northern Ireland
Amyloidoma is a rare soft tissue tumour and has been reported peripheral nerves as well as in viscera such as GI tract and lung. Amyloidoma can be a presenting manifestation of AL amyloidosis.

A 57-year-old female presented with profound fatigue, bilateral painful paresthesia in the hands, palpitations and transient right facial weakness. Examination revealed a mobile right neck mass. There was no clinical or neurophysiological evidence of peripheral neuropathy.

Imaging demonstrated a right greater auricular nerve mass. Biopsy was consistent with an amyloidoma demonstrating amorphous strongly congophilic deposits with patchy apple green birefringence. AL amyloid was confirmed by mass spectrometry. Additional investigations including SAP scintigraphy excluded cardiac and visceral amyloid.

Serological tests were abnormal with beta-2 microglobulin 3.5 mg/l (1.2-2.4), raised free kappa light chains 65.8mg/L (3.3-19.4) and raised kappa/lambda ratio but no paraprotein. CSF examination was unremarkable.

Whole body FDG PET-CT identified widespread FDG avid subcutaneous nodules and a prominent focus in right tibia. Right tibial biopsy was similar to the nerve biopsy. Biopsy of the subcutaneous nodules demonstrated lymphoplasmacytic lymphoma. Bone marrow was unremarkable. A breast lesion biopsied subsequently confirmed amyloid.

The patient developed progressive painful neuropathic symptoms and was commenced on bendamustine-rituximab followed by BEAM autologous stem cell transplant and is currently on maintenance rituximab.

Florbetaben PET-CT performed after treatment demonstrated widespread amyloid deposition in the tibial bone marrow consistent with known pre-treatment deposition.

This case demonstrates an atypical neurological presentation of AL amyloidoma associated with an underlying lymphoplasmacytic lymphoma. Despite presenting with localised disease this warranted systemic therapy to control symptoms.


Keywords: Amyloidosis

Grant Support: None.
Increased rate of pregnancy complications and occasional worsening of Charcot-Marie-Tooth (CMT) during pregnancy have been reported, but there are no large systematic studies.

Through an ad hoc online questionnaire, we investigated pregnancy and neuropathy course in CMT women adhering to the CMT Italian Registry. Controls were recruited among friends and unaffected relatives.

We collected data on 140 CMT women (aged 20-73 yrs) with detailed information on 194 pregnancies from 86 women. Results were compared to 31 age-matched controls and 59 pregnancies in 24 women. Age at pregnancy was 17-43 years (mean 28.7) for CMT patients and 17-41 years (mean 29.5) for controls. Complications occurred in 69 pregnancies (36%) for 30 CMT women (35%) and 10 pregnancies (16.9%) for 6 controls (26%) (p<0.05). Utero-placental hemorrhage occurred in 10% of CMT pregnancies vs 1.7% among controls (p=0.04); placenta previa occurred during 5 pregnancies in 5 CMT women and in no control (p=0.21). Delivery occurred in 158 cases for CMT (81.4%) and 46 for controls (78%) after a mean of 38.6 gestational weeks (range 26-44) vs 38.9 (range 32-42) for controls, with natural delivery in 93 CMT (16 of them with induction) (similar figures in controls). There were two post-partum hemorrhages in CMT patients. Nine newborns (6.3%) from CMT pregnancies had icterus vs one control (2.2%). CMT status worsened during 16 out of 194 pregnancies (8.25%) in 12/86 patients (14%), with no recovery in 11/16 instances. After pregnancy, three more patients needed assistance for walking and two patients needed new assistive devices.

Although pregnancy course and delivery are overall regular in CMT, we observed a relatively higher frequency of haemorrhages in CMT than controls. Worsening of CMT is not infrequent and occurs not only in CMT1A. Pregnant CMT women need to be monitored with particular care.

References: None.

Keywords: CMTR

Grant Support: Supported by Telethon Foundation grant GUP13006
The nerve echogenicity assessment in Charcot-Marie-Tooth disease type 1A

Yuta Kojima1, Yu-ichi Noto1, Yukiko Tsuji1, Fukiko Kitani1, Kensuke Shiga2, Toshiki Mizuno1, Masanori Nakagawa3

1Department of Neurology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, 2Neurology, Matsushita memorial hospital, Osaka, Japan, 3North Medical Center, Kyoto Prefectural University of Medicine, Kyoto, Japan

Introduction: Charcot-Marie-Tooth disease (CMT) is a heterogenous group of slowly progressive hereditary neuropathies. It is challenging to detect small changes in disease activity over a few years. This is thought to be one of the reasons why clinical trials are failed in CMT. Recently, quantitative nerve ultrasound assessment is increasingly used in neuropathies. Nerve echogenicity is one of quantitive parameters. Fisse et al. reported that nerve echogenisity of the arm could be a prognostic marker in chronic inflammatory demyelinating polyneuropathy (CIDP). The aim of this study is to elucidate changes in nerve echogenecity of patients with CMT type1A (CMT1A).

Methods: This study included 15 patients with CMT1A (M:F= 10:5, mean age: 55.1 years old) and 15 age-matched normal controls (M:F = 9:6, mean age: 55.4). Nerve ultrasound examination was performed in CMT1A patients twice (at the baseline and 5 years after the baseline) and in controls once. Nerve echogenicity in the median (at the wrist, forearm and upper arm) and sural nerves was measured in each stored image using a semiautomated and quantitative method by ImageJ(provided by NIH). Comparison of nerve echogenicity between CMT1A patients and normal controls at baseline was performed, and change from the baseline to the 5years after the baseline was analyzed.

Results: Nerve echogenicity at the forearm of the median nerve was lower in CMT1A (fraction of black: 66.2±7.9%) than in controls (57.1±8.0%) (p =0.0023), whereas there were no differences at the other sites. Regarding a longitudinal change in CMT1A patients, echogenicity of the sural nerve decreased over 5 years (p =0.016).

Conclusions: Hypoechoic change at the forearm of the median nerve was a remarkable finding in CMT1A patients when compared with controls. Additionally, echogenicity of the sural nerve may change along with the disease progression in CMT1A.


Keywords: CMTR

Grant Support: None.
Poster 122

OPA3-related autosomal dominant optic atrophy and cataract (ADOAC) plus syndrome.

Alejandro Horga1, Enrico Bugiardini1, Andreea Manole1, Fion Bremner2, Zane Jaunmuktane2, Lois Dankwa3, Adriana Rebelo4, Catherine Woodward2, Iain Hargreaves2, Andrea Cortese1, Alan Pittman1, Sebastian Brandner2, James Polke2, Robert Pitceathly1, Stephan Züchner4, Michael Hanna1, Steven Scherer3, Henry Houlden1, Mary Reilly1

1UCL Queen Square Institute of Neurology, London, United Kingdom of Great Britain and Northern Ireland, 2The National Hospital for Neurology and Neurosurgery, London, United Kingdom of Great Britain and Northern Ireland, 3University of Pennsylvania, Philadelphia, PA, USA, 4University of Miami, Miami, FL, USA

Background: Mutations in the OPA3 gene, which encodes a putative mitochondrial pro-fission protein, cause autosomal recessive 3-methylglutaconic aciduria and autosomal dominant optic atrophy and cataract (ADOAC). Neurological features have been reported in some patients with ADOAC; in one of them, peripheral neuropathy (PN) was confirmed by nerve conduction studies (NCS). The aim of this study is to describe the phenotype in individuals with OPA3-related ADOAC and PN. Methods: Two probands with several affected relatives and one sporadic case were referred for evaluation of a PN. Their phenotype was determined by clinical assessment and NCS. Neuropathologic evaluation of the sural nerve was performed in one individual. All probands underwent exome sequencing. Results: The main clinical features in one sporadic case and one family consisted of early-onset cataracts, gastrointestinal dysmotility symptoms, and PN. Impaired vision was an early-onset feature in another family, in which affected individuals had a variable combination of cataracts, gastrointestinal dysmotility symptoms, and PN. Other features among all affected individuals were hearing loss, symptoms of autonomic dysfunction, and recurrent pancreatitis. A subclinical PN, sensory-predominant PN, or motor and sensory PN were confirmed by NCS in five individuals. In one patient, sural nerve biopsy revealed loss of myelinated fibres without demyelinating features. Exome sequencing identified heterozygous OPA3 variants in all probands, including a novel missense variant and a known pathogenic mutation. Variant validation and cosegregation analyses were performed by Sanger sequencing. Conclusions: We confirm that dominant OPA3 mutations may be associated with a syndromic form of ADOAC (ADOAC plus) in which axonal PN and gastrointestinal dysmotility symptoms are common clinical features.

References: None.

Keywords: Human Genetics

Grant Support: MMR, SSR, AC, and LD are supported by the Inherited Neuropathy Consortium (INC), which is a part of the National Institutes of Health Rare Diseases Clinical Research Network (RDCRN) (U54NS065712). RDCRN is an initiative of the Office of Rare Diseases Research (ORDR), NCATS, funded through a collaboration between NCATS and the NINDS. SSS and LD are also supported by the Judy Seltzer Levenson Memorial Fund for CMT Research. MMR and SB are also supported by the National Institute for Health Research University College London Hospitals (UCLH) Biomedical Research Centre. AC is also funded by the Wellcome Trust (204841/Z/16/Z). HH is supported by the Medical Research Council and Wellcome Trust.
Neuropathic Pain and Clinical Characteristics in Charcot-Marie-Tooth Disease Subtypes

Elina Millere\textsuperscript{1}, Einar Kupats\textsuperscript{2}, Inese Kazaine\textsuperscript{3}, Ieva Micule\textsuperscript{3}, Dmitrijs Rots\textsuperscript{2}, Linda Gailite\textsuperscript{2}, Natalja Kurjane\textsuperscript{2}, Viktorija Kenina\textsuperscript{2}

\textsuperscript{1}Riga Stradins University, Children's Clinical University Hospital, Riga, Latvia, \textsuperscript{2}Riga Stradins University, Riga, Latvia, \textsuperscript{3}Children's Clinical University Hospital, Riga, Latvia

Introduction

Charcot-Marie-Tooth (CMT) disease is inherited neuropathy usually affecting both - motor and sensory peripheral nerves. There are two main CMT disease subtypes - CMT1 (demyelinating form) and CMT2 (axonal form). CMT1 subtype has mutations affecting the PMP22 gene (17p11.2 duplication) and it is the most common subtype of CMT. Few researches focused on pain in CMT, neuropathic pain is an occasional symptom noticed by patients. The goal of our study was to determine neuropathic pain prevalence and clinical characteristics in different CMT subtypes.

Methods

For neuropathic pain assessment the Neuropathic Pain Diagnostic Questionnaire (DN4) was used. CMT neuropathy score (CMTNS) and 6 minutes walking test (6MWT) was used to evaluate clinical characteristics. Data from peripheral nerve conduction study (NCS) for electrophysiological characteristics was evaluated.

Results

In this study data from 53 patients were analysed. There were 32 patients with CMT1A (17p11.2 duplication) and 21 with others CMT subtypes. CMT1A patients tend to be more severely clinically affected (CMTNS 26.5 vs 20.5; 6MWT 290 m vs 365 m (p>0.05). Neuropathic pain was significant more common symptom in group of CMT1A (DN4 18/32 vs 5/21 (p>0.05)).

Conclusions

CMT1A patients have significant more common neuropathic pain than patients with other CMT subtypes. Higher functional disability is more common in patients with neuropathic pain. Further studies are needed to investigate possible pain mechanisms in patients with CMT1A.

References: None.

Keywords: Pain

Grant Support: None.
Neuropathy-causing mutations in TRPV4 disrupt TRPV4-RhoA interaction and cytoskeletal modulation

Brett McCray, Jeremy Sullivan, William Aisenberg, Brian Woolums, Pamela Saveedra, Thomas Lloyd, Charlotte Sumner

Johns Hopkins School of Medicine, Baltimore, MD, USA

Dominant mutations in the calcium-permeable cation channel TRPV4 (transient receptor potential vanilloid 4) cause two distinct diseases: Charcot-Marie-Tooth disease type 2C, a form of peripheral neuropathy that causes muscle weakness and sensory loss, and various forms of skeletal dysplasia that cause abnormalities of bone development. While prior work has demonstrated that both neuropathy and skeletal dysplasia mutations cause a gain of ion channel function, this finding alone cannot account for tissue-specific toxicity. Importantly, neuropathy-causing mutations cluster within a cytosolic protein-protein interaction domain, suggesting that such interactions are critical to neuropathy pathogenesis. Using proteomics, we identified that TRPV4 functionally interacts with the small GTPase RhoA, which plays a fundamental role in regulating the actin cytoskeleton and in modulating neurite outgrowth. Notably, both wild-type (WT) TRPV4 and skeletal dysplasia TRPV4 mutants are able to bind RhoA, but neuropathy mutations dramatically disrupt RhoA interaction. WT TRPV4 specifically interacts with the inactive, GDP-bound form and inhibits RhoA activation, whereas neuropathy mutant TRPV4 fails to inhibit RhoA. Furthermore, RhoA interaction with WT TRPV4 inhibits ion channel activity in response to environmental and chemical stimuli. Our data also demonstrate that both WT TRPV4 and skeletal dysplasia mutants of TRPV4 promote neurite outgrowth in cultured motor neuron-like cells. In contrast, neuropathy mutant TRPV4 leads to impaired neurite outgrowth, and neurite outgrowth can be restored by pharmacologic inhibition of RhoA activity. Together, our results demonstrate robust reciprocal functional interactions of TRPV4 and RhoA that serve to regulate cytoskeletal dynamics. Furthermore, we show that neuropathy-causing mutations specifically disrupt interactions with RhoA, leading to disinhibition of TRPV4 ion channel activity and dysregulation of RhoA. Thus, disrupted TRPV4-RhoA interaction may represent a specific and fundamental pathologic feature in TRPV4-related neuropathy.

References: None.

Keywords: Human Genetics, Axonal Biology

Grant Support: None.
Functional Characterization of Human iPSC-derived Motor Neurons with Loss of Neurofilament Light

Svetlana Molchanova 1, Markus Sainio 1, Tiina Rasila 1, Julius Järvillehto 1, Jana Pennonen 1, Johanna Palmio 2, Emil Ylikallio 3, Henna Tyynismaa 1

1 Stem cells and metabolism research program, University of Helsinki, Helsinki, Finland, 2 Neuromuscular Research Unit, University of Tampere, Tampere University Hospital, Tampere, Finland, 3 Clinical Neurosciences, Neurology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

Neurofilament light (NEFL) is a gene encoding light chain of neurofilaments, and mutations in this gene cause Charcot-Marie-Tooth disease. We identified a novel homozygous nonsense mutation in NEFL, which is linked to early-onset axonal neuropathy in a Finnish family. To further characterize the mutation, we differentiated patient-derived induced-pluripotent stem cells (iPSC) to spinal motor neurons, and compare them to cells, differentiated from healthy donor iPSCs. We also generated NEFL knockout iPSCs from healthy donors by Crispr/Cas9-based gene editing.

The optimized differentiation protocol resulted in a nearly pure TUJ1+ neural population containing above 90% ISL1/2+ and 30-60% HB9+ motor neuron lineage cells. Neurons from control lines were functionally active, displaying spontaneous cytosolic calcium transients and action potentials with high frequency. All neurons recorded were able to produce repetitive action potentials upon membrane depolarization; and most of the cells exhibited spontaneous synaptic currents, which were blocked by AMPA-type glutamate receptor antagonist CNQX.

Neurons, differentiated from patient iPSCs and NEFL knockout neurons completely lacked NEFL protein, but did not show any structural disease-related phenotype. Loss of NEFL did not affect the initial differentiation into neurons or prevent elaborate neurite networks. The ongoing work is aimed at functional characterization of patient-derived and NEFL knockout motor neurons, using spontaneous calcium transients and action potential generation as readouts for functional maturity of the neurons; and synaptic currents as an indicator of the proper synaptic network formation. The results will hopefully elucidate the functional consequences of NEFL loss in motor neurons.


Keywords: CMTR, Human Genetics, Axonal Biology

Grant Support: This study is funded by the Academy of Finland Center of Excellence on Stem Cell Metabolism and Helsinki University Doctoral School of Biomedicine.
Serum neurofilament light chain is a sensitive biomarker for degeneration of immature SMA motor axons

Lingling Kong¹, Cera Hassinan¹, Jae Hong Park², Chloe Grzyb², Scotty McGaugh³, Christine Hatem¹, Thomas Crawford², Charlotte Sumner²

¹Johns Hopkins University, School of Medicine, Baltimore, MD, USA, ²Johns Hopkins University, Baltimore, MD, USA, ³Johns Hopkins University, Baltimore, MD, USA

Spinal muscular atrophy (SMA) has an unusual clinical course characterized by initial decline and subsequent stabilization. To uncover the pathologies that may account for these observations, we collected and analyzed tissues collected from SMA patients and age-matched controls and SMAΔ7 mice. Ventral roots (VRs) in type I SMA autopsy cases are 2-3 fold smaller and contain 50-75% less myelinated axons compared to age-matched controls. The immature axon marker, GAP43, is robustly expressed in every SMA VR analyzed, but not in the controls. At the EM level, 80% of the total axons in the SMA VRs are retained in polyaxonal pockets, 1-2 microns or less in size and unmyelinated. Degenerating unmyelinated axons takes up 10-20% of the total axons, while less than 5% of the degenerating axons are myelinated ones. Reconstructed EM images of the lumbar level 1 (L1) VR in SMA mice demonstrates significant defects in radial growth (starting at E13.5) and sorting (starting at E17.5). At P1, about 20% of the small unmyelinated axons in SMA are either swollen or atrophied, indicating axonal degeneration. By P2, the total number of L1VR axons in SMA mice is reduced by half with no further loss seen at P14. Serum neurofilament light (NF-L) levels correlated with degeneration of the unmyelinated axons with maximal elevations observed at P1 and P2 in SMA. NF-L levels subsequently declined in both groups but remained modestly elevated in SMA mice. Here we demonstrated markedly impaired axon sorting and radial growth of SMA motor axons that begins embryonically. These immature axons rapidly degenerate in the neonatal period and this is associated with an early onset elevations of NF-L in SMA sera. Together our results show that blood NFL levels may be a sensitive biomarker of early degenerative events in severe SMA infants.

References: None.

Keywords: Axonal Biology, Other, Other, Other, Other

Grant Support: Cure SMA, SMA foundation, NINDS RO1
Small Fibers impairment In Charcot-Marie-Tooth Disease: The Role Of Laser Evoked Potentials.

Alessia Peretti¹, Giovanna Squintani², Moreno Ferrari³, Federica Taioli³, Tiziana Cavallaro³, Gianmaria Fabrizi³

¹Ospedale S. Bortolo, Vicenza, Italy, Vicenza, Italy, ²Neuroscience Department, Azienda Ospedaliera Universitaria Integrata, Verona, Italy, Verona, Italy, ³Neurology Division, Department of Neuroscience, AOUI Verona, Verona, Italy., Verona, Italy

Introduction Pain is a common symptom in Charcot-Marie-Tooth (CMT) disease, either nociceptive or neuropathic (NP) in nature. Laser evoked potentials (LEPs) are the most reliable neurophysiological tool for Aδ fibers assessment.

Purpose We aim to investigate the small fiber involvement in different CMT through LEPs detection.

Methods Forty-six patients with different forms of CMT (19 CMT1A, 11 MPZ-CMT, 12 CMTX, 4 CMT2A) were enrolled. All subjects underwent a complete neurological examination; pain, whether present, was rated with the 11-point Numerical Rating Scale (NRS) and characterized by means of validated questionnaires (Neuropathic Pain Diagnostic Questionnaire -DN4- and Neuropathic Pain Symptoms Inventory -NPSI-). LEPs were recorded after right foot and hand stimulation, and patients’ N2-P2 complex amplitude and latency were compared with 46 age-matched control subjects.

Results Overall pain prevalence was 34,8%. NP was present in 15,2% of patients with a length-dependent distribution in 85,7% of cases and was significantly more frequent in CMT1A (p<0,001); all descriptors of NP were involved as emerged from NPSI. Prolonged latency of N2-P2 complex from foot stimulation was noted in 11 CMT1A patients (57,9%), 6 of which (63,6%) were asymptomatic. MPZ-CMT patients showed different clinical and neurophysiological phenotypes, strictly dependent on the underlying motor conduction velocity pattern. LEPs results were normal in all but one CMTX patients, but amplitude after foot stimulation was significantly lower in males compared to females (p=0,043). CMT2A patients were NP free and LEPs recordings were all normal. We found a significant association between LEPs alteration and NP (p=0,017).

Conclusions NP is frequent in CMT disease and is highly related to Aδ fibers impairment, although different and concomitant mechanisms could be hypothesized. Aδ fibers involvement greatly varies between CMT subtypes and reflects differences in genetic mutations and pathophysiologic mechanisms.

References: None.

Keywords: Pain, Small Fibers, CMTR

Grant Support: None.
Using C. Elegans to model X-linked Charcot-Marie-Tooth (CMTX6) disease.

Ramesh Narayanan1, Megan Brewer2, Emilie Wong3, Brent Neumann4, Garth Nicholson5, Marina Kennerson6

1Northcott Neuroscience Laboratory, ANZAC Research Institute, NSW, Sydney, Australia, 2ANZAC Research Institute NSW Australia, Sydney Medical School University of Sydney NSW Australia, Sydney, Australia, 3ANZAC Research Institute NSW Australia, Sydney Medical School University of Sydney NSW Australia, Sydney, Australia, 4Monash Biomedicine Discovery Institute, Monash University, Melbourne, Australia, 5ANZAC Research Institute NSW Australia, Sydney Medical School University of Sydney NSW Australia, Sydney, Australia, 6ANZAC Research Institute NSW Australia, Sydney Medical School University of Sydney NSW Australia, Sydney, Australia

Although mutations in more than 85 genes are known to cause Charcot-Marie-Tooth (CMT) neuropathy, the molecular and cellular mechanisms that underlie the pathogenesis of CMT still needs further elucidation. Animal models closely recapitulating pathogenic in vivo events in patients are crucial for investigating mechanisms of axonal degeneration and the development of drug therapies. C. elegans is a 1 mm long nematode with a simple nervous system that comprises of 302 neurons. The short life span along with a “toolkit” of various genetic and molecular assays available makes C. elegans a powerful system for modelling motor and sensory defects caused by CMT mutations. The p.R158H mutation in the pyruvate dehydrogenase kinase 3 (PDK3) gene has been reported by our group to cause an X linked form of CMT (CMTX6). Previously we generated a C. elegans model of CMTX6 overexpressing human wild type (PDK3WT) and mutant PDK3 (PDK3R158H) which demonstrates axonal degeneration. We have recently utilized the CRISP-cas9 system to engineer the p.R158H mutation into the worm ortholog of PDK3, pdhk-2R159H. Using behaviour studies in the PDK3 overexpression, knock-in and null mutants, we demonstrate that synaptic transmission is affected in our CMTX6 animal models. Defective synaptic transmission may lead to loss of signal at the neuromuscular junction resulting in muscle atrophy and neurodegneration. In addition, we have characterised the effect of PDK3 mutations on the morphology of cholinergic excitatory and GABAergic inhibitory neurons. Further investigation of PDK3 associated synaptic transmission loss will help identify genes and pathways impacted by the mutation that can be targeted for drug development and therapy in CMTX6.

References: None.

Keywords: CMTR

Grant Support: None.
Assessment of neuropathic pain in patients with Charcot-Marie-Tooth disease type 1A

Stojan Perić¹, Bogdan Bjelica¹, Ivo Bozovic¹, Ivana Basta¹, Vukan Ivanovic², Dragana Lavrnic¹, Vidosava Rakocevic-Stojanovic¹

¹Neurology Clinic, Clinical Center of Serbia, School of Medicine, University of Belgrade, Belgrade, Serbia, ²Neurology Clinic, Clinical Center of Serbia, School of Medicine, University of Belgrade, Belgrade, Serbia

Introduction: There have been a very few studies that have analyzed characteristics of neuropathic pain in CMT1A patients. Aim of this study was to determine frequency and features of neuropathic pain in CMT1A and to assess the association between neuropathic pain and clinical characteristics of patients.

Methods: Our research included 39 CMT1A patients with a genetically confirmed diagnosis. PainDETECT questionnaire (PD-Q) was used to assess neuropathic pain. The Medical Research Council (MRC) Sum Score, Overall Neuropathy Limitations Scale (ONLS) score, and Beck Depression Inventory were also applied.

Results: Neuropathic pain was present in 16 (41%) patients with CMT1A. The average severity of pain was 5.7±2.1 out of 10. The most sensitive neuropathic symptom was numbness which was present in all patients with neuropathic pain, while the most specific symptom was allodynia that was present in 50% of CMT1A subjects and virtually absent in patients without neuropathic pain. Patients with neuropathic pain were older (p=0.01) and they also had more pronounced disability of the upper extremities than patients without neuropathic pain (p<0.05). Depression was more frequent in patients with neuropathic pain compared to patients without it (56.2% vs. 13.6%, p<0.05).

Conclusions: Neuropathic pain was present in almost half of patients with CMT1A and it was moderate on average. Presence of neuropathic pain was associated with older age, worse functional disability and depression.

References: None.

Keywords: CMT1A, Pain

Grant Support: This study was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (grant #175083 granted to Prof. Vidosava Rakocevic-Stojanovic).
Two families with Charcot-Marie-Tooth-4H due to mutations in FGD4: Broadening the phenotype

Tara Jones, Glenn Pfeffer, John Graham, Robert Baloh, Richard Lewis

Cedars-Sinai Medical Center, Los Angeles, CA, USA

Purpose: We report the clinical features of three patients from two families with CMT4H due to mutations in FGD4 encoding frabin. This will expand our knowledge of the phenotype of this rare disorder.

Patients: One family consists of two sisters of a consanguineous Kuwaiti family with relatively mild neuropathy and homozygous p.Y443X mutations. The 13 year old was found to have neuropathy discovered incidentally when she underwent a genetic evaluation for short stature, markedly reduced weight, pectus carinatum, scoliosis, partial webbing of her fingers and short 4th metatarsals. There were no foot abnormalities and CMT exam score was 4/28. Whole exome sequencing revealed only the p.Y433X mutations, and chromosomal microarray was normal. Her 16 year old sister had cavovarus foot deformities, the right side treated with surgical tendon transfers and osteotomies of the calcaneus and first metatarsal. Median motor velocity was 7 m/sec, ulnar motor velocity was 8 m/sec, with absent sensory responses. The third patient, compound heterozygous for a whole gene deletion and p.R577X, was seen at age 44 but had disease onset at age 11. She had pes cavus, scoliosis, and four previous foot surgeries. Her ulnar motor velocity was 8 m/sec with absent sensory responses. Her CMTNS was 17 indicating moderate dysfunction.

Discussion: Less than twenty families from around the world with CMT4H have been described. Early age of onset, distal weakness and scoliosis are common. Myelin outfoldings have been seen on nerve biopsy. Despite very severe conduction slowing below 10 m/sec the disease severity is mild to moderate in many instances. This striking difference may be unique to this disorder and provide a clue as to the pathophysiology of this disorder. We will review the phenotype of our patients in context of those reported in the literature.


Keywords: CMTR, Human Genetics

Grant Support: None.
Early-onset hereditary motor and sensory neuropathies are rare disorders causing variable degrees of impairment and disability, presenting with high clinical variability, frequent sporadic presentation and genotype-phenotype heterogeneity. Few reports focused on large cohorts of Charcot-Marie-Tooth (CMT) patients in paediatric age. Data from a series of 288 patients, aged 0-17 years, will be reported. On the basis of neurophysiological studies they were classified as affected with demyelinating, axonal, pure motor (HMN) and pure sensory (HSN) forms. Genetic analyses were performed with Sanger sequencing for single genes or through customized gene panels. 70% of cases were affected with demyelinating forms, 20% with axonal, 7% with HMN, 2% with HSN. A definite genetic diagnosis was achieved in 79% of cases. Causative mutations were detected in 88% of patients affected with demyelinating forms, in 57% of axonal, in 35% of HMN and in only 1/6 cases of HSN. Considering the whole series of patients, CMT1A represents the most frequent form (45% of total, 65% of demyelinating forms). The other genetic defects are largely more rare, with mutations in MPZ, MFN2, GDAP1 and GJB1 genes accounting for 6% each, while mutations in other genes were detected in few or single cases. In some children specific clinical features allowed us to address the genetic studies. The analysis of our case series confirms that also in childhood age CMT1A is the most frequent form; the identification of specific genetic defect is reached more frequently in patients affected with demyelinating forms while children with axonal or HMN forms more often still lack a definite genetic diagnosis. Both demyelinating and axonal CMT can be associate with congenital or very early onset. Sporadic, or apparently sporadic presentation is frequent (38%), and makes it difficult to address the molecular analyses towards a rapid diagnosis, crucial for the appropriate familiar counselling.

References: None.

Keywords: CMTR

Grant Support: None.
Poster 133

Molecular analysis and clinical diversity of hereditary motor neuropathy

Xiaoxuan Liu, Dongsheng Fan

Peking University Third Hospital, Beijing, China

Objective: To identify the genetic distribution of hereditary motor neuropathies (HMNs) in a large cohort of Chinese patients with Charcot-Marie-Tooth disease (CMT) and evaluate the correlation of the HMNs with the clinical manifestations.

Methods: Next-generation panel testing or whole-exome sequencing was performed in 96 patients with clinically diagnosed HMNs out of 455 patients with CMT between January 2007 and October 2017. We recorded the clinical features, CMT neuropathy scores (CMTNS) and electrophysiological data at diagnosis.

Results: We identified 24 causative mutations in 70 index patients with HMNs (34.3%). If the patients with likely pathogenicity were included, the detection rate was 42.9% (30/70 families). HSPB1 mutations were the most common causative gene mutations in HMNs (10/32, 31.3%), followed by mutations in IGHMBP2 (3/32, 9.4%), GARS (2/32, 6.3%) and BSCL2 (2/32, 6.3%). Some CMT genes (MPZ, SH3TC2, GDAP1) were related to CMT disease (motor-CMT2) with minor sensory involvement. Patients with HMN-plus often had complicated phenotypes and included genes of hereditary spastic paraplegia (HSP), amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA) (FUS, KIF5A, KIF1B, ZFYVE26, DNAJB2).

Conclusions: Pure motor neuropathies and motor neuropathies with minor sensory involvement share many genes with CMT. HMN-plus may have a complicated phenotype, and some of the disease-causing genes were shared with ALS. Axonal transport defects and autophagic dysfunction may play a crucial role in the downstream pathogenesis of HMNs.

References: None.

Keywords: CMTR

Grant Support: None.
Charcot-Marie-Tooth disease is an incurable hereditary neurodegenerative disorder characterized by demyelination and/or axonal degeneration of the peripheral motor and sensory neurons. Aminoacyl-tRNA synthetases (ARS) represent the largest cluster of proteins implicated in CMT etiology. These are ubiquitously expressed enzymes involved in the initial step of protein biosynthesis and therefore they are indispensable for cell viability. So far, it remains mysterious how molecular defects in these essential enzymes cause specifically neurodegeneration and lead to dominant forms of neuropathies sharing common symptoms. We aim to investigate whether there is a common toxic pathway triggered by the CMT mutations in ARS. To streamline our studies, we developed new cellular and fly models of CMT induced by four different ARS. To ensure maximal comparability between the vertebrate and invertebrate models, we expressed the same transgenic constructs using a modified GeneSwitch™ technology. This inducible system allows for temporal and spatial modulation of ARS expression levels. After functional and morphological characterization of these new models, we aim to perform proteomics studies deciphering the ARS protein network and its molecular perturbations after induction of the mutant proteins in cellulo and in vivo. The knowledge gained will provide a comprehension towards the pathomechanism underlying ARS CMT causing mutation and might contribute to the development of common treatment strategies for all ARS-linked CMT neuropathies.

References: None.

Keywords: CMTR

Grant Support: None.
Acupuncture Management for Diabetic Neuropathy: A case report

Yun Jin Kim

Xiamen University Malaysia, Selangor, Malaysia

Introduction: Neuropathies are among the most common of all the long-term complications of diabetes, and it is most common form of neuropathy in the developed countries of the world, accounts for more hospitalizations than all the other diabetic complications combined[1], and is responsible up to 50% of patients of non-traumatic amputations[2]. It is defined as damage to peripheral nervous system and caused by a primary lesion or dysfunction[3]. Recently acupuncture is beneficial for management for neuropathic pain. Here, we reported a case reports of acupuncture management for diabetic neuropathy.

Methods: Thirty patients diagnosed with diabetic neuropathy patients were observed. Used acu points were LR4, LU5, LI11, KI27, ST 36, GB34, SP6, SP9, and LI4. The acupuncture needles (sterilised single- use stainless steel needle, size: 0.3X40mm; Hansol Medical Co. Reg. No.:141024)were punctured into the muscle layer, the acupuncture needles were kept in place for 20 minutes. Patients received acupuncture management three times per week, during four months. Clinical outcomes were measured by visual analogue scale, clinical signs and symptoms, and Hamilton anxiety rating scale (HAM-A).

Results: Thirty patients indicated improvement on the visual analogue scale, and its clinical signs and symptoms, also Hamilton anxiety rating scale (HAM-A).

Conclusion: This case reports describes the patients on acupuncture management of diabetic neuropathy experienced positive clinical outcomes during four months acupuncture treatments. Further studies need to be carried out on a larger sample size, with better designs for validation, and evidence-based scientific mechanisms.


Keywords: Diabetes, Pain

Grant Support: This presentation support from Xiamen University Malaysia research grants( No.: XMUMRF/2018-C2/ITCM/0001)
Multimodal Assessment Of Intensive Care Unit-Acquired Weakness (ICU-AW) In Severe Acute Stroke Patients

Berin İnan, Can Ebru Bekircan-Kurt, Çağrı Mesut Temuçin, Ethem Murat Arsava, Mehmet Akif Topcuoglu, Sevim Erdem-Ozdamar, Ersin Tan

Hacettepe University; Faculty of Medicine, Department of Neurology, Ankara, Turkey

Purpose: Intensive care unit-acquired weakness (ICU-AW) is an acute neuromuscular impairment that occurs in approximately 40% of critically ill patients (1,2), and associated with delayed weaning, longer ICU and hospital stays, higher mortality (3,4,5). In this study, we aim to investigate the frequency of ICU-AW in severe stroke patients in neurological ICU, and diagnostic correlations between electrophysiological studies and muscle biopsy. Methods: All stroke patients followed in our intensive care unit, with NIHSS ≥16 and a life expectancy longer than three weeks, without any known neuromuscular disease were included. The baseline unilateral electrophysiological (EP) studies and bioimpedance analysis (BIA) were evaluated within the first 72 hours of admission, and afterward with an interval of 3-5 days. Muscle biopsy was performed in patients whose EP studies revealed critical illness myopathy. Results: Fourteen patients met the inclusion criteria. Three patients refused to participate in the study, and 3 were excluded due to the presence of neuropathy in basal electrophysiological studies. Thus, eight patients were included. The mean age was 81.87 and seven patients were female. Myopathy developed in two and neuromyopathy developed in one patient almost within one month (31-st-33rd days). Peroneal and ulnar nerve CMAP and sural nerve SNAP amplitudes were the most affected parameters. The baseline phase angle values were below 4.5⁰ in all and continued to decrease during follow-up BIA tests. Muscle biopsy was performed in 2 patients. Type 2 muscle fiber atrophy was seen in accordance with critical illness myopathy. Inflammatory infiltrate or mitochondrial damage was not observed. Conclusions: Intensive care unit-acquired weakness developed in three of 8 patients within one month. Our preliminary findings suggest that the percent of the decrease in CMAP and SNAP amplitudes were associated with the degree of type 2 fiber atrophy and the decrease in phase angle values.


Keywords: Other

Grant Support: The study was supported by the Hacettepe University Scientific Research Projects Coordination Unit funds (Project ID:17114: THD-2018-17114).
Poster 137

Dose-dependent Chemotherapy-induced peripheral autonomic neuropathy: acute injury and slow recovery

Ying Liu¹, Ben Liu², Blessan Sebastian², Krystyna Wozniak², Ying Wu², Guido Cavaletti³, Barbara Slusher², Mohamed H Farah², Michael Polydefkis²

¹Johns Hopkins University, Baltimore, MD, USA, ²Johns Hopkins University, Baltimore, MD, USA, ³University of Milano-Bicocca, Monza, Italy

Most chemotherapy-induced peripheral neuropathy (CIPN) studies preferentially focus on sensory fiber loss and dysfunction. Here, we compared the structural and functional recovery of autonomic fibers in sweat glands (SGNFD) and sensory fibers (IENFD) in mouse footpads after exposure to a maximum tolerated dose (MTD) of several common chemotherapy agents. Additionally, we assessed footpad sweat production as a functional correlate to SGNFD reductions. Female Balb-c mice were treated with a MTD of four anti-tubulin agents: paclitaxel (PCA), ixabepilone, eribuline, vinorelbine, or corresponding placebo given intravenously over a two weeks (MWF dosing) period. Recovery was assessed at 7 post-treatment time points: 24hr, 1, 2, 4, 8, 12 and 24 weeks post chemotherapy exposure. Footpads were processed to visualize epidermal and sweat gland nerve fibers using PGP9.5 and TH. All four agents resulted in comparable or more severe loss of SGNFD compared to IENFD, and SGNFD was slower to recover than IENFD with PCA-treated animals showing the most severe and persistent changes. The dose-dependent and functional study on autonomic nerves was performed on Male Bl6 mice, treated (i.p) with PCA at doses of 10, 20, 25, 30 and 50 mg/kg. Sweat droplet formation (autonomic) and hot plate paw withdrawal (sensory) function was assessed at 24hr, 1 and 2 weeks following the last dose. Footpad sweat droplet number remained significantly reduced from baseline at 2 weeks while paw withdrawal normalized at 2-weeks. Together, these data indicate that in mouse models of CIPN, autonomic nerve fiber structure and function are affected to a greater degree than sensory nerve fibers, and recover more slowly. Autonomic dysfunction may be an important and under-appreciated consequence of chemotherapy exposure.

References: None.

Keywords: Axonal Regeneration, Small Fibers

Grant Support: None.
Quantitative gait analysis in patients with diabetic polyneuropathy

Dongah Lee, Kyong Jin Shin, Si Eun Kim

Department of Neurology, Haeundae-Paik Hospital, Inje University, College of Medicine, Busan, Korea (Republic of)

Neuropathic pain, sensory loss, and distal motor weakness are the main symptoms of diabetic polyneuropathy. Gait disturbance is also commonly observed in patients with diabetic polyneuropathy, especially as a form of sensory ataxia. However, the studies to quantitatively analyze gait in patients with diabetic polyneuropathy using several infrared cameras were few. The object of this study is to quantify the gait in patients with diabetic polyneuropathy and to determine the association between clinical and electrophysiological parameters and gait parameters.

Forty-seven patients with diabetic polyneuropathy were enrolled in this study. Diabetic polyneuropathy was clinically assessed by with Toronto clinical scoring system (TCSS). All enrolled patients underwent nerve conduction study and quantitative gait analysis using 3-dimensional motion analysis system. The correlation of various gait parameters according to TCSS, compound muscle action potential of the peroneal nerve (A-CMAP), and sensory nerve action potential of the sural nerve (A-SNAP) were analyzed.

Decreased step length and stride length were associated with increased TCSS. Increased stance phase and decreased step length, stride length and walking speed were associated with decreased A-CMAP. Increased anterio-posterior range of motion was also associated with decreased A-SNAP.

Gait parameters associated with decreased motor electrophysiological parameter were stance phase, step and stride lengths and walking speed, on the other hand, gait parameter associated with decreased sensory electrophysiological parameter was anterior-posterior range of motion which is associated with postural stability. Various quantitative gait parameters can be used in assessing neurological status in patients with diabetic polyneuropathy.

References: None.

Keywords: Diabetes

Grant Support: None.
Regeneration can occur in the peripheral nervous system after injury, but the mechanisms that underlie this process have not been fully determined. We have previously demonstrated the involvement of macrophages acting in peripheral ganglia in the enhanced regeneration that occurs in sensory and sympathetic neurons after a conditioning lesion (CL). Oncomodulin (Ocm) has been proposed as a macrophage and neutrophil secreted pro-regenerative molecule that stimulates optic nerve regeneration following inflammation in the eye. We have utilized an Ocm knockout (KO) mouse strain to investigate whether Ocm plays a role in the CL response in sensory neurons after sciatic nerve injury. First, we measured neurite outgrowth in cells maintained in dissociated culture after a CL. A robust increase in neurite outgrowth was seen in neurons from both wild type (WT) and Ocm KO mice after a CL. Next, we examined the CL response in explanted ganglia. Increased neurite outgrowth following a CL was seen in explants from both WT and KO mice; however, the magnitude of the effect was significantly smaller in the explants from KO animals. Finally, we examined the CL effect in vivo measured in response to a sciatic nerve crush. A CL response was seen in WT animals but not in KO animals. Flow cytometry studies measuring macrophage number in dissociated culture, explant culture, and DRG in vivo, demonstrated that the Ocm-dependent deficit in regeneration is seen only under experimental conditions in which a significant number of macrophages are present. To begin to determine how Ocm influences regeneration, Il-6 mRNA was measured in axotomized DRG from WT and Ocm KO animals where increased levels were significantly higher in ganglia from WT animals. Thus, our data shows that Ocm is necessary for the conditioning lesion response in vivo and may act to support regeneration through IL-6.

References: None.

Keywords: Axonal Regeneration, Inflammatory

Grant Support: None.
Aberrant DEGS1 activity alters sphingolipid metabolism and causes leukodystrophy and axonal degeneration

Thorsten Hornemann¹, Karsai Gergely², Florian Kraft³, Ingo Kurth³

¹University Zurich, University Hospital Zurich, Zurich, Switzerland, ²University Zurich, Zurich, Switzerland, ³UK Aachen, Aachen, Germany

BACKGROUND:

Sphingolipids are important components of cellular membranes and functionally associated with fundamental processes such as cell differentiation, neuronal signaling and myelin sheath formation. Defects in the synthesis or degradation of sphingolipids lead to various neurological pathologies, however, the entire spectrum of sphingolipid metabolism disorders is still elusive.

RESULTS:

By whole-exome sequencing in a patient with a multisystem neurological disorder of both the central and peripheral nervous system, we identified a homozygous p.(Ala280Val) variant in DEGS1, which catalyzes the last step in the ceramide synthesis pathway. The blood sphingolipid profile in the patient showed a significant increase in dihydro sphingolipid species which was further recapitulated in patient-derived fibroblasts, in CRISPR/Cas9-derived DEGS1 knockout cells, and by pharmacological inhibition of DEGS1. The enzymatic activity in patient fibroblasts was reduced by 80% compared to wild type cells which was in line with a reduced expression of mutant DEGS1 protein. Moreover, an atypical and potentially neurotoxic sphingosine isomer was identified in patient plasma and in cells expressing mutant DEGS1.

CONCLUSION:

We report DEGS1 dysfunction as a novel sphingolipid disorder with hypomyelination and degeneration of both the central and peripheral nervous system.


Keywords: Metabolic, Human Genetics, Schwann Cell, Axonal Biology, Small Fibers

Grant Support: None.
**Poster 141**

**Sensory nerve conduction studies in ALS patients: a retrospective study**

Aikaterini Papagianni¹, Nikos Karandreas², Thomas Zambelis², Panagiotis Kokotis²

¹Neurology University Clinic, Würzburg, Germany, ²Laboratory of Electromyography and clinical neurophysiology, Department of Neurology, University of Athens, Athens, Greece

**Introduction:** This retrospective research study aimed to evaluate abnormalities in the sensory nerve conduction studies in patients with ALS.

**Methods:** The results of the routine sensory nerve conduction studies (median, ulnar, superficial peroneal und sural nerve) of 104 patients with clinically definitive or probable ALS according to the El Escorial classification criteria (61.5±10.7 years) were compared to the results of 120 age-matched controls (58.6±11.7 years) suffering from radiculopathy (control subgroup A, n=63), myopathy or myasthenia gravis (control subgroup B, n=57). Patients with concomitant reasons for sensory polyneuropathy or with severe malnutrition were excluded from the study. According to results all patients were classified in three subgroups: one with normal values, one with abnormal findings in only one nerve and a one with abnormal findings in two or more nerves.

**Results:** 17.3% (median age 58.5, range 34-76 years) of the ALS patients had abnormal sensory nerve conduction studies in two or more nerves, compared to 24.2% (median age 67, range 45-80 years) of patients in the control group. Abnormal findings in one nerve was detected in 16.3% of ALS patients compared to 22.5% of patients in the control group.

There was no statistically significant difference in the percentage of pathological findings in the ALS patients versus controls (Chi square= 3.9, p=0.14, K: 0.13). The statistical comparison between the ALS patients and the two control subgroups provided same result (Chi square= 6.9, p=0.92).

**Conclusion:** A significant higher percentage of abnormal sensory nerve conduction studies in ALS patients could not be proved in this study.

**References:** None.

**Keywords:** Other

**Grant Support:** None.
Electrophysiological Findings in Critical Illness Neuropathy

Giuseppe Piscosquito¹, Vincenzo Provitera², Stefania Mozzillo¹, Francesco Lullo³, Annamaria Saltalamacchia³, Claudio Calabrese³, Maria Nolano⁴, Bernardo Lanzillo²

¹Istituti Clinici Scientifici “Maugeri” SPA SB, IRCCS of Telese Terme, Telese Terme, Italy, ²Istituti Clinici Scientifici “Maugeri” SPA SB, IRCCS of Telese Terme, Telese Terme (BN), Italy, ³Istituti Clinici Scientifici “Maugeri” SPA SB, IRCCS of Telese Terme, Telese Terme (BN), Italy, ⁴Istituti Clinici Scientifici “Maugeri” SPA SB, IRCCS of Telese Terme; University “Federico II” of Naples, Telese Terme (BN), Italy

About 80% of patients admitted to intensive care unit (ICU) develop ICU acquired weakness (ICUAW).¹ Critical illness neuropathy (CIN) is part of the ICUAW, a source of disability associated with debilitating outcomes. Significant knowledge gaps exist concerning CIN incidence, neurophysiological patterns and the impact in the neurorehabilitation setting.²,³ The aims of this study are to assess the occurrence of CIN, its electrophysiological patterns and rehabilitative outcomes in a series of severe brain-injured patients.

We enrolled 52 consecutive critically ill patients (male/female:44/8; mean age:51.6±19.0 years) treated for at least seven days in ICU without any previous known cause of neuropathy. Extensive electrophysiological investigation was performed. Rehabilitative outcome was assessed through 2 measures: the gain of the Functional Independence Measure (FIM) score at end of the treatment (ΔFIM = FIM at discharge − FIM at admission) and the rehabilitation length of stay (RLoS).

In 63.5% of patients, a diagnosis of CIN was achieved, while in the remaining 36.5% (no-CIN group) a diagnosis of single/multiple mononeuropathies (16.9%) or normal neurophysiological findings (19.6%) were found. Among the CIN patients, we identified three electrophysiological patterns: A) generalized sensory-motor neuropathy (75.7%); B) lower limb sensory-motor neuropathy (14.8%) and C) generalized motor neuropathy (9.5%). Most of the mononeuropathies were due to nerve entrapment (ulnar and peroneal nerves most involved). The ΔFIM was 20.4±20.6 for CIN patients and 50.1±31.3 for no-CIN patients (p=0.0007), RLoS was 191.5±97.0 days for CIN patients and 100.0±58.3 days for no-CIN patients (p=0.0002).

Peripheral nervous system damage is very common in patients with history of ICU hospitalisation admitted in rehabilitative setting. CIN is a spectrum of different electrophysiological patterns with axonal, sensori-motor, length-dependent polyneuropathy as the most common one. Entrapment neuropathies represent a frequent finding. The presence of CIN is associated with a worst functional outcome and a delayed discharge of patients.


Keywords: Metabolic, Axonal Biology, Inflammatory

Grant Support: None
Poster 143

Ischiofemoral impingement syndrome provoked by childbirth: an unusual case of a severe sciatic mononeuropathy

Elie Naddaf, Jacqui-Lyn Saw

Mayo Clinic, Rochester, MN, USA

Post-partum neuropathy is a recognized complication of childbirth occurring in up to 1% of deliveries. Risk factors include nulliparity and prolonged second stage of labor. While the femoral nerve is the most commonly involved, post-partum sciatic mononeuropathy has been rarely described without clear description of underlying mechanisms.

A 29 year-old Caucasian multiparous woman (gravida 4 para 2) presented with acute onset left lower limb weakness following the spontaneous vaginal delivery of twins. The second stage of her labor was 39 minutes. She had a routine uncomplicated epidural anaesthesia. When the anesthesia started to wear off, she noted she had no movement in her left foot associated with tingling and numbness. Examination revealed 0/5 strength in sciatic-innervated muscles and decreased pinprick sensation in the foot most severe in the superficial peroneal distribution. Day 13 following her presentation, nerve conduction studies/EMG demonstrated a severe acute left sciatic neuropathy with increased insertional activity, no fibrillation potentials and no activated motor unit potentials in all the left sciatic-innervated muscles. An MRI of the lumbar spine was normal. A lumbosacral plexus MRI showed flattening of the sciatic nerve as it passed through the ischiofemoral space, with mild edema of the quadratis femoris and T2 hyperintensity immediately distal to the sciatic notch. The space itself was noted to be tight (measuring at 8mm).

Ischiofemoral impingement syndrome is defined as a decreased ischiofemoral and quadratis femoris space affecting the contents within. As seen with our case, quadratis femoris muscle edema is prototypical. While patients usually present with chronic non-specific pain in the deep gluteal region, our patient had acute sciatic nerve compression in the ischiofemoral space during childbirth. Women with baseline tight ischiofemoral space may be at risk of postpartum sciatic nerve injury. Twin pregnancy and positioning during labor likely represent additional risk factors.

References: None.

Keywords: Axonal Regeneration

Grant Support: None.
**Poster 144**

**Autophagy inhibition affects from the spinal cord level which induces symptom change in PIPN mouse**

Ji Hyun Lee¹, Bohye Shin², Hwan Tae Park¹

¹Dong-A University, Busan, Korea (Republic of), ²Dong-A University, Busan, Korea (Republic of)

**Background:** Paclitaxel is a widely applied chemotherapeutic drug but neuropathic pain is a troublesome complication during treatment. Autophagic regulation has been proposed to alleviate neuropathic pain in chronic constriction injury model but the alteration of autophagy has not been studied in the paclitaxel-induced peripheral neuropathy (PIPN) mouse model.

**Method:** LC3 GFP-RFP mouse were administered with paclitaxel 16mg/kg 3 times/weekly for 4 weeks. Autophagy inhibition with 3-methyladenine (3MA) was done at 30 mg/kg, 30 minutes before the paclitaxel injection.

**Result:** Four groups in this study were injected with vehicle (group 1), 3MA (group 2) paclitaxel only (group 3), 3MA with paclitaxel (group 4). A marked reduction of the mean mechanical withdrawal threshold was observed by manual von Frey test after 4 weeks of paclitaxel injection (group 1 vs. group 2; group 1 vs. group 3; group 1 vs. group 4; group 2 vs. group 3; and group 2 vs. group 4, all P < 0.0001, respectively) but there was no statistical difference between group 3 and 4. By catwalk gait analysis, showed distinctive change in group 1 vs. group 3 and group 3 vs. group 4, especially in terms of single stands and step cycles in front and hind paws; initial dual stance in front paws; and body speed in hind paws. All these parameters which changed after paclitaxel injection showed reversal of changes when paclitaxel was injected in 3MA injected animals. Western blot of p62 showed a markedly increased level in spinal cord and sciatic nerve but not DRG in group 2, 3 and 4.

**Conclusion:** Suppression of autophagic activity alleviated symptom in PIPN mouse model which was observed to be the consequence affecting the spinal cord and sciatic nerve level but not DRG. Regulation of autophagy could be a therapeutic target for paclitaxel-induced peripheral neuropathy.

**References:** None.

**Keywords:** Pre-clinical Studies, Metabolic

**Grant Support:** This work was supported by the Korean National Research Fund (NRF-2017R1C1B5014853).
Evidence of Altered Peripheral Nerve Function in a Rodent Model of Pre-diabetes

Md Jakir Hossain, Brandon Wild, Michael Kendig, Margaret Morris, Ria Arnold

School of Medical Sciences, UNSW Sydney, Sydney, Australia

Objective: Peripheral neuropathy (PN) is one of the major microvascular complications of diabetes, affecting >50% of diabetic patients. While the pathophysiology remains unclear, recent evidence has linked obesity and pre-diabetes to PN risk prior to development of overt hyperglycemia. We utilised a translationally relevant rodent model of obesity to examine early changes in peripheral nerve electrophysiology.

Methods: Thirty adult male Sprague-Dawley rats were randomised to control (n=15) or cafeteria style (n=15) diet (pre-diabetes). After 12 weeks of diet, nerve conduction studies were undertaken in caudal (sensory) and tibial (motor) nerves. Nerve excitability, an indirect measure of ion channel function and membrane potential, was undertaken in the tibial nerve. Body composition, fasting blood glucose (FBG), triglycerides and HDL cholesterol were measured 1 week later prior to intra-peritoneal glucose tolerance test (ip-GTT). Fasting plasma insulin, IL-1β and IL-6 were measured by ELISA at cull (15 weeks of diet).

Results: The pre-diabetes group had significantly higher body weight, FBG, fasting insulin and adiposity. Pre-diabetic rats also showed dyslipidemia (higher triglycerides and lower HDL cholesterol), impaired glucose tolerance, insulin resistance (HOMA-IR) and increased IL-1β (all \( p<0.05 \)) although IL-6 remain unchanged. Standard nerve conduction parameters including amplitude and latency of motor or sensory nerves were not different between groups. However, nerve excitability measures demonstrated a significant difference in superexcitability (control: 2.18±0.77 [SEM], pre-diabetic: -0.54±0.64; \( p<0.05 \)), which was significantly positively correlated with fasting HDL and body composition (\( rs>0.4; p<0.05 \)). This suggests abnormal fast potassium conductances at the node of Ranvier. While sensory nerve amplitudes did not differ between groups, there was a significant negative correlation between FBG and sensory amplitudes (\( r=-0.48; p=0.008 \)).

Conclusion: This dietary pre-diabetes model demonstrates dyslipidemia, metabolic impairment, elevated IL-1β and changes in peripheral nerve function, thus providing a platform to investigate pathophysiological mechanisms and relationships between metabolic parameters and peripheral nerve damage.

References: None

Keywords: Diabetes, Metabolic, Inflammatory, Pre-clinical Studies, Axonal Biology

Grant Support: Animal work was supported by project grant funding by National Health and Medical Research Council (NHMRC) to MJM (Grant 1126929), Early Career Post-Doctoral Fellowship NHMRC support to RA (Grant 1091006) and Funding from the Rebecca Cooper Foundation (Grant RG160627). MJH was supported by a Scientia PhD scholarship from UNSW Sydney.
Caloric Restriction Improves Peripheral Nerve Function and Glucose Tolerance in Diet-Induced Obese Mice

Shayna Mason, Sarah Elzinga, Amy Rumora, John Hayes, Lucy Hinder, Eva Feldman

University of Michigan School of Medicine, Ann Arbor, MI, USA

Common diabetic complications like diabetic peripheral neuropathy (DPN) are becoming more prevalent with rising rates of obesity and diabetes. Tight glucose control is the only available treatment for DPN, but it does little to alleviate symptoms in patients with Type 2 diabetes. Lifestyle interventions such as diet and exercise are potential alternative therapeutics.

In diet-induced obese mice, changing the diet from 60% lard-based high fat chow to 12% corn oil-based chow (dietary reversal) completely reverses DPN and ameliorates the diabetic phenotype. However, it is unclear if these positive effects result from changes in diet composition or from decreased caloric intake. Therefore, this study aims to determine if caloric restriction alone improves DPN.

We fed male C57BL/6 mice a 60% lard-based high fat diet (HFD; n=16) or a standard 12% corn oil-based control diet (n=8) ad libitum until 18 weeks of age (wks). At this point, 8 HFD mice were placed on caloric restriction (CR), limited to 40% of food consumed by paired HFD controls. Neuropathy phenotyping was measured by sural and sciatic motor nerve conduction velocities (NCVs) at baseline (15 wks) and terminal (26 wks) time points. Baseline and terminal metabolic phenotyping was assessed by insulin and glucose responses to intraperitoneal glucose tolerance testing.

Following 8 weeks of caloric restriction, mice demonstrated improvement in their metabolic phenotype and partial restoration of their neuropathy phenotype. Terminal insulin and glucose area under the curve were significantly higher for HFD compared to CR and control mice. NCVs significantly improved from baseline to terminal for CR mice but remained significantly lower than controls. These data indicate that caloric restriction alone appears to partially restore peripheral nerve function and improve metabolic phenotype in diet-induced obese mice, but further studies are needed to fully differentiate the effects of caloric restriction versus dietary reversal on DPN.

References: None.

Keywords: Diabetes

Grant Support: None.
Poster 147

Bilateral abducens palsy associated with anti-GQ1b antibody: A single center experience

Kee Hong Park

Department of Neurology, College of Medicine, Chungnam National University, Daejeon, Korea (Republic of)

Introduction

Anti-GQ1b antibody is known to be associated with acute ophthalmoplegia without ataxia which is an atypical form of Miller Fisher syndrome. We evaluated clinical features and antigangliosde antibody profile of bilateral abducens palsy.

Methods

We retrospectively reviewed bilateral abducens palsy patients from 2016 to 2018. Those caused by structural lesions or increased intracranial pressure were excluded. Four patients were identified and their medical records were reviewed. Antiganglioside antibodies tests were done by enzyme-linked immunosorbent assay.

Results

Patient 1 and 2 were positive to antiganglioside antibodies (Pt 1: IgM GT1a (1+), IgM GQ1b (1+), IgG GQ1b (1+); Pt2: IgG GQ1b (2+)). Each age was 25 and 18 years old. Both were male and had a history of antecedent infection. Only patient 2 had areflexia and both did not show ataxia. Albuminocytologic dissociation was not observed. Ophthalmoplegia of patient 1 was fully recovered in 1 month after intravenous immunoglobulin infusion. Patient 3 and 4 were negative to antiganglioside antibodies. Clinical features, such as young age (24 and 17 years old), absence of albuminocytologic dissociation, ataxia, and favorable outcome, were similar to those of antibody-positive patients. Patient 4 had generalized ataxia and both did not have antecedent infection.

Conclusions

Patients of bilateral abducens palsy type acute ophthalmoplegia showed young age of onset and favorable outcome. Clinical features were not significantly different according to the presence of antibody except antecedent infection.

References: None.

Keywords: Inflammatory

Grant Support: None.
Reliability of Resynthesis technique to identify proximal conduction block: A series of 20 cases.

Roberto Pontes¹, Carolina Moreira¹, Lucas Clementino², Patricia Onofre¹, Vanessa Marques¹, Pedro Tomaselli¹, Camila Cruz¹, Lucas Silva², Luiza Barretto¹, Ana Silva¹, Isaac Maia¹, Wilson Marques Jr¹

¹University of Sao Paulo, Ribeirao Preto Medical School, Ribeirao Preto, Brazil, ²University of Sao Paulo, Ribeirao Preto Medical School, Sao Paulo, Brazil

Background: Detection of conduction block (CB) in generalized neuropathies is mainly associated to conditions susceptible to a variety of immunological treatments. However, routine nerve conduction studies (NCS) are not effective to identify a proximally located CB, frequently resulting in wrong diagnosis and unappropriated treatments. Furthermore, many patients are treated based on the presumption of a hidden CB that may not exist. Both situations should be avoided. Several techniques may be used to identify these proximal CB, including spinal root stimulation, triple stimulation and magnetic stimulation. Resynthesis is a technique that compares the summation of volitional evoked MUAP to the distal electrical evoked CMAP, aiming to identify a CB proximal to the stimulus. Additionally, in patients with few motor units we may try to evoke electrically MUAPs that are not evoked voluntarily. Purpose: To analyze the effectivity of Resynthesis to detect CB. Methods: We describe a series of 20 patients in whom Resynthesis was applied. Initially we applied the technique to check if it was effective to identify a CB that had already been demonstrated by routine techniques. Subsequently, we evaluated the response to therapy of patients that were treated based on the existence of a CB detected only by Resynthesis. Results: Resynthesis technique was effective to demonstrate the existence of CB in 13 patients already known to have CB by routine NCS. In 7 patients CB was identified only by Resynthesis at first. Six received the diagnosis of Multifocal Motor Neuropathy and one of CIDP. Six (85%) of them had clinical improvement after treatment and five (71%) had neurophysiologic improvement. In addition, two (25%) posteriorly developed CB on routine NCS. Conclusion: Resynthesis seems to be a useful technique to apply on clinical practice. It may be helpful in order to select candidates for immunotherapy based on detection of proximal CB.


Keywords: Inflammatory, Node, Other, Other

Grant Support: FAEPA, INCT Translational Medicine
Clinical Subtypes And Anti-Glycolipid Antibodies In Chronic Inflammatory Demyelinating Polyneuropathy

Motoi Kuwahara¹, Taro Matsui², Keisuke Yoshikawa¹, Masaki Yamana¹, Yuta Fukumoto¹, Kenichi Kaida², Susumu Kusunoki¹

¹Department of Neurology, Kindai University Faculty of Medicine, Osaka, Japan, ²Department of Neurology, Anti-aging and Vascular Medicine, National Defense Medical College, Saitama, Japan

Chronic inflammatory demyelinating polyneuropathy (CIDP) is classified into either typical or atypical CIDP. Characteristics of electrophysiological findings and treatment responses are different between typical and atypical CIDP, indicating varied pathogenetic mechanisms. Herein, we focused on the association between clinical subtypes and anti-glycolipid antibodies in CIDP. We retrospectively collected clinical features of CIDP patients for whom IgM and IgG antibodies to 10 glycolipids (GM1, GM2, GM3, GD1a, GD1b, GD3, GT1b, GQ1b, Gal-C, and LM1) were examined in 2015 and investigated the association between clinical subtypes and those antibodies. Clinical information including subtypes could be obtained in 146 patients with CIDP. Of the 146 patients, 103 (71%) were classified as typical CIDP, 14 (10%) as distal acquired demyelinating symmetric (DADS) neuropathy, 14 (10%) as multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy, 6 (4%) as pure motor neuropathy, 5 (3%) as pure sensory neuropathy, and 3 (2%) as focal neuropathy. Among IgM antibodies, anti-GM1 antibody was most common (27/146, 18%), whereas anti-LM1 antibody was the most frequently observed IgG antibody (8/146, 5%). While anti-GM1 IgM antibody was detected in various clinical subtypes, anti-LM1 IgG antibody was detected in 7 patients with typical CIDP and one with DADS. Additionally, IgG anti-LM1 antibodies belonged to IgG3. The frequency of each subtype of CIDP in the present series is almost the same as described in the previous reports. IgG antibodies to LM1, which is localized in the human peripheral nerve myelin, were detected in predominantly typical CIDP. Because IgG3 antibodies can cause complement activation, anti-LM1 IgG antibodies may be involved in the complement-mediated demyelinating mechanisms in typical CIDP.

References: None.

Keywords: Inflammatory

Grant Support: None.
Poster 150

Usefulness of subperineurial edema and C5b9 deposition in sural nerves for predicting treatment response

Wei Ping Kay Ng¹, Alan Pestronk²

¹National University Health System, Singapore, Singapore, ²Washington University St. Louis, St. Louis, MO, USA
Introduction

Subperineurial edema (SPE) is easily identified on sural nerve biopsies, and has been described to be associated with various etiologies, including inflammatory neuropathies. We investigated the clinico-pathologic features associated with SPE, and other histopathologic markers of treatment response.

Methods

We compared the patient and pathologic data of 68 sural nerve biopsies showing SPE with 33 biopsies showing axonal loss alone.

Results

More patients with SPE on their biopsies responded to treatment compared to patients with axonal loss alone (p<0.01), even when they had symmetric axonal neuropathies (p<0.05). More patients with SPE had symptom duration of ≤ 12 months prior to biopsy (p<0.01). SPE was more commonly associated with other histopathological markers of immune-mediated neuropathies (differential fascicular loss, p<0.05, alkaline phosphatase staining, p<0.05) and evidence of Wallerian degeneration (p<0.01). Other than inflammatory neuropathies, final diagnoses of patients with SPE on their biopsies included motor neuronopathy/motor neuron disease (n=4), Friedrich’s ataxia (n=1), and cerebellar syndrome associated with autoimmune encephalitis (n=1).

Treatment response was more likely if the nerve biopsy showed CD4 cells (p<0.05), and abnormal endoneurial or perineurial vessels (p<0.01). Patients with both SPE and microvascular C5b-9 deposition on biopsy were more likely to respond to treatment than those with SPE alone. More biopsies with C5b-9 deposition were also associated with other markers of immune-mediated neuropathies (abnormal alkaline phosphatase staining and CD4 cell foci, p<0.01). In patients with biopsies without SPE, more responded to treatment if their biopsies showed C5b-9 deposition and abnormal blood vessels (p<0.05).

There was no significant correlation of symptom duration prior to biopsy with treatment-response. Patients with microvascular C5b-9 deposition were more likely to be diabetic (p<0.05).

Conclusion

SPE and microvascular C5b-9 deposition, a probable marker of humoral immunity, may predict treatment response, even in symmetric axonal neuropathies.


Keywords: Inflammatory, Diabetes

Grant Support: Washington University Neuromuscular Research Fund
Poster 151

**MR neurography in differential diagnosis of CIDP, MMN and CMT**

Masaki Kobayashi¹, Megumi Takeuchi¹, Miki Suzuki¹, Kayoko Abe², Kazuo Kitagawa¹

¹Department of Neurology, Tokyo Women's Medical University, Tokyo, Japan, ²Department of Neuroradiology, Tokyo Women's Medical University, Tokyo, Japan

The aim of our study was to determine the usefulness of MR neurography (MRN) in the differential diagnosis of demyelinating neuropathies. Eight patients with chronic inflammatory demyelinating polyneuropathy (CIDP), five with multifocal motor neuropathy (MMN), and three with Charcot–Marie–Tooth disease (CMT) were included in this study. Mean patient age was 56.5 years (range, 41-81 years) in the CIDP group, 57.0 years (range, 45-72 years) in the MMN group, and 46.3 years (range, 33-67 years) in the CMT group. Brachial plexus MRN by using three-dimensional nerve-SHeath signal increased with INKed rest-tissue RARE Imaging (3D-SHINKEI), which was performed to measure nerve root diameter (NRD) at 15-mm distal from the dorsal root ganglion. Mean NRD was enlarged in all groups which the normal range has been reported as 3.39±0.80 mm according to a previous study using short inversion tau recovery imaging on MRI. CIDP group tended to have larger NRD value (5.4±1.7 mm) than in the MMN group (3.9±0.77 mm), but the difference was not significant. Mean NRD was 4.6±0.61 mm in the CMT group. With regard to CIDP subtype, NRD enlargement was prominent in NF-155- positive cases, moderate in multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy cases, and mild in typical CIDP cases. NRD was not related to disease duration; moreover, NRD showed negative association with age in the CIDP group probably due to the higher frequency of NF-155-positive cases in the younger population. In conclusion, enlarged NRD in CIDP, especially in NF-155-positive cases, was an important factor but did not influence definitive differential diagnosis from CMT. Moderate enlargement of NRD in MADSAM neuropathy cases could be a contributing factor to differentiate cases of dominant motor presentation from those of MMN.

**References:** None.

**Keywords:** Inflammatory, Other

**Grant Support:** None.
A case of Lewis-Sumner syndrome mimicking vasculitic neuropathy

Jin-Ah Kim, Seok-Jin Choi, Sangwon Han, Young Nam Kwon, Min Ju Cha, So Hyun Ahn, Je-Young Shin, Yoon-Ho Hong, Jung-Joon Sung

1Seoul National University College of Medicine, Seoul National University Hospital, Seoul, Korea (Republic of), 2Inha University College of Medicine, Inha University Hospital, Incheon, Korea (Republic of), 3Seoul National University College of Medicine, Seoul National University Boramae Hospital, Seoul, Korea (Republic of)

Lewis-Sumner syndrome (LSS), which is also called multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), is a rare disease characterized by asymmetrical and multifocal mononeuropathy commonly located in the upper limbs [1]. LSS is considered as one of the phenotypic variants of chronic inflammatory demyelinating polyradiculoneuropathy [2]. In this paper, we report a case of LSS which initially presented like vasculitic neuropathy. A 57-year-old woman visited our emergency room with weakness and tingling sense of left arm which had rapidly progressed from distal to proximal part within a few hours. She also presented with a two-week period of both calf pain with rash. Neurological examination revealed left upper extremity weakness which was more severe in distal part. All modalities of sensation were decreased on the left arm. Nerve conduction studies (NCS) demonstrated demyelinating sensorimotor neuropathy with conduction block between the elbow-axilla segment of the left median nerve and sensory nerve action potential showed reduced amplitude in the left median nerve. Her left posterior tibial nerve showed no potential and both peroneal nerves showed reduced compound muscle action potential amplitude. Cerebrospinal fluid examination showed normal findings. Antiganglioside antibodies were all negative including anti-GM1 antibodies. Other systemic vasculitis studies were all negative and the computed tomography angiography of four extremities showed no evidence of vasculitis. On the diagnosis of MADSAM, she was treated with intravenous immunoglobulin (IVIG) for 5 days and showed improvement of her weakness and sensory symptoms. At initial presentation, vasculitic neuropathy was compatible with both legs’ pain and rash were compatible with vasculitis. However, NCS revealed definite conduction block and sensory involvement, which led to the diagnosis of MADSAM. So we suggest that IVIG can be treatment of choice when NCS findings are compatible with MADSAM, even though the patients show clinically vasculitic manifestation.


Keywords: Inflammatory, Pain, Other

Grant Support: None.
A 59-year-old gentleman, with preceding diarrhoea, presented with rapidly progressive quadriplegia over 2 days. Serum anti-GM1 IgG was raised. Acute Motor Axonal Neuropathy (AMAN) subtype of Guillain-Barré syndrome (GBS) was diagnosed. He received 2 gm/kg of intravenous immunoglobulins. At day 3 of admission, Modified Erasmus GBS outcome score (MEGOS) was 11, Erasmus Guillain-Barré syndrome Respiratory Insufficiency Score (EGRIS) 7; GBS Disability score (GDS) 5. At Day 5, which was the nadir of weakness, MRC sum score was 0. He was intubated and stayed in the intensive care ward for 9 days. Nerve conduction study at 3 and 10 weeks showed inexcitable motor nerves. Sensory studies were normal. Microbiologic evaluation suggested recent exposure to Zika virus. Besides respiratory failure his clinical course was complicated by pneumonia and deep venous thrombosis. He stayed in acute hospital for 30 days and thereafter underwent in-patient rehabilitation for 9 months. At 3 months and 6 months GDS remained 4 while MRC sum scores were 6 and 14 respectively. GDS improved to 3 at 10 months and 2 at 13 months. He now walks with use of ankle-foot orthoses. Poor prognostic scores and marked impairment should not deter patients and physicians from persevering with prolonged intensive physical therapy. The expertise and finances needed to “Get Better Slowly” are unfortunately not available uniformly throughout the world. This and the morbidity associated with severe sustained disability underline the importance of finding better treatment to augment the effects of IVIg and plasma exchange for patients with severe GBS.

References: None.

Keywords: Inflammatory, Axonal Regeneration, Schwann Cell, Node, Node Biology

Grant Support: None.
Factors Associated with Residual Fatigue in Guillain-Barré Syndrome: Focus on Low-Income Countries

Nowshin Papri¹, Nirbachita Biswas¹, Tanura Chowdhury¹, Rufydha Azam¹, Zahirul Islam¹, Quazi Mohammad²

¹Laboratory Sciences and Services Division, icddr,b, Dhaka, Bangladesh, ²National Institute of Neurosciences and Hospital, Dhaka, Bangladesh

Fatigue accounts for an important residual symptoms experienced by patients with Guillain-Barré syndrome (GBS). This can surprisingly persist for many years of disease onset and lead to tremendous impairment of daily life and social activities. We investigated overall burden and factors associated with fatigue after one year of disease using one of the largest GBS cohorts from developing countries. We have included 147 GBS patients from Dhaka, Bangladesh based on the availability of data after one year of disease onset. Fatigue was assessed using Fatigue Severity Scale (FSS). An average score ≥4 was used to indicate fatigue, and ≥5 for severe fatigue. Associations of different factors with fatigue were tested using Fisher’s exact test or χ² test. Among 147 patients, 65% were male; median age 28 years. After one year, fatigue and severe fatigue was reported by 8% and 14% patients respectively. Fatigue interfered with physical functioning in 23% patients; 15% reported fatigue as one of the three most disabling symptoms. Fatigue was found significantly higher among females (35% vs. 15%; p=0.004). No significant associations were found between fatigue and age, disease severity, antecedent infections and serology, GBS subgroups or treatment. Fatigue was found significantly higher among patients with incomplete physical recovery measured by GBS Disability Score (36% among GBS-DS=2 and 64% among GBS-DS=3; p<0.001) and MRC score (75% and 17% patients with MRC 21-40 and 41-60 respectively; p<0.001). Fatigue was found significantly higher (78%) among patients having moderate anxiety/depression (self reported EQ-5D) compared to mild or no anxiety/depression (34% and 2% respectively; p<0.001). Fatigue as a residual complication of GBS was reported much lower among Bangladeshi GBS patients compared to developed countries (40-60%). However, more rigorous studies are needed to reconfirm the findings and develop integrative management of fatigue for GBS patients in developing counties.

References: None.

Keywords: Inflammatory, Other

Grant Support: None.
A Case Of Guillain-Barré Syndrome With Treatment-Related Fluctuation

Nghia Hoang¹, Ngan Pham¹, Umapathi Thirugnanam²

¹175 Military Hospital, Ho Chi Minh, Viet Nam, ²National Neuroscience Institute, Singapore, Singapore

Guillain-Barré syndrome (GBS) is the commonest cause of acute flaccid paralysis in Vietnam. Neurological deficits reach a nadir generally within 3 weeks and do not progress beyond 4 weeks. However, marked deterioration following a period of stabilization, usually after immune therapy, can occur. A forty-six-year-old man presented to a tertiary hospital at Ho Chi Minh City with a one-week history of progressive weakness and numbness of all four limbs. He had no antecedent infection symptoms. Clinical and electrodiagnostic features suggested acute inflammatory demyelinating polyneuropathy. At day 5, which was the nadir of weakness, Medical Research Council (MRC) sum score was 42 and GBS Disability score (GDS) was 3. His weakness and numbness improved after seven cycles of plasma exchange; MRC sum score 48 and GBS GDS 2. Three days later his condition worsened; MRC sum score 18 and GDS 5. He required mechanical ventilation. Intravenous immune globulin was administered; and the managing physician added methylprednisolone. He recovered almost fully three weeks later. Treatment-related fluctuations (TRF) is defined as an improvement in disability score of at least one grade or in MRC sum score of more than five points within 4 weeks, followed by a reduction in the MRC sum score of more than five points or a worsening in functional disability score of at least one grade. His subsequent, uneventful recovery ruled out acute–onset chronic inflammatory demyelinating polyradiculoneuropathy. Physicians should be aware of TRF in view of its potential to cause harm if unanticipated. The management of TRF is unclear; although most experts believe it warrants a second course of immunotherapy. Our patient was switched to IVIG. The role of methylprednisolone is controversial. However, many physicians in Vietnam use corticosteroids to treat GBS although there is no evidence to support its use


Keywords: Inflammatory

Grant Support: None.
Multicentre Study Investigating the Association of Guillain-Barre Syndrome with Flaviviruses and other Arboviruses in Singapore.

Christen Sheng Jie Lim1, Yiu-Wing Kam2, Nicholas K. W. Yeo2, Siti Naqiah Amrum2, Jonathan Jia Jing Pong3, Joshua Lim3, Wei Ting Wang3, Lisa F. P. Ng2, Thirugnanam Umapathi4

1National University Hospital, University Medicine Cluster, Singapore, Singapore, 2Singapore Immunology Network, Agency for Science, Technology and Research, Singapore, Singapore, 3National University of Singapore, Yong Loo Lin School of Medicine, Singapore, Singapore, 4National Neuroscience Institute, Department of Neurology, Singapore, Singapore

The aim of this study is to understand the relationship between Guillain-Barre Syndrome (GBS) and antecedent Flaviviruses and other arbovirus infections in South and South-East Asia. The study involves hospitals in Singapore, Myanmar, Laos, Vietnam, Thailand, Pakistan, Sri Lanka and India. GBS patients, hospital controls and community controls were examined for evidence of recent Dengue (DENV), Zika (ZIKV) and Chikungunya (CHIKV) infections. Multiplex real-time RT-PCR, ZCD multiplex PCR followed by single-plex PCR reconfirmation, and virion-based ELISA were performed on the patients’ sera and urine for ZIKV, DENV serotypes 1-4, and CHIKV. Neutralisation assays were performed to exclude cross-reactivity between ZIKV, DENV and CHIKV. We present the preliminary data of 16 patients and 2 hospital controls from Singapore, recruited from Dec 2017 to Jan 2019. Of 16 patients only 1 patient had evidence of recent ZIKV infection: positive serum ZIKV PCR obtained at days 43 and 89 from onset of GBS symptoms. Serum and urine had been negative for ZIKV on initial sampling on day 28. The patient had no significant IgM response against ZIKV, DENV and CHIKV. The positive ZIKV PCR in the convalescent rather than acute sera makes ZIKV unlikely to be the responsible antecedent infection. This patient reported diarrheal illness rather than symptoms suggestive of acute ZIKV infection prior to onset of GBS. There was no evidence of recent ZIKV, DENV or CHIKV infections in any of the other cases. As expected in an endemic region, the majority of cases and controls had evidence of previous exposure to various combinations of ZIKV, DENV and CHIKV. Our preliminary data suggests that Flaviviruses and other arboviruses might not be significant antecedent infections of GBS in Singapore. More prospective data from on-going recruitment as well as from our international collaborators will be presented at the PNS meeting.

References: None.

Keywords: Inflammatory, Other

Grant Support: Professor Umapathi and Dr Lisa receive support from the following funding agencies: 1) Professor Umapathi: GBS-CIDP Foundation 2) Dr Lisa Ng: - Biomedical Research Council (BMRC), Agency for Science And Technology (A*STAR) - partial support from BMRC A*STAR-led ZIKA Virus Consortium fund (project number: 15/1/82/87/001), Agency for Science And Technology (A*STAR)
Serial Studies Reveal “Covert” Sural-sparing Pattern in Guillain-Barre Syndrome

Jasmine Shimin Koh, Genevieve Lynn Yu, James Wei Min Tung, Si Min Seah, Lin Wee, Amanda Siew Hwee Tan, Amelia Rui Ying Tan, Thirugnanam Umapathi

1National Neuroscience Institute, Singapore, Singapore, Singapore, 2Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore, Singapore, 3Yong Loo Lin School of Medicine, National University Singapore, Singapore, Singapore, Singapore

Our previous studies established: i) Relative sural-sparing, defined as a greater reduction of median or ulnar sensory nerve action potential (SNAP) compared to sural SNAP, is seen in the initial nerve conduction studies (NCS) of more than one-third of Guillain-Barre syndrome (GBS) patients, ii) Sural-sparing pattern is seen in both demyelinating and axonal subtypes, including Miller-Fisher syndrome (MFS) and iii) Disruption of blood-nerve barrier at entrapment sites rather than terminal nerve endings is the likely cause of the sural-sparing pattern. We also encountered cases that initially did not demonstrate sural-sparing but serial NCS showed greater involvement of median or ulnar SNAPs compared to sural SNAP. We aim to understand the frequency of this “covert” sural-sparing pattern in GBS patients. We reviewed the serial NCS of consecutive patients enrolled into our prospective GBS database. Patients with relative sural-sparing pattern on initial NCS were delineated as shown, using age and height matched normal values derived from 245 controls: (Normal Median or Ulnar SNAP - patient’s Median or Ulnar SNAP)/(Normal Median or Ulnar SNAP) > (Normal Sural SNAP-patient’s Sural SNAP)/(Normal Sural SNAP). Serial NCS of those without initial sural-sparing were examined for significant change in SNAP, as validated by Capasso et al, i.e. at least 44%, 47% and 58% for median, ulnar and sural SNAP amplitudes respectively. “Covert” sural-sparing was defined as a greater change in median or ulnar SNAPs compared to sural SNAP. 55/86 (64%) patients had relative sural-sparing at initial study. 8 were AIDP, 11 AMAN/AMSAN, 28 MFS/MFS-GBS and 8 unclassified. Of the remaining 31 patients without initial sural-sparing pattern, 5 had “covert” sural-sparing. These were 2 AIDP, 2 AMAN/AMSAN and 1 MFS. We believe sural-sparing is a fundamental electrodiagnostic footprint of all GBS subtypes and, depending on the sensitivity of the methods used, is present in at least 2/3 of GBS patients.

References: None.

Keywords: Inflammatory

Grant Support: None.
Pharmacokinetic Modelling and Simulation of Flexible Dosing Regimens of Subcutaneous Immunoglobulin (IgPro20) in CIDP Patients

Xuwen Ma¹, Richard Lewis², David Cornblath³, Theresa Yuraszeck¹, Orell Mielke⁴, Vera Bril⁵, Hans-Peter Hartung⁶, Gen Sobue⁷, John-Philip Lawo¹, Billie Durn¹, Ingemar Merkies⁸, Ivo van Schaik⁹, Michael Tortorici¹

¹CSL Behring, King of Prussia, PA, USA, ²Cedars-Sinai Medical Center, Los Angeles, CA, USA, ³Johns Hopkins University School of Medicine, Baltimore, MD, USA, ⁴CSL Behring, Marburg, Germany, ⁵University of Toronto, Imam Abdulrahman Bin Faisal University, Toronto, Canada, ⁶Heinrich Heine University, Düsseldorf, Germany, ⁷Nagoya University Graduate School of Medicine, Nagoya, Japan, ⁸Maastricht University Medical Center, St Elisabeth Hospital, Maastricht, Netherlands, ⁹University of Amsterdam, Amsterdam, Netherlands

Introduction: A population pharmacokinetics (PopPK) model was developed to characterise the pharmacokinetics of immunoglobulin G (IgG) following intravenous (IV) or subcutaneous (SC) administration of IgPro10 (Privigen®, CSL Behring, King of Prussia, PA, USA) or IgPro20 (Hizentra®, CSL Behring) in CIDP patients. This model was used to simulate concentration-time profiles and PK parameters at steady state following various SC dosing regimens to enhance flexible dosing for patients’ convenience.

Methods: The PopPK analysis was conducted using the data from PRIMA (NCT01184846) and PATH (NCT01545076) studies, including 1558 observed IgG concentrations from 235 adult patients. Data exploration and PopPK modelling were conducted using R and nonlinear mixed-effects modelling software (NONMEM), respectively. Using the final PopPK model, IgG concentration–time profiles were simulated (300 simulated trials of 25 CIDP patients) and corresponding exposure metrics were calculated from different dose regimens (daily to bi-weekly dosing) and compared with the weekly dosing regimen.

Results: A two-compartment model with first-order absorption (for SC administration) and elimination described the observed IgG serum concentration data well. IgG disposition in patients was characterised by low clearance (CL, 0.45 L/day) and a small volume of distribution and (V2, 4.7 L). Relative bioavailability of the SC formulation was approximately 85% compared with the IV formulation. Additionally, body weight was a significant covariate on both CL and V2. The results of the simulations suggested that exposure (AUC, Cmax and Cmin) from flexible dosing (daily to bi-weekly) was comparable with that of a weekly dosing regimen within the equivalence boundaries of 0.8–1.25.

Conclusions: The PK of IgG following IV and SC administration to CIDP patients was well characterised by a two-compartment model with the first order absorption (for SC) and elimination. Based on the simulation results, flexible dosing from daily to biweekly is feasible resulting in equivalent exposure across dose regimens.

References: None.

Keywords: Inflammatory

Grant Support: This study was supported by CSL Behring.
**Poster 159**

**CSF neurofilament heavy chain: A possible biomarker of Guillain-Barré syndrome**

Jee-Eun Kim¹, Byung-Nam Yoon², Suk-won Ahn³, Ji Won Yang⁴, Su-yeon Park⁵, Kee-Hong Park⁶, Nam-Hee Kim⁷, Seoh Ah Lee⁸, Je-young Shin⁹, Jung-Joon Sung⁹, Yoon-ho Hong¹⁰, Jong-Suk Bae¹¹

¹Department of Neurology, Seoul Medical Center, Seoul, Korea (Republic of), ²Department of Neurology, Seoul Paik Hospital, Inje University College of Medicine, Seoul, Korea (Republic of), ³Department of Neurology, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, Korea (Republic of), ⁴Department of Neurology, Gachon University Gil Medical Center, Incheon, Korea (Republic of), ⁵Department of Neurology, Korea Cancer Center Hospital, Seoul, Korea (Republic of), ⁶Department of Neurology, Chung-Nam University Hospital, Daejun, Korea (Republic of), ⁷Department of Neurology, Dongguk University Ilsan Hospital, Goyang, Korea (Republic of), ⁸Research Institute, Seoul Medical Center, Seoul, Korea (Republic of), ⁹Department of Neurology, Seoul National University Hospital, Seoul, Korea (Republic of), ¹⁰Department of Neurology, Seoul National University College of Medicine, Seoul, Korea (Republic of), ¹¹Department of Neurology, Kangdong Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Korea (Republic of)

**Introduction:** Guillain-Barré syndrome (GBS) have diverse variants and mimics that might delay the diagnosis. About 20% of GBS develops permanent severe disability at long term follow up. From this reasons, early accurate diagnosis and predicting prognosis are important in treating GBS and improving outcome. We investigated the diagnostic and prognostic role of 4 cerebrospinal fluid (CSF) proteins which are axonal or glial markers – neurofilament heavy chain (NfH), tau, S100B and glial fibrillary acidic protein (GFAP) – in GBS.

**Method:** We prospectively recruited acute stage of GBS patients diagnosed by Asbury criteria (1990) from multicenter. Serial nerve conduction studies (NCS) were performed to classify subtypes of GBS. CSF levels of axonal (NfH and tau) and glial (S100B and GFAP) proteins were measure by ELISA. Outcome was assessed for 6 months and assessed with Hughes functional score (F-score). F-score ≥ 3, which indicates inability to walk independently, was determined as poor outcome. Thirteen healthy volunteers were used as control. Results: Total 40 GBS patients were recruited and 4 patients were excluded due to inappropriate CSF specimen. Analyzed 36 patients (Female to male ratio = 1:1) are classified as 17 AMAN, 11 AIDP, 8 Miller-Fisher syndrome or other anti-GQ1b antibody syndrome. Among 4 protein biomarkers, only NfH was significantly elevated in GBS compared to normal control. There is no significant difference in NfH, S100B, GFAP, tau CSF levels between subtypes of GBS. NfH level in CSF is distinctively dichotomized in GBS and NfH and S100B were associated with residual neurological deficit after 6 months. Conclusions: CSF NfH and S100B are possible diagnostic and prognostic biomarkers that can predict prognosis after 6 months in GBS. NfH, tau, S100B and GFAP might not be useful for differentiate GBS subtype, but rather it might be a marker for the severity of degree of inflammation.

**References:** None.

**Keywords:** Inflammatory

**Grant Support:** None.
Human Leukocyte Antigen (HLA)-DQB1 Polymorphisms and Their Haplotype Patterns in Patients with Guillain-Barré Syndrome

Zhahirul Islam1, Shoma Hayat1, Israt Jahan1, Avizit Das1, Md Zahid Hassan2, Md. Zakir Howlader3, Ishtiaq Mahmud3

1icddr,b, Dhaka, Bangladesh, 2Bangladesh University of Health Sciences (BUHS), Dhaka, Bangladesh, 3University of Dhaka, Dhaka, Bangladesh

The etiology of Guillain-Barré syndrome (GBS) is still an enigma although genetic and environmental factors are highly speculated for this autoimmunity. Among the genetic factors, the human leukocyte antigen (HLA)-DQB1 gene displays an impressive degree of polymorphism and haplotype structures may provoke autoimmune responses to infection and thereby influence GBS development. We determined HLA-DQB1 polymorphic alleles (*0201,*030x,*0401, *050x, *060x) among 151 patients with GBS and 151 ethnically matched healthy controls in Bangladesh using sequence-specific PCR. Pair wise linkage disequilibrium and haplotype patterns were analyzed based on D' statistics. Fisher’s exact test and logistic regression analysis were used for association studies. No association was observed between HLA-DQB1 alleles and susceptibility to GBS. In haplotype analysis, haplotype 9 (DQB1*0303-*0601) was significantly decreased in GBS patients compared to controls (P=0.006, OR=0.49, 95% CI=0.30-0.82). Frequencies of DQB1*0303 alleles were prevalent in patients with severe form (P=0.025, OR=2.49, 95% CI=1.13-5.48). Clinical and serological subgroup analysis revealed a higher frequency of DQB1*0201 allele in demyelinating subtype (P=0.027, OR=2.68, 95% CI= 1.17-6.17). Patients with haplotype 5 (DQB1*0501-*0602) were associated with C. jejuni-triggered axonal subtype of GBS (P=0.02, OR=4.06, 95% CI=1.25-13.18). Individuals with haplotype 9 (DQB1*0303-*0601) possess 53% less frequency of anti-GM1 antibody sero-positivity compared to healthy controls (P=0.029, OR=0.47, 95% CI=0.24-0.93). Finally, HLA-DQB1 polymorphism is not associated with disease susceptibility though haplotype 9 (DQB1*0303-*0601) is less likely to be found in patients with GBS and expression of GM1 is lower in the presence of haplotype 9. Nevertheless frequencies of DQB1*0303 alleles are significantly evident in severely affected patients with GBS.

References: N/A

Keywords: Human Genetics, Inflammatory, Other

Grant Support: N/A
Temporal Profile of Anti-Ganglioside Antibodies in Recurrent Guillain-Barre Syndrome

Takamasa Kitaoji¹, Yukiko Tsuji¹, Naoki Makita¹, Tomoyuki Ohara¹, Yu-ichi Noto¹, Masanori Nakagawa², Toshiki Mizuno¹

¹Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, ²North Medical Center, Kyoto Prefectural University of Medicine, Kyoto, Japan

Introduction: In the serum of patients with Guillain-Barre syndrome (GBS), the level of anti-ganglioside antibodies decreased after reaching its peak in several months after the onset. However, the temporal profile of serum anti-ganglioside antibodies in patients with recurrent Guillain-Barre syndrome (RGBS) is unclear. We demonstrate a longitudinal change of anti-ganglioside antibodies for 2 years in an RGBS case.

Case: A 36-year-old woman was admitted with a 3-day history of distal paresthesia and weakness in her extremities. She had two episodes of GBS at 13 and at 19-year-old. 10 days prior to admission, she developed diarrhea. Her Hughes grade scale was 3 and deep tendon reflexes were decreased on the day of admission. Nerve conduction study (NCS) demonstrated demyelinating changes including conduction block and reduced amplitude of sensory nerve action potentials in the median and ulnar nerves. 2 courses of intravenous immunoglobulin were administered after admission. The symptom reached nadir on the third day (Hughes grade scale: 4) and improved gradually thereafter. 4 months after admission, she recovered (Hughes grade scale: 1) with leaving mild paresthesia in her hands. The parameters of NCS were completely improved 1 year after admission. Anti-GD1b IgG antibody was strongly positive in both of sera obtained at the time of the second and last episodes, although symptoms of preceding infections were different between in these two episodes. She had respiratory symptoms at the first and second GBS episodes, whereas she had diarrhea at last GBS episode. In addition, we examined the levels of anti-ganglioside antibody in serum at 4 months, 1 year and 2 years after admission. Strongly positive level of anti-GD1 IgG antibody was kept at the respective points of time.

Conclusions: Continual strongly positive anti-ganglioside antibodies may be the recurrent risk of GBS.

References: None.

Keywords: Inflammatory

Grant Support: None.
Experimental autoimmune neuritis (EAN): Morphological evidence for mitochondrial damage

Ines Muke¹, Alina Sprenger¹, Ilja Bobylev¹, Mohammed Barham², Wolfram Neiss², Helmar Lehmann³

¹University Hospital Cologne, Cologne, Germany, ²University Cologne, Cologne, Germany, ³University Hospital Cologne, Cologne, Germany

Experimental autoimmune neuritis (EAN) is used as an animal model for Guillain-Barré syndrome (GBS). In this study we examine mitochondrial morphology in different cellular compartments by longitudinal histological examination including electron microscopy, qPCR and immunohistochemistry in EAN.

Lewis rats were injected with P0 Protein and adjuvants. 7 days after injection animals developed pathogenic signs, after 14 days the disease peaked, after 21 days severity decreased. Animals were sacrificed after 14 and 28 days. Sural, tibial and sciatic nerves were dissected. Semithin sections were used to study axon count and g-ratio. Electron microscopy was performed to examine mitochondrial diameter in myelinated and unmyelinated axon as well as in Schwann cells. Immunohistochemistry stainings and qPCR were performed to investigate spatial relationship between mitochondrial pathophysiology and immune reaction against myelin.

Histological examination revealed no changes in axon count, but significant changes in the g-ratio in all nerves after 14 and 28 days. There was a significant increase in mitochondrial diameter at the peak of the disease (14days) in myelinated and unmyelinated axon as well as Schwann cells. Furthermore, after 14 days changes where seen in mitochondrial physiology investigated by qPCR and immunohistochemical stainings. Pathological changes can be linked to changes in myelination and immune reaction.

Segmental demyelination in EAN is associated with profound changes in mitochondrial morphology. During the disease peak mitochondria tend to be swollen in axons and Schwann cells, slight differences are to be seen between the different nerves. These morphological changes in the mitochondria were correlated with formation of onion bulbs and axonal sprouts. Whereas in the recovery phase of the disease mitochondria show almost no significant differences compared to disease onset. In summary alteration in mitochondrial morphology correlated with the disease course in EAN, which could point to a role of mitochondrial dysfunction for disease severity and recovery potential.

References: None.

Keywords: Inflammatory, Schwann Cell, Axonal Regeneration, Axonal Biology, Other

Grant Support: None.
**Poster 163**

**Predominantly Abnormal Sensory Responses at Disease Onset and Electrophysiological Characteristics of Anti-Neurofascin 155 Neuropathy**

Stefanie Kar Yan Hung¹, Yuen Kang Chia², Luis Querol³, Fu Liong Hiew⁴

¹Hospital Kuala Lumpur, Department of Neurology, Kuala Lumpur, Malaysia, ²Department of Neurology, Queen Elizabeth Hospital, Kota Kinabalu, Sabah, Malaysia, ³Autoimmune Neurology, Neuromuscular Diseases Unit, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, ⁴Department of Neurology, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia

**Introduction**

Sensory ataxia is one of the prominent clinical features of patients with anti-neurofascin 155 (NF-155) neuropathy

**Methods**

We report the early electrophysiology characteristics of 2 Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) patients with NF-155 antibody, their clinical phenotype and treatment response

**Results**

Both patients had symptoms onset at 21-years-old. One had preceding febrile illness and the other had yellow fever vaccination, but no specific identifiable infections detected. Both patients presented with progressive distal upper and lower limbs paraesthesia and weakness with areflexia, sparing all cranial nerves. Clinical phenotype was consistent with atypical CIDP subtype of distal acquired demyelinating symmetric (DADS). Both patients showed prominent sensory ataxia and hand tremor. The first patient was more severely affected. Nodo/paranodal antibody testing was performed, and both patients were positive for anti-NF155 with the cell-based assay and anti-NF155 titers by ELISA of 1:24300 and 1:8100 respectively. Initial electrophysiology of both patients was performed within 2 months from symptoms onset. In the first, sensory nerve action potentials (SNAPs) were absent in all upper and lower limbs with typical compound motor action potentials (CMAPs) demonstrating demyelinating changes. For the second patient, SNAPs responses were predominantly reduced in amplitudes with mild conduction slowing, involving only the upper limbs, sparing the sural nerves. Motor neurography showed prolonged DML and F-wave latency. Follow-up electrophysiology studies demonstrated rapid deterioration of SNAPs responses to inexcitability. Treatment responses were variable. The first patient responded partially to IV immunoglobulin (IVlg), but not to corticosteroid and Azathioprine. The second patient responded partially to corticosteroids but stopped due to intolerance and did not respond to IVlg, Azathioprine and Mycophenolate mofetil. IV rituximab administered over the last 2 years stopped clinical progression, although anti-NF155 titers remained high

**Conclusion**

These cases demonstrated the predominant and rapid sensory nerve disturbance progression in patients with NF-155 neuropathy

**References:** None.

**Keywords:** Other

**Grant Support:** None.
Detection of IgG and IgM antibodies against nodo-paranodal proteins in CMT and CIDP

Lorena Martín-Aguilar¹, Elba Pascual-Goñi¹, Cinta Lleixà¹, Marina Frasquet², Herminia Argente², Angel Cano-Abascal³, Jordi Diaz-Manera⁴, Elena Cortés-Vicente¹, Ana Lara Pelayo⁵, Teresa Sevilla⁶, Ricard Rojas-García⁴, Luis Querol⁷

¹Neuromuscular Diseases Unit, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Spain, Barcelona, Spain, ²Hospital Universitari i Politècnic de la Fe, Valencia, Spain, Valencia, Spain, ³Hospital Universitario Marqués de Valdecilla, Santander, Spain, Santander, Spain, ⁴Neuromuscular Diseases Unit, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, CIBERER., Barcelona, Spain, ⁵Hospital Universitario Marqués de Valdecilla, Santander, Spain, Santander, Spain, ⁶Hospital Universitari i Politècnic de la Fe, Valencia, Spain., Valencia, Spain, ⁷Neuromuscular Diseases Unit, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, CIBERER, Barcelona, Spain

INTRODUCTION AND PURPOSE: A small percentage of patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) have IgG4 antibodies against Neurofascin and Contactin. Recently IgG and IgM antibodies against the same antigens have been described in patients with Charcot-Marie-Tooth (CMT)¹ and IgM antibodies against NF155 have been detected in CIDP and GBS patients by ELISA². Our objective is to study the presence of nodal and paranodal IgM and IgG antibodies in patients with CMT and CIDP.

METHODS: 70 patients fulfilling the EFNS/PNS diagnostic criteria for CIDP and 100 patients fulfilling diagnostic criteria for CMT from three different centers were included. The presence of IgG and IgM antibodies against Neurofascin 155 (NF155), nodal neurofascin (NF186 and NF140) and Contactin-1 (CNTN1) have been investigated by immunocytochemistry in transfected HEK293 cells. The presence for NF155 IgM was also tested by ELISA. Sera with positive or with uncertain results were further tested by ELISA and immunohistochemistry (IH) in pig teased-nerve fibers.

RESULTS: Seventy patients with CIDP and 52 patients with CMT have been analyzed until now. Five patients with CMT have a doubtful pattern staining for IgM against nodal neurofascin, which were not confirmed by ELISA. Two patients with CMT have a doubtful pattern staining for IgG against nodal neurofascin, not confirmed by ELISA or IH.

CONCLUSIONS: Our pilot study suggests that patients with CIDP have not IgM antibodies against nodal and paranodal antigens. Until now, we did not detect nodal or paranodal antibodies in patients with Charcot-Marie-Tooth and have not confirmed the presence of IgM antibodies against paranodal proteins in CIDP. Final results will be presented at the congress.


Keywords: Inflammatory, CMTR, Node, Node Biology

Grant Support: None.
Poster 165

Disability, Fatigue and Treatment Safety During Long-Term Intravenous Immunoglobulin (Gamunex® 10%) Therapy in CIDP Patients

Juliane Klehmet¹, Bernd Kieseier², Judith Haas³, Björn Tackenberg⁴

¹NeuroCure Clinical Research Center Berlin, Charité Universitätsmedizin Berlin, Berlin, Germany, ²Neurologische Klinik, Heinrich-Heine Universität, Düsseldorf, Germany, ³Jüdisches Krankenhaus Berlin, Berlin-Mitte, Germany, ⁴Klinik und Poliklinik für Neurologie, Marburg, Germany

Purpose: Chronic inflammatory demyelinating polyneuropathy (CIDP) is marked by disability progression and fatigue. Here, long-term assessment of these features in CIDP patients receiving intravenous immunoglobulin (IVIG) therapy in daily routine practice is described.

Methods: GAMEDIS was a multi-centre, prospective, non-interventional study performed on CIDP patients aged ≥18 years treated with IVIG (Gamunex® 10%), who were followed-up for 2 years. Inflammatory Neuropathy Cause and Treatment (INCAT) disability score, Hughes scale and Fatigue Severity Scale (FSS) were assessed at baseline and each quarterly visit. Dosing and treatment intervals, the change of clinical outcome parameters, and adverse events (AEs) were analysed.

Results: 158 patients were enrolled, of which 148 (93.7%) were evaluable and 81 (54.7%) had full dosing records available. 86.5 % of patients had a previous IVIG-treatment history and received a median maintenance IVIG dose of 0.9 g/kg per treatment cycle (median: 28 days) during a mean observational period of 83.3 weeks. Disability and fatigue remained stable throughout the study. Mean INCAT score was 2.4±1.8 at baseline and 2.5±1.9 at last observation. Patients regarded as healthy or with minor symptoms by Hughes score were 74.3% at baseline and 71.6% at the end of study. Mean FSS was 4.2 ± 1.6 and 4.1±1.7 at baseline and end of the study, respectively. Fifteen patients (9.5%) experienced 34 potentially treatment-related AEs. There were no AEs in 993% of all documented infusions.

Conclusion: Long-term treatment of CIDP patients with Gamunex® 10% in every day practice had a very good tolerability and safety records. Disability and fatigue remained stable through the 2 years observational period.

References: None.

Keywords: Inflammatory

Grant Support: None.
Time to Relapse After IVIG Withdrawal Predicts Relapse of Placebo-Treated CIDP Subjects in PATH Study

Richard Lewis 1, Ivo van Schaik 2, Orell Mielke 3, Vera Bril 4, Hans-Peter Hartung 5, Gen Sobue 6, John-Philip Lawo 7, Michaela Praus 7, Billie Durn 7, David Cornblath 8, Ingemar Merkies 9

1 Cedars-Sinai Medical Center, Los Angeles, CA, USA, 2 University of Amsterdam, Amsterdam, Netherlands, 3 CSL Behring, Marburg, Germany, 4 University of Toronto, Imam Abdulrahman Bin Faisal University, Toronto, Canada, 5 Heinrich Heine University, Düsseldorf, Germany, 6 Nagoya University Graduate School of Medicine, Nagoya, Japan, 7 CSL Behring, King of Prussia, PA, USA, 8 Johns Hopkins University School of Medicine, Baltimore, MD, USA, 9 Maastricht University Medical Center, St Elisabeth Hospital, Maastricht, Netherlands

Introduction: PATH was a randomised study of subcutaneous immunoglobulin (SCIG) for chronic inflammatory demyelinating polyneuropathy (CIDP) that included a preceding immunoglobulin (IgG) dependency test period. The time to relapse in the IgG dependency period as a predictor of subsequent relapse in subjects randomised to placebo was measured to evaluate the utility of the IgG dependency test as an enrichment strategy.

Methods: Subjects were withdrawn from their previous intravenous immunoglobulin (IVIG) regimen for up to 12 weeks unblinded. Those who relapsed were restabilised and randomised to receive SCIG or placebo for 24 weeks. Relapse was defined as a ≥1 point increase in adjusted INCAT score. In a post-hoc analysis, time to relapse in the IgG dependency period was analysed in relation to likelihood of relapse for subjects treated with placebo in the subsequent randomised treatment period.

Results: Of 57 patients treated with placebo in the randomised SCIG treatment period, 40 relapsed by INCAT relapse criteria in the preceding dependency period and 24 relapsed by the same criteria in the SCIG treatment period. Those who relapsed in the SCIG treatment period tended to have a shorter time to relapse in the IgG dependency period (median 4.5 weeks, interquartile range 3.0 to 6.0 weeks, versus 7.8 [6.1 to 10.8] weeks) than those who did not relapse in the IgG dependency period; 75% of relapers demonstrated IgG dependency within 6 weeks, whereas 75% of non-relapers (n=16) demonstrated IgG dependency only after 6 or more weeks.

Conclusion: Subjects who deteriorated within 6 weeks when withdrawn from IVIG in a non-blinded manner were more likely to relapse when treated with placebo in the randomised treatment period than those who remained stable for 6 weeks off therapy before relapsing. These facts should be taken into account in future clinical trials to minimise subject numbers and subject burden.

References: None.

Keywords: Inflammatory

Grant Support: This study was supported by CSL Behring.
Medical Research Council Grading System Revisited in CIDP Through Rasch Analyses: The PATH Study

Ingemar Merkies\textsuperscript{1}, Orell Mielke\textsuperscript{2}, Vera Bril\textsuperscript{3}, Hans-Peter Hartung\textsuperscript{4}, Richard Lewis\textsuperscript{5}, Gen Sobue\textsuperscript{6}, John-Philip Lawo\textsuperscript{7}, Michaela Praus\textsuperscript{7}, Billie Durn\textsuperscript{7}, David Cornblath\textsuperscript{8}, Ivo van Schaik\textsuperscript{9}

\textsuperscript{1}Maastricht University Medical Center, St Elizabeth Hospital, Maastricht, Netherlands, \textsuperscript{2}CSL Behring, Marburg, Germany, \textsuperscript{3}University of Toronto, Imam Abdulrahman Bin Faisal University, Toronto, Canada, \textsuperscript{4}Heinrich Heine University, Düsseldorf, Germany, \textsuperscript{5}Cedars-Sinai Medical Center, Los Angeles, CA, USA, \textsuperscript{6}Nagoya University Graduate School of Medicine, Nagoya, Japan, \textsuperscript{7}CSL Behring, King of Prussia, PA, USA, \textsuperscript{8}Johns Hopkins University School of Medicine, Baltimore, MD, USA, \textsuperscript{9}University of Amsterdam, Amsterdam, Netherlands

Introduction: The Medical Research Council (MRC) grading system (ranging from 0–5) has been used for decades in clinical practice for muscle strength assessment, but its applicability has been debated particularly as sum scores are being generated from what is an ordinal scale. In a recent analysis of the peripheral neuropathy outcome measures standardisation study (PeriNomS) group, the applicability of the MRC grades showed inconsistency when investigated through Rasch analyses using published data on 72 muscles in various neuromuscular illnesses. Fewer inconsistencies were seen in proximal versus distal muscles/muscle groups, mainly in inflammatory neuromuscular like chronic inflammatory demyelinating polyneuropathy (CIDP); however, the CIDP series was relatively small.

Methods: The PATH study, the largest worldwide randomised controlled trial currently performed in CIDP, provides a unique opportunity to examine whether the MRC grading system could meet Rasch-model expectations. Available initial data on all randomised patients (\textit{n}=172) with CIDP will be subjected to a Rasch model to examine whether 1) physicians could differentiate between the MRC grades in the 8 muscle pairs examined (shoulder abductors, elbow flexors, wrist extensors, first dorsal interosseous, hip flexors, knee extensors, ankle dorsiflexors, extensor hallucis longus), and 2) whether each muscle contributes to the same degree to the sum score used in CIDP.

Results: The findings of this analysis will be presented at the PNS congress. The PATH study data provides a unique opportunity to contribute to the methodological questions in the field of inflammatory neuropathies.

Conclusion: This analysis will provide further information on the use of Rasch-transformed MRC scores in neuropathies.

References: None.

Keywords: Inflammatory

Grant Support: This study was supported by CSL Behring.
Impact of Diagnosis Delay in Chronic Inflammatory Demyelinating Polyneuropathy: Results from a Global Patient Survey

Rajiv Mallick1, Noemi Hahn2, Daniel Riley2, Anne Haudrich1, Ann Leon1, Ingemar Merkies3

1CSL Behring, King of Prussia, PA, USA, 2Bryter, New York, NY, USA, 3Maastricht University Medical Center, St Elisabeth Hospital, Maastricht, Netherlands

Background: Chronic inflammatory demyelinating polyneuropathy (CIDP), a rare peripheral neuropathy, is often misdiagnosed. Diagnosis delay can adversely impact treatment decisions and disease progression.

Methods: Online global GBS CIDP Foundation survey data from 595 adult CIDP patients, with self-reported CIDP, was used to assess impact of diagnosis delay (after incident symptoms) on physical function (PF) based on PROMIS PF T-scores using Short Form-4 and Inflammatory Rasch-Built Overall Disability Scale (I-RODS) scores. Logistic models predicted the worst two tertiles per outcome, associated with work disability and residential changes. Diagnostic delay thresholds were evaluated using receiver operating characteristic curves.

Results: Patients were stratified into “Likely/somewhat likely CIDP” (n=426) and “Unlikely CIDP” (n=169, excluded from analysis) based on symptom patterns and EFNS/PNS guidelines. Median time to CIDP diagnosis after symptom recognition: 8 months (≥12 months: 43%; ≥30 months: 24%). Overall, mean [SD] PROMIS PF T-score was 36.5 [7.9] (internationally accepted population norm: 50 [range 23-57]), mean I-RODS centile score was 56.2 [16.9] (range 6-100); these were significantly lower (worse) (p=0.009, p=0.05 respectively) following ≥12 month diagnosis delay versus <12 month delay. A ≥12-month delay increased risk of being in lower two tertiles of PROMIS PF or I-RODS centile scores (1.7 times higher odds [p=0.015]) or I-RODS centile scores (1.6 times [p=0.04]). Assessing sensitivity versus false positive rate (FPR) of alternative diagnostic delay thresholds for being in lower two PROMIS PF or I-RODS tertiles, a 6-month delay had higher sensitivity and FPR, a ≥30-month threshold had lower sensitivity and FPR. Being female or a shorter time post-diagnosis to survey were associated with higher risk of being in lower two PF tertiles.

Conclusions: CIDP diagnosis delay beyond 12 months of symptom onset is associated with significant PF impairment. Limiting diagnosis delay to 6-months from symptom onset may be desirable, however this could increase FPR in identifying those at risk.

References: None.

Keywords: Inflammatory

Grant Support: This study was supported by CSL Behring.
Epitope Mapping for Anti-FGFR3 Autoantibodies in Sensory Neuropathy

Christian Moritz\(^1\), Martin Jung\(^2\), Evelyne Reynaud-Federspiel\(^1\), Lauriane Mohr\(^3\), Yannick Tholance\(^4\), Karine Ferraud\(^5\), Jean-Philippe Camdessanche\(^5\), Jean-Christophe Antoine\(^5\)

\(^1\)Institut NeuroMyoGène of the University of Lyon, Saint-Étienne, France, \(^2\)Medical Biochemistry and Molecular Biology of the Saarland University, Homburg, Germany, \(^3\)Institut NeuroMyoGène of the University of Lyon, Saint-Étienne, France, \(^4\)University hospital of Saint-Étienne, Institut NeuroMyoGène of the University of Lyon, Saint-Étienne, France, \(^5\)University hospital of Saint-Etienne, Institut NeuroMyoGène of the University of Lyon, Saint-Étienne, France

Sensory neuropathies (SNs) are rare diseases of the peripheral nerve system. Although being often classified as idiopathic, many cases are associated with immune-mediated diseases, suggesting an active involvement of the immune system. Indeed, autoantibodies against Fibroblast Growth Factor Receptor 3 (FGFR3) were recently identified in a subgroup of patients with sensory neuropathies.\(^1\) To assess these autoantibodies' pathobiological role, we aimed for detecting their epitope(s). In a first pre-screening approach, we synthesized and spotted 158 peptides covering the FGFR3 full-length sequence (806 amino acids (aa)) onto a cellulose membrane. Each peptide was 25 aa long, 20 aa overlapped between adjacent peptides. In a second step, we focused on the intracellular domain applying a higher resolution of peptide coverage (22 aa overlap) and on phosphorylated aa at their natural sites besides the unphosphorylated peptide. Upon these pre-screenings via immunostaining with four anti-FGFR3-positive patient sera, nine interesting cytosolic epitopes were selected and tested in a systematic screening array with 66 anti-FGFR3-positive SN patients and 34 healthy controls. The first pre-screening localized the major epitopes in the intracellular domain. The second, more detailed pre-screening showed that (1) reactivity of several epitopes is highly dependent on the phosphorylation state and (2) there are clear interindividual differences among the patients. In the systematic screening based on nine selected epitopes, 16 of 66 anti-FGFR3-positive SN patients and 2 of 34 healthy controls bound at least one epitope. The epitopes reacting with healthy control sera were rejected. Five epitopes remained, each significantly targeted by at least two patients: aa positions 415-436, 457-478, 634-652 with phosphorylated tyrosines 647/48, 634-652 with unphosphorylated tyrosines 647/48, and 742-760. These epitopes cover 7/14 functionally relevant sites, such as pathogenic mutation or phosphorylation sites. To our knowledge, our results represent the first description of phosphorylation state-dependent autoantibodies in a neurological disease.

References: \(^1\) Antoine JC, Boutahar N, Lassablière F, Reynaud E, Ferraud K, et al., Antifibroblast growth factor receptor 3 antibodies identify a subgroup of patients with sensory neuropathy, J Neurol Neurosurg Psychiatry, 86, 1347-55, 2015

Keywords: Inflammatory

Grant Support: German Research Foundation (DFG; MO 3240/1-1:1 and CRC894)
Multicentre Study Investigating the Association of Guillain-Barre Syndrome with Flaviviruses and other Arboviruses in Myanmar

Kyaw Hlaing, Nicholas Yeo, Ohnmar Ohnmar, Jason Kam, Siti Naqiah, Lisa Ng, Thirugnanam Umapathi

1University of Medicine (1)/Yangon General Hospital, Yangon, Myanmar, 2Singapore Immunology Network, Agency for Science, Technology and Research, Singapore, Singapore, Singapore, 3University of Medicine 1/Yangon General Hospital, Yangon, Myanmar., Yangon, Myanmar, 4Singapore Immunology Network, Agency for Science, Technology and Research., Singapore, Singapore, 5 Singapore Immunology Network, Institute of Infection and Global Health, University of Liverpool, UK, Singapore, Singapore, 6National Neuroscience Institute, Department of Neurology, Singapore, Singapore, Singapore

The aim of this study is to understand the relationship between Guillain-Barre Syndrome (GBS) and antecedent Flavi and other arboviruses infections in South and South-East Asia. The study involves hospitals in Singapore, Myanmar, Laos, Vietnam, Thailand, Pakistan, Sri Lanka and India. The methodology involves examining GBS patients, hospital and community controls for evidence of recent Dengue (DENV), Zika (ZIKV) and Chikukunya (CHIKV) infections, using various microbiologic assays that account for confounding cross and co-infections. To date we have recruited a total of 16 patients, 11 Hospital controls and 13 community controls from Yangon, Myanmar. Only 1 patient, MR 15, had a clinical diagnosis of DENV in Yangon. He presented with fever, epistaxis, positive Hess test and leucopenia. On days 3 of fever he developed acute flaccid paralysis and a diagnosis of GBS was made. On day 4, NS1 antigen (for DENV) was positive, but DENV Ig M and Ig G were negative. On day 10 he developed a typical DENV rash. Sera and urine specimens of all cases and controls have been transported to Singapore for the following tests: multiplex real-time RT-PCR, ZCD multiplex and single-plex PCR reconfirmation as well as virion-based ELISA, for ZIKV, DENV serotypes 1-4, and CHIKV. Neutralisation assays will then be performed to exclude cross-reactivity between ZIKV, DENV and CHIKV. Preliminary ELISA serology suggests that 10 out of the 16 GBS patients had one of these infections recently. As expected in an endemic region, there is evidence of previous exposure to various combination of ZIKV, DENV and CHIKV in the remaining cases. The pending PCR tests and neutralization assays will help delineate infections that could antedate, and therefore possibly trigger, GBS.

References: None.

Keywords: Inflammatory

Grant Support: International GBS-CIDP foundation
Poster 171

Patient Demographics and Clinical Features of Typical and Atypical CIDP—A Single-Center Experience from Turkey

Yesim Parman, Ayse Nur Ozdag Acarli, Hacer Durmus Tekce, Nermin Gorkem Sirin Inan, Arman Cakar

Istanbul University, Istanbul Medical Faculty, Istanbul, Turkey

Objective: To present the clinical features of 92 CIDP patients based on a retrospective analysis of a large cohort diagnosed at a reference center.

Methods: Among the 146 patients with immune mediated demyelinating neuropathy treated between March 1993 and January 2019, 92 patients (57 males) who fulfilled the EFNS/PNS diagnostic criteria for definite (n=90) or probable (n=2) CIDP were recruited. Patients were clinically classified into typical and atypical CIDP.

Results: Atypical CIDP group (52%) consisted of MADSAM (30%), DADS (16%), pure sensory (4%), and focal CIDP (1%). Gender, age at presentation, duration of follow-up, disease duration and course, CSF protein level were similar between groups. Childhood-onset disease was more frequent in typical CIDP (34%, p=0.018), and were more likely to have progressive disease course and less favorable disability scores in lower extremities (p=0.027). The overall response rate to the initial treatment was 64%. The response rates among CIDP subgroups were similar (p=0.565). In patients who deteriorated within 2 months, switching to a second immunotherapy increased the overall response rate to 75%. Compared with typical CIDP, the overall response to conventional therapies was similar in patients with MADSAM (p=0.203) but significantly lower in patients with DADS (p=0.023). Furthermore, patients with DADS and MADSAM responded less to steroids compared to typical CIDP (p=0.046, p=0.044 respectively). Although MADSAM patients had higher disability scores and were more likely to have unstable active disease according to CDAS, there was no significant difference in disability scores or disease outcome among subgroups.

Discussion: The frequency of atypical CIDP patients (52%) is high in our cohort compared to previous studies. Atypical cases are usually referred to our clinic which is one of the main centers in country. This probably explains the high number of atypical cases. Atypical CIDP patients tended to have less favorable response to therapy with a higher disability score. Early onset patients and atypical CIDP cases should be more closely followed and early initiation of third line treatment should be considered especially in atypical cases.

References: None.

Keywords: Inflammatory, Clinical Trials

Grant Support: None.
IVlg treatment in chronic inflammatory neuropathies – experience of single neuromuscular centre.

Marta Lipowska, Judyta Barańska, Justyna Kubiszewska, Anna Potulska-Chromik, Anna Kostera-Pruszczyk

Department of Neurology, Medical University of Warsaw, Warsaw, Poland

The aim of the study is characteristic of management protocols of IVlg- treated patients with chronic inflammatory neuropathies in experience of single neuromuscular centre. Since Jun 2015 reimbursement procedures allowed to treat with IVlg MMN as first line and CIDP as a second line regimen (contradiction to GCS or lack of effectiveness of GCS).

Material and methods: retrospective analysis of clinical response and dose regimen of patients diagnosed with MMN or CIDP who received at least one full course of IVlg between Jun 2015 and Feb 2019.

Results: 39 patients with CIDP and 11 with MMN were identified: In CIDP cohort 25 M and 14F, aged 21-89, mean 53 years; in MMN 7M and 4F, aged 34-61, mean 47 years. In CIDP group 17 patients are currently treated with IVlg: 14 at regular intervals (3-12 weeks, mean 5.4; dose 0.6-2g/kg, mean 1.2), and 3 in case of exacerbation of symptoms. 5 patients receive additional immunosuppressive treatment. In 22 subjects IVlg treatment was discontinued: 7 are in remission, one died (death not related to CIDP), one was lost to follow up, one due to side effects of IVlg- aseptic meningitis, 12 (30%) did not respond. In 3 of 7 patients remission was achieved by adding low doses of steroids to IVlg. 8 subjects with lack of response were re-diagnosed, two patients were treated with plasma exchange or GCS, two patients with poor response to IVlg had coexisting diabetic neuropathy.

In MMN cohort one patient was discontinued due to mild symptoms. In 10 patients long term IVlg treatment have been administrated (interval 3-7 weeks, mean 4.3; dose 1-2g/kg, mean 1.2). 3 patients receive additional immunosuppressive treatment.

Conclusion: In CIDP and MMN individualised IVlg regimens are used. 18% of CIDP patients achieved remission, while MMN need chronic treatment.

References: None.

Keywords: Inflammatory

Grant Support: no support
Poster 173

MUNIX: A Potential New Monitoring Tool of Treatment Response in Chronic Inflammatory Demyelinating Polyneuropathy

Andrew Lawley¹, Stefano Seri², Yusuf Rajabally¹

¹Aston University, Queen Elizabeth Hospital, Birmingham, United Kingdom of Great Britain and Northern Ireland, ²Aston University, Birmingham, United Kingdom of Great Britain and Northern Ireland
Background

Traditional outcome measures used to assess treatment response in chronic inflammatory demyelinating polyneuropathy (CIDP) include a mixture of clinical assessments and disability scores. Reports vary regarding usefulness of conventional electrophysiological parameters. A relatively new electrophysiological technique for assessing number of functioning motor units (motor unit number index; MUNIX) has been shown to correlate with muscle strength and disability scores in CIDP and improvements in MUNIX values have been reported in a single study following immunoglobulin therapy. We investigated short-term changes in MUNIX values in patients with CIDP on regular intravenous immunoglobulin (IVIg) therapy.

Methods

26 patients with pre-existing diagnosis of CIDP (15 on regular IVIg therapy) were recruited prospectively as part of an ongoing observational study. All patients had clinical assessment of strength and sensory function, disability scores and electrophysiological studies. MUNIX sumscores were calculated from 3 muscles unilaterally (APB, ADM and TA). 20 healthy controls had MUNIX studies for comparison. Patients receiving IVIg therapy had a baseline study immediately prior to a planned treatment and repeat study 15 days later. 5 patients not on treatment also underwent repeat studies.

Results

MUNIX sumscores were significantly lower in patients than healthy controls at baseline (mean 214.0 (SD 124.4) vs mean 516.9 (SD 91.4), respectively; p<0.001). MUNIX sumscores at baseline significantly correlated with MRC scores, grip dynamometry, INCAT sensory sumscores, R-ODS and ONLS scores. A significant increase from baseline in MUNIX values was seen in IVIg treated patients (mean 188.3 (SD 110.5) baseline vs 226.4 (SD 132.0) post-treatment; p<0.001). No significant change in MUNIX sumscores compared to baseline values was seen in untreated patients or controls.

Conclusion

MUNIX sumscores correlate with assessments of motor and sensory function and disability scores in CIDP. These findings highlight a potential role for MUNIX sumscores in monitoring response to IVIg therapy.


Keywords: Inflammatory

Grant Support: None.
Guillain-Barré syndrome (GBS) is the most common cause of acute paralysis globally. It is estimated to affect 1.3/100000 people/year. GBS is self-limiting, but can be lethal during the acute stage of the disease due to paresis of the respiratory muscles or catastrophic cardiac events from autonomic failure. Mortality of GBS is 3% in the developed world; however in the developing world it often exceeds 10%. This is largely because of inadequate intensive care facilities, the unaffordability of standard immunotherapy, namely plasma exchange (PE) and intravenous immunoglobulin, as well as the lack of specialised equipment and expertise. To circumvent these difficulties colleagues in Sri Lanka, Bangladesh and Myanmar have devised an innovative alternative solution, small volume plasma exchange (SVPE). SVPE is the repeated removal of small volumes of supernatant plasma over several days via sedimentation of the patient’s whole blood that eventually removes a therapeutic amount of plasma. SVPE generally achieves up to 50% of the volume exchanged in standard PE. SVPE is simple and in principle can be applied at basic medical facilities. This technique has been tested in a pilot-study in Bangladesh. Video link: [bmjopen-2018-022862-SP1.mp4]. The Bangladeshi protocol employs a very basic circuit without the need of a centrifuge. Preliminary studies indicate its safety. The SVPE set-up involves manually connecting several bags (containing blood, anti-coagulant solution and replacement fluid) with multiple infusion sets via three way taps. This risks inadvertent contamination and introduction of infections. We are currently working to customize this SVPE circuit into a continuous multichannel kit. Such a ready-made, cost-effective, continuous SVPE-kit, if successfully tested in additional studies, can potentially be used to treat not only GBS but also other neuro-immunological disorders that are currently untreated in under-resourced parts of the world.

References: None.

Keywords: Inflammatory

Grant Support: None.
Clinical spectrum of stiff person syndrome associated with glutamic acid decarboxylase antibodies

Anza Memon, Naganand Naganand

Henry Ford Health System, Detroit, MI, USA

Background: Stiff person syndrome (SPS) is an immune-mediated neurological disorder that can cause rigidity of the axial and limb muscles. About 80% of patient with SPS have had high-titer antibodies against glutamic acid decarboxylase (GAD), and 15% have antibodies to glycine receptors.

Objective: The aim of this study was to examine the clinical characteristics and associated diagnosis of the SPS.

Methods: Retrospective chart review of patients with SPS and positive GAD antibody who were seen over 5 years was performed. Demographics, detailed clinical information, and diagnostic data were recorded. Coexisting autoimmune diseases and serologies were reviewed.

Results: Nine patients were included in this study, 7 women and 2 men. The median age at symptom onset was 47 years. Six patients had positive Gad antibody and 3 were negative. Primary diagnosis was stiff person syndrome (n=4), cerebellar ataxia (n=2), PERM (n=2) and sensory neuropathy/neuronopathy (n=1). Commonly associated antibodies were islet cell antibody and neuronal voltage-gated potassium channel. Type 1 diabetes, seizures, and thyroid disease were commonly associated with the diagnosis. Three patients had an EMG finding suggestive of SPS and two of these patients had negative GAD antibody.

Conclusion: Women are commonly affected by the disease. There is a phenotypic variation of the disease as previously reported in the literature. EMG is helpful in the diagnosis of negative GAD antibody patients where clinical suspicion for SPS is high.

References: None.

Keywords: Inflammatory

Grant Support: None.
Poster 176

Peripheral neuropathy associated with neuroglial antibodies: clinical, electrodiagnostic and histopathological characteristics

Pritikanta Paul, Christopher Klein, Sean Pittcock, Andrew McKeon, Rocío Vazquez Do Campo, Elia Sechi, Eoin Flanagan, Michel Toledano, John Mills, Divyanshu Dubey

Mayo Clinic, Rochester, MN, USA

Introduction: Descriptions of aquaporin-4 (AQP4), glial fibrillary acid protein (GFAPα) and myelin oligodendrocyte glycoprotein (MOG) antibody associated neuropathies are limited. Furthermore, phenotypic and histopathological details are lacking.

Methods: We included patients from our institution's EMR and Neuroimmunology Laboratory database using the following criteria: 1) signs/symptoms of neuropathy, 2) electrodiagnostic/radiological evidence of peripheral nerve involvement 3) AQP4/GFAPα/MOG seropositivity 4) reasonable exclusion of alternative etiology. Clinical outcome was measured by change in Modified Rankin Score.

Results: Nineteen patients [42% females, age12-78 years (median 63)] seropositive for AQP4-IgG (n=9) or MOG-IgG (n=5) or GFAPα-IgG (n=5) with neuropathies were identified. Twelve patients (63%; AQP4, 4; MOG, 4; GFAPα, 4) had neuropathies as the initial presentation. Polyradiculoneuropathy/polyradiculopathy were the most common phenotypic presentations (n=16, 84%). Other phenotypes included bilateral sciatic neuropathies (n=1) and subacute length-dependent neuropathy (n=2). Neuropathic pain was common (74%). The majority of cases had co-existing myelopathy (68%). Four patients (GFAPα-IgG, 2; MOG-IgG, 1; AQP4-IgG, 1) had demyelinating features (slow conduction velocity [n=2], prolonged/absent F-waves [n=1], conduction block [n=1]) on nerve conduction studies. CSF studies showed inflammatory changes in 87% (13/15) of cases. Four patients (GFAPα-IgG, 2; AQP4-IgG, 1; MOG-IgG, 1) had nerve biopsies. AQP4-IgG case had evidence of increased axonal degeneration and small to moderate sized epineurial and endoneurial perivascular inflammatory collections. GFAPα-IgG and MOG-IgG cases demonstrated increased rate of demyelination and axonal degeneration, along with individual to small collections of inflammatory cells. Seventeen patients received immunotherapy. Clinical outcomes varied based on antibody specificities; 60% of MOG-IgG and GFAPα-IgG cases had favorable outcome at last follow-up, compared to 44% of AQP4-IgG cases.

Conclusion: Peripheral neuropathy with or without CNS involvement is a rare but severe manifestation of neuroglial antibodies. Neuropathies in these patients can contribute to substantial morbidity. Recognizing the inflammatory polyradiculoneuropathy/polyradiculopathy phenotype may help in early diagnosis and treatment.

References: None.

Keywords: Inflammatory, Pain

Grant Support: None.
Subcutaneous immunoglobulin administration via manual push technique in chronic inflammatory demyelinating polyradiculoneuropathy patients

Erdita Peci1, Carlotta Canavese2, Federico Cossa1, Yolanda Falcone1, Simona Rigaldo3, Dario Cocito1

1Istituti Clinici Scientifici Maugeri, Torino, Italy, 2A.O.U.Città della Salute e della Scienza di Torino - Dipartimento Pediatria e Specialità Pediatriche, Torino, Italy, 3A.O.U. Città della Salute e della Scienza di Torino - Dipartimento di Neuroscienze, Torino, Italy

Subcutaneous immunoglobulin (SCIg) represents an effective alternative to intravenous immunoglobulin (IVIg) for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Recently, SCIg administration via manual push technique (MPT) was presented as an option in a large cohort of PID patients requiring Ig replacement therapy. The aim of this study is to evaluate feasibility and (both clinical and laboratory) efficacy of a novel regimen of immunoglobulin administration, based on the delivery of lower volumes of SCIg administered daily using MPT in CIDP patients.

8 patients were randomly assigned 1:1 to receive SCIg either by MPT or pumps for 4 consecutive months at the same dose with crossover to the other. Clinical and laboratory efficacy parameters: IgG level, inflammatory neuropathy cause and treatment score (INCAT), medical research council scale (MRC), Martin vigorimeter handgrip strength test and the Rasch-built overall disability scale (RODS) were assessed monthly; while life quality index (LQI) was evaluated at the end of each treatment period.

The average plasma levels of IgG during the infusion period with pumps ranged from 1569.38±352.95 mg/dL (range 915-1866) to 1490.25±315.56 mg/dL (range 775-1743) while during MPT period ranged from 1556.63±337.8 mg/dL (range 775-1855) to 1554.13±340.64 mg/dL (range 1074-1866). Even if there is no significant difference between the two periods (p:0.70), there is an increase in IgG level at the end of the MPT period compared with the pump administration (from 1490.25±315.56 to 1554.13±340.64 mg/dL). LQI sub-scale I significantly improved (p:0.05), while no significant changes were observed in INCAT (p:0.99), MRC (p:0.78), grip strength test (p:0.62), RODS (p:0.96).

Our study reports a fluctuation of IgG after the MPT with a gradual increase of plasma levels probably due to the fact that serum IgG has a concentration-dependent catabolism. In conclusion our findings suggest that SCIg-MPT seems to have similar clinical efficacy and tolerability as SCIg weekly infusions administration.

References: None.

Keywords: Inflammatory, Clinical Trials, Other

Grant Support: None.
Characteristics and management of peripheral nervous system adverse events induced by anti-PD-1 or anti-PD-L1 immunotherapy

Léo Plaçais¹, Jean-Marie Michot², Adeline Not³, Céline Labeyrie³, Guillemette Beaudonnet³, Bénédicte Sensenbrenner³, David Adams³, Olivier Lambotte³, Cécile Cauquil⁴

¹Kremlin Bicêtre hospital, Neurology department, Le Kremlin Bicêtre, France, ²Gustave Roussy Institute, Villejuif, France, ³Kremlin Bicêtre University Hospital, Le Kremlin Bicêtre, France, ⁴Kremlin Bicêtre university hospital, Le Kremlin-Bicêtre, France

• Introduction: Anti-programmed cell death 1 (PD-1) and anti-programmed cell death ligand 1 (PD-L1) antibodies are novel immunotherapies for cancer that can induce neurologic immune-related adverse events (n-irAEs). N-irAEs occurrence often leads to immunotherapy withdrawal, and guidelines are needed. In this retrospective monocentric study, we describe n-irAEs patients with emphasis on clinical features, morbidity, mortality and treatment strategy.

• Material and methods: Patients registered in a national referral database of suspected irAEs from 10/1/2014 to 1/1/2019 were included. N-irAEs probability was assessed using the Uppsala monitoring center causality scale. All cases were thoroughly investigated by oncologists and neurologists using an extensive diagnostic workup.

• Results: Twenty-five patients treated with anti-PD-1/PD-L1 antibodies and presenting with peripheral nervous system (PNS) symptoms (CTCAE grade I to V) were included. Eleven n-irAEs were scored grade II CTCAE, 11 grade III and 3 grade IV. Eleven patients (44%) presented with inflammatory demyelinating polyneuropathy (IDP), seven (28%) had both central and PNS involvement, four (16%) had radiculopathy, 4 (16%) had cranial nerve alterations, 4 (16%) had neuromuscular junction (NMJ) disorders, including 3 with myasthenia gravis (MG) and 1 with Lambert-Eaton myasthenic syndrome (LEMS), and 2 (8%) had length-dependent axonal polyneuropathy. Mean time of onset was 94 days after treatment was started. Three patients with IDP presented with anti-gangliosides antibodies in serum. Treatment was withdrawn in 23/25 cases, and reintroduced in 2/23 cases. Twenty patients were treated with corticosteroids, five with intravenous immunoglobulins, and 1 with TNF-alpha inhibitors. One patient died from LEMS.

• Conclusion: PNS n-irAEs range from moderate to severe disorders involving roots, peripheral nerves, cranial nerves and NMJ. In our series of 25 patients, IDP represented 44% of n-irAEs cases, and only one patient died as a result of n-irAEs. In selected cases, n-irAEs may be managed without withdrawing immunotherapy.

References: None.

Keywords: Inflammatory, Clinical Trials

Grant Support: None.
Poster 179

Spontaneous Secretion Of Anti-GM1 Antibodies By Peripheral Blood Plasmablasts In A Patient With Guillain-Barré Syndrome

Ruth Huizinga, Wouter van Rijs, Anne Tio-Gillen, Willem Jan Fokkink, Bart Jacobs

Erasmus MC, Rotterdam, Netherlands

Introduction

Antibodies to gangliosides play an important role in the pathogenesis of the Guillain-Barré syndrome (GBS). These antibodies and their effects have been characterized extensively, but relatively little is known about the cells that produce these antibodies. Recently, we observed that plasmablasts are increased in the peripheral blood of approximately one-third of the GBS patients at the time of hospital admission. In some patients the number of plasmablasts further increases in response to treatment with intravenous immunoglobulins. Our hypothesis is that these plasmablasts are also the producers of the anti-ganglioside antibodies in GBS. Here we aimed to investigate whether the plasmablasts are functional and able to secrete anti-ganglioside antibodies in vitro.

Methods

Naive B cells, memory B cells and plasmablasts were sorted from peripheral blood mononuclear cells (PBMC) using flow cytometry. PBMC were obtained from four GBS patients with elevated numbers of plasmablasts. Cells were cultured in vitro with cytokines. IgM and IgG levels in supernatants were measured by ELISA specific for human immunoglobulins. Anti-ganglioside antibodies in sera and supernatants were measured by ELISA.

Results

The frequency of plasmablasts in patients with GBS was 15.5 ± 5.3% of the total CD19-positive B cells. Plasmablasts spontaneously produced IgM (65 ± 30 ng/ml) and IgG (371 ± 289 ng/ml) in vitro. This was significantly higher as compared to naive B cells and memory B cells (p<0.05). Two patients were positive for anti-GM1 antibodies in the serum. Of these, one clearly demonstrated anti-GM1 antibody production by plasmablasts in vitro. In contrast to serum anti-GM1 antibodies, which were IgM and IgG, the in vitro produced anti-GM1 antibodies were only IgG.

Conclusion

Our data indicate that ganglioside-reactive plasmablasts can be present in the peripheral blood of patients with GBS, suggesting ongoing B-cell activation in a subset of patients.

References: None.

Keywords: Inflammatory

Grant Support: Prinses Beatrix Spierfonds
Assessment of paranodal region in skin of Chronic Inflammatory Demyelinating Polyradiculoneuropathy patients

Raffaella Lombardi¹, Matilde Paolini¹, Daniele Cartelli², Mirna Andelic³, Diego Franciotta³, Andrea Cortese⁴, Jerome Devaux⁵, Giuseppe Lauria Pinter⁶

¹IRCCS “C.Besta” Neurological Institute Foundation, Milan, Italy, ²IRCCS “C.Besta” Neurological Institute Foundation, Milan, Italy, ³IRCCS C. Mondino National Neurological Institute, Pavia, Italy, ⁴IRCCS C. Mondino National Neurological Institute, Milan, Italy, ⁵Aix-Marseille University, Marseille, France, ⁶IRCCS “C.Besta” Neurological Institute Foundation, “Luigi Sacco” University of Milan, Milan, Italy

Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) is a heterogeneous disease that critically lacks of diagnostic and prognostic biomarkers. The identification of anti-neurofascin 155 (Nfasc155), anti-contactin 1 (CNTN1) and contactin-associated protein 1 (Caspr1) antibodies in a subset of patients has widened the spectrum of CIDP phenotypes. Nfasc155/CNTN1/Caspr1 complex is expressed on the paranodal region, and play key roles on sodium channel clustering and glia-axon interactions. Besides the quantification of unmyelinated intraepidermal nerve fibers (IENF), skin biopsy allows the immunohistochemistry evaluation of dermal nerve fibers to investigate morphological changes of myelin sheath and node of Ranvier structure. Of the 31 CIDP patients who underwent skin biopsy at the lower limb, 7 had antibodies against one of the component of the Nfasc155/CNTN1/Caspr1 complex. Of all seropositive patients, 3 had IgG4 antibodies against Nfasc155, two had IgG1-3 antibodies against Nfasc155, one had antibodies against CNTN1, and one had IgG4 antibodies against Caspr1. Skin tissues from seronegative and seropositive CIDP patients was assayed using a panel of antibodies including anti-Protein-Gene-Product (anti-PGP) 9.5 to visualize axons; anti-Myelin-Basic-Protein (anti-MBP) to identify the sheath of myelin; anti-panNeurofascin (anti-panNfasc), anti-Nfasc155, anti-Nfasc186, anti-Caspr1, anti-CNTN1, anti-Nav and anti-Kv channels to identify nodal/paranodal/juxtaparanodal structures. CIDP patients showed a significantly lower IENFD at distal leg (DL) and proximal thigh (PTh) compared to normative values. All the parameters used to assess the paranodal symmetry significantly differed between CIDP and healthy subjects. The mean fluorescence intensity to Caspr1 protein appeared significantly lower in CIDP patients. Dermal myelinated fibers showed significant elongation of the paranodal regions and increase of the area in CIDP patients compared to healthy subjects. Myelinated nerve fibers in Nfasc155-positive CIDP patients showed lack of staining in the paranodal site where Nfasc155 is expressed. Findings could provide evidence in support of a pathology driven stratification of CIDP patients to be correlated with personalized treatment.

References: None.

Keywords: Node, Inflammatory

Grant Support: GBS/CIDP Foundation Non-profit Grant 2017 Grant code: 501(c)(3)
MULTIFOCAL MOTOR NEUROPATHY (MMN) IN A 33 YEAR OLD female

Elene Nebadze, Giorgi Giorgidze, Nana Kvirkvelia

Petre Sarajishvili Institute of Neurology, Tbilisi, Georgia

Body: A 33-year-old female presented to hospital with a 2-years history of bilateral leg weakness that began after flu, progressed, accompanied by cramping. Physical examination revealed poor strength in the musculus tibialis anterior and bilateral feet drop, absent Achilles and knee reflexes. Nerve conduction studies showed motor polyneuropathy with conduction blocks (CB) in multiple motor nerves of the lower extremities. CB also revealed in motor fibers of nervus ulnaris dextra. Conduction velocity was normal in sensory fibers of upper and lower extremities. Lab. values including ESR, ANA, ANCA, CRP were all negative. Anti-GM1 IgM ratio was 1:1800, confirming diagnosis of MMN. Patient received 5 doses of IVIG, along with physical therapy, and responded well with improvement in motor function.

Conclusion: MMN is a rare, treatable, immune-mediated neuropathy, often associated with CB with slowly progressive weakness, fasciculations, and muscle cramping without loss of sensation.

The pathologic mechanism is secondary to autoantibodies against the GM-1 ganglioside within the Ranvier nodes, causing nerve conduction block. The disease could be detected according to clinical criteria, EMG studies and these antibodies in the blood. IVIG is the first choice of treatment with the hope of suppressing the over activity of the immune system, but other pharmacological therapies are available. Response to IVIG may occur quiet rapidly, but the dose and frequency may need to be individualized depending on the length and benefits.

We presented a 33 years old female with MMN. Diagnosis was based on EMG tests, clinical features, lab. values and positive treatments with immunoglobulins. MMN typically begins in elderly people; most patients are affected between the ages of 40-60 years and preferably in men.

It is important to consider MMN as the differential diagnosis of demyelinating disorders as MMN causes significant disability but does not shorten life, and the prognosis is generally good.

References: None.

Keywords: Other

Grant Support: None.
Poster 182

Intravenous Immunoglobulin (IVIG) Therapy in Idiopathic lumbosacral plexopathy: Report of two cases

Demet Ilhan Algin, Demet Ilhan Algin, Oguz Osman Erdinc

Eskisehir Osmangazi University, Medical Faculty, Eskisehir, Turkey

Introduction

Idiopathic lumbosacral plexopathy (ILSP), also called lumbosacral plexitis or non-diabetic lumbosacral (radiculo)plexus neuropathy is a rare clinical entity. Some studies suggest that the condition has an immune-mediated etiology. We report documented case of ILSP, which to dramatic response to intravenous immunoglobulins (IVIG) treatment.

Methods:

**Case 1:** A 36-year-old woman presented to the medical admissions unit with progressive weakness of her right limb, pain, and areflexia. Complete blood count, erythrocyte sedimentation rate (ESR), chemistries, hemoglobin A1c, fasting blood sugar, a 2-hour glucose tolerance and autoimmune screen were normal. Magnetic resonance imaging (MRI) of the lumbosacral plexus revealed gadolinium enhancement of mainly L5 on the right. The patient was started on intravenous immunoglobulins IVIG for 5 days repeated at monthly intervals. A dramatic response to IVIG within three months.

**Case 2:** A 56 year old woman started feeling sensation, pain, weakness, and numbness in her lower limb. On subsequent days the weakness was more progressed in lower extremities. In the examination performed, the left knee extension was found to be 4/5. Hypoesthesia was detected in left L4, L5 and S1 dermatomes. Left patellar reflex could not be taken when the patient was atrophic on the left thigh. Electromyography (EMG) findings were evaluated as compatible with dominant motor axonal degeneration in the upper part of lumbosacral plexus. Our patient responded to IVIG within two months which in view of her clinical findings.

Conclusions:

ILSP is characterized by an abrupt onset of sensory disturbances, weakness, and loss of deep tendon reflexes of lower extremities. The diagnosis requires clinical and electrophysiological demonstration of lesions affecting multiple nerves and root levels in the absence of other causes of lumbosacral plexopathy e.g. trauma, radiation, diabetes or mass lesions. Small series have reported response to intravenous immunoglobulin and steroids in high doses either alone or in combination.

References: None.

Keywords: Inflammatory

Grant Support: None.
Characteristics of Late-Onset Val30Met Transthyretin Amyloidosis with Polyneuropathy from the Transthyretin Amyloidosis Outcomes Survey

Marcia Waddington-Cruz1, Jonas Wixner2, Rajiv Mundayat3, Leslie Amass4, Yukio Ando5

1Federal University of Rio de Janeiro, National Amyloidosis Referral Center, CEPARM, Rio de Janeiro, Brazil, 2Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden, 3Pfizer Inc, New York, NY, USA, 4Pfizer Inc, Collegeville, PA, USA, 5Department of Neurology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan

Introduction: Transthyretin amyloidosis with polyneuropathy (ATTR-PN) is a clinically heterogeneous disease caused by mutations in the transthyretin (TTR) gene. The most common mutation is Val30Met which manifests as an early-onset or late-onset disease.

Methods: The Transthyretin Amyloidosis Outcome Survey (THAOS) is an ongoing, global, longitudinal, observational survey of patients with ATTR amyloidosis, including both inherited and wild-type disease, and asymptomatic patients with TTR mutations. This descriptive analysis compared symptomatic Val30Met ATTR-PN patients with late-onset (age ≥50 years) versus early-onset (age <50 years) disease in THAOS (data cut-off: January 16, 2019).

Results: Of 1327 Val30Met ATTR-PN patients in THAOS, 451 (34.0%) had late-onset disease. Regional differences were observed with late-onset more likely than early-onset patients to be from Sweden (28.8% of all late-onset versus 5.3% of all early-onset), Japan (8.9% versus 6.1%), or Spain (9.3% versus 6.5%) and not from Portugal (26.4% versus 62.1%) or Brazil (8.0% versus 10.4%). Late-onset patients: were more likely to be male (65.2% late-onset versus 53.4% early-onset); had an higher mean (SD) age at disease onset (62.6 [7.5] versus 33.3 [7.1] years); and had a longer time from onset to diagnosis (3.8 [3.5] versus 2.6 [4.0] years), potentially associated with more severe neurological impairment at enrollment (mean [SD] derived neuropathy impairment score in the lower limbs, 31.1 [24.3] versus 19.2 [21.9]; neurologic composite score, 58.7 [55.6] versus 38.1 [45.9]). Cardiac manifestations were more prominent in late-onset patients (versus early-onset), with 72.1% (versus 44.3% early-onset) having an overall interpretation of ECG as abnormal and 69.1% (versus 13.5%) having left-ventricular septum thickness of ≥12mm.

Conclusions: In THAOS, late-onset Val30Met ATTR-PN is relatively common, presenting with more severe neurologic and cardiac disease manifestations at enrollment but, due to heterogeneity of disease, may be more difficult to diagnose. Increased recognition of late-onset ATTR-PN could improve earlier diagnosis and patient outcomes.

References: None.

Keywords: Amyloidosis

Grant Support: THAOS and this analysis were sponsored by Pfizer. Rajiv Mundayat and Leslie Amass are full-time employees of Pfizer and hold stock and/or stock options with Pfizer. Medical writing support was provided by Joshua Fink, PhD, of Engage Scientific Solutions and was funded by Pfizer.
SCN9A Channelopathy Of Extremes: From Hyperexcitability, Hyperalgesia and Hypertension To Hypoplastic Limbs, Hyponatremia And Hypomineralization.

Isis Joosten1, Maurice Sopacua1, Monique Gerrits2, Stephen Waxman3, Ingemar Merkies4, Catharina Faber1, Janneke Hoeijmakers1

1Department of Neurology, School of Mental Health and Neuroscience, Maastricht University Medical Center+, Maastricht, Netherlands, 2Department of Clinical Genetics, Maastricht University Medical Center+, Maastricht, Netherlands, 3Department of Neurology and Center for Neuroscience and Regeneration Research, Yale University School of Medicine, New Haven, CT, USA, 4St. Elisabeth Hospital, Willemstad, Curacao

A 35-year-old man, with a history of hypertension since adolescence, presented with clinical features of erythromelalgia and small fiber neuropathy. In addition, he showed small stature with disproportionately small hands, feet and lower limbs. His father and brother had a similar, but less severe phenotype. All three were found to harbor a gain-of-function mutation in SCN9A (G856D; c.2567G>A). Functional analysis showed the mutation hyperpolarizes (-9.3 mV) channel activation, depolarizes (+6.2 mV) fast-inactivation, slows deactivation and produces a remarkable 10-11X enhancement of persistent and ramp current. During follow-up the patient developed an episode of confusion and myoclonic jerks as a result of a syndrome of inappropriate antidiuretic hormone secretion (SIADH). An X-ray showed an osteoporotic vertebral fracture. Subsequently, the patient's father was admitted to the hospital with SIADH. The family has expanded to include daughters with abnormal stature, and symptoms of erythromelalgia and small fiber neuropathy. One daughter has already been treated for hypertension beginning at age of six. Additional whole exome sequencing in the index patient did not reveal any other genetic causes for this remarkable phenotype. The finding of this mutation has extended the spectrum of SCN9A related human pain syndromes.

References: None.

Keywords: Small Fibers, Pain, Human Genetics

Grant Support: None.
A Comparative Study of Human Hairy and Glabrous Skins

Baohan Pan, Xin Pan, Mohamed Khoshnoodi, Joao Pan, Kelly Wagner, Michael Polydefkis

Johns Hopkins School of Medicine, Baltimore, MD, USA

Most human peripheral neuropathy and neuropathic pain studies using skin biopsy focus on hairy skin while experimental rodents and non-human primate models concentrate on glabrous skin. Differences in innervation patterns and distribution of nerve fiber subgroups between hairy and glabrous skin are poorly characterized. In the current study, we compared unmyelinated and myelinated nerve fiber innervation in human glabrous and hairy skin in normal healthy control subjects.

Three mm distal leg skin biopsies (hairy skin) and plantar foot biopsies (glabrous skin) were obtained from healthy control subjects (n=15). Immunohistochemistry for pan-neuronal marker (PGP 9.5), neurofilament H (NFH), peptidic sensory nerve marker (CGRP) was performed. Quantification of intraepidermal nerve fiber density (IENFD) and subepidermal nerve fiber density (SENFD) were carried out using conventional counting method and unbiased stereology protocol with CE<0.1, respectively. Double immunohistochemistry of PGP9.5 with NFH or CGRP was carried out to examine co-localization of markers.

We observed prominent differences between plantar and glabrous dermal and epidermal innervation. Glabrous skin had significantly lower (p<0.0001) PGP 9.5 IENFD than distal leg hairy skin while NFH+ innervation was significantly higher in plantar glabrous skin than hairy skin (p<0.0001). Similarly, CGRP+ dermal nerve fiber density was significantly higher than distal leg hairy skin (p<0.05). There are prominent differences between hairy and glabrous epidermal innervation. This may account for some of the disconnect between preclinical models and human neuropathic pain studies.

References: None.

Keywords: Small Fibers, Axonal Biology, Pain, Other

Grant Support: Blaustein Pain Foundation
Diagnostic Performance of Sudoscan in Young Patients Evaluated For Small-Fiber Neuropathy and Healthy Controls

Max Klein, Heather Downs, Ian Farquhar, William David, Anne Louise Oaklander

Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Introduction: Sudoscan is a rapid non-invasive screening device cleared by US FDA to aid in assessing sudomotor function (sweating) in the hands and feet, which often decrements in small-fiber polyneuropathy (SFN). It measures electrochemical skin conductance (ESC) of the hands and feet. It has reported utility in identifying diabetic neuropathy in adults,1 but there is only one study of normal children,2 and none of youngsters with neuropathy.3 We tested the hypothesis that Sudoscan can effectively screen for SFN in children and teenagers, where noninvasive testing is particularly desirable.

Methods: With consent and/or assent of all volunteers and/or parents to an IRB-approved protocol, we have thus far studied with Sudoscan 39 patients aged 4-19 years being evaluated by neurologists for SFN. 120 community-recruited screened healthy children aged 2-20 years provided controls. Outcomes were based on manufacturer’s interpretation of ESC. Among the patients, 30 had SFN confirmed by lower-leg PGP9.5 immunolabeled skin biopsies (epidermal neurite densities ≤5th centile of predicted) and/or autonomic function testing (AFT) interpreted as SFN by consensus criteria. 115 healthy controls had interpretable Sudoscan results.

Results: Among all 39 SFN-evaluated patients, none were interpreted by Sudoscan as “elevated risk” of peripheral neuropathy. 5 (13%) measured as “moderate risk”, among whom 2 had objective confirmation. Among the 30 with confirmed SFN, 28 had normal ESC and 2 were measured as “moderate risk”. Among 115 healthy controls, 15 (13%) were measured as “moderate risk”; the rest had normal results. Mean ESCs in patients were very close to those in healthy controls: hand ESC averaged 76.5µSi vs. 75.5µSi; p=0.65, and feet ESC 85.5µSi vs. 83.2µSi; p=0.16.

Conclusions: Sudoscan did not differentiate children and teenagers with neuropathy from demographically matched healthy controls. Sudoscan thus should not yet be used with current interpretive scales to screen for SFN in youngsters under age 21.


Keywords: Small Fibers

Grant Support: Supported in part by the National Institutes of Health (R01NS093653). Impeto Medical loaned a Sudoscan device for the early parts of this study.
Dynamic Sweat Test (DST) in Small Fiber Neuropathies

Maria Nolano¹, Vincenzo Provitera², Giuseppe Caporaso², Annamaria Stancanelli², Ilaria Borreca², Stefania Mozzillo², Giuseppe Piscosquito², Bernardo Lanzillo², Fiore Manganelli³, Lucio Santoro³

¹Istituti Clinici Scientifici “Maugeri” SPA SB, IRCCS of Telese Terme 2 University “Federico II” of Naples, Italy, Telese Terme (BN), Italy, ²Istituti Clinici Scientifici “Maugeri” SPA SB, IRCCS of Telese Terme, Telese Terme (BN), Italy, ³University “Federico II” of Naples, Italy, Naples, Italy

A sweating impairment has been described in painful small fiber neuropathies (SFN). Quantitative sudomotor axon reflex test (QSART) has been described as abnormal in 74% of SFN patients. Among functional testing, the sudomotor assessment may be an objective and sensitive tool to detect a small fiber pathology. Quantitative sensory testing (QST) abnormalities, associated to SFN symptoms contribute to reach a definite diagnosis of SFN. However, QST is not objective because implies patient collaboration. DST compared to QSART, provide a dynamic assessment of the sweating output, the number of activated sweat glands and the volume of produced sweat. We tested the hypothesis that autonomic sudomotor dysfunction may occur early in the course of SFN and can be revealed before the occurrence of intraepidermal nerve fibers (IENF) degeneration.

We recruited 138 patients (94 male, mean age 51±15 years) with symptoms and signs of SFN and normal NCV study. We assessed IENF density from distal leg and quantified sweating output with the DST on 2 body sites (leg and forearm), after stimulation with 1% pilocarpine by iontophoresis.

We found a sweating impairment in 77% of patients at the forearm and in 86% at the leg, while only 51% of patients showed an IENF density below the 5th percentile cut-off. Eighteen patients with normal IENF density and abnormal sudomotor function repeated skin biopsy over time, showing a reduced IENF density and therefore reaching a definite SFN diagnosis.

DST appears to be an objective and easy-to-perform test to assess autonomic function in SFN. In our population, it showed to be more sensitive than skin biopsy. The assessment of sudomotor function using a test as sensitive as DST may be able to detect a SFN even before the IENF loss. The DST should be considered to diagnose and to monitor SFN over time during disease-modifying treatment.

References: None.

Keywords: Small Fibers, Pain

Grant Support: None
Mutations in Cell Adhesion Molecules Belonging to the CADM Family Cause Charcot-Marie-Tooth Disease

Adriana Rebelo¹, Andrea Cortese², Lisa Abreu³, Steve Courel³, Eilior Peles⁴, Chelsea Bacon⁵, Shawna Feely⁵, Diane Castro⁶, Michael Shy⁵, Mary Reilly⁷, Stephan Zuchner³

¹Dr. John T. Macdonald Foundation Department of Human Genetics, University of Miami Miller School of Medicine, Miami, FL, USA, ²UCL Institute of Neurology Centre for Neuromuscular Diseases, UCL Institute of Neurology, London, United Kingdom of Great Britain and Northern Ireland, ³Dr. John T. Macdonald Foundation Department of Human Genetics, University of Miami Miller School of Medicine, Miami, USA, ⁴Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot, Israel, ⁵Department of Neurology, Carver College of Medicine, University of Iowa, Iowa, USA, ⁶Departments of Pediatrics, Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center, Dallas, USA, ⁷MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, London, United Kingdom of Great Britain and Northern Ireland

CADM family of proteins consists of four neuronal specific adhesion molecules (CADM1, CADM2, CADM3 and CADM4) that mediate the contact interaction between axons and glia. In the peripheral nerve, axonal-Schwann cell interaction is essential for the structural organization of myelinated fibers and it is primarily mediated by the binding of CADM3, expressed in axons, to CADM4, expressed by myelinating Schwann cells. We have identified by whole exome sequencing three families with axonal Charcot-Marie-tooth disease (CMT2) sharing the same private variant in CADM3 and one autosomal dominant CMT2 family with a private variant in CADM4. Although all families have CMT2, CADM3 and CADM4 families developed distinct subclinical features. The CADM3 families share the same peculiar phenotype consisting of axonal motor neuropathy affecting mainly the upper limbs with pyramidal features. In contrast, the CADM4 family developed a more typical length dependent CMT. The variant identified in CADM3, Y138C, was found to be de novo in two families, while in the third family the variant shows dominant segregation. High resolution mass spectrometry analysis coupled with nanoflow UPLC detected disulfide bonds modifications in the mutant CADM3 potentially modifying the native protein conformation. In addition, we observed a significant increased protein retention of the mutant in the endoplasmic reticulum leading to activation of the unfolded protein response (UPR). Interestingly, ablation of CADM4, but not CADM3, in mouse results in myelination abnormalities and impaired motor function. We are currently studying a CADM3 knockin (KI) mouse carrying the same variant observed in our patients to better mimic the human phenotype and its pathological mechanism. Preliminary results indicate increased muscle weakness in the CADM3-KI mouse compared to the wild-type. Our findings indicate a novel molecular pathway involving axon-glial interaction abnormalities in patients with CMT.

References: None.

Keywords: CMTR, Axonal Biology, Human Genetics, Schwann Cell

Grant Support: None.
<table>
<thead>
<tr>
<th></th>
<th>Title</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Novel NDRG1 mutations causing CMT4D with milder phenotype</td>
<td>Shawna Feely</td>
</tr>
<tr>
<td>2</td>
<td>Novel biomarkers and therapeutic approaches in Charcot-Marie-Tooth Disease (CMT)</td>
<td>Michael Sereda</td>
</tr>
<tr>
<td>3</td>
<td>Patisiran, a silencing RNA in Hereditary Transthyretin Amyloid polyneuropathy: First experience in real life</td>
<td>Thierry Gendre</td>
</tr>
<tr>
<td>4</td>
<td>Broadening The Spectrum Of Biallelic ADPRHL2 Mutations Into Complex Early-Onset Motor Neuropathy Phenotypes</td>
<td>Danique Beijer</td>
</tr>
<tr>
<td>5</td>
<td>IFB-088 treatment improves Charcot-Marie-Tooth type 1A disease phenotype of C3-PMP22 mice</td>
<td>Maurizio D'Antonio</td>
</tr>
<tr>
<td>6</td>
<td>Deep-learning based morphological profiling for rapid variant annotation in inherited neuropathies.</td>
<td>Wolfgang Pernice</td>
</tr>
<tr>
<td>7</td>
<td>Treatment of Arg98Cys MPZ Mice In Vitro and In Vivo with IFB088</td>
<td>Michael Shy</td>
</tr>
<tr>
<td>8</td>
<td>Long-term Safety and Efficacy of Patisiran in Patients with hATTR Amyloidosis: Global OLE Study</td>
<td>Michael Polydefkis</td>
</tr>
<tr>
<td>9</td>
<td>Plasma NIL concentration is increased in patients with ATTRm and correlates with clinical severity scores</td>
<td>Mahima Kapoor</td>
</tr>
<tr>
<td>10</td>
<td>Identification of TMPRSS5/Spinesin, a Novel Schwann Cell Derived Plasma Biomarker for CMT1A</td>
<td>Matthew Davison</td>
</tr>
<tr>
<td>11</td>
<td>Wildtype and Familial Transthyretin Amyloid Polyneuropathy: Distinct Cutaneous Biomarkers at the Distal Limb</td>
<td>Gigi Ebenezer</td>
</tr>
<tr>
<td>12</td>
<td>Preclinical Gene Therapy Studies for FIG4/CMT4J and GARS/CMT2D.</td>
<td>Robert Burgess</td>
</tr>
<tr>
<td>13</td>
<td>Nusinersen in Adults with Spinal Muscular Atrophy, A Single Center Experience</td>
<td>Orly Moshe-Lilie</td>
</tr>
<tr>
<td>14</td>
<td>Influence of Body Mass Index on disability in Children with CMT</td>
<td>Gabrielle Donlevy</td>
</tr>
<tr>
<td>15</td>
<td>GENE REPLACEMENT THERAPY FOR CMT1X NEUROPATHY</td>
<td>Alexia Kagiava</td>
</tr>
<tr>
<td>16</td>
<td>Gene Therapy For Peripheral Neuropathy CMT1A</td>
<td>Benoit Gautier</td>
</tr>
<tr>
<td>17</td>
<td>Efficacy and safety of PXT3003 in patients with CMT1A: International Pivotal Phase III trial.</td>
<td>Attarian Shahram</td>
</tr>
<tr>
<td>18</td>
<td>IVlg Treatment-Related Fluctuations in CIDP Patients Using Daily Grip Strength Measurements (GRIPPER): Study Update</td>
<td>Jeffrey Alllen</td>
</tr>
<tr>
<td>19</td>
<td>Immediate Effects of AFOs on Balance in Individuals With Inherited Neuropathies in the Clinical Setting</td>
<td>Reza Sadjadi</td>
</tr>
<tr>
<td>20</td>
<td>HémiCharcot-Marie-Tooth disease: an atypical and rare presentation</td>
<td>Marion Masingue</td>
</tr>
<tr>
<td>21</td>
<td>An unusual Recessive CMT2</td>
<td>Riccardo Zuccarino</td>
</tr>
<tr>
<td>22</td>
<td>Differentially expressed genes within peripheral nerve of a dog model of late-onset peripheral neuropathy</td>
<td>Susannah Sample</td>
</tr>
<tr>
<td>23</td>
<td>Role of Slit2 in peripheral nerve development and regeneration</td>
<td>Emanuela Porrello</td>
</tr>
<tr>
<td>24</td>
<td>A Novel Case of Demyelinating Neuropathy in Mitochondrial Trifunctional Protein Deficiency</td>
<td>Carla Zingariello</td>
</tr>
<tr>
<td>25</td>
<td>Nerve cross sectional area correlates to clinical severity in patients with Charcot Marie Tooth 1A</td>
<td>Stefano Tamburin</td>
</tr>
<tr>
<td>26</td>
<td>CK levels in CMT and related disorders</td>
<td>Mariola Skorupinska</td>
</tr>
<tr>
<td>27</td>
<td>Electrodiagnostic accuracy in polyneuropathies: supervised learning algorithms versus electrophysiologists</td>
<td>Antonino Uncini</td>
</tr>
<tr>
<td>28</td>
<td>Nerve Conduction in Patients with Transthyretin Amyloidosis with Polyneuropathy Enrolled in THAOS</td>
<td>Marcia Waddington-Cruz</td>
</tr>
<tr>
<td>Page</td>
<td>Title</td>
<td>Author</td>
</tr>
<tr>
<td>------</td>
<td>----------------------------------------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>29</td>
<td>Digitally assessed patient-reported real-world treatment patterns for Charcot-Marie-Tooth disease in the UK and US</td>
<td>Tjalf Ziemssen</td>
</tr>
<tr>
<td>30</td>
<td>Yeast Phenotypes of GDAP1 - Loss of Function Mutations</td>
<td>Weronika Rzepnikowska</td>
</tr>
<tr>
<td>31</td>
<td>Clinical Trial of Sural Nerve Grafts to the Substantia Nigra in Patients with Parkinson's Disease</td>
<td>Jorge Quintero</td>
</tr>
<tr>
<td>32</td>
<td>Impact of pathogenic DNMT1 mutations on human iPSC-derived sensory neuronal phenotypes and DNA methylation</td>
<td>Nathan Staff</td>
</tr>
<tr>
<td>33</td>
<td>Diagnostic Challenges for Familial Amyloid Polyneuropathy: An Illustrative Case</td>
<td>Supreet Sahai</td>
</tr>
<tr>
<td>34</td>
<td>Mitochondrial Malformation In The Optic Nerve Of A Transgenic Mouse Expressing Mitofusin 2S245R</td>
<td>Shinichiro Ukon</td>
</tr>
<tr>
<td>35</td>
<td>Mitochondrial Dysfunction as a Common Pathology in CMT</td>
<td>Verna Sarajärvi</td>
</tr>
<tr>
<td>36</td>
<td>Effect of Limb Position on Nerve Shear Wave Velocity In Situ</td>
<td>Chelsea Rugel</td>
</tr>
<tr>
<td>37</td>
<td>Novel Mutations in SH3TC2 and SNX10 in Chronic Demyelinating Sensorimotor Polyneuropathy with Congenital Thrombocytopenia</td>
<td>Kalpana Prasad</td>
</tr>
<tr>
<td>38</td>
<td>Gene delivery targeted to Schwann cell using a minimal myelin promoter</td>
<td>Natasa Schiza</td>
</tr>
<tr>
<td>39</td>
<td>Peripheral nerve ultrasounds in hereditary transthyretin amyloidosis patients and asymptomatic carriers. A multicenter Italian study.</td>
<td>Alessandro Salvalaggio</td>
</tr>
<tr>
<td>40</td>
<td>Testing An ShRNA Gene Silencing Approach In A Mouse Model Of Charcot-Marie-Tooth Disease Type 1A</td>
<td>Marina Stavrou</td>
</tr>
<tr>
<td>41</td>
<td>A new double homozygous GDAP1 mutation in two patients presenting an axonal Charcot-Marie-Tooth disease</td>
<td>Federica Miressi</td>
</tr>
<tr>
<td>42</td>
<td>Indirect Treatment Comparison of the Efficacy of Patisiran and Inotersen for hATTR Amyloidosis with Polyneuropathy</td>
<td>Laura Obici</td>
</tr>
<tr>
<td>43</td>
<td>A CRISPR/Cas9 knock-out screen to identify regulators of Hspb8 expression and stability</td>
<td>Leen Vendredy</td>
</tr>
<tr>
<td>44</td>
<td>Neuropathy with developmental delay in a young patient carrying chromosome 1q23.3-q24.2 deletion including MPZ</td>
<td>Anna Mazzeo</td>
</tr>
<tr>
<td>45</td>
<td>Histone deacetylase 3 inhibition improves Schwann cell differentiation in Charcot-Marie-Tooth disease 1A</td>
<td>Robert Prior</td>
</tr>
<tr>
<td>46</td>
<td>Effect of Balance Training on Posturography Variables and Functional Balance in People with Charcot-Marie-Tooth disease</td>
<td>Gita Ramdharry</td>
</tr>
<tr>
<td>47</td>
<td>MND-like presentation as the main manifestation of the p.Val142Ile FAP-TTR mutation</td>
<td>Ana Marina Silva</td>
</tr>
<tr>
<td>48</td>
<td>Phenotypic variability in a Portuguese family with AGel Amyloidosis</td>
<td>Ana Sousa</td>
</tr>
<tr>
<td>49</td>
<td>Develop pan-specific monoclonal antibodies against mutant GlyRS for treating CMT2D</td>
<td>Jiadong Zhou</td>
</tr>
<tr>
<td>50</td>
<td>HARS-related peripheral neuropathy with polyglucosan bodies, cerebellar atrophy and mild cognitive impairment</td>
<td>Pinelopi Tsouni</td>
</tr>
<tr>
<td>51</td>
<td>Trans-deletion of WHEP Domain in Glycyl-tRNA Synthetase Rescues CMT2D Neuropathy</td>
<td>Yao Tong</td>
</tr>
<tr>
<td>52</td>
<td>TTR gene sequencing in 100 Czech patients with unsolved late onset axonal neuropathies</td>
<td>Pavel Seeman</td>
</tr>
<tr>
<td>53</td>
<td>CNS phenotype in X linked Charcot-Marie-Tooth Disease</td>
<td>Vinojini Vivekanandam</td>
</tr>
<tr>
<td>54</td>
<td>SPORADIC TRANSTHYRETIN FAMILIAL AMYLOID POLYNEUROPATHY IN A BRAZILIAN COHORT</td>
<td>Pedro Tomaselli</td>
</tr>
<tr>
<td>55</td>
<td>The RAB7A K126R Mutation Associated with Predominantly Motor CMT2B</td>
<td>Paola Saveri</td>
</tr>
<tr>
<td>57</td>
<td>Association between Clinical Outcomes and Quality of Life in Patients with Hereditary Transthyretin Amyloidosis</td>
<td>Aaron Yarlas</td>
</tr>
<tr>
<td>58</td>
<td>Impact of Inotersen on Condition-Specific Quality of Life for hATTR Amyloidosis: Double-Blind Placebo-Controlled Trial Results</td>
<td>Spencer Guthrie</td>
</tr>
<tr>
<td>59</td>
<td>Characterizing Treatment Experience among Patients with Transthyretin Amyloidosis</td>
<td>Asia Sikora Kessler</td>
</tr>
<tr>
<td></td>
<td>Title</td>
<td>Authors</td>
</tr>
<tr>
<td>---</td>
<td>-----------------------------------------------------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>60</td>
<td>Safety and Efficacy of Switching Patients with Neuromuscular Disorders from one IVIG Preparation to Panzyga®</td>
<td>Lidia Cosentino</td>
</tr>
<tr>
<td>61</td>
<td>Development of a Ligand Conjugated Antisense Oligonucleotide for the Treatment of Transthyretin Amyloidosis (ATTR)</td>
<td>Li-Jung Tai</td>
</tr>
<tr>
<td>63</td>
<td>P75 and NCAM can Identify Pathologic Schwann Cells in Peripheral Neuropathies</td>
<td>Jong Kuk Kim</td>
</tr>
<tr>
<td>64</td>
<td>Examination of Risks/Benefit Profile of Medical Cannabis in CMT and HNPP and Chronic Pain Patients</td>
<td>Brian Piper</td>
</tr>
<tr>
<td>65</td>
<td>A mitochondrial ATP6 mutation causing a slowly progressive myeloneuropathy</td>
<td>Tanya Bardakjian</td>
</tr>
<tr>
<td>66</td>
<td>Genome-wide DNA Methylation Profiling Identifies Epigenetic Clues into Human Peripheral Neuropathy in Type 2 Diabetes</td>
<td>Stephanie Eid</td>
</tr>
<tr>
<td>67</td>
<td>INTRAEPIDERMAL NERVE FIBER REGENERATION IS DIFFERENT BETWEEN TYPE1 and TYPE2 DIABETES.</td>
<td>Mohammad Khoshnoodi</td>
</tr>
<tr>
<td>68</td>
<td>Epidermal Axon Changes in Patients with Prediabetes: The PACMAN Study</td>
<td>Dan Elliott</td>
</tr>
<tr>
<td>69</td>
<td>Expression of GAP-43 in type 2 diabetes and IGT: a longitudinal study</td>
<td>Xin Pan</td>
</tr>
<tr>
<td>70</td>
<td>Gut Microbiome and its Potential Role in Obesity-Induced Allodynia</td>
<td>Raiza Bonomo</td>
</tr>
<tr>
<td>71</td>
<td>A Keratinocyte-Derived Mechanism of Nicotinamide Riboside to Prevent and Reverse Diabetic Neuropathy</td>
<td>Cheng-Ying Ho</td>
</tr>
<tr>
<td>72</td>
<td>Mrgrpdr as a Potential Therapeutic Target for Painful Diabetic Neuropathy</td>
<td>Dale George</td>
</tr>
<tr>
<td>73</td>
<td>Real Time Analysis of ATP Levels in DRG Neurons Derived from Normal or Diabetic Rats</td>
<td>Reza Aghanoori</td>
</tr>
<tr>
<td>74</td>
<td>Bortezomib neurotoxicity is associated with altered MAP2 levels and distribution within human iPSC-derived sensory neurons</td>
<td>Nathan Staff</td>
</tr>
<tr>
<td>75</td>
<td>INTRINSIC GROWTH AND PLASTICITY PATHWAYS WITHIN SENSORY NEURONS: An expanding list</td>
<td>Douglas Zochodne</td>
</tr>
<tr>
<td>76</td>
<td>Mitochondrial vacuolation occurs independent of axon degeneration in paclitaxel-induced peripheral neuropathy</td>
<td>Anthony Cirrincione</td>
</tr>
<tr>
<td>77</td>
<td>Asymmetry in Chemotherapy-induced Peripheral Neuropathy: Differences in patient report and objective assessment</td>
<td>Hannah Timmins</td>
</tr>
<tr>
<td>78</td>
<td>Incidence and characteristics of neurological adverse events secondary to immunotherapy with checkpoint inhibitors</td>
<td>Roser Velasco</td>
</tr>
<tr>
<td>79</td>
<td>Elevated Neurofilament Light Chain (NF-L) Levels in Pancreatic Cancer Patients with CIPN Receiving Abraxane</td>
<td>Catherine Stehman-Breen</td>
</tr>
<tr>
<td>80</td>
<td>Bortezomib Neuropathy: Clinical and Electrophysiological Features and Its Predictive Factor</td>
<td>Nagaaki Katoh</td>
</tr>
<tr>
<td>81</td>
<td>Outcome Measures in the Assessment of Chemotherapy Induced Peripheral Neuropathy- Which Tools are Most Responsive?</td>
<td>Tiffany Li</td>
</tr>
<tr>
<td>82</td>
<td>Molsidomine provides neuroprotection against vincristine-induced peripheral neurotoxicity</td>
<td>Francesco Lotti</td>
</tr>
<tr>
<td>83</td>
<td>Improving Neuropathy and Mobility in Diabetes: the INMED trial</td>
<td>Lindsay Zilliox</td>
</tr>
<tr>
<td>84</td>
<td>Cervical Radiculoplexus Neuropathy As The First Presentation Of Type 2 Diabetes</td>
<td>Piyumi Wijewickrama</td>
</tr>
<tr>
<td>85</td>
<td>The Critical Involvement of Neutrophils in Wallerian Degeneration After a Peripheral Nerve Injury.</td>
<td>Richard Zigmond</td>
</tr>
<tr>
<td>86</td>
<td>Diagnosing Vitamin B12 Deficiency In Patients With Polyneuropathy</td>
<td>Janna Warendorf</td>
</tr>
<tr>
<td>87</td>
<td>Risk of Developing Treatment-Induced Neuropathy of Diabetes (TIND) in hospitalized patients: A Prospective Cohort Study</td>
<td>Amanda Siew Hwee Tan</td>
</tr>
<tr>
<td>88</td>
<td>Reduced glycolysis–TCA cycle flux in IMS32 Schwann cells under high glucose and pyruvate-deficient conditions.</td>
<td>Kazunori Sango</td>
</tr>
<tr>
<td>No.</td>
<td>Title</td>
<td>Author</td>
</tr>
<tr>
<td>-----</td>
<td>----------------------------------------------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>90</td>
<td>A Case of Female Adrenoleukodystrophy Carrier Presenting Like Nonsystemic Vasculitic Neuropathy</td>
<td>Jin Myoung Seok</td>
</tr>
<tr>
<td>91</td>
<td>TIND and Diabetic Lumbosacral Radiculoplexus Neuropathy – Is Fluctuating Glycemic Control an Etiologic Link?</td>
<td>Genevieve Yu</td>
</tr>
<tr>
<td>92</td>
<td>Footwear neuropathy: the diagnostic usefulness of ultrasonography</td>
<td>HIROSHI TSUKAMOTO</td>
</tr>
<tr>
<td>93</td>
<td>The association between electrophysiological severity and pain and paresthesia in diabetes</td>
<td>Chieko Suzuki</td>
</tr>
<tr>
<td>94</td>
<td>The characteristics of immobilization-induced rhabdomyolysis patients with peripheral neuropathy</td>
<td>JUNG IM SEOK</td>
</tr>
<tr>
<td>95</td>
<td>Chronic Axonal Polyneuropathy in The Rotterdam Study: A Population-based Cohort Study</td>
<td>Noor Taams</td>
</tr>
<tr>
<td>96</td>
<td>ULTRASONOGRAPHY FINDING FOR THE DIAGNOSIS OF CARPAL TUNNEL SYNDROME IN DIABETIC AND NON-DIABETIC PATENTS</td>
<td>Yasufumi Sekiguchi</td>
</tr>
<tr>
<td>97</td>
<td>Vascular factors and neuropathy in lower limb of diabetic patients</td>
<td>Kyong Jin Shin</td>
</tr>
<tr>
<td>98</td>
<td>Atypical Sensorimotor Neuropathy Related to Cutaneous Toxigenic Diphtheria Infection In A World Traveller</td>
<td>Penelope Spring</td>
</tr>
<tr>
<td>99</td>
<td>Electrophysiological findings in axonal-demyelinating polyneuropathy in diabetes</td>
<td>Anna Potulskachromik</td>
</tr>
<tr>
<td>100</td>
<td>Systemic Transplantation of Adult Stem Cells Restores Aging Neuromuscular Tissue Structure and Function</td>
<td>Seth Thompson</td>
</tr>
<tr>
<td>101</td>
<td>Antibodies directed against peripheral neurons, Schwann cells and myelin are frequently found in Zika-exposed subjects</td>
<td>Simon Rinaldi</td>
</tr>
<tr>
<td>102</td>
<td>Immunomodulatory effects of bortezomib in experimental autoimmune neuritis in lewis rats.</td>
<td>Rafael Klimas</td>
</tr>
<tr>
<td>103</td>
<td>POEMS syndrome: characterization of neuropathy and post-treatment outcome in 36 patients</td>
<td>Nathalie DESCHAMPS</td>
</tr>
<tr>
<td>104</td>
<td>Outcomes after single-cycle rituximab in patients with anti-MAG polyneuropathy: an average eleven years follow-up analysis</td>
<td>Martina Garnero</td>
</tr>
<tr>
<td>105</td>
<td>Difference of Clinical and Paraclinical Patterns in anti-FGFR3-Positive Sensory Neuropathy Cases from Brazil and Europe</td>
<td>Yannick Tholance</td>
</tr>
<tr>
<td>106</td>
<td>Holistic Characterization of the Repertoire of Targeted Autoantigens of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)</td>
<td>Christian Moritz</td>
</tr>
<tr>
<td>107</td>
<td>Misdiagnosis and Diagnostic Pitfalls of CIDP</td>
<td>Merel Broers</td>
</tr>
<tr>
<td>108</td>
<td>One year closer to clinical trials with a new antigen specific treatment for anti-MAG neuropathy</td>
<td>Pascal Hanggi</td>
</tr>
<tr>
<td>109</td>
<td>Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) Associated With Sarcoidosis Or Connective Tissue Disease.</td>
<td>Clément Vialatte de Péville</td>
</tr>
<tr>
<td>110</td>
<td>Incidence of antibodies against the node of Ranvier in a prospective cohort of 1000 CIDP</td>
<td>Emilien Delmont</td>
</tr>
<tr>
<td>111</td>
<td>Secondary Endpoints (PATH Extension Study): Long-term Outcomes of Subcutaneous Immunoglobulin IgPro20 in CIDP Maintenance Treatment</td>
<td>Ivo van Schaik</td>
</tr>
<tr>
<td>112</td>
<td>The overlapping spectrum of Chronic Inflammatory Demyelinating Polyradiculoneuropathy and anti-MAG neuropathy</td>
<td>Giuseppe Liberatore</td>
</tr>
<tr>
<td>113</td>
<td>International Validation of the modified Erasmus GBS Outcome Score (mEGOS) for Guillain-Barré Syndrome</td>
<td>Alex Doets</td>
</tr>
<tr>
<td>114</td>
<td>The impact of eculizumab on neurological improvement in Guillain–Barré syndrome: Subanalysis of JET-GBS study</td>
<td>Sonoko Misawa</td>
</tr>
<tr>
<td>115</td>
<td>A Dose Response RCT Of IV immunoglobulin In Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)/DRIP Study</td>
<td>Krista Kuitwaard</td>
</tr>
<tr>
<td>116</td>
<td>Title: Intravenous Immunoglobulin Overdose in Chronic Inflammatory Demyelinating Polyneuropathy: Double-Blind Randomized Controlled Non-Inferiority Trial (IOC-TRIAL)</td>
<td>Max Adrichem</td>
</tr>
<tr>
<td>117</td>
<td>RECIPE: a phase II randomized controlled trial of rituximab for refractory CIDP with IgG4 autoantibodies</td>
<td>Masahiro Iijima</td>
</tr>
<tr>
<td>118</td>
<td>Restabilization after intravenous immunoglobulins (IVIg) withdrawal in patients with chronic inflammatory demyelinating polyneuropathy (CIDP)</td>
<td>Ilse Lucke</td>
</tr>
<tr>
<td>Page</td>
<td>Title</td>
<td>Authors</td>
</tr>
<tr>
<td>------</td>
<td>----------------------------------------------------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>119</td>
<td>Second IVIG Course in Guillain-Barré Syndrome Patients with Poor Prognosis (SID-GBS); Double-blind Randomized Controlled Trial.</td>
<td>Christa Walgaard</td>
</tr>
<tr>
<td>120</td>
<td>A Randomized, Single-Blinded, Non-Inferiority Cross-Over Trial of Facilitated Subcutaneous Immunoglobulin in Multifocal Motor Neuropathy</td>
<td>Ali Al-Zuhairy</td>
</tr>
<tr>
<td>121</td>
<td>Guillain-Barré Syndrome in the United States, 2009–2015</td>
<td>James Sejvar</td>
</tr>
<tr>
<td>122</td>
<td>A Case of Peripheral Sensory Ataxia Causing Recurrent Falls</td>
<td>Wei Min James Tung</td>
</tr>
<tr>
<td>123</td>
<td>Anti-GM1 complex antibodies in patients with different electrophysiological subtypes of Guillain-Barré syndrome</td>
<td>Min Wang</td>
</tr>
<tr>
<td>124</td>
<td>Predictive Modelling for Acute Inflammatory Demyelinating Polyneuropathy</td>
<td>Cheng-Yin Tan</td>
</tr>
<tr>
<td>125</td>
<td>Impairment of reflex sensory pathway in multifocal motor neuropathy (MMN): an electrophysiological demonstration</td>
<td>Eglė Sukockienė</td>
</tr>
<tr>
<td>126</td>
<td>Japanese Nationwide Epidemiologic Survey of POEMS syndrome</td>
<td>Tomoki Suichi</td>
</tr>
<tr>
<td>127</td>
<td>Different distributions of nerve conduction slowing/block in typical and atypical chronic inflammatory demyelinating polyneuropathy</td>
<td>Kazumoto Shibuya</td>
</tr>
<tr>
<td>128</td>
<td>The Difference in the Distribution of Fasciculations Between Multifocal Motor Neuropathy and Amyotrophic Lateral Sclerosis</td>
<td>Yukiko Tsuji</td>
</tr>
<tr>
<td>129</td>
<td>Evaluation of complement proteins and cleavage fragments in CSF samples from Guillain-Barre syndrome patients</td>
<td>Sethu Sankaranarayanan</td>
</tr>
<tr>
<td>130</td>
<td>Multicentre Study Investigating Association of GBS with Flaviviruses and other Arboviruses in Asia- Patient Characteristics</td>
<td>Lai Lim Yip Ivy</td>
</tr>
<tr>
<td>131</td>
<td>The variety of peripheral neuropathies in eosinophilic granulomatosis with polyangiitis</td>
<td>Makoto Samukawa</td>
</tr>
<tr>
<td>132</td>
<td>Neuropathy by B-cell chronic lymphocytic leukemia involvement of the central nervous system: a case report</td>
<td>Tiziana Rosso</td>
</tr>
<tr>
<td>133</td>
<td>Reversible conduction failure of sensory in acute axonal subtypes of Guillain Barré syndrome</td>
<td>Shuo Yang</td>
</tr>
<tr>
<td>134</td>
<td>Repeater F-waves in demyelinating and axonal polyneuropathies</td>
<td>Dimitra Veltsista</td>
</tr>
<tr>
<td>135</td>
<td>Exposure-Response of Serum IgG Levels and INCAT Scores in CIDP Patients Receiving Subcutaneous Immunoglobulin (IgPro20)</td>
<td>Theresa Yuraszeck</td>
</tr>
<tr>
<td>136</td>
<td>Current treatment practice of Guillain-Barré syndrome</td>
<td>Christine Verboon</td>
</tr>
<tr>
<td>137</td>
<td>IgM anti-MAG(+/−) peripheral Neuropathy: from proper assessment to trial needs (IMAGiNe study)</td>
<td>Mariëlle Pruppers</td>
</tr>
<tr>
<td>138</td>
<td>Different Clinical Findings Between Anti-GQ1b Antibody-Positive And -Negative Bickerstaff Brainstem Encephalitis</td>
<td>Keisuke Yoshikawa</td>
</tr>
<tr>
<td>139</td>
<td>Guillain-Barré Syndrome And Related Diseases After Influenza Virus Infection</td>
<td>Masaki Yamana</td>
</tr>
<tr>
<td>140</td>
<td>Neurophysiological and Imaging Features can Differentiate between GBS with Treatment-Related Fluctuations and Acute-Onset CIDP</td>
<td>Tsun Haw Toh</td>
</tr>
<tr>
<td>141</td>
<td>Guillain-Barre syndrome as an initial manifestation of antiphospholipid syndrome</td>
<td>Sung-Yeon Sohn</td>
</tr>
<tr>
<td>142</td>
<td>Is testosterone a potential agent for patients with delayed recovery from Guillain-Barre syndrome?</td>
<td>Anomali Vidanagamage</td>
</tr>
<tr>
<td>143</td>
<td>Temporal-Spatial Activation of Spinal Microglia after Peripheral Nerve Injury</td>
<td>Hauke Wüstenberg</td>
</tr>
<tr>
<td>144</td>
<td>BENDAMUSTINE–RITUXIMAB (BR) COMBINED THERAPY FOR TREATMENT OF IMMUNO-MEDIATED NEUROPATHIES ASSOCIATED TO HEMATOLOGICAL DISORDERS</td>
<td>Angela Zuppa</td>
</tr>
<tr>
<td>145</td>
<td>Including Sensory Nerve Conduction Studies in a Modified Electrodiagnostic Criteria for Guillain-Barré Syndrome</td>
<td>Wei Ting Wang</td>
</tr>
<tr>
<td>146</td>
<td>Antecedent infection spectrum in patients with Guillain-Barré syndrome: a single center, prospective study</td>
<td>Yuzhong Wang</td>
</tr>
<tr>
<td>147</td>
<td>Electrophysiologic assessment of eculizumab efficacy in severe Guillain-Barré syndrome: A post-hoc analysis of JET-GBS study</td>
<td>Yukari Sekiguchi</td>
</tr>
<tr>
<td>Page</td>
<td>Title</td>
<td>Author</td>
</tr>
<tr>
<td>------</td>
<td>----------------------------------------------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>148</td>
<td>Anti-glycolipid antibodies and clinical features in recurrent Guillain-Barre syndrome</td>
<td>Ayumi Uchibori</td>
</tr>
<tr>
<td>149</td>
<td>Prognosis and clinical features of acute motor axonal neuropathy with conduction block</td>
<td>Eun Hee Sohn</td>
</tr>
<tr>
<td>150</td>
<td>Difference in seasonality of CIDP research volume on google trends</td>
<td>Emanuele Spina</td>
</tr>
<tr>
<td>151</td>
<td>Predicting IVlg Treatment Response In CIDP – A Substudy Of INCbase</td>
<td>Luuk Wieske</td>
</tr>
<tr>
<td>152</td>
<td>MRI of neuralgic amyotrophy in the subacute phase</td>
<td>Paolo Ripellino</td>
</tr>
<tr>
<td>153</td>
<td>Three Cases of Early Tremor in the Course of Guillain-Barré Syndrome</td>
<td>Susanne Ten Holter</td>
</tr>
<tr>
<td>154</td>
<td>Vasculitic neuropathy associated with IgA vasculitis (Henoch-Schönlein purpura) as an unusual manifestation: Clinicopathological analysis</td>
<td>Kazuma Sugie</td>
</tr>
<tr>
<td>155</td>
<td>Suspected paraneoplastic Guillain-Barre syndrome with anti-CASPR2 antibodies</td>
<td>Phuongthao Quan</td>
</tr>
<tr>
<td>156</td>
<td>A severe case of neuro-Sjögren’s syndrome induced by pembrolizumab</td>
<td>Alex Vicino</td>
</tr>
<tr>
<td>157</td>
<td>Modification of the I-RODS to Assess Outcome of Guillain-Barré Syndrome Using the IGOS Cohort</td>
<td>Melissa Mandarakas</td>
</tr>
<tr>
<td>158</td>
<td>Ex vivo modulation of Schwann cell differentiation by neuritogenic T cells</td>
<td>Alicia Wang</td>
</tr>
<tr>
<td>159</td>
<td>Non-inflammatory Demyelinating Polyradiculoneuropathy associated with monospecific anti-GD1b IgM antibody: a case report</td>
<td>Matteo Tagliapietra</td>
</tr>
<tr>
<td>160</td>
<td>Impact of lysophosphatidic acid signaling on Schwann cell differentiation in experimental autoimmune neuritis</td>
<td>Fabian Szepanowski</td>
</tr>
<tr>
<td>161</td>
<td>Rat neuron / human Schwann cell co-cultures to assess demyelinating properties of patient-derived serum factors</td>
<td>Leon-Phillip Szepanowski</td>
</tr>
<tr>
<td>162</td>
<td>Distribution of Natural Killer cells in the peripheral nerve in experimental autoimmune neuritis</td>
<td>Bernice Walter</td>
</tr>
<tr>
<td>163</td>
<td>Guillain-Barré Syndrome and Autoimmune Hemolytic Anemia Following an Allogeneic Bone Marrow Transplantation.</td>
<td>Marta Ruiz</td>
</tr>
<tr>
<td>164</td>
<td>Predictors Of Respiratory Failure In Guillain-Barré Syndrome In Children</td>
<td>Joyce Roodbol</td>
</tr>
<tr>
<td>165</td>
<td>Comparison of high-frequency and ultra-high-frequency probes in chronic inflammatory demyelinating polyneuropathy</td>
<td>Angela Puma</td>
</tr>
<tr>
<td>166</td>
<td>Mechanism of Action and Long-term Safety of Hyaluronidase-Facilitated Subcutaneous Immunoglobulin 10% in Primary Immunodeficiency Disease</td>
<td>Leman Yel</td>
</tr>
<tr>
<td>167</td>
<td>High-Dose Therapy and Autologous Transplant for POEMS Syndrome: Effective, but how to optimise?</td>
<td>Stephen Keddie</td>
</tr>
<tr>
<td>168</td>
<td>Combined central and peripheral demyelination - new insight into clinical features and potential risk factors.</td>
<td>Łukasz Rzepiński</td>
</tr>
<tr>
<td>169</td>
<td>Long-term Observation In A Cohort of IgM Associated Neuropathies.</td>
<td>James Triplett</td>
</tr>
<tr>
<td>170</td>
<td>The Role of Dipeptidyl Peptidase IV in the Pathogenesis of Inflammatory Neuropathies</td>
<td>Gang Zhang</td>
</tr>
<tr>
<td>171</td>
<td>Multifocal motor neuropathy: a rare and complex disease - an university center’s experience.</td>
<td>Camila Pupe</td>
</tr>
<tr>
<td>172</td>
<td>Chronic Inflammatory Demyelinating Polyneuropathy – First Epidemiological Insights From A National Prospective Cohort Study</td>
<td>Stephan Ratzlaff</td>
</tr>
<tr>
<td>173</td>
<td>Biomarker Profiling of Neuropathic Pain in Idiopathic Peripheral Neuropathy</td>
<td>Perry Van Doormaal</td>
</tr>
<tr>
<td>174</td>
<td>Rate of progression of Utah Early Neuropathy Scale (UENS) score in diabetic neuropathy</td>
<td>J. Robinson Singleton</td>
</tr>
<tr>
<td>175</td>
<td>Long-Term Efficacy and Safety of Inotersen for Hereditary Transthyretin Amyloidosis: NEURO-TTR Open-Label Extension 2-Year Update</td>
<td>Thomas Brannagan</td>
</tr>
<tr>
<td>176</td>
<td>Autoantibodies and Pain: The Role of Leucine-Rich Glioma Inactivated 1 in Primary Sensory Neurons</td>
<td>John Dawes</td>
</tr>
<tr>
<td>177</td>
<td>Effects of candesartan on mouse models of vincristine- and oxaliplatin-induced neuropathy</td>
<td>Hichem Bouchenaki</td>
</tr>
<tr>
<td>Page</td>
<td>Title</td>
<td>Author</td>
</tr>
<tr>
<td>------</td>
<td>----------------------------------------------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>178</td>
<td>Presence of red flags in Transthyretin familial amyloid polineuropathy (TTR-FAP) at the moment of diagnosis</td>
<td>Lorenzo Silva Hernández</td>
</tr>
<tr>
<td>179</td>
<td>Chronic Pain Following Non Freezing Cold Injury is Caused by an Acquired Sensory Neuropathy</td>
<td>Thomas Vale</td>
</tr>
<tr>
<td>180</td>
<td>Neurotrophic Strategy for Subacute Ophthalmic Herpetic Neuralgia at 6 months: Randomized, Single-center, Clinical trial Study</td>
<td>Gang Xu</td>
</tr>
<tr>
<td>181</td>
<td>Clinical characteristics and nerve conduction study of the patients with carpal tunnel release; 261 cases.</td>
<td>Byung-Nam Yoon</td>
</tr>
<tr>
<td>182</td>
<td>Responsiveness of Neuropathy Symptom and Change (NSC) Scores With Inotersen for Hereditary Transthyretin Amyloidosis Polyneuropathy</td>
<td>P. James Dyck</td>
</tr>
<tr>
<td>183</td>
<td>Talking of Mesenchymal Stem Cells with Astrocytes Under Inflammatory Condition</td>
<td>Gulay Sezer</td>
</tr>
<tr>
<td>184</td>
<td>Whole Exome Sequencing Study in Italian Families and Early-Onset Patients affected by Painful Peripheral Neuropathy</td>
<td>Silvia Santoro</td>
</tr>
<tr>
<td>185</td>
<td>Bioequivalency/Bioavailability Clinical Trials Of Neuropathic Pain Medications In Healthy Subjects</td>
<td>Zafer Sezer</td>
</tr>
<tr>
<td>186</td>
<td>CHEMOTHERAPY INDUCED PERIPHERAL NEUROTOXICITY: THE SEARCH FOR THE IDEAL OUTCOME MEASURE</td>
<td>PAOLA ALBERTI</td>
</tr>
<tr>
<td>187</td>
<td>Modulators of Burn-Injury-Related Pain: The Search for Important Risk Factors in the Acute-Chronic Pain Transition.</td>
<td>PAU YEN WU</td>
</tr>
</tbody>
</table>
Novel NDRG1 mutations causing CMT4D with milder phenotype

Shawna Feely, Riccardo Zuccarino, Rosemary Shy, Michael Shy

University of Iowa, Iowa City, IA, USA

N-Myc Downstream-Regulated Gene 1 (NDRG1) mutations have previously been reported to cause a demyelinating, recessive form of Charcot Marie Tooth (CMT) disease, specifically CMT4D. The phenotype is typically severe with onset in the first or second decade, motor and sensory impairment with hearing loss. We describe novel mutations in NDRG1, Cys289fs and Ala143Thr, which are likely causing CMT4D in our patient with a mild phenotype. Patient was a product of a normal pregnancy and delivery. Early milestones were on time and she kept up with peers. At 12 years her parents noticed that she was toe walking. She had muscle atrophy noted at ankles, could not get up on her heels, and structural changes noted in feet. She started to trip and fall, and had frequent ankle sprains. She was 15 years of age at her initial examination which showed weakness in her hands, as the FDI, APB, and ADM was 4-/5 on the left and 4/5 on the right. She also had weakness in her lower extremities getting 4/5 bilaterally for her anterior tibialis, foot eversion, and great toe dorsi flexion. Sensory examination was normal for pinprick, vibration, and joint position sense. She had diffusely reduced reflexes. Overall CMT Exam Score version 2 (CMTESv2) was in the mild range at 3/28 and the CMT Pediatric Score (CMTPeds) was also mild with a score of 10/44. Nerve conduction studies were performed and revealed intermediate median NCV of 38 m/s with 3.5mV amplitude. Parents were each found to be carriers of the NDRG1 mutations identified in the proband confirming phase. The other more common mutations identified in this gene lead to a truncated protein and loss of function. These mutations may allow for partial protein function thus leading to a milder phenotype and NCVs that are intermediate compared to significantly slowed.

References: None.

Keywords: CMTR, Human Genetics

Grant Support: None.
Poster 2

Novel biomarkers and therapeutic approaches in Charcot-Marie-Tooth Disease (CMT)

Michael Sereda

University Medical Centre Goettingen, Max-Planck-Institute of Experimental Medicine, Goettingen, Germany

Charcot-Marie-Tooth disease 1A (CMT1A) is the most common inherited neuropathy caused by a duplication of the gene encoding PMP22. CMT1A is characterized by slow disease progression and a high variability, even among twins. The cause of disease variability is unknown and epigenetic disease modifiers have been suggested. Previously, we could identify skin-derived disease and progression biomarkers in a rat model of CMT1A, which was translated to patients and was validated in a large European and US-based cohort. We now found that differentially methylated DNA regions and transcriptomic target genes correlate with disease severity in peripheral nerves in CMT1A rats. Clinically relevant, we also identified novel candidates from blood in both rats and CMT1A patients that may serve as easily accessible novel biomarkers. We are currently validating these candidates in blood of patients with CMT1A but also other CMT forms within the German CMT Disease Network (CMT-NET). Apart from the clinical projects we focus on the molecular understanding of failed myelin assembly in CMT in order to identify novel therapeutic approaches. I will present preclinical therapeutic approaches targeting different molecular mechanisms of mutant Schwann cells that contribute to failed myelination in CMT1A: dysdifferentiation, altered intracellular signaling and reduced lipid synthesis. I will also show how these therapeutic strategies may be relevant for other demyelinating neuropathies and how these findings may become relevant for therapeutic trials in patients.

References: None.

Keywords: Pre-clinical Studies, Schwann Cell, Clinical Trials

Grant Support: MWS was supported by the German Ministry of Education and Research (BMBF, CMT-BIO, FKZ: 01ES0812, CMT-NET, FKZ: 01GM1511C, CMT-NRG, ERA-NET 'ERARE3', FKZ: 01GM1605). MWS was awarded a DFG Heisenberg Professorship (SE 1944/1-1).
Patisiran, a silencing RNA in Hereditary Transthyretin Amyloid polyneuropathy: First experience in real life

Thierry Gendre¹, Abir Wahab¹, Farida Gorram¹, Amandine Ladaïque², Philippe Le Corvoisier³, Diane Bodez⁴, Jean-Pascal Lefaucheur⁵, Violaine Planté-Bordeneuve¹

¹Department of Neurology, Henri Mondor Hospital, East Paris University, Créteil, France, ²Department of Pharmacy, Henri Mondor Hospital, East Paris University, Créteil, France, ³Department VERDI, Inserm, CIC1430, Créteil, France, ⁴Department of Cardiology, Henri Mondor Hospital, East Paris University, Créteil, France, ⁵Department of Neurophysiology, Henri Mondor Hospital, East Paris University, Créteil, France

Background: Patisiran, a transthyretin silencing RNA, is a new effective therapeutic in hereditary transthyretin amyloid polyneuropathy (hATTR-PN) evaluated in the phase 3 Apollo trial.

Aim: To report our first experience on the safety and efficacy of patisiran in hATTR-PN patients previously treated by TTR stabilizers.

Methods: After premedication, patisiran 0.3mg/kg was administered intravenously every 3 weeks. An assessment was performed at baseline and every 6 months, including the Neuropathy Impairment Score (NIS), polyneuropathy disability (PND) score, Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN), and serum TTR level. Adverse events were recorded.

Results: Twenty-one hATTR-PN patients (17 males, 13 ATTR-Val30Met, mean age: 66 years [range: 45-86]) received patisiran. Four were enrolled in the Apollo open-label extension study, since April 2016, 17 others in the early access program since May 2018. Disease course averaged 7.2 years [range: 1.9-19.1]. Eleven patients had a PND score ≥IIIA. The mean NIS was 62 [range: 12-128] at baseline. Twenty patients received a prior TTR stabilizer. Under TTR stabilizer, the mean delta-NIS during the past 12 months was 9.6 (range: 0-58) and the PND score worsened in 10 patients. Under patisiran, the NIS was unchanged in all cases evaluated at 6 months (N₁=8) and at 12 months (N₂=2). The delta-NIS change was less than 5 at 24 months (N₃=2). Under patisiran, PND score was stable in all patients but one. At last evaluation, the mean serum TTR level had decreased by 75% from baseline (18 cases). All patients but two had an improved Norfolk QOL-DN score (mean change: -13.6). Safety was generally good. Local erythema or flush occurred in 3 cases. Two patients presented a serious adverse event attributable to the premedication (dexamethasone) including hyperglycemia and a cardiac failure episode.

Conclusion: Patisiran appears an effective and well-tolerated treatment to stabilize hATTR-PN. Longer follow-up will be presented.

References: None.

Keywords: Amyloidosis

Grant Support: Dr. Planté-Bordeneuve received supports for meeting, traveling fees and consulting from Alnylam, Pfizer, and Akcea.
ADP-ribosylation is circular process of posttranslational modification of proteins and is mediated by several factions of enzymes: poly-ADP-ribose polymerases, like PARP1, which catalyze the attachment of poly-ADP-ribose (PAR) units to proteins using NAD+ as a donor for ADP-ribose. Subsequently, mono-or poly-ADP hydrolases, like PARG, catalyze the removal of single or strings of ADP-ribose units. A stress response initiates a rapid breakdown of PAR, preventing excessive PAR accumulation that would result in cell death via the parthanatos pathway. The ADP-ribosylation pathway is an ubiquitously expressed pathway controlling cellular stress. However, impairment in this pathway seems to primarily affect neuronal tissues in a neurodegenerative fashion. Recently, recessive ADPRHL2 mutations were shown to cause a neurodegenerative stress-induced epileptic ataxia syndrome with early pediatric onset, and neurodegeneration with developmental delay, ataxia, and axonal neuropathy. In this study, we present two families with homozygous mutations in ADPRHL2 with a complex juvenile-onset neurodegenerative peripheral neuropathy phenotype, further validating the neuronal vulnerability for dysregulation of the ADP-ribosylation pathway. In vitro studies of the identified ADPRHL2 missense mutations were performed in order to assess the expression levels, stability and localization of the mutant and wild-type proteins. In addition, patient fibroblast cells were investigated to validate the in vitro experiments.

References: None.

Keywords: Human Genetics

Grant Support: None.
Charcot-Marie-Tooth disease (CMT) is a group of rare inherited peripheral neuropathies with no therapeutic cure to date. The most common type of CMT, CMT1A, is due to a large 1.4 Mb duplication on chromosome 17p11.2 encompassing the peripheral myelin protein 22 gene (PMP22) gene. It is widely accepted that the increased dosage of PMP22, an integral component of the Schwann cell myelin, is the main cause of CMT1A. PMP22 protein folds with low efficiency under normal conditions. Nearly 80% of newly synthesized PMP22 is rapidly degraded by the proteasome, and only a small proportion of PMP22 is fully matured and reaches the myelin sheath. The maintenance of correct protein homeostasis is tightly controlled by protein quality control mechanisms. When they fail, stress response pathways are activated leading to phosphorylation of the alpha subunit of eukaryotic translation initiation factor 2 (eIF2α) causing a reduction of global protein synthesis while allowing the translation of selected genes supporting stress recovery. By inhibiting eIF2α dephosphorylation, IFB-088 prolongs protein translation attenuation in response to stress to allow the cells to restore cellular homeostasis. We previously demonstrated that IFB-088 rescues phenotype in CMT1B mice with activated unfolded protein response. We hypothesized that in CMT1A the overproduction of PMP22 may overload the degradative system causing a failure of protein homeostasis. Here, we show that the P-eIF2α pathway is activated in the C3-PMP22 mice, validated animal model of CMT1A. IFB-088 treatment ameliorates motor, neurophysiological and morphological parameters of C3-PMP22 mice, confirming previous data generated in the CMT1A rat model. Through its mode of action, IFB-088, currently in phase I clinical trial, represents a new therapeutic option for CMT1A and has the unique potential to be effective in the treatment of different CMT subtypes.

References: None.

Keywords: Pre-clinical Studies, CMTR, Schwann Cell, Human Genetics

Grant Support: None.
Deep-learning based morphological profiling for rapid variant annotation in inherited neuropathies.

Wolfgang Pernice¹, Sultan Kenjeyev², Jonathan Shintaku³, Leonard Pernice⁴, Liza Pon⁵, Michio Hirano ³

¹Columbia University Medical School, New York, NY, USA, ²University College London, London, United Kingdom of Great Britain and Northern Ireland, ³Columbia University Medical Center, New York, NY, USA, ⁴Free University of Berlin, Berlin, Germany, ⁵Columbia University, New York, NY, USA

Neuromuscular disease (NMD) researchers are faced with the challenge of discerning pathophysiological mechanisms and treatment opportunities for hundreds of disease genes identified to date. At the same time, a large fraction of NMD-genes remains to be discovered – a daunting task, as variants in any particular disease gene are often exceedingly rare. Leveraging advanced deep learning algorithms, we have developed a high-content, unbiased, and scalable method to rapidly identify disease-associated phenotypes in high-resolution, multiplexed, fluorescent microscopy images of primary, NMD-patient derived cells. Our approach outperforms human-experts and traditional image-analysis methods by at least 5-fold in single-cell classification accuracy, improves image-analysis throughput by orders of magnitude, and allows for the efficient generation of a standardized, deep, and quantitative map of cellular phenotypes across NMD-subtypes, that facilitates the identification of shared disease pathways. At the same time, our method maintains patient-specific granularity, and efficiently identifies disease-associated cellular phenotypes in NMD-patients with unknown genetic etiology. The identified phenotypes (a) can be functionally interpreted by their similarity to profiles of cells with established genotype-phenotype associations, and (b) enable direct experimental validation of candidate variants in NMD-cases with pending genetic diagnosis. Moreover, (c) the high-content nature and cost-efficiency of our approach compared to orthogonal methods such as RNA-Seq, renders it suitable for small-molecule screens on a patient-specific, cellular level.

References: None.

Keywords: Human Genetics, CMTR, Pre-clinical Studies, Other

Grant Support: Postdoctoral Training Fellowship jointly sponsored by the Inherited Neuropathy Consortium (U54 NS065712-10) and the North American Mitochondrial Disease Consortium (U54 NS078059-08).
Poster 7

Treatment of Arg98Cys MPZ Mice In Vitro and In Vivo with IFB088

Michael Shy¹, Yunhong Bai¹, Mason LaMarche¹, David Wang¹, Rosa Mastrangelo², Caroline Treins³, Philippe Gueda³, Maurizio D'Antonio², Michael Shy¹

¹University of Iowa, Carver College of Medicine, Iowa City, IA, USA, ²San Raffaele Scientific Institute, Milano, Italy, ³InFlectis BioScience, Nantes, France

Objective: To determine whether IFB088 provides therapeutic benefit for a second model of Myelin Protein Zero (MPZ) induced Charcot Marie Tooth 1B (CMT1B) in which the unfolded protein response (UPR) contributes to the neuropathy.

Background: Patients with Arg98Cys mutations in myelin protein zero (MPZ) develop a severe infantile onset CMT1B. Arg98Cys MPZ mice recapitulate the disease and have demonstrated that activation of the UPR contributes to the pathogenesis of the neuropathy. IFB088, a specific inhibitor of the Gadd34/Ppp1r15a phosphatase, successfully treated Ser63del MPZ mice by prolonging the P-eIF2a - mediated attenuation of protein synthesis. We hypothesized that similar treatment may prove effective with Arg98Cys MPZ animals.

Methods: Arg98CysMPZ/+ DRGs were treated with 50, 75, 100 and 125nM of IFB-088 and assessed for myelination. IFB088 or vehicle was fed by gavage BID to Arg98Cys MPZ or WT mice from P30 through P180 and evaluated clinically, physiologically and morphologically. Western blot and immunohistochemistry (IHC) were used to analyze expression of relevant proteins including transcription factors that regulate PNS myelination.

Results: Most concentrations IFB-088 increased myelination in MPZArg98Cys DRGs and at 100 and 125 nM, the number of myelinating internodes approached wild-type levels. Treated Arg98Cys/+ mice increased holding time on the accelerating rotarod, increased their grip strength and increased both motor and sensory conduction velocity. Morphological and molecular studies are ongoing.

Conclusions: These data demonstrate that IFB088 improved the phenotype of Arg98Cys MPZ CMT1B in vitro and in vivo. This suggests that IFB088 may prove beneficial in other cases of CMT1B involving UPR activation.

References: None.

Keywords: CMTR, Schwann Cell

Grant Support: Support from InFlectis BioScience
Introduction: Hereditary transthyretin-mediated (hATTR) amyloidosis is a progressive, life-threatening disease; majority of patients develop a mixed phenotype including polyneuropathy and cardiomyopathy. Patisiran’s efficacy and safety over 18-24 months have been demonstrated in Phase 2 and Phase 3 (APOLLO) studies in hATTR amyloidosis with polyneuropathy. Safety and efficacy from an interim analysis of the ongoing Global Open-Label extension (OLE) study are presented.

Methods: Multicenter, international, OLE, safety and efficacy study (NCT02510261) in eligible patients who completed parent studies, including APOLLO patients randomized to placebo (APOLLO/placebo, n=49) or patisiran (APOLLO/patisiran, n=137) and Phase 2 OLE patients (n=25).

Results: 211 patients enrolled into Global OLE; 189 had 12-month assessments by September 24, 2018. Safety profile remained consistent with previous studies. After 12 months of additional patisiran treatment in the Global OLE, durable improvement was seen for mNIS+7 (mean change [SEM]) in APOLLO/patisiran (-4.0 [1.9]) and Phase 2 OLE (-4.7 [3.5]) groups compared to their parent study baselines. Norfolk QOL-DN (only measured at parent study baseline in APOLLO) also showed durable improvement in APOLLO/patisiran patients (-3.9 [2.1]) following additional 12-months treatment in OLE. In the Global OLE, APOLLO/placebo patients experienced improvement on average after 12 months of patisiran (mNIS+7: -1.4 [2.4], Norfolk QOL-DN: -4.5 [2.5]), although they had progressed relative to APOLLO baseline (mNIS+7: +24.0 [4.2], Norfolk QOL-DN: +15.0 [3.4]) given the progression while on placebo in APOLLO.

Conclusions: Long-term patisiran treatment continues to show a positive benefit:risk profile, including patients dosed for 4 years or more. Overall, patients with longer-term exposure to patisiran demonstrated durability of effect. Despite marked progression on placebo during the 18-month APOLLO study, previously untreated patients exhibited halting of disease progression and QOL improvement following 12 months of patisiran. However, delay in treatment resulted in these patients accumulating greater disease burden compared to patients treated earlier with patisiran.

References: None.

Keywords: Amyloidosis

Grant Support: None.
Plasma NfL concentration is increased in patients with ATTRm and correlates with clinical severity scores

Mahima Kapoor¹, Julian Gillmore², Michael Lunn³, Andrea Malaspina⁴, Amanda Heslegrave⁶, Henrik Zetterberg⁶, Alex Rossor¹, Mary Reilly¹

¹MRC Centre for Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, United Kingdom of Great Britain and Northern Ireland, ²National Amyloidosis Centre, University College London (Royal Free Campus), London, United Kingdom of Great Britain and Northern Ireland, ³National Hospital for Neurology and Neurosurgery, London, United Kingdom of Great Britain and Northern Ireland, ⁴Centre for Neuroscience and Trauma, Blizard Institute, Queen Mary University of London, London, United Kingdom of Great Britain and Northern Ireland, ⁵Department of Neurodegenerative Disease, UK Dementia Research Institute, UCL Queen Square Institute of Neurology, London, United Kingdom of Great Britain and Northern Ireland, ⁶UCL QS ION, Inst. Neuroscience & Physiology, Uni of Gothenburg, Clinical Neurochemistry Lab, Sahlgrenska Uni Hosp, London, United Kingdom of Great Britain and Northern Ireland
Background

The success of gene silencing therapies in hereditary transthyretin amyloidosis (ATTRm) is a breakthrough for adult-onset, neurodegenerative diseases. A biomarker for peripheral nerve damage would be useful in detecting early peripheral nerve involvement and monitoring response to therapy. Neurofilament light chain (NFL) has been studied in several neurological disorders.

Aim

1) Evaluate whether plasma NFL (pNFL) concentration is elevated in patients with ATTRm compared to controls; 2) Investigate the association between pNFL and Neuropathy Impairment Score (NIS); 3) Assess the correlation between NIS and weighted examination score of the CMT Neuropathy Score (CMTES-R).

Methods

Blood samples were collected in 15 healthy controls and 85 patients with genetically-confirmed ATTRm, 42 (49.5%) had a neurological examination within four months of venepuncture. PNFL concentration was measured using a commercially available Simoa assay (Quanterix, Lexington, MA).

Results

Of the 85 patients with ATTRm, the most common genotypes were ATTRV30M (57.6%), ATTRS77Y (25.6%) and ATTTRT60A (22.9%). The control group was significantly older than the ATTRm group (70.7 years vs. 56.7 years, p = 0.04). NFL concentration was significantly higher in patients with ATTRm compared to healthy controls (44.3 pg/ml vs. 16.8 pg/ml, p < 0.001). Disease severity measured by NIS was a significant predictor of pNFL (β = 1.167, p = 0.006), whereas age was not (β = 0.04, p = 0.94). There was a tight correlation between NIS and CMTES-R (r = 0.89, p < 0.0001). 10 patients had received treatment for ATTRm prior to venepuncture; 8 patients had or were currently taking Diflunisal, 2 patients had undergone liver transplantation, 2 patients received patisiran and 1 patient was taking tafamidis.

Conclusion

NFL is a biomarker that is significantly raised in patients with ATTRm and correlates with the NIS. Further work is required to assess its clinical value in monitoring response to treatment.

References: None.

Keywords: Amyloidosis, Axonal Biology

Grant Support: None.
Identification of TMPRSS5/Spinesin, a Novel Schwann Cell Derived Plasma Biomarker for CMT1A

Matthew Davison1, Hongge Wang1, Kathryn Wang1, Katherine Call1, Xingyao Wu2, Riccardo Zuccarino2, Chelsea Bacon2, Yunhong Bai2, Laurie Gutmann2, Daniel Anderson2, Alexander Rosser3, Mary Reilly3, John Svaren4, Michael Shy2

1Sanofi, Framingham, MA, USA, 2University of Iowa, Iowa City, IA, USA, 3University College London, Queen Square Institute of Neurology, London, United Kingdom of Great Britain and Northern Ireland, 4University of Wisconsin, Madison, WI, USA

The development of biomarkers for Charcot-Marie-Tooth disease is critical for implementing effective clinical trials. A recent report1 identified neurofilament light (NEFL) as upregulated in the plasma of CMT disease patients (including CMT1A, SPTLC1, CMT2, CMTX1 and other CMT disease subtypes) compared to healthy controls, and NEFL correlated with disease severity clinical scores. However, no plasma/serum biomarker has been identified that is specific to the Schwann cells of peripheral nerve, the most directly affected cells in CMT1A.

We have used the new Olink immunoPCR platform, which provides high multiplex, good sensitivity detection, to profile CMT1a patient (n= 47, 2 cohorts) and normal control plasma (n= 41, two cohorts). Using five different Olink panels, each profiling 92 different proteins, we profiled a total of 400 unique proteins. The most promising candidate biomarker that was consistently elevated across independent cohorts of CMT1A samples relative to controls, was the TMPRSS5/Transmembrane protease serine 5 gene (also known as spinesin). The average upregulation was 2.05 fold (p = < 0.0001). Expression databases show that TMPRSS5 is most highly expressed in human peripheral nerve and central nervous system, and mouse studies show high levels in purified Schwann cells and oligodendrocytes.

In parallel, we found elevated levels of NEFL in the same samples, using the Olink detection system. These results confirmed the previously reported upregulation of NEFL in CMT1A patient samples, across multiple disease and normal cohorts (average of 1.58 fold, p < 0.0001); and also a positive correlation to disease clinical score. The levels of TMPRSS5 and NEFL were tested for correlation with CMT1A disease clinical scores and conduction velocities. These data provide the first identification of a Schwann cell specific protein that is elevated in plasma of CMT1A patients, and may provide a sensitive treatment-responsive biomarker, with good disease specificity, for clinical trials.


Keywords: CMTR, Schwann Cell

Grant Support: Charcot-Marie-Tooth Association NINDS/NCATS-ORD U54NS065712
Poster 11

Wildtype and Familial Transthyretin Amyloid Polyneuropathy: Distinct Cutaneous Biomarkers at the Distal Limb

Gigi Ebenezer, Mohammad Khoshnoodi, Daniel Judge, Ashley Marascalchi, Kelly Wagner, Boahan Pan, Michael Polydefkis

Johns Hopkins School of Medicine, Baltimore, MD, USA

We examined clinical and pathological peripheral nerve features among hATTR and wtTTR patients including (1) pathogenic TTR carriers with peripheral neuropathy (PN): hATTR-PN (n=19), (2) hATTR pathogenic carriers without PN: hATTR-noPN (n=9), (3) patients with ATTRwt presenting with cardiomyopathy (ATTRwt-CM, n=7), (4) PN patients found to have TTRwt amyloid on biopsy (TTRwt-PN, n=4), (5) 40 age/gender matched disease controls, and (6) non-TTR amyloidosis (AL (N=2), gelsolin (N=2). Patients underwent examination (NIS), electrophysiology and 3mm skin biopsies at the distal limb. 50µM skin sections were assessed for IENFD, SGNFD (PGP9.5), and TTR amyloid by anti-misfolded TTR immunohistochemistry and Congo red.

Amyloid was detected in d.leg skin with higher sensitivity by anti-misfolded TTR-immunohistochemistry than with Congo red staining (in hATTR: 57%vs.93%, hATTR-PN: 58%vs.100% with no controls or AL/gelsolin patients being positive (100% specificity). Amyloid burden was higher in hATTR-PN vs hATTR-noPN (% mean±SD, hATTR-PN: 17.5±25.8, TTR-noPN: 7.1±13.2) and inversely correlated with d.leg IENFD (p=0.02, r=-0.45). While amyloid was detected in 100% of hATTR-PN subjects in least at one leg site, the amyloid burden varied greatly with dense deposits in V30M patients to mild in V122I. IENFD correlated inversely with NIS-LL (d.leg: p<0.0001, r=-0.70; p.thigh: p<0.001, r=-0.63), and positively with sural (p=<0.001, r=0.69) and peroneal nerve (p<0.001, r=0.68) amplitudes. TTRwt-PN and TTRwt-CM patients had scanty amyloid deposits, primarily on ascending sweat ducts and nerve fibers while amyloid deposited in many dermal adenexal structures in hATTR.

3mm skin biopsies have high diagnostic yield in detecting amyloid of different etiologies. Immunohistochemistry against anti-misfolded TTR is more sensitive than Congo red in detecting amyloid and differentiates hATTR from TTRwt. TTRwt may represent a rare unrecognized etiology for peripheral neuropathy analogous to TTRwt-CM. The pattern of amyloid deposition in hATTR is distinct from ATTRwt.


Keywords: Amyloidosis, Small Fibers

Grant Support: None.
Preclinical Gene Therapy Studies for FIG4/CMT4J and GARS/CMT2D.

Robert Burgess¹, Kathryn Morelli², Maximiliano Presa³, Laurent Bogdanik³, Rachel Bailey⁴, Steven Gray⁴, Nettie Pyne⁵, Lindsay Wallace⁵, Allison Fowler⁵, Scott Harper⁵, Cathleen Lutz³

¹The Jackson Laboratory, Bar Harbor, ME, USA, ²The Jackson Laboratory, The University of Maine, Bar Harbor, USA, ³The Jackson Laboratory, Bar Harbor, USA, ⁴University of Texas Southwestern, Dallas, USA, ⁵The Research Institute at Nationwide Children’s Hospital, Columbus, USA

Inherited peripheral neuropathies are candidates for gene therapy approaches, although the diversity of mutations will require a variety of strategies. Here, we report the results of two preclinical studies for Charcot-Marie-Tooth types 4J and 2D. In both studies, mouse models were dosed with adeno-associated virus 9 (AAV9) to deliver the gene therapy payload to peripheral neurons. For CMT4J, recessive loss-of-function mutations in mouse Fig4 were rescued by a codon-optimized human FIG4 gene. Treatment by intracerebroventricular (ICV) injection at postnatal day (PND) one or four resulted in survival up to a year, compared to a median lifespan of ~35 days in untreated mice. Treatment by intrathecal delivery at PND seven or eleven also increased life span (median ~100 days in PND7 treated mice). Motor neurons showed improved conduction velocity, decreased vacuolization in the ventral horn, and decreased axon loss in the femoral motor nerve. Treated mice showed grip strength and motor performance that closely approximated wild type littermates. Thus, this treatment is effective within the limited treatment window provided by the aggressive Fig4 mouse model.

To treat dominant mutations in GARS underlying CMT2D, we used AAV9-delivered RNAi specifically targeting mutant GARS transcripts. This induce allele-specific knockdown was tested in two mouse models of CMT2D, one of which is an engineered human disease allele. When delivered ICV at birth, this approach was able to almost completely prevent the neuropathy, which otherwise develops by three weeks-of-age. Body weight, grip strength, sciatic nerve conduction velocity and femoral nerve axon number were all indistinguishable from wild type littermates. However, treating after the onset of symptoms did not promote regeneration, and had limited benefit that went down quickly with age. Thus, our studies show that allele-specific knockdown is technically feasible and is efficacious for dominant mutation in GARS, but early treatment is needed for maximal benefit.

References: None.

Keywords: Pre-clinical Studies, Axonal Biology

Grant Support: Muscular Dystrophy Association, National Institutes of Health U54 OD020351, R21 NS105116, Talia Duff Foundation
Objective: To report a single center’s experience of treating adult SMA patients with Nusinersen. Studies in adult SMA patients are lacking, especially of those treated with Nusinersen.

Design/Methods: We conducted a chart review of adult patients with genetically confirmed SMA types 2 or 3 seen between 2017-2019. Results: Twenty-three patients were included, 9 type 2 and 14 type 3, median age was 35 (range 20-71). Twenty-two were nonambulatory. Seventeen had severe scoliosis, 12 had undergone thoracolumbar fusion. Of those, 6 were referred for bone laminectomy to establish access for treatment and three underwent procedure. Ten had significant respiratory impairment necessitating ventilation and 2 underwent tracheostomy. Ten were treated with Nusinersen for median of 10 months (range 4-16). All treated patients exhibited stability in %MRC at 4-6 months. 5 were treated for 12 months. Of those, 2 exhibited stability, three demonstrated very modest improvement with %MRC change mean of 3.5% and 5% in upper and lower limbs respectively. Two patients were treated for 16 months, exam in one patient remained stable, the other had modest improvement with %MRC change mean of 7.5%. One patient died shortly after treatment initiation from respiratory failure. One stopped treatment due to recurrent pneumonias and lack of improvement at 12 months. All untreated patients’ % MRC remained stable. Four patients declined treatment due to comorbidities, lack of data in adults or advanced stage. Four patients awaiting treatment. Treatment side effects included post lumbar puncture headache in 5 patients, two of which necessitated blood patch, 1 developed bacterial meningitis requiring admission for long term antibiotics. Conclusions: The degree of impact on strength and function in adult SMA treated with Nusinersen remains unclear, and complications secondary to its intrathecal administration can be serious. More data is needed to better understand the role of Nusinersen in adult SMA patients.
Influence of Body Mass Index on disability in Children with CMT

Gabrielle Donlevy¹, Sarah Garnett¹, Kayla Cornett², Marnee McKay³, Jennifer Baldwin⁴, Joshua Burns (Joint Senior Author)¹, Manoj Menezes (Joint Senior Author)¹

¹The University of Sydney, The Children’s Hospital at Westmead, Sydney, New South Wales, Australia, Sydney, Australia, ²The University of Sydney, New South Wales, Australia, Columbia University, Irving Medical Center, New York, NY, USA, Sydney, Australia, ³The University of Sydney, Sydney, New South Wales, Australia, Sydney, Australia, ⁴School of Clinical Sciences, Auckland University of Technology, Auckland, New Zealand, Auckland, New Zealand

Growth and body mass influence disability in many childhood neuromuscular disorders. In this study we examined the relationship between Body Mass Index (BMI) and disability in children with CMT. We conducted a cross sectional analysis of 477 patients with CMT aged 3-20 years from the Inherited Neuropathies Consortium, and 316 age-and-sex matched controls from the 1000 Norms Project[1]. BMI was categorised according to the International Obesity Task Force (IOTF)[2], and compared with scores on the CMT Pediatric Scale (CMTPedS) [3]. ITOF categories were collapsed into five age-and-sex equivalent BMI groups: severely underweight (BMI <17kg/m²); underweight (≥17kg/m² to <18.5kg/m²); healthy weight (≥18.5kg/m² to <25kg/m²), overweight (BMI ≥25 kg/m²to <30 kg/m²); obese (BMI ≥30 kg/m²). Compared to normative reference data, there was a significantly higher proportion of children with CMT categorised as severely underweight (5.6% vs 0.3%), underweight (10.4% vs 5.1%), and obese (7.6 vs 3.8%) (p<0.05). There was fewer children categorised as healthy weight (61.2% vs 74.4%) (p<0.05), and the distribution of overweight (15.1 % vs16.5%) between the two groups was comparable. Mean CMTPedS scores for each group were: severely underweight (27 ±9), underweight (20 ±8), healthy weight (17± 9), overweight (17± 9) and obese (22 ±10). Compared to healthy weight children with CMT, being severely underweight with CMT was significantly more disabling (p< 0.0001), as was being obese (p=0.015). There is a higher frequency of underweight and obese children with CMT compared to age-and-sex matched healthy children. Underweight and obese children with CMT are more disabled than children of healthy weight. A longitudinal study is required to determine the need for specific nutritional intervention to reduce the burden of CMT.


Keywords: CMTR, Other

Grant Support: None.
Mutations in the GJB1 gene, encoding gap junction protein connexin32 (Cx32), cause X-linked Charcot-Marie-Tooth disease, one of the commonest forms of inherited demyelinating peripheral neuropathy. Our previous studies have shown that gene addition mediated by an intrathecally injected lentiviral vector carrying the GJB1/Cx32 gene under the myelin protein zero (Mpz) promoter, ameliorates the phenotype of the Cx32 knockout (KO) mouse model of the disease, through Schwann cell-targeted expression. In order to develop a more translatable approach, we cloned the Mpz.Egfp (mock vector) and Mpz.GJB1 (full vector) expression cassettes into the AAV transfer plasmid and used the AAV9 vector serotype with established safety in clinical trials for other disorders to target Schwann cells. Following lumbar intrathecal injection of the AAV9-Mpz.Egfp vector in 2-month old wild type (WT) mice, EGFP reporter gene expression was detected in the perinuclear compartment of Schwann cells in lumbar roots, sciatic and femoral nerves, at rates similar to those observed after lentiviral delivery. After delivery of the AAV9-Mpz.GJB1 therapeutic vector into 2-month old Cx32 KO mice, Cx32 expression was detected in the paranodal non-compact myelin areas of myelinated fibers. We then performed a post-onset treatment trial in which 6-month old Cx32 KO mice were randomized to receive either the mock or the full AAV9 vector. Outcome was assessed at 8 and 10 months of age by behavioral, electrophysiological and morphological analyses. We observed improved motor performance and sciatic nerve conduction velocities along with improved myelination and reduced inflammation in PNS tissues of treated mice. Blood neurofilament light levels, a clinically relevant biomarker, were also significantly ameliorated in treated compared to mock-treated mice. This study provides evidence that a more clinically translatable AAV9-mediated gene therapy approach targeting Schwann cells could be potentially used for the treatment of CMT1X, even after the onset of the disease.

References: None.

Keywords: CMTR, Schwann Cell

Grant Support: Muscular Dystrophy Association and Charcot-Marie-Tooth Association (Grants MDA 480030 and MDA603003 to KAK). Dr. Kagiava is a recipient of a Young Research’s Award by the Cyprus Research Promotion Foundation (KOYΛΤΟΥΡΑ/ΒΡ-ΝΕ/0416/07).
CMT1A, the most common of Charcot-Marie-Tooth diseases, results from the duplication of the Peripheral Myelin Protein 22 (PMP22) gene. This gene encodes for a small protein of 22 kDa, PMP22, mainly produced by Schwann cells and the excess of PMP22 leads to demyelination. There is still no cure for this disease, but one approach for a treatment is gene therapy. A transgenic rat model exists for CMT1A, which possesses 3 copies of the mouse PMP22 gene. Our goal is to provide a proof of principle for gene therapy in peripheral nerves using this rat model of CMT1A. Our strategy is to reduce the overexpression of mouse PMP22 protein in rats Schwann cells using short hairpin RNAs (shRNAs). shRNAs are small non-coding RNAs that specifically bind to targeted mRNAs resulting in their degradation. Adeno-associated serotype 9 (AAV9) viral vector was used to deliver these molecular tools to cells affected by the disease. AAV9 was selected for its high transduction rate of myelinating Schwann cells for its good diffusion and low immunogenicity. We performed bilateral injections in the sciatic nerve of control and CMT1A rats. The efficiency of this gene therapy was high as muscle strength (grip test), mobility (Rotarod) and nerve conduction velocity of treated CMT1A rats were maintained to wildtype levels on a long range of time (at least 12 months, which represent the third of the life expectancy). AAV9 injection did not generate an immune response in most of the animals and the unwanted AAV9 off target infection was very limited as well. All together, these results highlight this strategy as a promising one to treat CMT1A disease. We are now looking for a preclinical validation of the molecular tools and injection methods on large animal model, such as non-human primates, before entering the clinical phase.

References: None.

Keywords: CMTR, Pre-clinical Studies, Schwann Cell

Grant Support: None.
CMT1A is a rare, inherited, chronic peripheral neuropathy affecting 1 patient out of 5000. Patients suffer from distal dominant muscle atrophy compromising gait and activities of daily living, stocking-glove sensory loss, and overall reduced quality of life. To date, no treatment is available to stabilize or reverse the disease. PXT3003 is a novel oral fixed-dose 3 drug combination: baclofen, naltrexone and D-sorbitol targeting multiple disease pathways. Methods: PLEO-CMT is an international, multi-center, randomized, double-blind, placebo (Pb)-controlled pivotal phase III trial, assessing the efficacy and safety of 2 doses of PXT3003 given twice daily for up to 15 months to mild-to-moderate severity, genetically confirmed, CMT1A patients aged 16 to 65, with Dose 1 (D1) (3 mg baclofen, 0.35 mg naltrexone and 105 mg sorbitol), and Dose 2 (D2) at twice D1. Primary Objective: To assess the effect of PXT3003 on disability measured by the mean change from baseline of Overall Neurology Limitations Scale (ONLS) score at month 12 and 15. The 10-meter Walk Test (10-mWT) constituted one of the secondary efficacy endpoints. Results: 323 patients were randomized 1:1:1 in the study (D1=109, D2=113, Pb=101). Characteristics of the three groups were comparable at baseline. PXT3003 D2 met the primary endpoint: a clinically meaningful reduction of 0.37-point ONLS (95% CI [0.1,0.64], p=0.008) was observed vs. Pb. In addition, in group D2 a trend for improvement in the ONLS score was observed vs. baseline -0.20 (95% CI [-0.447, -0.039], p=0.098). A reduction of 0.47 sec (95%CI [0.09,0.85], p=0.016) was observed on the 10-mWT with D2 vs. Pb. The rate of treatment-emergent adverse events leading to treatment withdrawal was low and similar between groups (D2=5.3%, D1=5.5%, Pb=5.6%). Conclusion: PXT3003 is the first treatment for CMT1A demonstrated to be effective, safe and well tolerated.

References: For the Pleo CMT Investigators

Keywords: Clinical Trials, Human Genetics, Schwann Cell

Grant Support: None.
Although IVIg efficacy for the treatment of CIDP has been demonstrated in randomized controlled trials, the optimal treatment approach for patients on chronic therapy is unknown. Herein we update progress on the investigator-initiated, multi-center “GRIPPER” study that prospectively evaluates “wear-off” or other IVIg treatment-related fluctuations in patients with CIDP. The primary outcome measure is Jamar grip strength (GS), performed daily for 6 months. Home nursing visits also capture Rasch-built Overall Disability Score (R-ODS), Timed Up and Go Test (TUGs), Overall Neuropathy Limitations Scale (ONLS), Modified Fatigue Severity Scale (mFSS), and Visual Analog Pain Severity Scale (VAS) weekly for 6 months. The QOL Short Form Physical Component Summary (SF-36v2®) is collected at baseline, week 12, and week 24. Serum IgG levels are collected at 3 time-points surrounding IVIg infusions (peak, trough, and mid-cycle). Study “wear-off” frequency data is currently being analyzed by assessing the proportion of subjects with any given degree of GS and R-ODS intracycle fluctuation and the proportion of cycles in which GS and R-ODS fluctuation occurs. To determine the extent of “wear-off” the degree of difference between maximum and minimum GS, R-ODS, TUGs, ONLS, and VAS scores are being analyzed. Study enrollment (n=29) and data collection are now complete. Preliminary study results are forthcoming. By better understanding the frequency and extent of IVIg treatment-related fluctuations we expect that these results will help facilitate development of CIDP treatment optimization strategies.

References: None.

Keywords: Inflammatory, Clinical Trials, Other

Grant Support: None.
Immediate Effects of AFOs on Balance in Individuals With Inherited Neuropathies in the Clinical Setting

Reza Sadjadi¹, Katherine Burke², Amy Swartz Ellrodt², Natalie Grant², Kenneth Cornell³, Sabrina Paganoni¹

¹Massachusetts General Hospital, Department of Neurology, Boston, MA, USA, ²Massachusetts General Hospital, Department of Neurology, Boston, USA, ³Cornell Orthotics and Prosthetics, Peabody, MA, USA

Purpose: Inherited neuropathies cause weakness and atrophy of the muscles generally in distal extremities, with or without sensory changes. These impairments contribute to impaired balance and gait, and increase risk for falls and secondary injuries. Dynamic carbon ground reaction ankle foot orthoses (AFOs) are one type of lower extremity orthosis that can be prescribed to help improve gait. To our knowledge, there are no studies that evaluate the immediate impact of these AFOs on balance in this population in a clinical setting. Methods: Participants were seen in clinic by a physical therapist and orthotist. Patients with gait impairment due to combination of distal weakness and sensory ataxia were asked to complete the modified Clinical Test of Sensory Interaction and Balance (mCTSIB) and the 4-item Dynamic Gait Index (DGI) with and without AFOs on to assess static and dynamic balance. To minimize the ceiling effect with the DGI, AFOs were not considered an assistive device for any of the items. Results: Nine individuals with confirmed hereditary neuropathies participated in this study. The average DGI scores were 6/12 without the AFOs on and 10/12 with the AFOs on. All participants improved on at least one of the conditions of the mCTSIB with use of the AFOs; however, there were no significant changes noted on any of the individual components of the mCTSIB. Conclusions: The findings in this study suggest a significant and immediate improvement in dynamic balance during ambulation with the use of carbon fiber ground reaction AFOs, as assessed by the 4 Item DGI. Data on static balance did not reach significance suggesting the need for future studies to further assess the effects of AFOs on static standing balance, as well as the impact of training with physical therapists.

References: None.

Keywords: CMTR

Grant Support: None
Charcot-Marie-Tooth disease (CMT) is a hereditary sensorimotor neuropathy, usually presenting in childhood with areflexia, distal amyotrophy mostly in the legs, associated with foot deformities and walking impairment. Asymmetric weakness may be observed in 30% of patients. We describe here two very unusual patients who displayed a sensorimotor weakness strongly predominant in one hemibody. Patient 1 is a 28 years old female, with a history of scoliosis in childhood, who presented a motor weakness and wasting since age 18, preferentially affecting the right side. She also displayed peripheral right facial palsy and diffuse areflexia. Electroneuromyography (ENMG) showed a bilateral but asymmetric demyelinating neuropathy, confirmed by the nerve biopsy. The disease evolution was marked by respiratory involvement and laryngeal palsy. Corticosteroids, immunoglobulins and plasmapharesis were inefficient. Patient 2, a male aged 63, had difficulties walking since the age of 10 years old due to a right stepping. He underwent several surgeries on his right leg during childhood and early adulthood. Clinical examinations also showed an atrophic right sensorimotor deficit, with right hearing loss and diffuse areflexia. ENMG displayed bilateral but asymmetric sensorimotor axonal neuropathy. Nerve MRI did not show any neural tumor. CMT disease gene panel, performed for these 2 patients on DNA extracted from the white blood cells, disclosed no mutation in the known genes. In very rare cases, CMT might present as a hemicorporeal deficit, prompting differential diagnosis such as chronic inflammatory demyelinating neuropathy (CIDP) or neural tumors. In our patients the long lasting disease, scoliosis, pes cavus and the absence of nerve tumor as well as the inefficacy of CIDP treatment comforted us in the hereditary hypothesis. A somatic mutation occurring in the development of embryo in a gene expressed in peripheral nerve could explain the asymmetry. DNA analysis on nerve biopsy is ongoing in Patient 1.

References: None.

Keywords: Human Genetics

Grant Support: None.
CMT2A is the most frequent form of CMT2 (20% of patients), and is caused by mutations in the nuclear encoded mitochondrial gene Mitofusin-2 (MFN2). MFN2 is highly conserved, and is a component of the outer mitochondrial membrane regulating fusion of mitochondria to each other or to membranes of the ER. Most MFN2 mutations cause autosomal dominant CMT2A, and the typical onset is in childhood with a severe axonal neuropathy (Verhoeven et al., 2006). Recessive mutations in MFN2, classified as CMT2A2B, are rare (Nicholson et al., 2008). Here we describe a patient with childhood onset predominantly motor axonal neuropathy who was found to have homozygous c.748C>T mutations resulting in amino acid substitution p.Arg250Trp. The patient was evaluated at 28 years of age. Milestones were on time. She developed an abnormal gait in early childhood and was a slow runner. She required tendon transfers in hands and feet at age 5. At 16 years she required bilateral AFOs. Hand function decreased around 20s. She reported no abnormal sensations. On exam, there was no movement below the knees and proximal weakness in the lower extremities. Strength was significantly reduced in the distal upper extremities. Sensory evaluation was normal. There was an evidence for severe axonal polyneuropathy on the nerve conduction study. R250W is predicted to be not tolerated and possibly damaging (SIFT, PolyPhen), and the frequency in population database ExAC is 0.00002%. Homozygous c.748C>T is present in two affected siblings who have heterozygous carrier parents with no symptoms, signs or abnormalities on nerve conductions. Further Arg250 is moderately conserved across species and it is located in the GTPase domain. CMT2A2B, a recessive disorder, is caused by a loss of function mechanism, and this patient demonstrates the importance of R250 for the normal GTPase activity and function of MFN2.

References: None.

Keywords: CMTR

Grant Support: None.
Poster 22

Differentially expressed genes within peripheral nerve of a dog model of late-onset peripheral neuropathy

Susannah Sample1, Emily Binversie2, Lauren Baker2, Jordan Gruel2, Mark Berres3, Josh Hyman3, Peter Muir2, John Svaren2

1University of Wisconsin - Madison, School of Veterinary Medicine, Madison, WI, USA, 2University of Wisconsin-Madison, School of Veterinary Medicine, Madison, WI, USA, 3University of Wisconsin-Madison, Biotechnology Center, Madison, WI, USA

Naturally occurring diseases in dogs can serve as valuable models of corresponding human conditions, particularly for neurodegenerative conditions. Dogs are affected by a variety of breed-associated peripheral neuropathies, the most common of which is a late-onset peripheral neuropathy (LPN) found in Labrador Retrievers. The clinical features of LPN are similar to human peripheral neuropathy. The most prominent features of LPN, laryngeal paralysis and pelvic limb weakness, are associated with the longest peripheral motor nerves in the dog. Labrador Retrievers typically present with signs of LPN by 10-12 years of age. A GWAS from our laboratory has highlighted two regions that significantly associate with LPN, both of which contain genes known to influence axonal regulation. Further preliminary data indicates that LPN is likely an autosomal dominant disease. Alterations in gene expression from pertinent tissues associated with LPN are not defined. We aim to identify transcriptome alterations in peripheral nerve from LPN affected dogs. We collected peripheral nerve biopsies from Labrador Retrievers who died as a result of LPN, unaffected aged control dogs and young control dogs. Differential gene expression profiles were evaluated. Further data from spinal cord and dorsal root ganglia are being obtained and analyzed. Since our data suggest that the causative mutation may be noncoding, we will test the hypothesis that affected dogs have deregulated gene expression in genes proximal to the GWAS hits. Understanding alterations in gene expression profiles in affected dogs, with a focus on early clinical or preclinical animals, will help clarify the underlying genetic basis of LPN. Genetic discovery in this model could help explain late onset human peripheral neuropathy, where many cases

References: None.

Keywords: Axonal Biology, Other

Grant Support: Susannah Sample received support from the National Institutes of Health (K01OD019743-01A1)
Poster 23

Role of Slit2 in peripheral nerve development and regeneration

Emanuela Porrello1, Michaela Horner2, Alessio Gioia3, Francesca Bianchi4, Sundararajan Srinivasan5, Luca Massimino6, Paola Podini7, Ubaldo Del Carro4, Cinthia Farina8, Angelo Quattrini7, Jian-Guo Geng8, Alain Chetodal9, Stefano Previtali10

1San Raffaele Scientific Institute, Division of neuroscience, Neuromuscular repair Unit, Milan, Italy, 2San Raffaele Scientific Institute, Division of neuroscience -Neuromuscular repair Unit, Milan, Italy, 3San Raffaele Scientific Institute, Division of neuroscience - Neuromuscular repair Unit, Milan, Italy, 4San Raffaele Scientific Institute, Division of neuroscience, Movement disorders Unit, Milan, Italy, 5San Raffaele Scientific Institute, Division of neuroscience, Immunobiology of neurological disorders Unit, Milan, Italy, 6San Raffaele Scientific Institute, Division of neuroscience, Stem Cell and Neurogenesis Unit, Milan, Italy, 7San Raffaele Scientific Institute, Division of neuroscience, Experimental neuropathology, Milan, Italy, 8Department of Biologic and Materials Sciences, University of Michigan School of Dentistry, Ann Arbor, MI, USA, 9Sorbonne Universités, UPMC Université Paris 06, INSERM, CNRS, Institut de la Vision, Paris, France, 10San Raffaele Scientific Institute, Division of neuroscience, Neuromuscular repair Unit, Milan, Italy

Background- Radial sorting of axons is the process by which Schwann cells choose larger axons to myelinate during development. This process is perturbed and arrested in human diseases, such as LAMA2, due to mutations in genes coding for laminin211 and associated molecules. Recently, we described Jab1 as a new molecule downstream the laminin211 pathway, as loss of Jab1 in Schwann cells results in axonal sorting defect and dysmyelination, which is a phenocopy of laminin211 disease. By performing transcription analyses searching for other molecules involved in the process of axonal sorting and dysmyelination in Jab1 null mice we identified a number of cell-cell adhesion molecules abnormally expressed in these mice. Among them, we found Slit2, known to play a role in axonal pathfinding in the brain. The aim of this study was to investigate the role of Slit2 in peripheral nerve development and regeneration, and to examine possible implications of Slit2 in LAMA2 disease.

Materials & Methods- We analyzed gain and loss of function of Slit2 in mouse models. We generated mice with conditional inactivation of Slit2 in Schwann cells using the P0-Cre transgene (Slit2cKO) and we used the Slit2 trasgenic mutant mouse overexpression the human Slit2 gene (Slit2tg). We carried out morphological, biochemical and neurophysiological analyses to evaluate the peripheral nerve development and regeneration in both mouse lines. Results- We provide evidence that both Slit2cKO and Slit2tg mice develop axonal sorting defects consisting of disorganized Remak bundles containing tightly packed and large-caliber axons. Moreover, Slit2tg mice showed hypomyelination whereas Slit2cKO mice increased myelin thickness. Accordingly, neurophysiology showed reduced motor nerve conduction in Slit2tg mice but not in Slit2cKO mice. Finally, we provided evidence that Slit2 did not affect regeneration after nerve crush injury. Conclusions- Slit2 plays a role in the process of axonal sorting and myelination.

References: None.

Keywords: Schwann Cell, Axonal Biology, Axonal Regeneration

Grant Support: None.
A Novel Case of Demyelinating Neuropathy in Mitochondrial Trifunctional Protein Deficiency

Carla Zingariello¹, Sabrina Yum², Tim Estilow³

¹University of Florida, Gainesville, FL, USA, ²Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA, USA, ³Children's Hospital of Philadelphia, Philadelphia, PA, USA
INTRODUCTION

Mitochondrial trifunctional protein deficiency (MTPD) is a clinically heterogeneous disorder due to biallelic mutations in HADHA or HADHB leading to disruption in the last three steps of the long-chain fatty acid beta oxidation cycle. There are three main manifestations: a fatal, neonatal-onset cardiac form, a severe infantile hepatic form, and a milder, later-onset neuromyopathic form associated with axonal sensory or sensorimotor neuropathy with episodic rhabdomyolysis.

METHODS

We report a male child presenting with delayed walking, followed by frequent falls and gait instability starting at age 3. He had normal newborn screen, no reported episodes of rhabdomyolysis, and family history was negative for neuropathy. He underwent extensive laboratory, electrodiagnostic and genetic work-up, as well as sural nerve biopsy.

RESULTS

Neurologic exam was notable for bilateral foot drop with intact reflexes, distal leg atrophy, and later sensory ataxia. Laboratory work-up showed normal CK, pyruvate, lactate, and VLCFA.

Nerve conduction studies revealed absent sensory nerve responses, with uniform slowing in the demyelinating range in motor responses. Needle EMG showed severe chronic reinnervation in selected leg muscles. Sural nerve biopsy revealed moderate to severely decreased density of myelinated fibers, increased number of empty nerve strands, possible onion bulbs, and individual-to-small perivascular epineurial inflammatory collections.

A hereditary neuropathy NextGen sequencing panel was unrevealing. Whole-exome sequencing analysis revealed a known pathogenic homozygous missense mutation (c.703C>T, p.Arg235Trp) in HADHA. Repeat CK was elevated (12,906 U/L) and acylcarnitine profile was abnormal, though patient remained asymptomatic. Carnitine, plasma amino acids and urine organic acids were normal.

CONCLUSIONS

We describe a novel case of demyelinating neuropathy confirmed by electrodiagnostic testing and nerve biopsy, and that preceded by years the diagnosis of MTPD due to HADHA mutation. Our patient is unusual in having only asymptomatic elevated CK, as his mutation has been associated with recurrent episodes of rhabdomyolysis.


Keywords: Metabolic, Human Genetics

Grant Support: None.
**Poster 25**

**Nerve cross sectional area correlates to clinical severity in patients with Charcot Marie Tooth 1A**

Stefano Tamburin¹, Giampietro Zanette², Federica Taioli¹, Matteo Lauriola², Andrea Badari², Moreno Ferrarini¹, Tiziana Cavallaro³, Gian Maria Fabrizi¹

¹University of Verona, Department of Neurosciences, Biomedicine and Movement Sciences, Verona, Italy, ²Pederzoli Hospital, Neurology Division, Peschiera del Garda, Italy, ³Verona University Hospital, Neurology Division, Verona, Italy

**Introduction.** Nerve cross sectional area (CSA) was reported to be on average larger than normal in Charcot-Marie-Tooth disease type 1A (CMT1A), although to a variable extent in single patients. We explored whether CSA is correlated with clinical severity of CMT1A explored by CMT neuropathy score version 2 (CMTNS2) and its examination subscore (CMTES2). Methods. We assessed 56 patients (mean age 46.5, SD 2.2; 28 men, 28 women; 42 families) with CMT1A. They underwent nerve conduction study (NCS), including left median and ulnar nerve CMAP amplitude and MNCV, and high-resolution ultrasound (HRUS) of the left median and ulnar nerves across their whole course and peroneal nerve at the fibular head. Results. Univariate analysis showed NCS and HRUS variables to be significantly correlated to CMTNS2 and CMTES2 and to each other. Multivariate analysis showed that ulnar MNCV was significantly correlated with CMTNS2 only, while median nerve CSA at the forearm was significantly correlated with CMTNS2 and CMTES2. Conclusions. Nerve CSA explored with HRUS was significantly associated to clinical scores in patients with CMT1A. These data suggest that HRUS findings might represent a potential instrumental biomarker of CMT damage and progression. Future longitudinal studies should explore whether nerve CSA might be sensitive to change and potentially useful in clinical trials.

**References:** None.

**Keywords:** CMT

**Grant Support:** None.
Creatine kinase (CK) is influenced by numerous factors including gender, race, muscle bulk and physical activity. An elevated CK may indicate a myopathic disorder but mildly elevated levels are also seen in neuropathies including Charcot Marie Tooth disease (CMT). The aim of this study was to assess CK levels in CMT and related disorders. Serum CK was collected in 161 patients with CMT and related disorders. Our cohort consisted of 63 female and 98 male patients. The CK range was 39-2205 IU/L. Overall in our cohort the highest CK level was recorded in a male patient with CMTX (2205). 118 (73%) of patients had the following subtypes of CMT (CMT1, CMT2, intermediate CMT), 24 HMN (15%), 8% HSN (13) and 4% HNPP (6). 77 (48%) of patients had an elevated CK level and the majority were male. Abnormal CK levels (normal range Male: 38-204, Female: 26-140) were found in 40% of CMT1 patients (average 271 IU/L, range 141-831), 55% of CMT2 (average 383 IU/L, range 154-1218), 40% of intermediate CMT (average 496 IU/L; range 149-2205), 67% of HMN (average 431 IU/L; range 144-1618) and 38% of HSN (average 226 IU/L; range 141-400) subtypes. Out of 87 genetically confirmed patients, 44 had an abnormal CK level, the three most common genotypes being Chromosome 17 duplication (23%), HSPB1 (12%), MPZ (5%). and average CK level for these three was 254 IU/L for Chromosome 17 dup., 396 IU/L for HSPB1, and 396 IU/L for MPZ. In conclusion, this study highlights that patients with HMN were most likely to have elevated CK levels. Assessment of a CMT cohort with larger numbers could evaluate for a correlation between CK and disease severity in various CMT subtypes and related disorders. We also found no correlation between CK levels and disease severity as measured by the CMTES.

References: None.

Keywords: CMTR

Grant Support: None.
**Electrodiagnostic accuracy in polyneuropathies: supervised learning algorithms versus electrophysiologists**

Antonino Uncini¹, Graziano Aretusi², Fiore Manganelli³, Yukari Sekiguki⁴, Laurent Magy⁵, Stefano Tozza³, Astuko Tsuneyama⁴, Sophie Lefour⁵, Satoshi Kuwabara⁴, Lucio Santoro³, Luigi Ippoliti⁶

¹Department of Neuroscience, Imaging and Clinical Sciences, University “G. d’Annunzio”, Chieti, Italy, ²Department of Neurosciences, Imaging and Clinical Sciences University “G. d’Annunzio”, Chieti, Italy, ³Department of Neurosciences, Reproductive Sciences and Odontostomatolog, University of Naples “Federico II”, Naples, Italy, ⁴Department of Neurology, Graduate School of Medicine, Chiba University, Chiba, Japan, ⁵National reference center for rare peripheral neuropathies and Department of Neurology, University of Limoges, Limoges, France, ⁶Statistic Unit, Department of Economics, University “G. d’Annunzio”, Pescara, Italy

Introduction. Electrodiagnosis is a mainstay in the evaluation of polyneuropathies. However, up to 47% of chronic inflammatory demyelination polyneuropathy (CIDP) patients received an alternative diagnosis at reevaluation and the interpretation of nerve conduction studies was a major factor in misdiagnosis. Supervised learning algorithms (SLAs) can predict the electrodiagnostic classification of a subject on the basis of a training data set based on the leave out one cross validation method. Methods. In this study we investigated the diagnostic accuracy of four SLAs, shrinkage discriminant analysis, multinomial logistic regression, classification and regression trees, support vector machine (SVM), and of three expert and three trainee electrophysiologists. Three academic tertiary neuromuscular centers participated in the study and 434 subjects were enrolled with the following reference diagnoses: CIDP (99), Charcot-Marie-Tooth disease type 1 (124), hereditary neuropathy with liability to pressure palsy (46), diabetic polyneuropathy (67), and controls (98). The final data set contained, for each subject, three motor and three sensory nerves with 27 electrophysiological parameters. Results. SVM showed the highest (91%) diagnostic accuracy for all five diagnostic classes when compared with other SLAs (76.3-86.6%), expert neurophysiologists (74.9-82%), and trainees (54.6-77%). SVM demonstrated also the best balance between sensitivity and specificity. In particular, regarding CIDP, SVM had sensitivity of 80.8% and specificity of 95.2% compared with other SLAs (52.5-75.8%; 89.2-98.8%), expert neurophysiologists (51.5-77.8%; 80.9-96.4%) and trainees (36.4-52.5%; 68.4-98.5%). Conclusions. Overall SVM exhibits the best diagnostic performances compared with other SLAs and neurophysiologists. Moreover SVM, as other SLAs, has the advantage of assigning to a subject the probability of belonging to each of the five diagnostic classes. SLAs are already available in statistical packages and electromyographic machines could be easily equipped with a software to introduce this robust diagnostic support system in clinical practice to reduce misdiagnoses of polyneuropathies.

References: None.

Keywords: Inflammatory, Diabetes, Other

Grant Support: None.
Nerve Conduction in Patients with Transthyretin Amyloidosis with Polyneuropathy Enrolled in THAOS

Marcia Waddington-Cruz¹, Yukio Ando², Leslie Amass³, Rajiv Mundayat⁴, Yoshiki Sekijima⁵

¹Federal University of Rio de Janeiro, National Amyloidosis Referral Center, CEPARM, Rio de Janeiro, Brazil, ²Department of Neurology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan, ³Pfizer Inc, Collegeville, PA, USA, ⁴Pfizer Inc, New York, NY, USA, ⁵Shinshu University School of Medicine, Matsumoto, Japan

Introduction: Patients with transthyretin amyloidosis with polyneuropathy (ATTR-PN) show altered motor and sensory nerve conduction, namely decreases in amplitude and velocity [1]. Characterization of these changes over time may be useful in assessing disease progression. The Transthyretin Amyloidosis Outcomes Survey (THAOS) is an ongoing, global, longitudinal, observational registry of patients with transthyretin amyloidosis, including both inherited and wild-type disease, and asymptomatic patients with TTR mutations. The primary objective of the present analysis was to assess nerve conduction over annual visits for ATTR-PN patients enrolled in THAOS.

Methods: ATTR-PN patients were included in the analysis (data cut-off: January 16, 2019) if they had a TTR mutation, one or more neurologic symptoms reported at any time during the study, and left and right values of sural or peroneal amplitude, both non-missing and greater than zero, at any time during the study. Both the amplitude and velocity of sural and peroneal conduction were measured at annual visits.

Results: Patients (N=1,009), both male (43.8%) and female (56.2%), had the following baseline characteristics: predominant TTR genotype, Val30Met (83.9%); mean (SD) age at onset and enrollment, 38.9 (13.1) and 42.6 (14.2) years; mean (SD) duration of symptoms, 8.6 (6.0) years; and mean (SD) amplitude and velocity of sural, 20.1 (12.5) μV and 51.5 (33.4) m/s, and peroneal conduction, 17.6 (17.2) μV and 46.5 (5.7) m/s. Across annual visits, the mean (SD) change from baseline in sural nerve amplitude generally decreased (year 1: -1.1 [7.5], n=553; year 8: -5.1 [10.8] μV, n=52), with a concomitant decline in velocity (year 1: -0.2 [5.8]; year 8: -2.1 [6.0] m/s). For the peroneal nerve, decreases in amplitude, but not velocity, were observed; however, smaller sample sizes may have contributed to variability.

Conclusions: These data suggest that progressive deterioration in nerve conduction may be a useful indicator of ATTR-PN disease progression.


Keywords: Amyloidosis

Grant Support: THAOS and this analysis were sponsored by Pfizer. Leslie Amass and Rajiv Mundayat are full-time employees of Pfizer and hold stock and/or stock options with Pfizer. Medical writing support was provided by Diane Hoffman, PhD, of Engage Scientific Solutions and was funded by Pfizer.
Digitally assessed patient-reported real-world treatment patterns for Charcot-Marie-Tooth disease in the UK and US

Tjalf Ziemssen\textsuperscript{1}, Shahram Attarian\textsuperscript{2}, Florian Thomas\textsuperscript{3}, Allison Moore\textsuperscript{4}, Daniel Tanesse\textsuperscript{5}, Xavier Paoli\textsuperscript{6}, Viviane Bertrand\textsuperscript{6}, Youcef Boutalbi\textsuperscript{6}, Emma Bagshaw\textsuperscript{7}, Hara Kousoulakou\textsuperscript{7}, Mark Larkin\textsuperscript{7}

\textsuperscript{1}Universitätsklinikum Carl Gustav Carus an der Technischen Universität Dresden, Germany, Dresden, Germany, \textsuperscript{2}Assistance Publique - Hopitaux de Marseille, Marseille, France, \textsuperscript{3}Hackensack University Medical Center, Hackensack, USA, \textsuperscript{4}Hereditary Neuropathy Foundation, New York, USA, \textsuperscript{5}CMT France, Fougères Cedex, France, \textsuperscript{6}Pharnext SA, Issy-les-Moulineaux, France, \textsuperscript{7}Vitaccess Ltd., Oxford, United Kingdom of Great Britain and Northern Ireland

Introduction:

The objective of this analysis was to examine patient-reported treatment patterns for Charcot-Marie-Tooth disease (CMT) in UK and US real-world practice.

Methods:

Adults with CMT were recruited to a two-year international observational study exploring the real-world impact of the disease. Data were collected via CMT&Me, a ‘bring your own device’ app specifically developed for this study, through which participants were asked questions about demographic, CMT management-related and quality-of-life variables. This interim analysis examined CMT treatment patterns, including use of surgical and physical therapies, medicines, and rehabilitative aids/orthoses in UK and US participants.

Results:

The majority of study participants reported having received some form of physical therapy for their CMT, the most common being physio/physical therapy and occupational therapy, each received by over half of participants. Analgesics/painkillers and antidepressants were the most frequently used medicines. Antianxiety medications, cannabidiol oil and neuroleptics were also used by substantial proportions of participants. Use of pain medication for CMT was often long-term, with many participants reporting several decades of analgesic use. Most participants used some form of orthosis or walking aid, insoles and ankle/leg braces being the most common, with walking sticks and other walking aids also frequently reported. Additionally, around half of participants had received a surgical procedure for their CMT. Common procedures included osteotomy, arthrodesis, and plantar fascia-, achilles-, or tendon release. On average, US participants received a slightly greater number of different types of physical therapy, medication, and surgical procedure than UK participants did, who used a greater number of aids/orthoses.

Conclusions:

The management of CMT in the UK and US is multifaceted, involving the use of physical and surgical therapies, as well as multiple medications, orthoses and aids. This ongoing registry will provide further real-world insights into the treatment CMT to enable gaps in care to be identified and addressed.

References: None.

Keywords: Other

Grant Support: None.
Charcot-Marie-Tooth type 4A disease (CMT4A) is incurable and severe peripheral nerve disorder caused by GDAP1 gene mutations. One of the potential approach to the experimental therapy of CMT4A is construction of low-cost, repeatable platforms for testing of GDAP1 mutations toxicity and for drug screening. In this study we characterized a yeast-based model of CMT4A disease caused by loss of function hGDAP1 mutations like hGDAP1-tc, coding truncated form of GDAP1. The transformation of the yeast with human full length cDNA of hGDAP1 or hGDAP1-tc resulted in a stable protein expression. The yeast expressing hGDAP1 or hGDAP1-tc did not show any reduced viability in comparison to wild-type non transformed yeast. The GDAP1 have been shown to be localized within mitochondria whereas GDAP1-tc in cytoplasm. The hGDAP1 expression seems to result in the consolidated network of mitochondria, whereas GDAP1-tc causes dispersed mitochondrial phenotype. Finally, we have found a yeast-growth phenotype of hGDAP1- and hGDAP1-tc transformed yeast which could be used for testing of GDAP1 mutations pathogenicity.

References: None.

Keywords: Pre-clinical Studies

Grant Support: This work was supported by the National Science Centre, Poland grant UMO-2016/23/B/NZ3/02035
Clinical Trial of Sural Nerve Grafts to the Substantia Nigra in Patients with Parkinson's Disease

Jorge Quintero¹, Andrew Welleford², John Slevin², Julie Gurwell², Greg Gerhardt², Craig van Horne²

¹University of Kentucky, Lexington, KY, USA, ²University of Kentucky, Lexington, USA

Parkinson's disease is a progressive neurodegenerative disease affecting 10 million individuals worldwide. Parkinson's disease is characterized as a movement disorder where the locus of the disorder is thought to be the substantia nigra of the basal ganglia. There are no treatments to alter the progression of the disease although preclinical evidence points to a beneficial effect of growth factors in slowing the progression or repairing damaged neurons. Injured Schwann cells (SC) transdifferentiate into repair SCs that release a variety of growth factors. In an exploratory Phase I trial (NCT02369003) focused on safety and feasibility, we have been implanting, at the time of deep brain stimulation surgery (an FDA approved treatment for symptoms of Parkinson's disease), activated autologous sural nerve to the substantia nigra in patients with Parkinson's disease. As part of Stage I of the surgery, the sural nerve is transected. Two weeks later, for Stage II, the nerve is harvested and implanted unilaterally to the substantia nigra. Following surgery, participants undergo Parkinson's disease motor testing and MRI brain scans. In a subset of participants, a comparison, using RNA sequencing, of nerve biopsies between Stage I and Stage II revealed significant upregulation of growth factor activity. Twenty seven participants have received graft(s). MRI brain scans at 1 or 2 years after surgery have been unremarkable. Most prevalent adverse event related to the study was paresthesia on the lateral aspect of the foot or ankle. Otherwise, adverse event profile consistent with standard deep brain stimulation surgery. Unified Parkinson's Disease Rating Scale scores showed a 22% improvement in motor scores at 1 year after surgery compared to baseline for single graft (N=14) and 19% improvement for dual grafts (N=8). Employing repair phenotype of SCs could be a potential strategy for supporting cells of the substantia nigra that are affected in Parkinson's disease.

References: None.

Keywords: Axonal Regeneration, Clinical Trials, Other

Grant Support: Support provided the Ann Hanley Research Fund. Additional support through the NIH National Center for Advancing Translational Sciences through grant number UL1TR001998. The content is solely the responsibility of the authors and does not necessarily represent the official views of
Poster 32

Impact of pathogenic DNMT1 mutations on human iPSC-derived sensory neuronal phenotypes and DNA methylation

Nathan Staff1, Soneela Ankam2, Saurabh Baheti2, Amandine Rovini2, Ron Hrstka2, Yanhong Wu2, Zachary Resch2, Christopher Klein2, Zhifu Sun2

1Mayo Clinic, Rochester, MN, USA, 2Mayo Clinic, Rochester, USA

INTRODUCTION: DNA methylation plays an important role in embryonic development, and mutations in DNA Methyltransferase-1 (DNMT1) have been associated with a number of disorders, including hereditary sensory and autonomic neuropathy type IE (HSAN1E). In this study, we utilize human induced pluripotent stem cells (iPSC) and their derived sensory neurons (iSN) to explore DNA methylation, gene and protein expression during sensory neuronal differentiation, and the impact of pathogenic DNMT1 mutations on these processes.

METHODS: Skin fibroblasts from patients with pathogenic DNMT1 mutations (HSAN1E) and healthy volunteers (HV) were reprogrammed into iPSC. iPSC were differentiated to neural crest iSN in vitro in order to examine iSN differentiation, protein expression (immunochemistry), gene expression (RT-PCR) and DNA methylation (genome wide reduced representation and bisulfite sequencing) in HV samples, which were then compared with HSAN1E lines.

RESULTS: Fibroblasts from HV and those with HSAN1E were readily reprogrammed into iPSCs and differentiated into iSN. iPSC and iSN from HV and HSAN1E were morphologically indistinguishable on light microscopy and immunofluorescence for markers of sensory neurons. In HV and HSAN1E, we observed decreasing DNA methylation with iSN differentiation that was reflected in increasing numbers and proportions of hypomethylated individual CpGs and regions, as well as lowered DNMT3b expression. When comparing DNA methylation between HV and HSAN1E; however, there were increasing numbers and proportions of hypermethylated individual CpGs and regions in the HSAN1E samples throughout iSN differentiation. Finally, genes with changes in DNA methylation near their Transcription Start Site suggested key pathways that may be involved in iPSC-derived sensory neuronal differentiation.

CONCLUSIONS: Pathogenic DNMT1 mutations in patients with HSAN1E do not result in obvious alterations of iPSC reprogramming and iSN differentiation on the timeframe analyzed in this study. Paradoxical increasing DNA hypermethylation in HSAN1E during iSN differentiation is intriguing and warrants further studies in longer-term cultures and animal models.

References: None.

Keywords: Human Genetics, Axonal Biology, Other

Grant Support: National Institutes of Health: CA211887 (NPS), Mayo Clinic Center for Regenerative Medicine (NPS)
Poster 33

Diagnostic Challenges for Familial Amyloid Polyneuropathy: An Illustrative Case

Supreet Sahai, Robert Vescio, Richard Lewis

Cedars-Sinai Medical Center, Los Angeles, CA, USA

Purpose: To demonstrate difficulties in recognizing hTTR Familial Amyloid Polyneuropathy (hTTR-FAP).

Case: 79-year-old man with a three-year history of progressive upper and lower extremity paresthesias and distal weakness. He noted skin changes on his hands. He was previously treated for CIDP with intravenous immunoglobulin and steroids without benefit. There was no history of cardiac or autonomic disturbance. He walked with a walker with ankle braces, unable to hold a cup, had marked weakness and atrophy of his hands, flail feet, good proximal muscle strength, marked sensory reduction, and diffuse areflexia. EMG showed absent sensory responses, prolonged distal motor latencies of median> ulnar nerves, and conduction velocities of 20-30 m/s. CSF protein was 21 mg/dl; small IgG lambda paraprotein was present; VEGF = 550 (normal < 90 pg/ml); negative bone survey. Bone marrow biopsy revealed amyloid deposition but there was too little to type by mass spectrometry. Based on the above, he was considered to have either POEMS or AL amyloidosis, partially treated by a long course of steroids. VEGF levels and the monoclonal protein normalized with Lenalidomide and Dexamethasone followed by Daratumumab, but the neuropathy progressed. Genetic testing revealed a V50M transthyretin mutation. He has started Inotersen and has stabilized.

Discussion: This case demonstrates some of the difficulties in identifying hTTR-FAP. Suspicion was blunted by the older age, lack of family history, and no cardiac or autonomic problems. Laboratory abnormalities raised concerns for AL amyloid, POEMS. Amyloid deposition can occur due to AL amyloid, wild-type, or TTR mutations. The coexistence of two sources of amyloid deposition, which could be hereditary or acquired, has been reported.

Conclusions: With the recent advances in the treatment of hTTR-FAP, clinicians must be vigilant in identifying the disorder, even in older patients with other potential causes of the neuropathy and amyloid

References: None.

Keywords: Amyloidosis, Human Genetics, Schwann Cell, Inflammatory, Other

Grant Support: None.
Charcot-Marie-Tooth disease type 2A (CMT2A) is the most commonly inherited form of autosomal dominant axonal CMT. It is caused by mutations in the mitofusin 2 (MFN2) gene. Some patients with MFN2 gene mutations develop optic neuropathy, but pathological changes of the optic nerve of CMT2A remain unclear. In this study, we detected a heterozygous MFN 2 gene mutation (c.733A>C: p. Ser245Arg) in a family lineage of CMT2A, which presented abnormal visual evoked potentials. Then, we generated a transgenic mouse expressing the S245R MFN2 mutation specifically in neurons. The transgenic mice showed significantly larger g-ratio in the sciatic nerve compared with control mice. Subsequently, we investigated the optic nerves of the transgenic mice and found that the size of mitochondria was significantly smaller in the transgenic mice on both transverse and longitudinal sections. Small mitochondria would derive from the impairment of mitochondrial fusion. The mutant MFN2 might affect mitochondrial fusion and cause optic neuropathy.

References: None.

Keywords: CMTR

Grant Support: None.
Charcot-Marie-Tooth (CMT) disease is a group of inherited peripheral neuropathies with over 80 causative genes identified to date. The mutations affect proteins with wide ranging cellular functions which include cytoskeletal structure, mitochondrial function, protein translation, vesicle trafficking as well as the cellular stress response. Despite the identification of several CMT-causing mutations, the underlying disease pathomechanisms remain unclear. It is possible that common pathomechanisms may be involved in different forms of CMT, or conversely, there may be great specificity in the cellular changes caused by different mutations.

In this project we used patient-derived fibroblasts and primary mouse neuronal cultures as models of CMT and investigated basic cellular functions and morphology to try and identify unique and common pathomechanisms between different CMT-causing mutations, focusing particularly on mitochondrial abnormalities and axonal transport. Patient fibroblasts with the following CMT-causing mutations were studied: A) CMT-causing mutations in mitochondrial proteins – MFN2 and MT-ATP6; B) the optic atrophy causing OPA1 mutation; C) CMT-causing mutations in non-mitochondrial proteins expressed in fibroblasts – HSPB1 and FIG4; D) CMT-causing mutations in non-mitochondrial proteins not expressed in fibroblasts – SH3TC2 and NEFL. In addition we used primary motor and sensory neurons transduced with 3rd generation lentiviruses to express CMT-causing mutations (MFN2, HSPB1 and NEFL).

Mitochondrial function and morphology were studied in fibroblasts and primary neurons, and axonal transport was examined in primary neurons. As expected, alterations in mitochondrial membrane potential and morphology were observed in fibroblasts and primary neurons expressing mutations linked to mitochondrial function; surprisingly, similar functional and morphological mitochondrial abnormalities were also present in some cells expressing non-mitochondrial CMT-causing mutations. The extent of mitochondrial dysfunction varies between different mutations but is not limited to mutations in genes linked to mitochondrial function. Therefore, mitochondrial dysfunction may be a common pathomechanism across different CMT subtypes.

References: None.

Keywords: Axonal Biology, Other

Grant Support: None.
Effect of Limb Position on Nerve Shear Wave Velocity In Situ

Chelsea Rugel¹, Colin Franz², Sabrina Lee¹

¹Department of Physical Therapy and Human Movement Sciences Northwestern University, Chicago, IL, USA, ²Shirley Ryan AbilityLab, Department of Physical Medicine and Rehabilitation Northwestern University, Chicago, IL, USA

Evaluation of nerves for inflammation, demyelination, and axonal loss is critical in neuropathy diagnosis. Nerve biopsies allow for detailed visualization of these pathological features, but often result in further impairment. Techniques that enable indirect structural assessment, such as electrodiagnostic testing, are thus essential. However, these tests can be painful and are not sensitive enough to detect certain neuropathies.

Shear wave (SW) ultrasound elastography, a real-time in vivo technique that induces and measures the rate of SW propagation, has the potential to detect changes in tissue mechanical properties that often accompany changes in structure. Greater nerve SW velocity is often presented synonymously with greater stiffness; however, tension is also known to influence SW velocity in other tissues. The purpose of this study was to assess if nerve SW velocity is influenced by limb position, and thus nerve tension, in a cat model.

Three exposed cat sciatic nerves were examined in situ at proximal and distal locations along the nerve with the hip at a fixed angle. The knee was manipulated into three positions with increasingly greater nerve tension: 70° flexion, 90° flexion, and 180° extension. No differences in nerve morphology (cross-sectional area and thickness) were observed between positions or locations. Shear wave ultrasound elastography was applied to a region of interest encapsulating the nerve in the longitudinal plane. At both proximal and distal locations, nerve SW velocity was greater at 180° knee extension (mean±SD: proximal 6.79±0.26m/s, distal 6.49±0.40m/s) than at 90° (proximal 2.93±0.35m/s, distal 3.13±0.34m/s) and 70° flexion (proximal 3.02±0.24m/s, distal 2.98±0.45m/s). These results suggest that although SW velocity might be indicative of nerve stiffness, it is also influenced by external factors such as tension. Therefore, parameters affecting nerve tension, including limb position, should be standardized when evaluating nerve SW velocity to minimize influences unrelated to structure.

References: None.

Keywords: Axonal Biology, Other

Grant Support: None.
A 28-year-old woman, third child of asymptomatic consanguineous parents, was diagnosed with congenital thrombocytopenia at birth; and presented with gradually progressive weakness and numbness in lower limbs at age 24. Her sister, who was also diagnosed with congenital thrombocytopenia in childhood, did not have any neurological symptom. Clinical findings of the patient were scoliosis, mild facial weakness, areflexia, mild distal weakness in upper limbs, proximal and distal weakness in lower limbs, bilateral foot drop, and sensory deficits in lower limbs. Nerve conduction study showed reduced or absent sensory nerve action potentials, heterogeneous slowing of motor nerve conduction, conduction block and temporal dispersion of compound muscle action potentials. She was diagnosed with chronic inflammatory demyelinating polyneuropathy. Cerebrospinal fluid showed mildly elevated protein (0.66 g/L) but no white blood cell. Serum and urine analysis did not reveal monoclonal protein. As there was no improvement in polyneuropathy with intravenous immunoglobulin and steroid, we performed whole exome sequencing (WES) for patient and parents to identify mutations inherited in an autosomal recessive pattern that can explain patient’s polyneuropathy (Charcot-Marie-Tooth disease type 4 or CMT4) and congenital thrombocytopenia. WES analysis revealed two novel variants that may represent candidates as causative events underlying the traits. A missense mutation, c.1129C>T (p.Arg377Trp) was identified in the CMT4C-related SH3TC2. This variant is predicted as damaging by two different computer algorithms. The other frameshift mutation, c.66delC (p.Tyr23ThrfsTer4) in SNX10, which is predicted to be pathogenic, has not been reported in CMT4 disease. Both SH3TC2 p.Arg377Trp and SNX10 p.Tyr23ThrfsTer4 have not been reported in 1000 Genomes or GnomAD databases. Sanger sequencing analysis validated the mutations were homozygous in the proband and heterozygous in her parents. The clinical presentation and sequencing results suggest that these novel mutations may contribute to the patient’s phenotype of chronic demyelinating sensorimotor polyneuropathy and congenital thrombocytopenia.

References: None.

Keywords: CMTR

Grant Support: None.
Charcot-Marie-Tooth disease (CMT) is a genetically heterogeneous group of inherited neuropathies, the majority of which are demyelinating in nature. Demyelinating neuropathies are typically caused by mutations in genes expressed specifically by myelinating Schwann cells and remain without effective treatment. An optimal gene therapy approach would require effective gene delivery and restricted expression in Schwann cells. Adeno-associated viral (AAV) vectors are valuable tools for direct in vivo clinical applications. However, their limited DNA transport capacity makes their use for many of the demyelinating CMT neuropathies challenging. In order to facilitate an AAV-mediated gene therapy for demyelinating CMT, we cloned a minimal version of the 1.2 kb myelin protein zero (Mpz) promoter which is known to drive gene expression specifically in Schwann cells. We PCR-amplified the 400 bp upstream of the start codon predicted to include functional regulatory elements of the full-length Mpz promoter. This mini-Mpz promoter was cloned into the AAV transfer plasmid along with downstream Egfp as a reporter gene. The AAV9-miniMpz.Egfp vector was produced and delivered by lumbar intrathecal injection into 2-month old wild type mice. EGFP expression was analyzed 4 weeks later in spinal cord, spinal roots, and sciatic nerve sections. We found widespread expression of the vector mostly restricted to myelinating Schwann cells in PNS tissues, with over 50% expression ratios and high vector copy numbers (VCNs) in roots and peripheral nerves. EGFP expression was found only in a very small subset of around 2-3% of both neurons and glia cells in the CNS as quantified from n=3-5 mice. This study provides evidence that Schwann cells can be targeted with AAV vectors offering a valuable tool to deliver several neuropathy-associated genes to treat demyelinating neuropathies.

References: None.

Keywords: Schwann Cell

Grant Support: Funding: Muscular Dystrophy Association and Charcot-Marie-Tooth Association (Grants MDA 480030 and MDA603003 to KAK).
Poster 39

Peripheral nerve ultrasounds in hereditary transthyretin amyloidosis patients and asymptomatic carriers. A multicenter Italian study.

Alessandro Salvalaggio¹, Alessandro Salvalaggio¹, Daniele Coraci², Mario Cacciavillani³, Laura Obici⁴, Anna Mazzeo⁵, Marco Luigetti⁶, Giulia Bisogni⁷, Luca Gentile⁸, Tiziana Cavallaro⁹, Marina Grandis¹⁰, Francesca Pastorelli¹¹, Chiara Gemelli¹², Marta Ruiz¹, Marta Campagnolo¹, Francesca Castellani¹, Mario Ermani¹, Rosaria Plasmati¹³, Gianmaria Fabrizi¹⁴, Carlo Martinoli¹⁵, Roberto Gasparotti¹⁶, Luca Padua¹⁷, Chiara Briani¹
The most common neurological manifestations of hereditary transthyretin amyloidosis (ATTR) are an axonal symmetric polyneuropathy and carpal tunnel syndrome (CTS). In idiopathic CTS, ultrasound of median nerve at wrist presents an increased cross-sectional area (CSA) which correlates with CTS neurophysiological severity. Recently new therapies are available for the treatment of hereditary ATTR, making an early diagnosis crucial for the care of the patients. The main aim of the present study was To assess the relationship between neurophysiology and ultrasound of median nerve at wrist in ATTR patients with CTS. Secondary aim was to assess the morphological pattern of ATTR polyneuropathy along the course of nerve trunks, both proximally and distally.

Sixty-one subjects (median age 60 years, 33 males, 28 females) with transthyretin gene mutation were recruited. Most prevalent mutations were Phe64Leu (22 subjects), Val30Met (13) and Glu89Gln (10). All the patients underwent electrophysiological and ultrasound evaluation of peripheral nervous system. Median nerve of patients with and without polyneuropathy and paired controls with idiopathic CTS were evaluated. 33/61 patients presented with axonal polyneuropathy. Twenty-one median nerves of subjects without polyneuropathy showed CSA within the normal values, no direct correlation between CTS severity and CSA were detected (r = -0.473). In controls with idiopathic CTS there was instead a direct correlation between CTS severity and CSA (r = 0.517). Increased CSA were detected in brachial plexus bilaterally in patients with polyneuropathy (mean values 95 mm² at right and 100 mm² at left) but not in carriers (p<0.001). The results of our study highlight that the absence of positive correlation between CTS severity and ultrasound findings seems to be peculiar of ATTR patients. In conclusion, the results of the present study identify a morphological pattern which can be considered as a red flag in the early diagnosis of hereditary ATTR.

References: None.

Keywords: Amyloidosis

Grant Support: None.
Poster 40

Testing An ShRNA Gene Silencing Approach In A Mouse Model Of Charcot-Marie-Tooth Disease Type 1A

Marina Stavrou¹, Irene Sargiannidou², Alexia Kagiava³, Jan Richter⁴, Christina Tryfonos⁴, Christina Christodoulou⁴, Christos Karaiskos³, George Lapathitis³, Kleopas Kleopa¹

¹Neuroscience Lab, The Cyprus Institute of Neurology and Genetics and Cyprus School of Molecular Medicine, Nicosia, Cyprus, ²Neuroscience Lab, The Cyprus Institute of Neurology and Genetics and Cyprus School of Molecular Medicine, Nicosia, Cyprus, ³Neuroscience Lab, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus, ⁴Molecular Virology Lab, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus

Charcot-Marie-Tooth disease type 1A (CMT1A) is the commonest inherited demyelinating peripheral neuropathy mainly resulting from the duplication of the peripheral myelin protein 22 gene (PMP22). The duplication of PMP22 creates a gene dosage effect that destabilizes the structure of the myelin sheath leading to demyelination and ultimately to secondary axonal loss and disability. Despite the early characterisation of the disease, none of the various therapeutic approaches that have been studied so far has provided effective treatment to improve the disease phenotype. We have previously compared two gene silencing approaches for CMT1A via the in vitro overexpression of microRNA29a and a PMP22-specific shRNA in a human PMP22 line, as they were predicted to post-transcriptionally downregulate PMP22 protein. We found that a PMP22-targeting shRNA was the most efficient and specific for downregulating human PMP22 gene. Therefore, the aim of this project was to test the potency of this shRNA in the C61 model of CMT1A which overexpresses the human PMP22 gene. In order to test this, we intrathecally injected adult C61 mice with an AAV viral vector expressing the human PMP22-targeting shRNA under the U6 promoter, along with TurboGFP as a reporter gene. Four weeks after injection mice were sacrificed and their PMP22 levels were evaluated in repeated experiments using immunocytochemistry, western blot and Real time PCR analysis. TurboGFP expression was detected both in Schwann cells and in axons. Human PMP22 protein and mRNA levels were reduced in roots and sciatic nerves, with the roots being more significantly affected by the shRNA. Currently, we are working on comparing two alternative AAV serotypes in order to establish the most efficient approach to transduce Schwann cells as well as to demonstrate a therapeutic benefit in the disease model. This study may provide a promising and translatable approach to treat CMT1A.

References: None.

Keywords: CMTR, Schwann Cell, Pre-clinical Studies

Grant Support: Cyprus School of Molecular Medicine, Telethon Cyprus and CMT Research Foundation
Charcot-Marie-Tooth (CMT) disease is the most frequent inherited dysfunction of peripheral nervous system, with an occurrence of 1/2500. The main genetic cause of CMT is the duplication of PMP22 gene, but mutations in more than 90 genes have already been identified as responsible of different forms of CMT. Mutations in GDAP1 gene, coding for the ganglioside-induced differentiation associated protein 1, are generally associated to axonal forms of CMT, with an autosomal, dominant or recessive, mode of inheritance.

Our study focuses on two clinical cases of Charcot-Marie-Tooth disease due to a double homozygous mutation on GDAP1 gene, identified by Sanger sequencing and never described before. Both mutations create an amino acidic substitution in the GST-N domain, at the beginning of GDAP1 protein. If the first mutation seems to be tolerated, the second one, located in a very conserved position, is predicted as possibly pathogenic according to different prediction tools.

Here we describe the clinical profile of these two CMT patients and we try to explain the pathological effect of the double homozygous GDAP1 mutation on the peripheral dysfunction and phenotypic manifestations.

References: None.

Keywords: CMTR, Human Genetics

Grant Support: Région Nouvelle Aquitaine, University of Limoges
**Poster 42**

**Indirect Treatment Comparison of the Efficacy of Patisiran and Inotersen for hATTR Amyloidosis with Polyneuropathy**

Laura Obici1, Peter Gorevic2, Hollis Lin3, Jaclyn Franklin3, Jihong Chen3, Tim Lin3, Gautam Sajeev4, Jessie CH Wang4, and Thomas H Brannagan5

1Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; 2Mount Sinai Medical Center, New York City, USA; 3Alnylam Pharmaceuticals, Cambridge, USA; 4Analysis Group, Inc, Boston, USA; 5Department of Neurology, Columbia University, New York City, USA

**Introduction:** Hereditary transthyretin-mediated (hATTR) amyloidosis is a rapidly progressive disease that leads to significant morbidity and disability. Patisiran and inotersen demonstrated efficacy for the treatment of hATTR amyloidosis with polyneuropathy in their respective, placebo-controlled, Phase 3 trials: APOLLO and NEURO-TTR. In the absence of direct comparative data, this analysis indirectly compares the efficacy of patisiran and inotersen on neuropathy and QOL.

**Methods:** A systematic literature scan identified publicly available randomized trial data on the efficacy of inotersen in hATTR amyloidosis with polyneuropathy. Patisiran data was extracted from the APOLLO trial. Indirect treatment comparisons between patisiran and inotersen were conducted using the Bucher approach and matched-adjusted indirect comparisons (MAIC). Indirect comparisons were conducted on the co-primary endpoints of the NEURO-TTR study - mNIS+7 and Norfolk QOL-DN – for which data is publicly available. Primary analyses adjusted for differences in discontinuation and duration between studies.

**Results:** The systematic literature scan identified one randomized, placebo-controlled trial of inotersen in hATTR amyloidosis patients with polyneuropathy. Patisiran demonstrated a favorable treatment effect relative to inotersen with statistically significant differences in mean change from baseline to 15 months for mNIS+7 (Bucher: -16.2 [95% CI -26.0, -6.3]; MAIC: -12.3 [95% CI -21.4, -3.3]) and Norfolk QOL-DN (Bucher: -11.6 [95% CI -20.3, -2.8]; MAIC: -11.3 [95% CI -19.8, -2.9]). Similar results were observed in sensitivity analyses.

**Conclusions:** Despite the lack of head to head trials and other limitations associated with this type of methodology, the results of this indirect treatment comparison analysis suggest that patisiran had a favorable treatment effect on neuropathy and QOL compared to inotersen in patients with hATTR amyloidosis with polyneuropathy.

**References:** None.

**Keywords:** Amyloidosis

**Grant Support:** None.
A CRISPR/Cas9 knock-out screen to identify regulators of Hspb8 expression and stability

Leen Vendredy, Elias Adriaenssens, Vicky De Winter, Manisha Juneja, Vincent Timmerman

Peripheral Neuropathy Research Group, Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium

HSPB8 belongs to the family of small heat shock proteins (sHSPs), a group of proteins operating as ATP-independent molecular chaperones to maintain cellular proteostasis. By binding to non-native and misfolded proteins, sHSP prevent irreversible protein aggregation until refolding takes place by ATP-dependent chaperones. Mutations in HSPB8 have been reported to be causative of autosomal dominant Charcot-Marie-Tooth type 2L (CMT2L) and distal hereditary motor neuropathy (dHMN). More recently, the disease spectrum was even expanded to distal myopathy (DM). To delineate the molecular deficits and functional consequences of HSPB8 mutations, we generated a knock-in (KI) mouse model for the K141N missense mutation mimicking the human neuropathy phenotype. In addition, we generated Hspb8 knock-out (KO) mice, which showed no overt phenotype. Based on these findings, we hypothesize that replicating a KO-like phenotype in our Hspb8-KI mice might alleviate the symptoms associated with CMT2L/dHMN/DM. However, it is incompletely understood how HSPB8 expression is regulated and which factors determine its protein stability. We will therefore perform a genome-wide CRISPR/Cas9 knock-out screen on endogenously tagged Hspb8-eGFP-P2A-mCherry reporter lines. Data obtained from this screen will provide us with novel targets to regulate the expression and stability of HSPB8.

References: None.

Keywords: Pre-clinical Studies, CMTR

Grant Support: PhD fellowship strategic basic research, Research Foundation - Flanders (FWO), 2018-2022
Neuropathy with developmental delay in a young patient carrying chromosome 1q23.3-q24.2 deletion including MPZ

Anna Mazzeo¹, Federica Taioli², GianMaria Fabrizi², Luca Gentile¹, Maria Bonsignore³, Adriana Tisano⁴, Giuseppe Vita¹

¹Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy, Messina, Italy
²Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy, Verona, Italy
³Dep. of Human Pathology of the Adult and Developmental Age, University of Messina, Messina, Italy
⁴Physical and Rehabilitation Medicine, AOU G. Martino, Messina, Messina, Italy

Introduction. MPZ mutations in humans cause the inherited demyelinating neuropathy CMT1B. Patient and Results. We describe an unusual case of a young patient carrying a wide deletion, de novo onset, in the chromosome 1q23.3-q24.2 also including MPZ. Our patient is a 11-year-old man with motor milestone delay, impaired communication skills and psychomotor disability. He presented with gait disturbance and difficulty climbing stairs. Neurological examination showed unsteady gait and deep tendon areflexia. Neurophysiological studies revealed moderately decreased conduction velocities (ranging from 32 to 37 m/s). Brain MRI was normal. Whole genome array-CGH was performed using Human Genome CGH Microarray Kit 60K (Amadini21924, Agilent Technologies) with an average resolution of 41,5 kb. The array-CGH data evidenced in the proband the presence of a deletion in the 1q23.3-q24.2 critical region spanning approximately 7 Mb (161.041.425-168.272.1789); the analysis in both parents showed that the rearrangement had a de novo origin. The deleted region involved several genes, including MPZ at position 1q23.3. MLPA analysis using probemix P143, specific for detection of MFN2-MPZ rearrangement, confirmed the deletion of all MPZ probes.

References: None.

Keywords: Human Genetics

Grant Support: None.
Histone deacetylase 3 inhibition improves Schwann cell differentiation in Charcot-Marie-Tooth disease 1A

Robert Prior¹, Stijn Verschoren², Liesbeth Minnoye³, Jasper Wouters³, Stein Aerts³, Philip Van Damme¹, Catherine Verfaillie⁴, Robert Baloh⁵, Ludo Van Den Bosch¹

¹KU Leuven - Department of Neurosciences. VIB - Center for Brain and Disease Research, Leuven, Belgium, ²KU Leuven - Department of Neurosciences, VIB - Center for Brain and Disease Research, Leuven, Belgium, ³KU Leuven - Department of Human Genetics. VIB - Center for Brain and Disease Research, Leuven, Belgium, ⁴KU Leuven - Stem Cell Institute Leuven (SCIL), Leuven, Belgium, ⁵Cedars-Sinai Medical Center - Board of Governors Regenerative Medicine Institute, Los Angeles, CA, USA

The most common form of Charcot-Marie-Tooth disease, type 1A (CMT1A), is caused by the duplication of the peripheral myelin protein 22 gene (PMP22). PMP22 is mainly expressed in Schwann cells, and the overexpression of PMP22 is known to cause defects in Schwann cell differentiation in CMT1A [1]. Histone deacetylase 3 (HDAC3) has recently being shown to an antagonist to myelination [2] and may offer as a way to help switch Schwann cells to a myelinating phenotype.

Using the CMT1A transgenic mouse line, C3-PMP22, we were able to observe Schwann cell developmental defects in the peripheral nerves of the C3-PMP22 mice. Using HDAC3 inhibitors (HDAC3i) to treat P6 C3-PMP22 pups, our preliminary data show an improvement in the compound muscle action potential amplitudes and latencies in comparison to littermate controls at 1 month old mice. In addition, we could detect and increase in axon diameters and myelin thickness in HDAC3i treated CMT1A mice. We are currently looking at Schwann cell differentiation-associated gene expression in the sciatic nerves of HDAC3i treated CMT1A mice.

To see if these results could be seen in human CMT1A cells, we used a protocol we recently developed to differentiate induced pluripotent stem cells (iPSC) to a Schwann cell lineage (iPS-SC). We mapped out the expression profile of Schwann cell markers throughout the protocol using single-cell RNA sequencing in a control iPSC line. Using CMT1A patient derived iPSCs and an isogenic control, we were able to show that the treatment of HDAC3i could improve the CMT1A iPSC-SC differentiation in terms of expression of the Schwann cell markers GFAP and S100β. Moreover, our preliminary work indicates that the treatment with HDAC3i was able to improve the CMT1A iPSC-SC lipid profiles in comparison to control iPSC-SCs. Future research includes investigating whether cholesterol metabolism is perturbed in these CMT1A iPSC-SCs.


Keywords: CMTR, Schwann Cell, Metabolic, Pre-clinical Studies

Grant Support: None.
Effect of Balance Training on Posturography Variables and Functional Balance in People with Charcot-Marie-Tooth disease

Gita Ramdharry¹, Magdalena Dudziec², Laurence Lee³, Mariola Skorupinska⁴, Matilde Laura¹, Mary Reilly¹

¹University College Hospitals NHS Foundation Trust, University College London, London, United Kingdom of Great Britain and Northern Ireland, ²Kingston University, London, United Kingdom of Great Britain and Northern Ireland, ³Kingston University, University College London, London, United Kingdom of Great Britain and Northern Ireland, ⁴University College Hospitals NHS Foundation Trust, London, United Kingdom of Great Britain and Northern Ireland

Background: People with Charcot-Marie-Tooth disease (CMT) report a high incidence of falls (1,2). There is sparse evidence to support rehabilitation interventions to improve balance in this population (3).

Aims: This study explored the feasibility and effect of delivering a home based programme using multi-sensory rehabilitation and strength training.

Methods: In this randomised controlled feasibility trial, 14 participants with CMT1A were randomised to either a 12 week home based exercise programme of multi-sensory balance exercises and proximal strengthening plus falls management, or a falls management session only. Participants self-recorded falls for 20 weeks. Outcome measures included static and dynamic balance with static posturography and a forward reach test; functional balance tests; lower limb strength tests (CITEC dynamometer). Effect sizes were calculated using a Hedge’s G

Results: No significant differences in disease severity existed between the two groups at baseline. Training was well tolerated with high participation levels. There was an overall positive effect with training. Laboratory based posturography measures demonstrated moderate improvements in visual dependency during static posturography (centre of pressure velocity with feet apart & eyes closed, Hedge’s G =0.48). Dynamic balance testing showed moderate to strong improvement (forward reach distance, Hedge’s G = 0.68). Functional measures of balance showed larger effect sizes (Berg Balance Score, Hedge’s G = 1.14; BESTest, Hedge’s G 1.04, 10MTW, Hedge’s G = 0.97, Functional Gait Assessment = 0.87). No significant difference in lower limb muscle strength were observed. Total reported falls were not significantly different (Intervention mean = 7 SD±5.2; Control mean= 4 SD±4; P=0.32).

Conclusions: This study was safe and feasible. The improvements in balance measures are encouraging and the effect sizes will be used to power a phase 3 trial. Lower limb strength did not change so improvements may have been due to changes in sensory processing.


Keywords: CMTR, Clinical Trials

Grant Support: This study was funded by a research grant from the CMT United Kingdom charity (Principle Investigator: GMR) and a PhD studentship from Kingston University (PhD student: MD).
Poster 47

MND-like presentation as the main manifestation of the p.Val142Ile FAP-TTR mutation

Ana Marina Silva, Ryann Paseto, Roberto Pontes, Davi Haddad, Wilson Marques Jr

University of Sao Paulo, Ribeirao Preto Medical School, Ribeirao Preto, Brazil

Case report: A 43 y/o man attended to our Neuromuscular outpatient clinic with a history of alternating periods of diarrhea and constipation since the age of 27, with marked weight loss. At the age of 33, he noticed progressive muscle atrophy at the scapular region and arms. He denied sensory or visual abnormalities, sphincter incontinence, erectile dysfunction, postural hypotension, cardiac manifestations or family history. On physical examination there was a severe weakness at axial and upper limbs muscles, fasciculations on hands, and a mild proximal weakness in lower limbs. Ankle reflexes were diminished but all the others were absent. Plantar reflexes were down. Furthermore, there was a persistent dissociated suspended hypoesthesia on upper limbs. Nerve conduction studies were normal, but needle examination showed a diffuse acute denervation with reinervation in all four segments, fulfilling neurophysiological criteria for lower motor neuron disease. Brain MRI, spinal MRI and CSF studies were normal. TTR sequencing showed the p.Val142Ile mutation. Additional workup, including skin sympathetic response, cardiac MRI and 99mTc-DPD scintigraphy, were unremarkable. The same mutation was found in his asymptomatic mother and in his sister, that had bilateral carpal tunnel syndrome.

Discussion: The clinical variability of the TTR mutations are well known. The p.Val142Ile is a known mutation mainly associated to cardiac amyloidosis, although there are case-reports showing the presence of neurologic symptoms, including motor neuropathy, sensory-motor polyneuropathy, dysautonomia and the presence of a concomitant Inclusion-Body Myositis. Stancanelli et al (2016), reported a caucasian patient with Val122Ile mutation, presenting with axonal neuropathy and no cardiac involvement at age 73. It is suggested that the presence of non-coding variants of TTR gene may be responsible for phenotypic differences seen between the Africans and non-Africans carrying the p.Val142Ile.

Conclusion: This case shows a unique presentation of an atypical motor neuron disease associated to TTR p.Val142Ile.


Keywords: Amyloidosis, Small Fibers, Other, Other, Other

Grant Support: FAEP, INCT TRANSLATIONAL MEDICINE, CAPES
Phenotypic variability in a Portuguese family with AGel Amyloidosis

Ana Sousa¹, Carolina Lopes², Sara Cavaco¹, José Pereira¹, Ana Silva¹, Teresa Coelho¹

¹Centro Hospitalar Universitário do Porto, Porto, Portugal, ²Centro Hospitalar Universitário S. João, Porto, Portugal

Introduction

AGel amyloidosis is an autosomal dominant inherited systemic amyloidosis, characterized by a triad of neurological, ophthalmological and dermatological findings. This form of amyloidosis was originally described in Finland, but the worldwide occurrence was later demonstrated.

Methods

Patient registries were consecutively assessed. Data on clinical, neurophysiological studies (electromyography, quantitative sensory testing, sympathetic skin response, quantitative sudomotor axon reflex test, electrochemical skin conductance, heart rate deep breathing test and evoked potentials), magnetic resonance imaging and neuropsychologic evaluations were analysed.

Results

We describe eight members from three generations of a Portuguese family with AGel amyloidosis with G654A mutation. Age at onset of neurological symptoms ranged from the late twenties to the early seventies. Bilateral facial nerve palsy was present in all patients and dysarthria and dysphonia in two. Cutis laxa was demonstrated by all patients. Three patients presented central nervous system involvement (focal epileptic seizures, focal transient neurological symptoms and cognitive impairment involving multiple cognitive domains). Corneal lattice dystrophy affected seven family members. Renal involvement was documented in one patient. Cardiovascular evaluation was normal in all cases. Five patients revealed upper limb mononeuropathies (three with median and two with mixed median and cubital mononeuropathies). Large and small fiber and autonomic neuropathy occurred only in one patient. Magnetic resonance imaging was abnormal in three patients.

Conclusions

We report eight additional cases of AGel amyloidosis, demonstrating phenotypic variability mainly regarding neurological aspects. This disease is rare and increased awareness on the typical presentation can help with the diagnosis.

References: None.

Keywords: Amyloidosis, Other

Grant Support: None.
Charcot-Marie-Tooth (CMT) disease patients have significant unmet medical need, as currently there is no medicine to treat the disease or to slow down the disease progression. Aminoacyl-tRNA synthetases (aaRS) constitute the largest gene family implicated in CMT. Among them, GARS or GlyRS, is the first member identified and whose mutations cause a dominant axonal form of CMT (CMT2D). Although aaRSs are best known as cytoplasmic enzymes essential for protein synthesis, a defect in aminoacylation activity is not necessary for them to be associated with the neuropathy. Evidence has been accumulated to indicate that dominant mutations in GlyRS cause CMT through toxic gain-of-function effects.

We have previously established that a major source of toxicity of the mutant GlyRS (GlyRS\textsuperscript{CMT2D}) originates from the extracellular space, where GlyRS\textsuperscript{CMT2D} aberrantly interacts with Nrp1 receptor and antagonizes a signaling pathway important for motor neuron maintenance (1). Here we generate monoclonal antibodies (mAbs) against GlyRS to block the aberrant Nrp1 interaction for CMT2D treatment. Ideally, the mAbs should selectively bind to GlyRS\textsuperscript{CMT2D} but not GlyRS\textsuperscript{WT} to avoid potential toxicity arising from blocking normal function of the extracellular GlyRS. In addition, considering the large number of different mutations linked to CMT2D and the small number of patients affected by each mutation, it is important to generate mAbs with pan specificity against various GlyRS\textsuperscript{CMT2D} mutants.

We designed a novel strategy based on our insights in the structure of GlyRS\textsuperscript{CMT2D} mutants. Previously, we found that different CMT2D mutations cause a similar conformational opening in GlyRS that exposes new protein surfaces to solution (2). By using peptides from the new protein surfaces as antigens for immunization, we have successfully obtained mAbs with pan-mutant selectivity and that can block the aberrant Nrp1 interaction. Experiments are ongoing to evaluate their in vivo toxicity, efficacy, and dose response in a CMT2D mouse model.


Keywords: CMTR

Grant Support: NIH R01 GM088278
HARS-related peripheral neuropathy with polyglucosan bodies, cerebellar atrophy and mild cognitive impairment

Pinelopi Tsouni1, Alexander Lobrinus2, Joseph Ghika1, Christel Tran1, Carlo Rivolta3, Andrea Superti-Furga4, Thierry Kuntzer1

1Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland, 2University Hospital Geneva (HUG), Geneva, Switzerland, 3Department of Computational Biology, Lausanne University, Lausanne, Switzerland, 4Division of Genetic Medicine, Lausanne University Hospital (CHUV), Lausanne, Switzerland

We present the case of a 49 year-old male with late-onset demyelinating motor neuropathy, cerebellar atrophy and cognitive deficit. Nerve biopsy revealed polyglucosan bodies (PGB) suggestive of adult PGB disease. Testing for known genes associated with PGB storage was negative. Whole exome sequencing identified a novel heterozygote variant, c.397G>T (p.Val133Phe) in the histidyl-tRNA synthetase (HARS) gene recently associated with inherited neuropathies. However, no cognitive deficit has yet been reported in patients with HARS-related neuropathy due to known variants. Mutations in aminoacyl-tRNA synthase genes are associated with many clinical conditions, most of which are both pleiotropic and highly variable. The association of mutations in the HARS gene with peripheral neuropathy is known. It thus seems likely that the novel variant found in our patient is causative. The presence of axonal PGB in peripheral nerve biopsy as well as central nervous system involvement suggest a wider clinical and pathophysiological spectrum than hitherto assumed.

References: None.

Keywords: Axonal Biology, Metabolic

Grant Support: None.
Poster 51

Trans-deletion of WHEP Domain in Glycyl-tRNA Synthetase Rescues CMT2D Neuropathy

Yao Tong¹, Weiwei He¹, Calin Dan Dumitru², Ge Bai², Na Wei², Xiang-Lei Yang²

¹Department of Molecular Medicine, Scripps Research, La Jolla, CA, USA, ²Department of Molecular Medicine, Scripps Research, La Jolla, USA

The largest protein family causally linked to Charcot–Marie–Tooth (CMT) disease is aminoacyl-tRNA synthetases (aaRSs). While every cell requires the tRNA aminoacylation function of aaRSs during protein synthesis, dominant mutations in aaRS only impair the peripheral nervous system for reasons that are unclear. Glycyl-tRNA synthetase (GlyRS or GARS) was the first aaRS linked to CMT. In addition to the enzymatic core, human GlyRS has an evolutionarily new N-terminal domain that is only found in animals and is dispensable for aminoacylation. It has a helix-turn-helix structure and is named WHEP domain. Remarkably, we found that the WHEP domain directs GlyRS to be secreted out of the cell, where protein synthesis does not occur. To understand the physiological significance of the WHEP domain and the secretion of GlyRS, we generated WHEP domain deleted mice (GarsΔWHEP). The homozygous mutant mice are neonatal lethal, indicating that the extracellular presence of GlyRS is essential for mice to survive. Unexpectedly, while GarsP234KY/+ mice exhibit strong hallmark phenotypes of CMT, the compound heterozygous GarsP234KY/ΔWHEP mice are normal and free of CMT-like phenotypes. Thus, trans-deletion of WHEP domain rescues CMT2D neuropathy. This is a strong indication that the WHEP domain and the extracellular function of GlyRS is relevant to the pathogenesis of CMT.

References: None.

Keywords: CMTR, Axonal Biology, Axonal Regeneration

Grant Support: NIH R01 GM088278
Amyloidotic polyneuropathy or transthyretin-related familial amyloidotic polyneuropathy (TTR FAP) is caused by pathogenic mutations in the TTR gene. There is a spectrum of phenotypes, but usually a late onset progressive sensorimotor polyneuropathy or with a severe autonomic dysfunction or cardiomyopathy.

Disease modifying therapy for TTR FAP is available now. Only one Czech patient with TTR mutation has been reported yet. Patients with FAP especially in the early stages of symptoms may be easily misdiagnosed as hereditary neuropathy or cardiomyopathy.

We examined the contribution of TTR mutations and FAP in Czech patients with suspicion for hereditary neuropathy send for DNA testing in our DNA laboratory.

A representative cohort of 100 Czech patients with late onset axonal neuropathy which remained unsolved after DNA testing of relevant genes associated with late onset hereditary neuropathies was tested by Sanger sequencing of all four coding exons of TTR.

No pathogenic mutation was detected in this cohort, showing that TTR mutations are not a relevant cause of late onset axonal polyneuropathies among Czech patients tested for hereditary neuropathy. Only one previously reported synonymous benign variant (c.76G>A, rs 1800458) was found in heterozygous state in 12 patients (12%).

After this study we received a requirement for TTR sequencing in a 64 years patient with suspicion for FAP made by his neurologist, due to a very unusual severe and rapid progression of neuropathic weakness. Sanger sequencing of all 4 coding exons in this patient revealed a previously reported pathogenic mutation p.Val50Met (c.148G>A) in heterozygous state, which is the most common in Europea countries. The patient is wheelchair bound since last year. Neuropathic symptoms with pain started at the age of 54 years, he had a lumbar surgery and later a carpal tunnel surgery. No amyloid was detected in the sural nerve biopsy at the age of 61 years.


Keywords: Amyloidosis, CMTR, Human Genetics, Pain

Grant Support: Supported by AZV 16-31173A and 16-30206A
CNS phenotype in X linked Charcot-Marie-Tooth Disease

Vinojini Vivekanandam¹, Hoskote Chandrashekar², Alexander Rossor³, Mary Reilly³

¹MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, Queen Square, London, United Kingdom of Great Britain and Northern Ireland, ²Department of Radiology, National Hospital for Neurology and Neurosurgery, London, London, United Kingdom of Great Britain and Northern Ireland, ³MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, London, UK, London, United Kingdom of Great Britain and Northern Ireland

CMTX1 is an inherited neuropathy secondary to GJB1 mutations coding for connexin 32. The phenotype is characterised by progressive peripheral neuropathy. Additional upper motor neuron (UMN) features reported include transient central features and fixed UMN signs. Some reports have highlighted co-existence of Multiple Sclerosis. However, the extent of CNS involvement and MRI changes in GJB1 remains incompletely characterised. To explore this CNS phenotype in GJB1, we reviewed our large cohort of patients with a genetic diagnosis of CMTX1 at the National Hospital for Neurology and Neurosurgery, Queen Square, London, UK.

Patients with confirmed GJB1 mutations (n=133) were identified from the internal database of individuals with CMT. The brain MRI scans of patients with CMTX1 who underwent imaging (n=26) were reviewed. Of the 26 MRI scans performed, 10 were identified as being abnormal and reviewed with a neuroradiologist. This translates to 7.52% of all patients with CMTX1 in our cohort. Of the 10 abnormal scans, only 1 patient had T2 white matter lesions (T2WML) resembling those seen in MS. This patient at age 61 has accumulated only one new lesion over 4 years, has not had a clinical attack and as such, does not meet criteria for either radiologically isolated syndrome (RIS) or MS. Four patients had serial imaging which did not demonstrate any new lesions.

The clinical indications for performing a MRI in our cohort were subtle upper motor neuron signs, predominantly extensor plantars and brisk reflexes. 6.77% of our cohort were found to have T2WML. However, no patients fulfilled diagnostic criteria for MS or RIS. The presence of T2WML, brisk reflexes or extensor plantar responses are part of the CNS phenotype of CMTX1. While several case reports exist, large scale cohort studies are needed to fully define the MRI changes in GJB1.


Keywords: CMTR

Grant Support: None.
Objective: To evaluate the prevalence and clinical features of hereditary transthyretin amyloidosis (ATTR) in a cohort of patients referred to neuromuscular outclinic for clinical investigation where no clear family history was present. Methods: We retrospectively evaluate the clinical notes of 80 consecutive patients that have been submitted to TTR sequencing. Patients included may have typical or atypical phenotype. Atypical cases were tested after excluding the commonest causes for their presentation. Results: 46 out of 80 patients were syndromic classified as having a progressive sensorimotor and autonomic neuropathy and considered to have the typical phenotype. The rest of patients had wide clinical presentations including chronic demyelinating polyradiculoneuropathy (3), myelopathy (1), predominant motor neuropathy (1), mononeuritis multiplex (6), familiar carpal tunnel syndrome (2). Regarding the etiology, only 34 patients (42,5%) received the initial diagnostic impression of ATTR. The remaining initial etiological diagnosis were idiopathic neuropathy (30; 37,5%), CIDP (3; 3,75%), leprosy (3; 3,75%), diabetic neuropathy (3; 3,75%), motor neuron disease (1; 1,25%), paraproteinaemic neuropathy (1; 1,25%), and vasculitis (1; 1,25%). Conclusion: In this Brazilian series of FAP-ATTR, a large number of syndromic and etiological diagnosis was found. The diversity of syndromic presentations certainly contributes to the difficulty in recognizing the presence of FAP-TTR. Although CIDP is usually said to be the main differential diagnosis of FAP-TTR, this was not the case in our series. We additionally draw attention that leprosy neuropathy was considered in 3 cases, resulting in an unnecessary treatment. Given the broad spectrum of FAP-ATTR related disorders genetic testing should also be considered in patients with atypical presentations.

References: None.

Keywords: Amyloidosis, Human Genetics, Small Fibers

Grant Support: CNPq, FAPESP, FAEP, PRONAS (MINISTRY OF HEALTH), INCT
The RAB7A K126R Mutation Associated with Predominantly Motor CMT2B

Paola Saveri1, Maria De Luca2, Veronica Nisi2, Chiara Pisciotto3, Giuseppe Piscosquito4, Mary Reilly5, James Polke6, Tiziana Cavallaro7, Gian Maria Fabrizi7, Raffaella Lombardi3, Francesca Caravello3, Giuseppe Lauria Pinter3, Stefania Magri8, Franco Taroni8, Cecilia Bucci2, Davide Pareyson3

1Department of Clinical Neurosciences, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, 2Department of Biological and Environmental Sciences and Technologies, University of Salento, Lecce, Italy, 3Department of Clinical Neurosciences, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, 4Functional Neuromotor Rehabilitation Unit, IRCCS ICS Maugeri Spa - SB, Scientific Institute of Telese Terme, Telese Terme (BN), Italy, 5MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, London, United Kingdom of Great Britain and Northern Ireland, 6Department of Neurogenetics, National Hospital for Neurology and Neurosurgery, UCL Institute of Neurology, London, United Kingdom of Great Britain and Northern Ireland, 7Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy, 8Unit of Medical Genetics and Neurogenetics, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

Autosomal dominant Charcot-Marie-Tooth type-2B (CMT2B) is associated with mutations in RAB7A, with five missense changes reported thus far. The encoded RAB7 protein is a ubiquitously expressed small GTPase that controls late endolysosomal trafficking and autophagy, and influences mitochondrial fission by regulating mitochondria-lysosome contacts. CMT2B is usually characterized by prominent sensory involvement, frequent ulcers and amputations, minor or absent motor deficits. We have recently found a novel RAB7A mutation (p.K126R) in a family (a 38-year-old woman and her father) with a predominantly motor presentation of CMT2B. We are characterizing the mutation by different approaches. In vitro analysis of bacterially purified K126R protein showed altered biochemical properties: the mutation affects affinity for guanine nucleotides and causes impaired GTPase activity. In addition, experiments with transfected Neuro2A cells, demonstrated that K126R mutant protein interacts more strongly with the intermediate filament peripherin as compared to wt protein and inhibits neurite outgrowth as described earlier for other CMT2B mutants. Total peripherin amount appeared also to be increased in proband as compared to control in immunohistochemistry on skin nerves. Notably, in NCI-H1299 cells, this mutation strongly reduced epidermal growth factor receptor degradation (EGFR) as confirmed also by specular studies on cultured skin fibroblasts and preliminary experiments on the proband’s sural nerve. We are currently exploring in ex vivo studies the expression of peripherin and Rab interacting lysosomal protein (RILP), a key RAB7 effector. Altogether our results confirm a pathogenic role for the p.K126R variant. The mutation shares similar properties with other previously reported RAB7A mutations (biochemical dysfunction, impairment of late endocytic trafficking and neurite outgrowth). It also shows differences, particularly in the EGFR degradation process, which might be a possible explanation of the different clinical presentation in this family.

References: None.

Keywords: CMTR

Grant Support: None.
Association between Clinical Outcomes and Quality of Life in Patients with Hereditary Transthyretin Amyloidosis

Aaron Yarlas¹, Spencer Guthrie², Michael Pollock², Andrew Lovley¹, Michelle White¹

¹Optum, Johnston, RI, USA, ²Akcea Therapeutics, Boston, MA, USA

Introduction: Hereditary transthyretin (hATTR) amyloidosis is a rare, systemic, progressive disease that often clinically manifests as polyneuropathy. The current analysis assesses associations of clinical outcomes with neuropathic-specific and generic health-related quality of life (HRQOL).

Methods: Data were from the NEURO-TTR trial (NCT01737398), a double-blinded, placebo-controlled randomized trial of inotersen in patients with hATTR accompanied by polyneuropathy. Clinical and patient-reported outcomes were assessed at baseline and week 66. Neuropathic-specific HRQOL was measured using the Norfolk QOL-diabetic neuropathy (DN) questionnaire, with the SF-36v2® Health Survey (SF-36v2) measuring generic HRQOL. Polyneuropathy symptoms and impairment were assessed by the polyneuropathy disability (PND) score (Stages I – IV, with higher stages indicating worse ambulatory disability), the modified Neuropathy Impairment Score+7 (mNIS+7), and the Neuropathy Symptoms and Change (NSC) questionnaire. Transthyretin (TTR) concentration was measured. Analysis of covariance models tested for differences in baseline HRQOL scores across baseline PND scores. Correlations measured associations between clinical outcomes and HRQOL measures at baseline. Ordinary least squares regression models tested associations between change-from-baseline HRQOL scores at week 66 and changes in clinical outcomes.

Results: Significantly worse scores in the majority of Norfolk QOL-DN and SF-36v2 scores were observed for patients in higher PND stages. mNIS+7 and NSC scores showed strong univariate correlations with Norfolk QOL-DN activities of daily living, large fiber neuropathy, and small fiber neuropathy domains, and SF-36v2 physical functioning and role-physical domains. In multivariable regression models, decreases in NSC scores were associated with improvement in Norfolk QOL-DN domains, while decreases in both NSC scores and TTR concentration were associated with improvements in SF-36v2 physical functioning and role-physical domains.

Conclusion: Differences and changes in the severity of neuropathy predicted both neuropathic-specific and generic HRQOL. Decreased TTR concentration predicted improvement in generic HRQOL. Thus, treatments that reduce TTR and neuropathy should produce better HRQOL in patients with hATTR amyloidosis.

References: None.

Keywords: Amyloidosis, Clinical Trials

Grant Support: None.
Impact of Inotersen on Condition-Specific Quality of Life for hATTR Amyloidosis: Double-Blind Placebo-Controlled Trial Results

Spencer Guthrie¹, Asia Sikora Kessler², Aaron Yarlas², Andrew Lovley², Michael Pollock¹, Michelle White²

¹Akcea Therapeutics, Boston, MA, USA, ²Optum, Johnston, RI, USA

Introduction: Hereditary transthyretin amyloidosis (hATTR) is a rare, systemic, progressive, and fatal condition in which misfolded proteins, produced in the liver, deposit in muscle and organ tissue leading to symptoms of peripheral neuropathy, and possible cardiomyopathy and autonomic neuropathy. Analyses examined the impact of an investigational therapy, inotersen, versus placebo on condition-specific quality of life (QOL), as captured by the Norfolk QOL – Diabetic Neuropathy (Norfolk QOL-DN) questionnaire, in hATTR patients.

Methods: Data were from the NEURO-TTR trial of inotersen, a multicenter, multinational, double-blind trial (NCT01737398) of 172 adults with hATTR. The Norfolk QOL-DN, a co-primary endpoint that was administered at baseline, week 35, and week 66 produces a total score and five subscale scores capturing symptoms associated with nerve damage: physical functioning (PF)/large fiber neuropathy, activities of daily living (ADL), symptoms, small fiber neuropathy, and autonomic neuropathy. Treatment impacts on mean Norfolk QOL-DN scores were tested using mixed-effects models for repeated measures (MMRM). Responder analysis compared the percentage of patients whose scores got better (i.e., decreased by at least one-half standard deviation [SD]), got worse (i.e., increased by at least one-half SD), or stayed the same using Fisher’s exact tests.

Results: At week 66, MMRM showed significant treatment effects supporting inotersen over placebo for most Norfolk QOL-DN scores, with better changes in mean scores on the ADL, PF/large fiber, and symptoms subscales, and total score, all p<0.01. Responder analysis indicated the percentages of patients whose scores were the same or meaningfully improved from baseline to week 66 was significantly higher for those on inotersen than for placebo for the total score (81% vs. 56%), ADL (81% vs. 52%), PF/large fiber (80% vs. 58%), and symptoms subscale scores (84% vs. 65%), all p<0.02.

Conclusion: Inotersen exhibited positive treatment effects on condition-specific QOL, providing evidence of efficacy for hATTR patients.

References: None.

Keywords: Amyloidosis, Clinical Trials

Grant Support: None.
Poster 59

Characterizing Treatment Experience among Patients with Transthyretin Amyloidosis

Asia Sikora Kessler1, Sean O'Connor1, Michael Pollock2, Spencer Guthrie2, Kristen McCausland1

1Optum, Johnston, RI, USA, 2Akcea Therapeutics, Boston, MA, USA

Introduction: Transthyretin amyloidosis (ATTR) is a rare, systemic, progressive and fatal condition resulting from amyloid deposits of misfolded transthyretin proteins in peripheral nerves and organs. Little is known about patients’ experience and satisfaction across available therapies. This study examined treatment-related tolerability, hospitalizations, and satisfaction experienced by patients with ATTR amyloidosis.

Methods: Adults with ATTR amyloidosis were enrolled in an online longitudinal observational study (n=92). Survey items assessed patients’ current treatment regimens; ability to tolerate treatment; hospitalizations due to treatment side effects; and treatment satisfaction. Treatment tolerability was characterized with a single 4-point scale item, and treatment-related hospitalizations with a single “Yes/No” item. Treatment satisfaction was assessed using the Treatment Satisfaction Questionnaire for Medication (TSQMvII) along four domains: Side Effects, Effectiveness, Convenience, and Global Satisfaction; greater satisfaction was represented by higher scores (range: 0-100). Responses for all outcomes were summarized descriptively by treatment.

Results: 63% of patients were currently receiving treatment for their ATTR amyloidosis (n=58). The 4 most prevalent treatments were: diflunisal (n=28), doxycycline + tauroursodeoxycholic acid (TUDCA; n=11), patisiran (n=13), and inotersen (n=10). Median treatment duration for common treatments was 0.3 to 2.0 years. Among patients receiving these treatments, tolerability was high (≥70% reported tolerating their treatment “very well”). Treatment-related hospitalizations were uncommon; only 3 reported diflunisal-related hospitalizations and 1 patisiran-related hospitalization. Patients receiving diflunisal reported highest satisfaction related to Side Effects (mean score=94.8); whereas patients receiving inotersen reported highest satisfaction related to Effectiveness (68.3). Convenience was similar for diflunisal, inotersen, and doxycycline + TUDCA (71.1-79.4). Across all treatments, patients receiving inotersen reported the highest Global Satisfaction (82.5); however, the ability to statistically compare the scores was limited by small sample sizes.

Conclusion: Patient treatment experience for available ATTR therapies showed high levels of tolerability and low incidence of hospitalizations. Overall, treatment satisfaction was highest with inotersen.

References: None.

Keywords: Amyloidosis

Grant Support: None.
Safety and Efficacy of Switching Patients with Neuromuscular Disorders from one IVIG Preparation to Panzyga®

Lidia Cosentino¹, Natasha Campbell¹, Sylvia DeMelo², Rami Massie³

¹Octapharma Canada Inc., Toronto, Canada, ²Montreal Neurological Institute & Hospital, McGill University, Montreal, Canada, ³Montreal Neurological Institute & Hospital, McGill University, Montreal, Canada

PURPOSE: Intravenous immunoglobulin (IVIG) is used to treat a number of immune-deficiencies and autoimmune disease. Patients established on one preparation may be changed to another for either tolerability issues, economic reasons or availability. In Québec, Canada, a tender process determines the availability of IVIG preparations. It is possible that the outcome of these tenders will result in some patients having to switch from their current IVIG to another for reasons other than product safety or efficacy. A transition of this nature took place in 2017. Panzyga® (Octapharma), was allocated the largest IVIG market share through their tender process. This resulted in several patients, including patients with neuromuscular disorders, having to switch from their current IVIG preparation to Panzyga®. This retrospective chart review was conducted to assess the efficacy, safety and tolerability during this switch in patients receiving IVIG treatment for neuromuscular disorders.

METHODS: Tolerability and efficacy of Panzyga® were assessed pre- and post-switch using the motor component of the Neuropathy Impairment Score (NIS-motor) and the Clinical Global Impression Scale-Improvement (CGI-I). Pre- and post-switch adverse events (AEs) were recorded.

RESULTS: Fourteen patients were included in the chart review. Diagnoses included chronic inflammatory demyelinating polyneuropathy (9 patients), multifocal motor neuropathy (1 patient) and myasthenia gravis (4 patients). There was no difference in pre- and post-switch mean NIS-motor scores. For the majority of patients, symptoms remained unchanged after switching brands as measured by the CGI-I. Most patients on IVIG did not experience AEs; for those who did, most were mild both pre- and post-switch. The most frequently reported AE was headache.

CONCLUSIONS: In summary, the results suggest that the safety, tolerability and efficacy of Panzyga® in neuromuscular patients is comparable to existing IVIG preparations. Future studies may wish to validate these findings with a larger cohort of patients.

References: None.

Keywords: Inflammatory, Other

Grant Support: None.
Development of a Ligand Conjugated Antisense Oligonucleotide for the Treatment of Transthyretin Amyloidosis (ATTR)

Li-Jung Tai

Ionis Pharmaceuticals, Inc., Carlsbad, CA, USA

Hereditary transthyretin amyloidosis (hATTR) is a rare, progressive, fatal disease caused by pathogenic variants in the transthyretin (TTR) gene. Amyloidogenic variants destabilize the normal tetrameric structure of TTR oligomers leading to the aggregation of insoluble, extracellular amyloid deposits in multiple organs systems. hATTR patients predominantly develop neuropathy and/or cardiomyopathy. Formation of wild-type TTR amyloid deposits can also occur, referred to as wtATTR.

Advances in Ligand Conjugated Antisense Oligonucleotide (LICA) strategies have increased drug potency 20 to 30-fold and improved safety and tolerability profiles of antisense oligonucleotides with targets expressed in the liver. Inotersen is an antisense oligonucleotide that reduces the production of both mutant and wild-type TTR protein by degradation of TTR messenger RNA. Treatment with inotersen demonstrated significant benefit in patients and has been approved for the treatment of hATTR patients with polyneuropathy. AKCEA-TTR-LRx (ION-682884) is a second-generation antisense oligonucleotide conjugated to a triantennary N-acetyl galactosamine (GalNAc3) moiety for selective, receptor-mediated delivery to hepatocytes, the principal source of systemically circulating TTR. AKCEA-TTR-LRx and inotersen target the same sequence of the TTR messenger RNA. Inotersen and AKCEA-TTR-LRx were tested in both a human hepatocyte culture system (Hepatopac) and a human TTR transgenic mice (hTTR-Tg) expressing the human TTR genomic sequence containing the Ile84Ser mutation.

In Hepatopac culture, free-uptake of AKCEA-TTR-LRx produced reductions in wild-type TTR expression that was approximately 50-fold more potent than inotersen. Subcutaneous administration of AKCEA-TTR-LRx in male hTTR-Tg mice produced significant dose-dependent reductions of mutant TTR mRNA and protein levels, demonstrating a 28 and 15-fold improvement in potency compared to inotersen, respectively. AKCEA-TTR-LRx was primarily confined to liver hepatocytes with limited distribution to non-parenchymal liver cells.

AKCEA-TTR-LRx is currently under clinical investigation in a double-blind, placebo-controlled phase 1/2 study conducted in healthy volunteers and patients with transthyretin-mediated amyloidosis (NCT03728634).

References: None.

Keywords: Pre-clinical Studies, Amyloidosis, Clinical Trials

Grant Support: None.
Poster 62

A novel variant for MORC2 Charcot-Marie Tooth (CMT2Z).

Alberto Martinez1, Felipe da Graça1, Lucas Resende1, Leticia Souza1, Jordana Tartaglia1, Fabricio de Lima1, Melina Martins1, Anamarli Nucci1, Marcondes França Jr2

1University of Campinas, Campinas, Brazil, 2Campinas, Campinas, Brazil

Introduction: Charcot-Marie Tooth (CMT) disease is an inherited peripheral neuropathy with heterogeneous clinical presentations and striking genetic variability. More than 80 different genes have been implicated to different forms of CMT. CMT2Z is a rare subtype of CMT characterized by axonal damage related to the MORC2 gene mutation. Full phenotypic spectrum of MORC2-related CMT is still unknown since few families were described to date.

Objective: To report a novel MORC2 mutation in a CMT2Z patient.

Case report: A 37 years old male patient presented with a 6-year history of sensory loss in distal lower limbs with slowly progressive weakness and muscular wasting. He reported no family history of similar clinical picture. Nerve conduction studies disclosed a symmetrical and distal axonal sensory-motor involvement. The NGS CMT panel revealed a novel mutation in MORC2 gene (c 2194+1G>A).

Conclusion: MORC2 mutations are still sparse in the literature. The report of novel mutations may be relevant to provide new insights on pathophysiological disease mechanisms especially for the recently described CMT2Z. Although clinical evaluation is essential in the approach of inherited peripheral nerve disorders, NGS is becoming paramount as a valuable and accessible tool for the accurate classification of CMT patients. Continuous efforts are needed to adequate the current classification with the evolving genetic discoveries, not only for clinical classification but also for further clinical trials.

References: None.

Keywords: CMTR, Human Genetics

Grant Support: None.
P75 and NCAM can Identify Pathologic Schwann Cells in Peripheral Neuropathies

Jong Kuk Kim1, Young Hee Kim1, Young Hye Kim2, Yoon Kyung Shin1, Young Rae Jo1, Da Kyeong Park2, Min-Young Song2, Byeol-A Yoon1, Soo Hyun Nam3, Jong Hyun Kim3, Byung-Ok Choi3, Ha Young Shin4, Seung Woo Kim4, Se Hoon Kim4, Je Woong Byeon1, Hana Go1, Hye Ran Kim1, Hwan Tae Park1

1Dong-A University, Busan, Korea (Republic of), 2Korea Basic Science Institute, Cheongju, Korea (Republic of), 3Sungkyunkwan University, Seoul, Korea (Republic of), 4Yonsei University, Seoul, Korea (Republic of)

Myelinated Schwann cells (SC) in adult peripheral nerves dedifferentiate into immature cells in peripheral demyelinating neuropathies and Wallerian degeneration, and this plastic Schwann cell change is actively involved in the myelin destruction and clearance as the demyelinating SC. In inherited demyelinating peripheral neuropathy, pathologically differentiated and dysmyelinated SC constitute the main nerve pathology. In this study, we applied the idea of that development of disease-relevant serum biomarkers representing these SC plastic status in human neuropathic nerves. Based on proteomics analysis on the secreted exosomes from immature SC, we traced p75 neurotrophin receptor (p75) and neural cell adhesion molecule 1 (NCAM) in the patient sera of peripheral neuropathy. ELISA tests revealed that p75 and NCAM are subtype-specifically expressed in the patient sera of peripheral neuropathy. In conjunction with these ELISA data on human sera, pathological analyses of neuropathic peripheral nerves from animal models and human patients specimen suggested that the presence of demyelinating SC in inflammatory demyelination neuropathy and supernumerary non-myelinating or dysmyelinating SC in inherited demyelination neuropathy could clearly be distinguishable by the selective expression of p75 and NCAM in human serum. This study indicates that the identification of disease-specific pathological SC stages could be a valuable tool for differential diagnosis of peripheral neuropathies.

References: None.

Keywords: Schwann Cell, Inflammatory, CMTR

Grant Support: This study was supported by grants from the National Research Foundation of Korea (NRF; 2016R1A5A2007009, 2016R1A5A2921654) and the National Institutes of Health (RO1 NS094388), both funded by the Korean government.
Poster 64

Examination of Risks/Benefit Profile of Medical Cannabis in CMT and HNPP and Chronic Pain Patients

Brian Piper¹, Allison Moore², Meg D’Elia³, Leah Perkinson⁴, Joy Aldrich⁵, Marion McNabb⁶, Andy Westerkamp⁷, Robert Moore², Gregory Carter⁸, Courtney Hollett⁹

¹Geisinger Commonwealth School of Medicine, Scranton, PA, USA, ²Hereditary Neuropathy Foundation, New York, NY, USA, ³Champlain Valley Dispensary & Southern Vermont Wellness, Burlington, VT, USA, ⁴Evergreen Evaluation and Consulting, Burlington, VT, USA, ⁵Hereditary Neuropathy Foundation, Seattle, WA, USA, ⁶Cannabis Community Care Research Network, Boston, MA, USA, ⁷AMW Cannabis Consulting, Boston, MA, USA, ⁸St. Lukes Rehabilitation Institute, Spokane, WA, USA, ⁹Hereditary Neuropathy Foundation, Chesterfield, VA, USA
Introduction:

Charcot-Marie-Tooth (CMT) disease is a group of hereditary sensory and motor neuropathies. A review of various treatment guidelines determined that the evidence base was substantial for medical cannabis (MC) for chronic pain (CP) and moderate to substantial in peripheral neuropathy. The objectives of this study were to: 1) obtain a deeper appreciation of the risks and benefits of MC in CMT and hereditary neuropathy patients; and 2) contrast this profile with that obtained previously with CP (Piper et al. 2017 J Psychopharmacology 2017; 31:569-575.).

Methods:

CMT participants (N=82, 65.9% female, age=52.0) were recruited from the Global Registry for Inherited Neuropathies and completed an online survey. Two-fifths (44.1%) were type 1A and one-fifth (20.6%) were Hereditary Neuropathy with Liability to Pressure Palsy. CP (N=705, age=47.7) were recruited from New England.

Results

CMT cohort respondents were primarily (88.9%) from the US. Among the subset that use medical cannabis for CMT (N = 34), one-third (32.4%) had completed the certification process and one-third (34.5%) communicated with their health care providers about their use of medical cannabis. The primary route of administration was smoked for half (51.6%) and edibles for one-third (29.0%). MC use was reported as 78.3% medical on a continuum from 0% medical (i.e. 100% recreational) and 100% medical (0% recreational). CP cohort respondents were 100.0% Caucasian and reported pain from multiple sources including back/neck (71.6%), neuropathic (34.3%), trauma (22.3%), post-surgery (19.7%), abdominal (12.5%), menstrual (5.1%), and cancer (1.4%). Qualitative analyses identified strengths (efficacy) and limitations (cost) of MC. Preliminary analyses across cohorts are suggestive of patients reducing their use of opioids after starting MC.

Discussion

These studies provide a detailed patient-centric understanding of the utility of MC. This research may form the foundation for additional controlled trials in CMT and other neuropathies.


Keywords: CMTR, Inflammatory, Pain, Clinical Trials, Other

Grant Support: None.
A mitochondrial ATP6 mutation causing a slowly progressive myeloneuropathy

Tanya Bardakjian, Steven Scherer

University of Pennsylvania, Philadelphia, PA, USA

We report on a 53-year-old man with an insidiously progressive myeloneuropathy that progressed over 20 years to more typical picture of CMT. The proband has had high arches for as long as he can remember, and developed hammertoes in his teens. He presented to a neurologist at the age of 32, and was found to have hammer toes and high arches, brisk reflexes in the arms and knees (but absent at the ankles) and prominent extensor plantar reflexes. Nerve conduction studies and EMG showed a motor > sensory axonal neuropathy, with severe, chronic denervation in distal leg muscles. At age 52, he reported more difficult ambulating. His exam showed minimally worsened deficits, reflexes were less pronounced at the knees, vibration sense was absent at the toes, pinprick sensation was normal above the knees, and he had subtle extensor plantar responses. Nerve conduction and EMG showed little change from the prior study. His CMT neuropathy score was 17. His mother was examined at age 68. She had hammertoes, mild (4+) weakness in extensor hallucis longus and tibialis anterior. Vibration was absent in her toes, and she had bilateral extensor plantar responses. Her nerve conduction (showed reduced motor but not sensory amplitudes in the feet, and EMG showed moderate, chronic denervation in distal leg muscles. A hereditary neuropathy panel of the proband through GeneDx identified a VUS in the SCN9A. Reflex testing to whole exome sequencing with mitochondrial sequencing identified a homoplasmic pathogenic variant in MT-ATP6 - m.9176T>C/p.Leu217Pro in the proband and his mother. These findings add to the evidence that MT-ATP mutations can present as CMT or evolve into a CMT-like presentation. The presence of a mitochondrial disorder changes the genetic counseling and risk assessment for a patient. Therefore, mitochondrial sequencing should be a part of a complete CMT evaluation.


Keywords: Human Genetics

Grant Support: The work was supported by the Judy Seltzer Levenson Memorial Fund for CMT Research, and by the Inherited Neuropathy Consortium (INC; U54 NS065712), which is a part of the NCATS Rare Disease Clinical Research Network (RDCRN), an initiative of the Office of Rare Disease Research (ORDR), NCATS. TB is supported by the Neurogenetics Translational Center of Excellence, Department of Neurology, the Perelman School of Medicine at the University of Pennsylvania.
Diabetic peripheral neuropathy (DPN) is one of the most common complications of diabetes worldwide, affecting up to 60% of subjects with diabetes. Emerging evidence suggests that aberrant DNA methylation is implicated in the pathogenesis of diabetes and diabetic complications, but its role in DPN is not well understood. In this study, we aimed to examine the association between DNA methylation and DPN progression in type 2 diabetes.

Using reduced-representation bisulfite sequencing, we performed genome-wide DNA methylation profiling of 12 human sural nerve samples from subjects with type 2 diabetes and DPN. These subjects were divided into two groups based on changes in sural nerve myelinated fiber density over a 52-week period: subjects with significant nerve regeneration (regenerators) and subjects with significant nerve degeneration (degenerators).

Between the two groups, we identified 3,460 differentially methylated CpG dinucleotides and 246 differentially methylated regions. The genes associated with differentially methylated CpGs were highly enriched in biological processes such as nervous system development, neuron development, and axon guidance, as well as glycerophospholipid metabolism and mitogen-activated protein kinase (MAPK) signaling.

To our knowledge, this is the first study to identify changes in sural nerve methylome associated with myelinated nerve fiber regeneration and degeneration in type 2 diabetes. Our results suggesting that pathophysiological pathways known to be implicated in DPN pathogenesis may be under epigenetic control will facilitate the development of new mechanism-based therapies.

**References:** None.

**Keywords:** Diabetes, Axonal Regeneration

**Grant Support:** This work was supported by the U.S. National Institutes of Health (NIH R24 DK082841 to E.L.F. and J.H.), the American Diabetes Association (to E.L.F.), the Novo Nordisk Foundation (to E.L.F.), the Program for Neurology Research and Discovery at University of Michigan, the A. Alfred Taubman Medical Research Institute, the Juvenile Diabetes Research Foundation (Postdoctoral Fellowship to J.H.), the Applied Systems Biology Core of the George M. O’Brien Michigan Kidney Translational Core Center (NIH P30 DK081943), the NIDDK Diabetic Complications Consortium Pilot Grant (DiaComp, www.diacomp.org; DK076169; Sub-award #25034-75 to J.H.), the University of North Dakota (UND) Epigenetics Center of Biological Research Excellence (CoBRE) Pilot Grant (to J.H.), and UND Post-Doc Pilot Grant (to K.G.).
Prediabetic and diabetic patients often complain of debilitating neuropathic pain. However, not everyone with prediabetes or diabetes develops pain and the predisposing risk factors to painful neuropathy remain elusive. The epidermis receives dual innervation via peptidergic and nonpeptidergic axons and our previous studies in mice show that a high fat diet induces mechanical allodynia and increases peptidergic epidermal axons. We hypothesize that patients with prediabetes and painful neuropathy have an abnormal proportion of epidermal peptidergic axons. In our ongoing clinical trial, patients are recruited into 3 groups, dependent on their metabolic status: 1) normal (n=6), 2) prediabetes (n=7), or 3) prediabetes with neuropathic symptoms (n=5). Metabolic status (healthy vs. prediabetic) is determined using ranges established by the 2016 American Diabetes Association (ADA) Guidelines. Assignment to prediabetic category requires lab values within each of the following three ranges: A1c (5.7-6.4%), fasting glucose (100-125 mg/dl), or oral glucose tolerance (140-199 mg/dl). Data (vitals, demographic, social/lifestyle, medical history) is collected, and fasting patients undergo a blood draw (insulin, lipid panel, hematocrit, hemoglobin, and HBA1c) and a glucose tolerance test and to identify their metabolic status. In a second visit, patients undergo a clinical evaluation of their sensory status (Brief Pain Inventory for Diabetic Neuropathy (BPI-DPN), Michigan Neuropathy Screening Instrument, Utah Early Neuropathy Scale) and an ankle skin biopsy is obtained to quantify intraepidermal nerve fiber density (IENFD). PGP 9.5 is used to identify all axons, and TrkA+ fibers are used to identify peptidergic axons. Our analysis will compare differences in peptidergic fiber measures to neuropathy symptoms among the 3 groups. Our goal is to identify risk factors that modify peripheral innervation and increase the risk of pain associated with neuropathy. Discussion of this ongoing clinical study will be presented at the meeting.

References: None.

Keywords: Diabetes, Metabolic, Small Fibers, Pain, Clinical Trials

Grant Support: None.
INTRAEPIDERMAL NERVE FIBER REGENERATION IS DIFFERENT BETWEEN TYPE1 and TYPE2 DIABETES.

Mohammad Khoshnoodi, Shaun Truelove, Michael Polydefkis

Johns Hopkins University, Baltimore, USA

Regeneration of cutaneous unmyelinated axons has been shown to be reduced in subjects with diabetes compared to healthy controls. However, it is not clear if the regeneration of sensory distal axons ever fully recovers in diabetic subjects if given sufficient time, or if there are regeneration differences between type I and type II diabetes.

Here we measured the rate of axonal regeneration 6 months after chemical denervation using a capsaicin model in 47 diabetic patients (N=11 T1, N=36 T2) without neuropathy. Punch skin biopsies (thigh) were obtained at baseline, 48hrs after applying capsaicin, and then at 30, 90, 150 and 180 days. Blood glucose level and HgbA1C were serially measured. Comparisons between groups were made using analysis of variance and linear regression models. The effect of other covariates (height, weight, BMI, HbA1C, and cholesterol) was assessed through multiple linear regression and the rate of regeneration with time was estimated using a linear mixed-effects model.

Sural responses, blood glucose level, hypercholesterolemia status, and HbA1C were similar between patients with type 1 and type 2 diabetes at baseline and subsequent measurements. After six months, IENFD levels in both type 1 and type 2 diabetic patients remained significantly below baseline levels, with type 1 patients 5.2 [95% CI, 2.1-8.3] fibers/mm below baseline levels and type 2 patients 8.6 [95% CI, 6.8-10.4] fibers/mm below. Patients with type 1 attained a significantly higher percentage of baseline levels (80% versus 60%, p=0.01) than type 2 subjects.

While we found significant differences between study groups in age, weight, height, and BMI, we found no significant effect for any of these covariates on absolute regeneration amount, percent of baseline regeneration, or rate of regeneration, when controlling for diabetes type. These results suggest that the long-term outcome of intraepidermal nerve fiber regeneration is affected by the type of diabetes.

References: None.

Keywords: Axonal Regeneration, Diabetes, Small Fibers

Grant Support: None.
Tale of two states: A comparison study of baseline health data of neuropathy patients

Mamatha Pasnoor¹, Gordon Smith², Patricia Kluding¹, Laura Herbelin¹, Robin Marcus³, Cathy Revere³, Alexis Hawks¹, Mazen Dimachkie¹, Richard Barohn¹, Robinson Singleton³

¹The University of Kansas Medical Center, Kansas City, KS, USA, ²Virginia Commonwealth University, Richmond, VA, USA, ³The University of UTAH Health, Salt Lake City, UT, USA

Introduction: Utah ranked 5th in the United Health Foundation 2018 America’s health rankings whereas Kansas is ranked 27th. We compared the baseline data on the diabetic peripheral neuropathy (DPN) patients in the Activity for Diabetic Polyneuropathy (ADAPT) study.

Objective: Compare the baseline health data of DPN patients between the two states.

Methods: Data collected included demographic, weight, body mass index (BMI), glycosylated hemoglobin (HgbA1C), lipid profile, activity information (number of steps), Norfolk Quality of Life - Diabetic Neuropathy (N-QOL), cholesterol, skin biopsy, Utah Early Neuropathy Scale (UENS), nerve conduction studies and 6-minute walk distance.

Results: Total number of subjects screened at Kansas and Utah was 95 and 67 respectively. There was no significant difference in the mean age 62.6 ±7.5 years and 62.4 ±10.5 years (p=0.89). Mean body mass index (BMI) was not different 34.9±8.8 and 33.4±5.9 (p=0.22). Significant difference was seen in HgbA1C (p=0.005) and high-density lipoprotein- cholesterol (HDL-C) (p=0.002) with higher mean HgbA1C and lower HDL-C in the Kansas DPN patients. There was no significant difference in LDL (p=0.83) and triglycerides (TG) (p= 0.88). The Utah Early Neuropathy Scale (UENS) and distal thigh IENF density did not show significant difference (p=0.63; p=0.67). Mean N-QOL was significantly different (11.0±10.9 vs 16.8 ±11.7; p=0.001). Sural amplitude, peroneal distal latency (DL) and conduction velocity (CV) showed significant difference (p<0.0001, p=0.038, 0.017). The activity level and fitness measured by step count and 6-minute walk total distance was higher in Utah compared to Kansas (p=0.02, p<0.0001). VO2max was higher in Utah than Kansas (mean 17.4±  5.5 vs. 15.8±5.0, p=0.05).

Conclusions: Baseline significant differences were seen in hgbA1C, HDL, sural amplitude, peroneal CV, total step count and VO2max indicating Utah has a healthier population compared to Kansas.

References: None.

Keywords: Diabetes, Clinical Trials, Pain

Grant Support: NIH/ NIDDK: R01 DK064814
Expression of GAP-43 in type 2 diabetes and IGT: a longitudinal study

Xin Pan¹, Baohan Pan¹, Yanning Shou¹, Krish Chandrasekaran², Lindsay Zilliox², Neda Ilieva², James Russell², Michael Polydefkis¹

¹Johns Hopkins School of Medicine, Baltimore, MD, USA, ²University of Maryland, Baltimore, MD, USA

Diabetes is a common cause of peripheral neuropathy and loss of intraepidermal nerve fiber density (IENFD) is described in impaired glucose tolerance (IGT) and DM2. Here, we examined GAP-43 expression and its relation to IENFD among newly-diagnosed, well-controlled DM2 (N=22), IGT (N=15) and age/gender matched controls (N=30) in a 12 month longitudinal study. 3mm skin biopsies were obtained at the distal leg (DL) and proximal thigh (PT) at baseline and after 12 months. Immunohistochemistry (IHC) for GAP-43 and PGP9.5 were performed. Double IHC assessed co-localization. Subepidermal nerve fiber density (SENFD) of GAP-43+ fibers was assessed using a validated, unbiased stereology protocol (CE<0.1). IENFD was determined with PGP and GAP-43.

GAP-43 and PGP were co-expressed in most nerve fibers. DM2 and IGT subjects had similar age, gender and MNSI scores. Both had excellent A1c values (6.6±0.2% vs. 5.8±0.1%, p<0.05); TG levels were elevated in DM2 vs. IGT (124±13 vs. 85±13 mg/dl, p<0.05). IENFD-PGP and GAP43-IENFD were similar in IGT and DM subjects and significantly reduced compared to controls at both sites.

At 12 month, DM2 (N=11) and IGT (N=6) showed similar patterns. Combining the groups, IENFD-PGP remained reduced at DL and increased (0.85±0.38 fibers/mm, p=0.04) at PT. Proximal thigh SENFD-GAP43 (p=0.01) and IENFD-GAP43 (p=0.10) levels increased at 12-months vs. baseline, while DL SENFD-GAP43 (p<0.01) values increased but DL IENFD-GAP43 did not.

Cutaneous nerve GAP43 expression is dynamic in IGT/early well-controlled DM2. Surprisingly, GAP43 expression increased at 12-months to a similar degree in both IGT and DM2 subjects, approaching control subject levels. This was associated with a small but significant increase in IENFD at the proximal thigh. These results suggest that increased GAP43 expression can be associated with IENFD increases in the setting of well controlled early-onset diabetes.

References: None.

Keywords: Diabetes, Small Fibers, Axonal Regeneration, Axonal Biology, Metabolic

Grant Support: NIDDK 1R01DK107007-01A1 and Department of Veterans Affairs (Rehabilitation Research and Development, 101RX001030 (JR)
Obesity is considered a 21st century epidemic, affecting over 2 billion people worldwide. This condition is accompanied by complications, including peripheral neuropathy (PN): a prevalent disease with no available treatment. The initial stages of PN are clinically presented as peripheral allodynia and hyperalgesia, that later may progress to loss of sensation. Despite the high prevalence, the molecular mechanisms underlying disease onset are poorly understood and affected patients have no other choice than to use pain killers. In addition, an increasing body of evidence has now linked metabolic disorders to alterations of gut microbiome composition and their secreted metabolites, such as short-chain fatty acids (SCFAs – acetate, butyrate, propionate). Notably, we observed a decreased abundance of gut butyrate-producing bacteria in hypersensitive, Western-diet (WD)-fed mice. This change in bacteria composition was associated with changes in plasma SCFAs’ concentration. We hypothesize that there is a relationship between gut microbiome and PN onset. To test our hypothesis, we subjected WD-fed mice to fecal microbiome transplantation (FMT) or to butyrate treatment. We evaluated changes in i) mechanical and thermal sensitivities, ii) glucose homeostasis, iii) gut bacterial composition, iv) plasma SCFA levels, v) gene expression and protein acetylation in the dorsal root ganglia (DRG) and in the sciatic nerve (SN). We observed that FMT protects from obesity-induced allodynia, indicating that gut microbiota may play a role in PN onset in obese mice. Our results also suggest that gut bacteria may change sensory neurons function via modulating gene expression and histone deacetylases activity in the DRGs and SN of neuropathic mice. The gut microbiome and its metabolites could be novel valuable targets to delay or cure pain associated with obesity. More studies need to be done in humans and mice models to better understand the cellular and molecular neurobiology underlying these findings to identify specific targets.

References: None.

Keywords: Pain, Small Fibers

Grant Support: Loyola Cardiovascular Research Institute Collaborative Grant
A Keratinocyte-Derived Mechanism of Nicotinamide Riboside to Prevent and Reverse Diabetic Neuropathy

Cheng-Ying Ho¹, Krish Chandrasekera², James Russell²

¹University of Maryland School of Medicine, Baltimore, MD, USA, ²University of Maryland School of Medicine, Baltimore VA Medical Center, Baltimore, MD, USA

Skin keratinocytes produce neurotrophins to provide trophic support to cutaneous sensory axons. Early studies have suggested deficient neurotrophin signaling as a potential pathogenic mechanism of diabetic neuropathy (DN). Attempts to treat DN by exogenous neurotrophin administration, however, have failed due to intolerable injection site pain. We hereby presented a novel mechanism of nicotinamide riboside (NR) to ameliorate DN by physiologically inducing the expression of keratinocyte-derived neurotrophins.

For the reversal study, C57BL6 mice were fed either a control diet (CD) or high-fat diet (HFD) for 5 months. The mice subsequently received a daily oral dose of 300 mg/kg NR or saline for 4 months. For the prevention study, the diet modification and NR administration started simultaneously. Neuropathy was determined by mechanical allodynia thresholds (MAT) and intraepidermal nerve fiber density (IENFD). HFD-fed mice in both the prevention and reversal group demonstrated increased MAT and decreased IENFD. These findings of DN were ameliorated in mice treated with NR for two months. Of note, BDNF expression levels were decreased in the paw skin of HFD-fed mice. Since BDNF is a known target of SIRT1, a protein deacetylase activated by NR, a potential neuroprotective mechanism of NR is to enhance expression of keratinocyte-derived BDNF. In primary human keratinocyte cultures, we demonstrated that NR treatment increased NAD+ levels and induced BDNF expression over time. In addition to BDNF, transcriptome analysis by RNA-seq showed a substantial increase of other neurotrophins including FGF18 and ciliary neurotrophic factor (CNTF) in keratinocytes treated with NR. We are currently using transgenic mouse models and sensory neuronal cultures to evaluate the effect of keratinocyte-derived neurotrophins on sensory nerve protection and neurite outgrowth.

Our findings not only provide a novel neuroprotective mechanism for DN, but also highlight induced expression of keratinocyte-derived neurotrophins by pharmacological compounds as a potential treatment strategy for DN.

References: None.

Keywords: Diabetes, Small Fibers

Grant Support: NIH NINDS K08NS102468 (CH) Passano Foundation (CH) NIH NIDDK R01DK107007 (JR)
Diabetes is a major global health problem and about 25% of these patients develop painful diabetic neuropathy (PDN), a debilitating complication of diabetes. In patients with PDN, nociceptors within the dorsal root ganglion (DRG) become hyperexcitable and eventually degenerate. Despite the prevalence of the disease, the pathogenesis of the disease is unclear. Our overall aim is to identify changes in the gene expression profile in PDN pathology for the discovery of novel druggable targets. To specifically study changes to the nociceptive neurons in PDN, we used the Na,1.8-Cre; Ai9 mice fed a regular or a high-fat diet for 10 weeks. The Na,1.8+ nociceptors from the DRG were sorted and followed by deep RNA sequencing. We identified 58 overexpressed and 360 underexpressed genes and observed overexpression of several GPCRs, including the Mas-related G protein-coupled receptor D (Mrgprd), a gene implicated in neuropathic pain. Mrgprd+ neurons are a subset of the Na,1.8 population and interestingly, we discovered several of the candidate genes clustered to the Mrgprd subpopulation, indicating a functional role of Mrgprd and associated genes in the pathogenesis of PDN. Mrgprd neurons are unmyelinated axons and do not express the neurofilament-200 (NF200), a marker of myelination. Interestingly, we observed Mrgprd expression within a population of NF200+ neurons in diabetic mice. Additionally, we examined the hairy skin of Mrgprd-EGFP reporter mice and saw a significant reduction of the Mrgprd intra-epidermal nerve fiber innervation in diabetic mice. Currently, efforts are directed towards the transcriptomic analysis of Mrgprd neurons and examining the effects of reducing the expression of Mrgprd receptors using CRISPR based approaches. Overall, we propose Mrgprd as a viable target for the development of disease-modifying therapeutics for PDN.

References: None.

Keywords: Small Fibers, Pain, Diabetes

Grant Support: NIH/NINDS R01 NS104295-01 (DMM)
The distal dying-back of nerve fibers is a hallmark of many neurodegenerative disorders including diabetic sensorimotor polyneuropathy (DSPN). There is a high energy demand at the nerve ending and provision of energy in the form of ATP is challenging for neurons with long axons where the primary metabolite is glucose. We hypothesized that energy supplementation via glycolysis and/or mitochondrial oxidative phosphorylation is compromised in nerve endings thus contributing to axonal degeneration in diabetic conditions. DRG neuron cultures from age-matched control or streptozotocin (STZ)-induced type 1 diabetic rats were used for in vitro studies. Three plasmids containing ATP sensors of varying affinities (medium to low affinity, and one mutant; detectable by FRET technology and live cell confocal imaging) were transfected into neurons to study endogenous ATP levels in real time. FRET efficiency (YFP/CFP ratio) of the ATP sensors AT1.03 (low affinity) and AT1.03 YEMK (medium affinity) were significantly higher than the mutant (AT1.03 R122/6K) in DRG neurons in both cell bodies and neurites (P<0.0001). Using the AT1.03 YEMK construct, treatment with oligomycin (an ATP synthase inhibitor in mitochondria) decreased the ATP levels in neurites and cell bodies of DRG neurons (P<0.05). Blockade of glycolysis using 2-Deoxy-D-glucose (2-DG: a glucose analog) also lowered ATP levels (P<0.001). Both neurites and cell bodies of DRGs from diabetic rats showed a diminishment of ATP levels when compared to neurons from control rats (P<0.01). In conclusion, low ATP levels in cell bodies and distal axons may contribute to the energy deficit in nerve in diabetes and could trigger distal dying-back nerve degeneration.

References: None.

Keywords: Axonal Biology, Diabetes, Axonal Regeneration

Grant Support: None.
INTRODUCTION: The neurotoxic effects of the chemotherapeutic agent bortezomib are well documented, yet the mechanistic underpinnings that govern these cellular processes remain incompletely understood. In this study, system-wide proteomic changes were identified in human induced pluripotent stem cell (iPSC)-derived sensory neurons (iSN) exposed to a clinically relevant dose of bortezomib.

METHODS: Our CIPN-in-a-dish model involved the differentiation of iPSCs created from 3 healthy individuals into neural crest derivatives followed by neuronal subtype specification and maturation using an established, directed approach with typical iSN yields of 60-70%. At 21 days post-induction, iSN were treated with 100nM bortezomib, DMSO, or left untreated for 48h.

RESULTS: Bortezomib treatment of iSN led to altered axonal morphology, microtubule distribution and decreased mitochondrial motility. Label-free mass spectrometry facilitated the identification of approximately 2800 differentially expressed proteins in iSN exposed to bortezomib. Pathway analysis revealed microtubule dynamics, cytoskeletal and cytoplasmic organization, and molecular transport as significantly affected cellular processes. Microtubule Associated Protein-2 (MAP2) emerged as a topmost influential candidate, which was reduced in proteomics and confirmatory Western blot analyses. Furthermore, 24h bortezomib exposure was sufficient to lead to the accumulation of MAP2 proximal to the plasma membrane.

CONCLUSIONS: Studying neurotoxicity of bortezomib is challenged by its broad effects on multiple protein pathways. Unbiased proteomics followed by pathway analysis aided the discovery of putative pathomechanisms. One of these molecules, MAP2, was further discovered to be concentrated in the perisomatic region and through pathway analysis was associated with processes of axonogenesis, neurite extension and branching, and neurite morphology.

References: None.

Keywords: Axonal Biology, Other

Grant Support: National Institutes of Health: CA211887 (NPS)
The plasticity of adult sensory neurons is relevant to their ability to mount a regenerative response following injury or disease. Outcomes following axonal damage to nerves remain unsatisfactory, rendering permanent disability. Manipulation of neurons downstream of growth factor receptors offers a newer approach to improve regenerative success. Here we summarize recent work on four, apparently independent pathways that impact adult sensory neuron plasticity. PTEN (phosphatase and tensin homolog deleted on chromosome 10) a tumour suppressor, impairs downstream signaling of PI3K/pAkt. Its inhibition or knockdown (KD) enhances neurite outgrowth in vitro and improves early axon regeneration in vivo. PTEN is upregulated in sensory neurons from experimental diabetes mellitus that have a regenerative deficit. Rb1 (retinoblastoma 1) inhibits a divergent transcriptional growth signal E2F1 and like PTEN, its KD improves outgrowth in vitro and regeneration in vivo. Both PTEN and Rb1 KD have greater impacts on neurons already ’preconditioned’, a unique instance of regrowth beyond that offered by preconditioning paradigms. BRCA1 (breast cancer 1) acts to repair damaged DNA, a previously unrecognized feature of both intact and regenerating sensory neurons. Unlike PTEN and Rb1, its KD inhibits growth, indicating a role in maintaining the integrity of regenerating adult neurons. The latest addition to this list is APC (adenomatous polyposis coli) that binds to and inhibits nuclear translocation of β-catenin, a widely acting transcription factor that supports growth. APC KD is associated with increases in neurite growth in vitro and improved regeneration in vivo. β-catenin localization to sensory neuron nuclei is enhanced. Both APC and PTEN have heightened expression in slower growing IB4 nonpeptidergic neurons. Overall, the commonalities among these intrinsic growth pathways requires additional investigation, but they each offer new approaches to enhance nerve regeneration.

References: None.

Keywords: Axonal Regeneration

Grant Support: Supported by the Canadian Institutes of Health Research
Mitochondrial vacuolation occurs independent of axon degeneration in paclitaxel-induced peripheral neuropathy

Anthony Cirrincione, Sandra Rieger

University of Miami Department of Biology, Coral Gables, FL, USA

Treatment with the chemotherapeutic agent paclitaxel causes peripheral neuropathy in the majority of patients. The mechanisms underlying this process have remained elusive. Evidence suggests that paclitaxel damages mitochondria in the axons, which is consistent with observations in other neuropathy models. Whether mitochondrial dysfunction underlies axon degeneration has however not been explored in detail. To re-examine this, we used our larval zebrafish paclitaxel model in combination with transmission electron and confocal microscopy to study mitochondrial function. Quantitative image analyses in transgenic zebrafish expressing the hydrogen-peroxide sensor, HyPer, shows a stronger mitochondrial oxidation in keratinocytes upon paclitaxel treatment compared with controls, suggesting a defect in keratinocyte-specific mitochondria. Nevertheless, transmission electron microscopy analyses shows that similar to mammalian studies, also axonal mitochondria show signs of damage. Axonal mitochondria form vacuoles within 3 hours of treatment and these persist up to 4 days of treatment with paclitaxel, when axon degeneration has initiated. We previously demonstrated that paclitaxel treatment upregulates MMP-13 in the epidermis and that pharmacological inhibition of MMP-13 prevents paclitaxel neurotoxicity. We therefore tested whether axonal mitochondrial vacuolation can be prevented in the presence of the MMP-13 inhibitor, DB04760. We found that this is not the case. These results suggest that vacuolation may not play a role in axon degeneration given that 1) axonal mitochondrial vacuoles form rapidly, long before axon degeneration occurs, and they do not differ over time, 2) we previously established that keratinocyte damage due to MMP-13 activity is the primary cause of axon degeneration, however vacuoles do not form in this cell type, and 3) MMP-13 inhibition prevents axon degeneration but not vacuolation of axonal mitochondria.

References: None.

Keywords: Axonal Biology, Axonal Regeneration, Pre-clinical Studies, Pain, Small Fibers

Grant Support: 7R01CA215973-02
Asymmetry in Chemotherapy-induced Peripheral Neuropathy: Differences in patient report and objective assessment

Hannah Timmins¹, Tiffany Li¹, Matthew Kiernan¹, Sally Baron-Hay², Gavin Marx³, Josie Rutovitz³, David Goldstein⁴, Susanna Park¹

¹University of Sydney, Sydney, Australia, ²Royal North Shore Hospital, Department of Oncology, Sydney, Australia, ³Sydney Adventist Hospital, SAN Integrated Cancer Centre, University of Sydney, Sydney, Australia, ⁴Prince of Wales Clinical School, Sydney, Australia

Chemotherapy-induced peripheral neuropathy (CIPN) is a dose-limiting side-effect of cancer treatment, typically producing symmetrical, length-dependent sensory symptoms and functional impairment. However, patients may report asymmetric-symptoms and the degree of concurrence with objective neurological assessment remains ill-defined. This study aimed to compare reported symptoms and objective assessments.

45 taxane-treated patients (F=43, 66±1.5 years, 24.3±2.4 months post-treatment) completed bilateral neurological assessments via the Total Neuropathy Score clinical version (TNSc) and bilateral sensory nerve conduction studies (NCS; sural: lateral malleolus, median: digit2). Patients reported symptom severity via FACT/GOG-Ntx13 questionnaires and were asked to report symptom symmetry. The laterality index (LI) was calculated as a ratio of smaller to larger side-to-side differences in CSAP amplitudes and TNSc scores indicating asymmetry.

Symptoms of neuropathy were reported by 88% of the cohort. On clinical examination, 83% had ≥2 abnormalities, with 35% having sural amplitudes below normative range. 35% indicated side-to-side symptom asymmetry, with 53% reporting discrepancy in upper limbs and 66% in lower limbs. Patients reporting asymmetry reported greater symptom burden (mean FACT-score=39.8±1.3) than those with symmetrical distribution (41.5±1.4, p<.05), as well as greater asymmetry on neurological examination (TNSc LI Asym=.72±.08, Sym=.85±.03, p<.05). However, there was no significant asymmetry in TNSc scores once patient report items were removed (LI Asym=.60±.10, Sym=.76±.05, NS) and no difference in side-to-side NCS (Median LI:Asym=.69±.06, Sym=.81±.04, NS; Sural LI:Asym=.80±.04, Sym=.81±.04, NS).

Discrepancies in symptom severity between hands and feet were reported by 31% of the cohort, with more severe symptoms typically in the feet. Of those reporting discrepancy, 54% demonstrated increased objective severity of neuropathy on clinical examination, in-line with patient report.

Discrepancies may exist between the patient experience of CIPN and objective assessments. Understanding these discrepancies may help to elucidate underlying mechanisms and inform treatment strategies. Accurate and early assessment of neuropathy, including identifying symptom asymmetry, may also assist to identify patients at-risk of severe neuropathy.

References: None.

Keywords: Other

Grant Support: None.
Objective: To explore the incidence and clinical phenotype of serious neurological adverse events (NAEs) in cancer patients who received immunotherapy with checkpoint inhibitors (ICIs). Patients and methods: We reviewed files of cancer patients who were treated with ICIs from 2010 to 2018 and then searched for ICIs-related NAEs. Results: We identified 1185 ICIs-treated patients. Males and females were 63.7% and 36.3%, respectively, with a mean age of 63.4±7.3 years-old. Nivolumab was given to 536 (45.2%) patients, Pembrolizumab to 301 (25.4%) patients, Atezolizumab to 135 (11.4%), Ipilimumab to 104 (8.8%), Durvalumab-Tremelimumab to 77 (6.5%), and other ICIs to 32 (2.8%). Of those patients, 24 (2%) developed a ICI-related NAE. No differences were identified in age, sex, tumor type and class of ICIs between patients who developed neurotoxicity compared to those without neurologic adverse events. The distribution of NAEs by agent was: Nivolumab (2.1%), Pembrolizumab (2%), Atezolizumab (1.5%), Ipilimumab (1%), Durvalumab-Tremelimumab (3.9%), and others (2.8%). The median number of cycles received before NAEs onset were 4.5 (1-10), and the median time was 110 days. PNS involvement was evident in 14 patients (58.3%) and CNS involvement in 41.7%, while 2 patients with aseptic meningitis also presented polyradicular involvement. Among PNS complications, there were 5 cases (20.8%) with axonal sensory neuropathies, 4 (16.7%) with Guillain-Barre-like syndromes, 4 (16.7%) with muscle involvement (myositis and myasthenias), and one with other syndromes. Seven patients (50%) with PNS-related NAEs were treated with steroids, 2 (14.3%) with IVIG, and 5 (35.7%) remained untreated. In general the outcome was good after ICIs discontinuation, with about half of patients improving or completely resolving NAEs. Conclusion: ICIs-related NAE although rare overall, might be severe, and are mostly represented by neuromuscular complications. Early discontinuation of ICIs and possibly treatment with immune-modulating therapies should early be commenced to achieve a favourable neurological outcome.

References: None.

Keywords: Other

Grant Support: None
Elevated Neurofilament Light Chain (NF-L) Levels in Pancreatic Cancer Patients with CIPN Receiving Abraxane

Catherine Stehman-Breen¹, Thomas Engber¹, Christine Alewine²

¹Disarm Therapeutics, Cambridge, MA, USA, ²National Institute of Health; National Cancer Institute, Bethesda, MD, USA

Neurofilaments have gained significant attention as a biomarker of axonal injury. They are abundant structural scaffolding proteins expressed only in neurons and are critical for radial growth and the stability of axons, enabling effective nerve conduction. Mutations in genes that encode neurofilament proteins are associated with Charcot-Marie-Tooth disease type 2E or 1F, amyotrophic lateral sclerosis, and familial Parkinson disease.

Abnormal levels of NF-L in the CSF and blood reflect axonal damage in a variety of neurodegenerative, inflammatory, vascular and traumatic diseases. Because neurofilaments are specific for axonal injury, they offer significant advantages over other biomarkers. Ultra-sensitive assay technology (SIMOA) has allowed for the reliable quantification of NF-L levels in blood. Data in acquired neuropathies suggest that NF-L levels are higher than in controls. However, there are no data assessing NF-L levels in CIPN. Since axonal damage and loss is observed in CIPN, detecting and monitoring CIPN with a serum biomarker would be advantageous in identifying those at risk and monitoring and evaluating treatment. We measured serum NF-L levels in 17 samples from 6 patients with previously treated metastatic and/or locally advanced pancreatic ductal adenocarcinoma and mesothelin expressing solid tumors who participated in an NCI sponsored trial where they received LMB-100, a mesothelin-targeted immunotoxin in combination with nab-paclitaxel. Patients received 125 mg/m2 abraxane chemotherapy on D1 and D8 of the 21 day cycle. One patient had received prior abraxane and all received oxaliplatin. Three subjects had CIPN at baseline and an additional subject had a prior history of CIPN. These 4 patients exhibited CIPN during treatment and had substantially greater increases in NF-L (115.2 pg/mL) than the 2 patients that did not develop CIPN (13.2 mg/mL). This is the first description of changes in NF-L in patients receiving neurotoxic chemotherapy. Additional studies should be conducted to confirm these findings.

References: None.

Keywords: Axonal Biology

Grant Support: NIH Center for Cancer Research Intramural Program
Bortezomib Neuropathy: Clinical and Electrophysiological Features and Its Predictive Factor

Nagaaki Katoh, Akihiro Ueno, Nobuhiko Ohashi, Minori Kodaira, Yoshiki Sekijima

Shinshu University, Matsumoto, Japan

【Purpose】Bortezomib is one of the proteasome inhibitors which are now considered as a major treatment option for systemic light chain (AL) amyloidosis. However, its neurotoxic side effect has emerged as a problem because some bortezomib-treated patients develop subsequent peripheral polyneuropathy. The aim of this study is to clarify the clinical and electrophysiological features of bortezomib-induced neuropathy and to investigate the possible predictive factor of this side effect. 【Methods】All AL patients, except for those with amyloid neuropathy, who were treated with bortezomib-dexamethasone (BD) between Oct. 2012 and Apr. 2018 were enrolled. Clinical and electrophysiological findings of the patients with bortezomib-neuropathy were retrospectively investigated. 【Results】Among 40 enrolled patients, ten patients (25.0%) were found to develop bortezomib-neuropathy. Mean cumulative dose of bortezomib at neuropathy onset was 15.8 mg/m². Clinical presentation was length-dependent symmetrical sensory neuropathy without any motor-nerve symptom. Electrophysiological examination revealed sensory-nerve axonal involvement. Although this abnormal electrophysiological findings recovered within 6 to 12 months after treatment, clinical symptom remained in all patients (the number of patients with complete recover: 0, partial improvement: 7, no improvement: 3). Many clinical parameters were compared between patients who developed bortezomib-neuropathy and who did not, but no significant predictive factor was detected. Neuropathy development did not affect hematological response rate or overall survival. 【Conclusion】25% of bortezomib-treated AL patients developed sensory-nerve axonal neuropathy with mean cumulative dose of bortezomib 15.8 mg/m². There was no significant relationship between neuropathy development and treatment outcomes. It is important to pay attention to cumulative dose of bortezomib because neuropathy onset was unpredictable but clinical symptom was likely to remain.

References: None.

Keywords: Amyloidosis, Other

Grant Support: None.
Poster 82

Outcome Measures in the Assessment of Chemotherapy Induced Peripheral Neuropathy- Which Tools are Most Responsive?

Tiffany Li¹, Hannah Timmins¹, Michelle Harrison², Lisa Horvath³, Michael Friedlander⁴, Siobhan O’Neill ⁴, Terry Trinh⁵, James McCrany⁵, David Goldstein⁶, Matthew Kiernan¹

¹University of Sydney, Sydney, Australia, ²Chris O’Brien Lifehouse, Sydney, Australia, ³Chris O’Brien Lifehouse, University of Sydney, Sydney, Australia, ⁴Prince of Wales Hospital, Sydney, Australia, ⁵Prince of Wales Clinical School, Sydney, Australia, ⁶Prince of Wales Hospital, University of New South Wales, Sydney, Australia
Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a major dose-limiting side effect of many cancer treatments, often leading to dose reduction or treatment cessation. Although multiple outcome measures are utilised to quantify CIPN, there is disagreement on whether quantitative sensory outcomes or patient reported outcomes (PRO) are most sensitive at detecting change in CIPN symptoms. This study compared the responsiveness of quantitative sensory outcomes (Von Frey Monofilament (VF), Grating Orientation Task (GOT) and 2-Point Discrimination (2PD)) and PROs (FACT/GOG-NTX13 and CIPN20) to the extensively validated composite neurological grading scale, Total Neuropathy Score (TNSc).

Methods

237 patients (73 males; 54.6±12.8 years) receiving neurotoxic chemotherapies (taxanes, platinums, vinka-alkaloids, bortezomib, thalidomide) were prospectively assessed prior to receiving, and upon completion of treatment. Sensitivity to change for each outcome (TNSc, GOT, VF, 2PD, FACT/GOG-NTX13 and CIPN20) was calculated using Cohen’s d effect sizes (95% CI), with 0.2 representing minimal clinically important difference. Pearson’s correlation coefficients were used to compare outcomes to the TNSc.

Results

From baseline to follow-up assessment, participants exhibited increased neuropathy symptoms, evident by larger TNSc scores (mean difference=2.7±0.18, P<0.005), PRO report and declining performance on quantitative outcomes. Effect sizes for all outcomes were clinically significant, however PROs demonstrated the most responsiveness (FACT/GOG 1.23(1.01-1.44); CIPN20 1.24(1.03-1.46)), compared to quantitative outcomes (VF 0.21(0.02-0.41); 2PD 0.52(0.30-0.73); GOT 0.56(0.36-0.76)) and neurological grading scale (TNSc 1.18(0.96-1.40)). PROs were more strongly correlated to TNSc than quantitative outcomes (VF r=0.15; 2PD r=0.14; GOT r=0.21; FACT/GOG r=0.40; CIPN20 r=0.37), suggesting concurrent validity.

Discussion

These results demonstrate that PROs are valid and responsive measures of CIPN. Although quantitative sensory outcomes provide objective assessment of sensory dysfunction, use of PROs allow for a more global and sensitive measure of neuropathy. Further investigation in comparing psychometric properties of PROs will provide insight into the optimal assessment of CIPN.

References: None.

Keywords: Other

Grant Support: None.
Molsidomine provides neuroprotection against vincristine-induced peripheral neurotoxicity

Francesco Lotti¹, Irina Utkina-Sosunova¹, Alessia Chiorazzi², Valentina Carozzi³, Annalisa Canta², Laura Monza², Paola Alberti², Giulia Fumagalli², Serge Przedborski⁴, Guido Cavaletti²

¹Department of Pathology & Cell Biology, Columbia University Medical Center, New York, NY, USA, ²Experimental Neurology Unit, School of Medicine and Surgery, University Milano-Bicocca, Monza, Italy, ³Experimental Neurology Unit, School of Medicine and Surgery, University Milano-Bicocca, Monza, Italy, ⁴Departments of Neurology, Pathology & Cell Biology, Columbia University Medical Center, New York, NY, USA

Peripheral neuropathy is the principal dose-limiting adverse reaction of the major frontline chemotherapeutic agents. Neupathy can be so disabling that many patients will drop out of potentially curative therapy, negatively impacting cancer prognosis. Chemotherapy-induced peripheral neuropathy (CIPN) is refractory to treatment and persists in about 50% of cancer survivors limiting their quality of life.

Vincristine is highly active, but its use is limited by the severe neurotoxicity leading to autonomic, sensory and motor impairment. The hallmark of vincristine peripheral neurotoxicity is axonopathy. Yet the underpinning mechanisms of vincristine-induced axonopathy remains uncertain. We hypothesize that agents preventing vincristine-induced axonopathy will effectively mitigate CIPN symptoms, hence improving cancer treatment outcomes and survivors’ quality of life. Based on this premise, we developed a comprehensive drug discovery pipeline to identify small molecules with neuroprotective activity against vincristine-induced axon degeneration. Among the hits identified, SIN-1 – an active metabolite of molsidomine (Covaryl) – prevents VCR-induced axon loss in both motor and sensory neurons, and it does so without compromising vincristine anti-cancer potency.

To determine the neuroprotective effect of molsidomine, we used an extensively validated rat model of vincristine-induced peripheral neuropathy. Vincristine (0.2mg/kg/week) was administered via the tail vein for 4 weeks and molsidomine (10mg/kg/day or 20mg/kg/day) was administered orally for 4 weeks, starting the first day of vincristine treatment. As expected, the selected schedule of vincristine administration induced severe sensory and motor nerve damage. Importantly, vincristine-treated rats showed a significant decrease in the sensory threshold determined by the dynamic test that was prevented by molsidomine administration in a dose-dependent manner. A similar protective effect of molsidomine was evident on digital nerve amplitude and velocity.

This study provides preliminary evidence of the neuroprotective properties of molsidomine and opens the way to further investigations of this drug as a therapeutic agent to prevent vincristine-induced peripheral neuropathy.

References: None.

Keywords: Axonal Biology, Pre-clinical Studies, Pain, Axonal Regeneration

Grant Support: This work is supported by the Thompson Family Foundation Initiative at Columbia University (TFFI) Innovation Award.
Poster 84

Improving Neuropathy and Mobility in Diabetes: the INMED trial

Lindsay Zilliox, Neda Ilieva, Min Zhan, James Russell

University of Maryland, VA Maryland Health Care System, Baltimore, MD, USA

Introduction

Currently there are no effective disease modifying treatments for diabetic neuropathy (DN). Short term, uncontrolled trials in DN have been performed. However, data from randomized control trials is lacking. To test the effect of a lifestyle intervention on subjects with impaired glucose tolerance (IGT) or type 2 diabetes mellitus (T2DM), a blinded, randomized, intention-to treat, parallel group intervention study was performed over 12 months.

Methods

The lifestyle intervention program consisted of a weight-loss dietary intervention that was tailored to the participants’ caloric expenditure and a graded, increasing, moderate intensity aerobic physical activity intervention that was tailored to the participants’ baseline physical activity (TDPA). The TDPA intervention group was compared to a standard care (SC) group receiving general dietary and exercise advice. The primary caregivers, those measuring endpoints, and the statistician were completely masked to the trial intervention. Masking to the trial intervention was achieved in 81% of participants. The primary efficacy measure was improvement in the 6 minute walk test (6MW) and the secondary efficacy measure was improvement in the intraepidermal nerve fiber density (IENFD).

Results

72 subjects were randomized into the study with equal numbers completing the study in each group. Baseline measurements in each group were not statistically different. At 6 months, the difference in the 6MW (change from baseline) was >25 meters (P=0.02) and >6 meters at 12 months in the TDPA compared to SC groups (P=0.03). At 12 months the change from baseline in the mean thigh IENFD was +1.29 in the TDPA and -0.39 fibers/mm in the SC group (P = 0.04).

Conclusions

In this randomized, blinded, intention-to-treat study of a lifestyle intervention in diabetic neuropathy, there is improvement in the IENFD, as a measure of neuropathy, and mobility in the tailored lifestyle intervention group. This offers a potential therapy for diabetic neuropathy.

References: None.

Keywords: Diabetes, Clinical Trials, Metabolic, Small Fibers, Other

Grant Support: Supported in part by the Office of Research Development, Department of Veterans Affairs (Rehabilitation Research and Development, 101RX001030 and 1K2RX001651, Diabetes Action Research and Education Foundation, and the GRECC.)
Cervical Radiculoplexus Neuropathy As The First Presentation Of Type 2 Diabetes

Piyumi Wijewickrama, Sathyajith Ambawatte, Kamal Gunaratne, Noel Somasundaram

National Hospital of Sri Lanka, Colombo, Sri Lanka

Diabetic radiculoplexus neuropathy (DRPN) or Bruns–Garland syndrome is an acute or subacute asymmetrical, progressive, painful weakness of proximal muscles. As established via postmortem histopathological studies, DRPN occurs as a result of ischemic nerve injury due to immune mediated microvasculitis [1]. DRPN is rare in upper limbs [2]. Our patient presented with cervical radiculoplexus neuropathy as the first presentation of Diabetes. A 49 year old heavy smoker presented with subacute painful weakness and wasting of proximal muscles of left upper limb for 3 months, associated with weight loss. There was no history of trauma, recent infection or osmotic symptoms. He has taken ayurvedic treatments and Diclofenac sodium without improvement. On examination, left upper limb proximal muscles were wasted with reduced power and diminished reflexes. Rest of the neurological examination was normal. His Full blood count was normal. Erythrocyte sedimentation rate was elevated with 60 mm/hr and cerebrospinal fluid was acellular with elevated protein level of 70 mg/dl. Nerve conduction showed comparative amplitude reduction. Needle examination revealed positive sharp waves, frequent fibrillations and high amplitude polyphasic motor unit potentials with reduced recruitment in proximal muscles of left upper limb. Rheumatoid factor, Antinuclear antibodies and Antineutrophil cytoplasmic antibodies were negative. His fasting blood glucose was 198mg/dl and hemoglobin A1c was 9%. He was diagnosed as Diabetic cervical radiculoplexus neuropathy (DCRPN). Treatment with oral hypoglycemics, and Pregablin was started, together with physiotherapy. Patient was advised to stop smoking. In two months review, his diabetes was controlled with significant improvement in proximal muscle power of left upper limb. He was informed that the recovery may be incomplete and treatment was continued. DCRPN is rarer than Diabetic lumbosacral radiculoplexus neuropathy (DLRPN), especially as the first presentation of diabetes. Our case report is an eye opener to think of DCRPN even in undiagnosed diabetes patients.


Keywords: Diabetes, Metabolic, Inflammatory, Other

Grant Support: None.
The Critical Involvement of Neutrophils in Wallerian Degeneration After a Peripheral Nerve Injury.

Richard Zigmond, Jane Lindborg
Case Western Reserve University, Cleveland, OH, USA

Wallerian degeneration has been extensively studied in models of peripheral nerve injury. Clearance of myelin and axonal debris is considered essential to nerve regeneration, as it involves removal of molecules that inhibit regeneration. Infiltrating CCR2+ macrophages have long been thought to be indispensable for nerve debris clearance after injury. It was therefore completely unexpected when we discovered that Ccr2-/- mice, which lack the primary receptor required for infiltration of monocytes/macrophages, displayed comparable myelin and axonal clearance to that of wild-type mice 7 d after sciatic nerve transection (Niemi et al., 2013). Since the Ccr2-/- mouse is a global knockout, we examined myelin clearance after an acute decrease in macrophage infiltration. This was accomplished by using the anti-CCR2 antibody MC-21. MC-21 decreased monocytes/macrophages in the blood and in the nerve; however, myelin clearance in these injected animals was comparable to that in mice given an isotype control antibody (MC-67). In a search for an alternative phagocyte, we injected fluorescent beads into the distal sciatic nerve and identified neutrophils and Schwann cells as capable, along with macrophages, of phagocytosing the beads. We also found that CXCL1 and CXCL2, two chemokines for neutrophils, were increased in the nerve after injury. Neutrophil accumulation in the distal nerve was not restricted to the injury site nor was it concentrated within blood vessels in the nerve, meaning that neutrophils were in a position to phagocytose myelin and axonal debris. Circulating neutrophils can be depleted by injecting animals systemically with an antibody to Ly6G. In these animals, neutrophils were reduced in both the blood and the sciatic nerve, and the clearance of myelin from the nerve was impaired. These results demonstrate for the first time that neutrophils play a pivotal role in mediating Wallerian degeneration.


Keywords: Inflammatory, Axonal Regeneration

Grant Support: Supported by grants DK097223, NS095017, and a predoctoral fellowship NS093694.
Poster 87

Diagnosing Vitamin B12 Deficiency In Patients With Polyneuropathy

Janna Warendorf

UMC Utrecht Brain Center, Utrecht, Netherlands

Background: Diagnosing clinically relevant metabolic Vitamin B12 deficiency can be challenging, especially because of a large variation in cut-off values for laboratory results. Currently used cut-off values are largely based on hematological or asymptomatic patients. Few studies assessed polyneuropathy separately, often preselecting patients with lower B12 values, without excluding folate deficiency or vitamin supplement use. These studies provide insufficient information to establish cut-off values for metabolic Vitamin B12 deficiency in patients with polyneuropathy. The aim of this study was to evaluate Vitamin B12 and metabolites levels in patients with polyneuropathy and establish which cut-off values are most suitable. Methods: A retrospective cohort study in patients with polyneuropathy was carried out. Exclusion criteria were folate deficiency, vitamin supplement use, missing values for methylmalonic acid (MMA), homocysteine, Vitamin B12 or folate. We compared several currently used diagnostic criteria for metabolic vitamin B12 deficiency. ROC curves, sensitivity, specificity, positive and negative predictive values were calculated for different cut-off values. Results: Over 300 patients were included. MMA was elevated (>0.29μmol/l) in 12%, Vitamin B12 ranged from 77 to 408pmol/L in this group, 27% had elevated homocysteine (>14μmol/l), in 32% both were increased. AUC for Vitamin B12, using increased MMA (>0.29μmol/l) as golden standard was 0.76 with a maximum sensitivity and specificity at 174pmol/L, AUC was similar for MMA>0.35μmol/l. AUC of homocysteine, and MMA or Homocysteine combined was lower, 0.67 and 0.75 respectively. A threshold of 300pmol/L for vitamin B12 resulted in a sensitivity of over 90%, and specificity of 30%, using increased MMA as golden standard. Conclusion: In order not to miss patients with metabolic vitamin B12 deficiency in patients with polyneuropathy higher cut-off values for Vitamin B12 might be suitable, such as 300pmol/L. The added value of homocysteine for diagnosing metabolic Vitamin B12 deficiency seems limited.

References: None.

Keywords: Other

Grant Support: None.
Risk of Developing Treatment-Induced Neuropathy of Diabetes (TIND) in hospitalized patients: A Prospective Cohort Study

Amanda Siew Hwee Tan1, Amelia Rui Ying Tan2, Si Min Seah2, Wei Min James Tung3, Jasmine Shimin Koh4, Thirugnanam Umapathi4

1Yong Loo Lin School of Medicine, Singapore, Singapore, 2Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore, 3Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore, 4National Neuroscience Institute, Singapore, Singapore

We previously showed, using retrospective studies on 2 large cohorts of unselected diabetes mellitus (DM) patients in endocrine clinics, an estimated Treatment-Induced Neuropathy of Diabetes (TIND) prevalence of 0.3% to 1.24%. This is lower than that reported in tertiary neuropathy clinics (10.9%), suggesting a difference in TIND occurrence across populations studied. We also reported 5 patients who developed TIND after aggressive in-hospital glycemic control. Common to these patients were high, double-digit admission HbA1c that dropped precipitously, accompanied by hypoglycemic episodes, and hospitalization for serious conditions warranting strict glycemic control. These circumstances, we believe, conspire to make TIND more common in hospitalized DM patients. Current literature lacks studies on what we have termed as “nosocomial” TIND. The role of glycemic variability (GV) in development of TIND is also uncertain. We hypothesize that risk of TIND may be higher in hospitalized patients with poorly controlled DM subjected to strict glycemic control, and GV, together with rate of HbA1c decline, contribute to TIND. We are conducting a prospective case-control study to estimate the prevalence of TIND in hospitalized patients. Patients with HbA1c ≥12% will be recruited, with baseline screening for pre-existing neuropathic or autonomic symptoms, neurologic examination, postural blood pressure and body-mass-index measurements performed. They will be tracked for minimum HbA1c decline required for TIND development (≥2% in 3 months or ≥4% in 6 months) and TIND symptoms at 4 and 8 weeks. Pre - and post-meal capillary blood glucose will be measured to compute standard deviation and coefficient of variance to reflect GV. Patients with suspected TIND would be reviewed using clinical and electrodiagnostic tests at the physician’s discretion. Patients who do not develop TIND would serve as controls in a logistic regression analysis of possible factors affecting TIND development, namely rate of HbA1c decline, GV and weight loss.

References: None.

Keywords: Diabetes, Small Fibers, Pain

Grant Support: None.
Reduced glycolysis–TCA cycle flux in IMS32 Schwann cells under high glucose and pyruvate-deficient conditions.

Kazunori Sango¹, Hideji Yako¹, Ayako Kato², Naoko Niimi¹, Shizuka Takaku¹, Koichi Kato²

¹Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan, ²Aichi Gakuin University School of Pharmacy, Nagoya, Japan

Endogenous pyruvate produced from glucose via glycolysis plays a key role in energy production under aerobic and anaerobic conditions, whereas exogenous pyruvate incorporated into cells via monocarboxylate transporters works as an antioxidant and a glycolysis accelerator. It has been shown that the treatment of experimental diabetic animals with pyruvate alleviates oxidative stress and ameliorates retinopathy and nephropathy. However, the beneficial effects of pyruvate on diabetic neuropathy and the role of exogenous pyruvate in the functional maintenance of neurons and Schwann cells under hyperglycemic environments remain unknown. In this study, immortalized adult mouse Schwann cells (IMS32) were exposed to normal (5 mM) and high glucose (>15 mM) conditions in the presence or absence of sodium pyruvate (1 mM) for up to 24 h, and the viability and glucose metabolism under each culture condition were evaluated using MTS cell proliferation assay, liquid chromatography coupled with tandem mass spectrometry, metabolome and the Extracellular Flux Analyzer. Surprisingly, rapid (<6 h) and massive IMS32 cell death under the high glucose and pyruvate-deficient conditions was observed. Pyruvate starvation had no influence on glucose uptake, but exerted inhibitory effects on glycolytic flux, mitochondrial respiration, and ATP synthesis. The same conditions significantly increased the intracellular contents of polyol pathway products, such as sorbitol and fructose. Moreover, treatment with TCA cycle intermediates (e.g., 2-oxoglutarate), as well as pyruvate, completely prevented IMS32 cell death, mitochondrial dysfunction and ATP depletion. These findings suggest that pyruvate starvation under high glucose conditions accelerates glucose flux in the polyol and other collateral glycolysis pathways and diminishes flux in the glycolysis–TCA cycle and ATP production in mitochondria, thereby being a cause of rapid Schwann cell death.

Keywords: Diabetes, Schwann Cell, Metabolic

A Case of Female Adrenoleukodystrophy Carrier Presenting Like Nonsystemic Vasculitic Neuropathy

Jin Myoung Seok¹, Hye-Jin Cho²

¹Department of Neurology, Soonchunhyang University College of Medicine, Cheonan Hospital, Cheonan, Korea (Republic of), ²Department of Neurology, Bucheon St. Mary’s Hospital, College of Medicine, The Catholic University of Korea, Bucheon, Korea (Republic of)

Background: Adrenoleukodystrophy (ALD) is an X-linked genetic disorder caused by mutations of ABCD1 gene. Male patients with ALD could show various clinical phenotypes including isolated adrenocortical insufficiency, slowly progressive myelopathy and peripheral neuropathy (adrenomyeloneuropathy), and rapidly progressive cerebral demyelinating disease. Female carriers also develop signs and symptoms of myelopathy or peripheral neuropathy; sensory complaints or disturbance were observed in more than half of female carriers of ALD. Here, we report a case of female diagnosed as ALD carrier who present with acute painful weakness mimicking non-systemic vasculitic neuropathy.

Case: A 47-year-old female presented with acute onset of leg pain and weakness. Her leg pain started acutely and lasted for one week, then her ankle weakness began with the sensory disturbance on her sole and dorsum of left foot. Neurologic exam revealed asymmetric distal dominant weakness of both lower limbs with hypesthesia on both sole and the dorsum of left foot, and the increased deep tendon reflexes (DTR) of both legs with a negative Babinski sign were observed. Nerve conduction study (NCS) showed decreased CMAP amplitude of motor nerves in both lower limbs, and mildly decreased SNAP amplitude of sural. Serologic tests for autoimmune vasculitis were all negative. Evaluations for myelopathy were also done because of the increased DTR, but showed no remarkable findings. The genetic analysis of ABCD1 gene showed a heterozygous missense mutation in ABCD1 gene (c.1661G>A; p.Arg554His) which was previously reported as pathogenic variant.

Conclusion: Female carriers of ALD usually present with adrenomyeloneuropathy having variable sensory symptoms. This case represents that the clinical picture of mononeuritis multiplex could be also a presenting feature of female carriers with ALD, which can be a diagnostic challenge.

References: None.

Keywords: Metabolic, Other

Grant Support: None.
TIND and Diabetic Lumbosacral Radiculoplexus Neuropathy – Is Fluctuating Glycemic Control an Etiologic Link?

Genevieve Yu, Jasmine Shimin Koh, Thirugnanam Umapathi

National Neuroscience Institute, Singapore, Singapore

Treatment-induced neuropathy of diabetes (TIND), a rare form of painful autonomic small-fiber neuropathy that occurs after abrupt improvement in glycemic control, and diabetic lumbosacral radiculoplexus neuropathy (DLRPN) share several features. Both present acutely-subacutely with severe, refractory neuropathic pain followed by incomplete improvement over 18-24 months. Weight loss is prominent in both. While DLRPN typically involves several nerve segments asymmetrically and tends to be proximal, recent studies describe involvement of autonomic and distal small sensory fibers as seen in TIND. They conceivably share common pathophysiological factors such as microvasculitis, inflammation, endoneurial ischemia secondary to relative hypoglycemia and glycemic fluctuation. We present 2 patients with DLRPN associated with rapid HbA1c decline. Patient 1 presented with subacute, severe neuropathic pain over the proximal left leg which later went on to involve the right leg. Clinical and electrodiagnostic evaluation confirmed lumbosacral plexoradiculopathy and mild length-dependent sensory polyneuropathy. He was recently diagnosed with diabetes mellitus. Neuropathic pain worsened tremendously and became distal-predominant over several weeks. This was associated with hypoglycemic spells and orthostatic dizziness. HbA1c had plunged from 12% to 6%. Further history revealed prolonged hospitalization with intensive glycemic control. He also lost weight substantially. Patient 2 was a known diabetic who presented with subacute, painful left foot drop. Clinical, electrophysiologic and radiologic findings were consistent with non-compressive left L5-S1 and right L4 radiculopathy. HbA1c had dropped from 13.1% to 10% over 4 weeks after intensive blood glucose control with 4 oral hypoglycemic agents was instituted. She also lost significant amount of weight. Both patients required multiple neuropathic pain medications including opioids. Common to both cases is the severe subacute neuropathic pain, high initial HbA1c, abrupt HbA1c decline and weight loss. We believe that DLRPN, like TIND, might be related to glycemic fluctuation; and the two are different entities of the same spectrum.

References: None.

Keywords: Diabetes, Pain, Small Fibers, Other, Other

Grant Support: None.
Footwear neuropathy: the diagnostic usefulness of ultrasonography

HIROSHI TSUKAMOTO1, TATSUYA ABE2, DAISUKE WATANABE3, TETSUO KOMORI4, KAORU YAMAZAKI5

1Tokyo Medical University Ibaraki Medical Center, Ibaraki, Japan, 2National Hakone Hospital, Odawara, Japan, 3Teikyo University School of Medicine Mizonokuchi Hospital, Kawasaki, Japan, 4National Hakone University, Odawara, Japan, 5Tokyo Medical University Ibaraki Medical Center, Ami, Japan

【Introduction】Footwear neuropathy defined as the neuropathy resulted from tighten by shoes or socks, is often experienced. But unfortunately there is few opportunities to be given the diagnosis because the clinical symptoms are very unusual. And, nerve conduction study shows normal findings in almost cases. To investigate the ultrasonographic imaging of foot wear neuropathy, we performed ultrasonography (US) procedure in three patients with foot wear neuropathy.

【Methods】Three patients, 13 to 78 years old (1 female, 2 men) who suffered from painful sensation in foot after wearing shoes or socks. High-frequency linear probe (more than 14MHz) were used. US was performed continuously among the affected nerves and compared with opposite side. The nerve cross-sectional area (CSA) was measured and judged as abnormal if the CSA of affected side increased more than 1.5 times of the healthy side. In addition, the anterograde sensory nerve conduction studies were performed at the same time, and the sensory nerve action potential (SNAP) amplitude is judged as abnormal if SNAP amplitude was less than 50% of the healthy side.

【RESULTS】The affected nerves were observed two sural nerves where compressed at the ankle and lateral side of the fifth metatarsal bone, one saphenous nerve at the ankle by US investigation. The causes compressed the nerves were shoes in two cases and sock in one. All cases showed Tinel’s sign at the point compressed by footwear. US showed the increased CSA reflecting nerve enlargement in the same point. However, SNAP amplitude was normal in all cases.

【Conclusion】The fact of the CSA was extremely enlarged in the patient with footwear neuropathy, although SNAP was normal. Moreover, US was very useful to detect morphological change and gives important information to suspect this neuropathy.

References: None.

Keywords: Other

Grant Support: None.
Poster 93

The association between electrophysiological severity and pain and paresthesia in diabetes

Chieko Suzuki, Masayuki Baba, Tatsuya Ueno, Haruo Nishijima, Akira Arai, Jin-ichi Nunomura, Masahiko Tomiyama

Department of Neurology, Aomori Prefectural Central Hospital, Aomori, Japan

Positive symptoms, such as paresthesia and pain, are very important in the diagnosis of diabetic polyneuropathy. However, the association between these symptoms and the severity of neuropathy is unclear. The aim of this study was to clarify whether patients with positive symptoms show severe neuropathy. We recruited 171 patients with diabetes. We performed nerve conduction studies and surveyed the patients for paresthesia and pain. From the results of the nerve conduction studies, we classified patients into 5 groups according to the stage of diabetic polyneuropathy, with Stage 0 being the mildest stage and Stage 4 being the most severe stage. The percentage of patients with pain and paresthesia was 25% in Stage 0, 32.4% in Stage 1, 45.2% in Stage 2, 21.0% in Stage 3 and 44% in Stage 4. No correlation between electrophysiological severity and percentage of patients with positive symptoms was observed. Stage 4 is a group with advanced neuropathy with compound muscle action potentials of the tibial nerve at less than 2 mV. More than half of the patients in this group were asymptomatic. Our results show that it is not appropriate to use positive symptoms for evaluating therapeutic effect and severity of diabetic neuropathy.

References: None.

Keywords: Diabetes, Metabolic, Pain

Grant Support: None.
The characteristics of immobilization-induced rhabdomyolysis patients with peripheral neuropathy

JUNG IM SEOK
Catholic University of Daegu, School of Medicine, Daegu, Korea (Republic of)

Introduction: Rhabdomyolysis is caused by injury to skeletal muscle, and is characterized by myalgia and swelling of the affected muscles. Peripheral nerve injury rarely occurs in patients with rhabdomyolysis. Based on our experience and previous reports, we consider prolonged immobilization a risk factor for peripheral neuropathy development in rhabdomyolysis patients.

Methods: This study included 28 patients with rhabdomyolysis due to prolonged immobilization. We analyzed their demographic and laboratory data, clinical and imaging findings, and outcomes, and compared the patients with and without neuropathy and assessed the factors associated with the development of peripheral neuropathy in patients with rhabdomyolysis caused by prolonged immobilization.

Results: Of the 28 patients, 7 had peripheral neuropathy, including sciatic neuropathy or lumbosacral plexopathy. The patients with neuropathy were younger and had higher peak creatine kinase (CK) levels than those without neuropathy. Muscle uptake on bone scan was also higher in the patients with neuropathy. On computed tomography (CT), abnormal muscle findings were frequently observed in the patients with neuropathy.

Conclusions: Prolonged immobilization-induced rhabdomyolysis patients with neuropathy had higher CK levels, increased uptake on bone scans, and more frequent abnormal muscles on CT than those without neuropathy. Peripheral neuropathy is more likely to develop in patients with severe muscle injury.

References: None.

Keywords: Clinical Trials, Metabolic

Grant Support: None.
Introduction: Chronic axonal polyneuropathy (CAP) is a common disease affecting the peripheral nervous system with a prevalence of 1-7% worldwide and 4% in The Netherlands. CAP is a disabling disease that impedes with daily activities and results in high morbidity. This study aims to find risk factors for CAP.

Methods: In June 2013, we implemented a polyneuropathy screening in The Rotterdam Study, a population-based cohort study running since 1990 that aims to identify risk factors for chronic diseases in the general population aged>40 years. Participants are screened every 3-5 years. The polyneuropathy screening consists of 3 components including a symptom questionnaire, neurological examination and nerve conduction studies (NCS) of the legs. Based on this screening, participants are categorized in consensus-meetings as definite, probable, possible or no polyneuropathy. Since July 2018 we started with re-screening, which allows us to study incidence, biological factors and NCS data related to the development of CAP.

Results: From June 2013 until November 2018, 3445 participants were screened of which 225 participants were excluded due to insufficient data. Of the remaining 3220 participants, 4.5% (N=146) had definite, 5.8% (N=188) probable, 18.9% (N=610) possible and 70.7% (N=2276) had no polyneuropathy. Participants with definite polyneuropathy were on average older (76.3y) than participants with no polyneuropathy (63.3y). Males more often had definite polyneuropathy than women (54.8% vs 45.2%). Previously we have focused on metabolic factors (N=1310 participants). Using the still increasing group of participants we will investigate these and other putative risk factors like dietary habits, cardio-metabolic health, medication use and genetic changes.

Conclusion: CAP is a common and disabling disease for which currently no treatment is available. This highlights the importance to conduct further research to identify risk factors that may not only lead to a better understanding, but hopefully also to treatment or even prevention of cases with CAP.

References: None.

Keywords: Metabolic, Diabetes, Other

Grant Support: None.
Poster 96

ULTRASONOGRAPHY FINDING FOR THE DIAGNOSIS OF CARPAL TUNNEL SYNDROME IN DIABETIC AND NON-DIABETIC PATIENTS

Yasufumi Sekiguchi

Fukushima Medical University School of Medicine, Fukushima, Japan

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy. Diabetes mellitus (DM) is reported as a significant independent risk factor for CTS. Some studies reported peripheral nerve changes in DM patients and described enlarged median nerve cross-sectional area (CSA) by Ultrasonography. The purpose of this study was to investigate the diagnostic value of CSA in patients with electro-diagnosed CTS with or without DM. We retrospectively studied 50 CTS wrists and 20 healthy wrists in a single center between January 1, 2013 and January 1, 2018. The CSA was calculated for each wrist. Patients were classified into four groups according to the presence of DM and CTS: group 1, non-DM and non-CTS patients; group 2, non-DM and CTS patients; group 3, DM and non-CTS patients; and group 4, DM and CTS patients. The CSA were 8.7 in non-DM+non-CTS, 14.8 mm² in non-DM+CTS, 12.5 mm² in DM+non-CTS and 15.7 mm² in DM+CTS. They were not significant differences between DM+non-CTS and non-DM+CTS. We conclude that the CSA has a low diagnostic accuracy in diabetic patients and should be used with caution in those patients.

References: None.

Keywords: Clinical Trials, Diabetes, Pain

Grant Support: None.
Asymmetric clinical presentation in some patients with diabetic polyneuropathy may result from the different vascular environments in both lower limbs. The aim of the study is to determine the association of neuropathy with vascular factors in each lower limb of diabetic patients. A total of 102 patients (204 lower limbs) given a diagnosis of diabetic polyneuropathy were enrolled. The primary end points are sensory nerve action potential (SNAP) amplitude and conduction velocity (CV) of the sural nerve and independent variables are vascular and nonvascular factors. Vascular factors include mean arterial pressure and pulse pressure at the ankle, ankle-brachial index, and arterial stiffness assessed by pulse wave velocity. Nonvascular factors include age, gender, height, body weight, body mass index, total cholesterol, and hemoglobin A1C. Age, hemoglobin A1C, and ankle pulse pressure were inversely correlated with SNAP amplitude of the sural nerve, while no factors were correlated with CV of the sural nerve. Increased arterial stiffness was significant in the limbs group with abnormal SNAP amplitude of the sural nerve, while increased height was significant in the limbs group with abnormal CV of the sural nerve. Vascular factors were more significantly associated with decreased SNAP amplitude rather than decreased CV of the sural nerve in the nerve conduction study of diabetic patients.

References: None.

Keywords: Diabetes

Grant Support: None.
Atypical Sensorimotor Neuropathy Related to Cutaneous Toxigenic Diphtheria Infection In A World Traveller

Penelope Spring¹, Alice Powell¹, Nilanthy Vigneswaran¹, Stephen Reddel¹, Genevieve McKew², Verlaine Timms³, Min-Xia Wang⁴, Judith Spies⁴, John Pollard⁴

¹Department of Neurology, Concord Repatriation General Hospital, Sydney, NSW, Australia, ²Department of Infectious Diseases and Microbiology, Concord Repatriation General Hospital, Sydney, NSW, Australia, ³Centre for Infectious Diseases, Microbiology-Public Health, Westmead Hospital and University of Sydney, Sydney, NSW, Australia, ⁴Institute of Clinical Neurosciences, University of Sydney and Royal Prince Alfred Hospital, Sydney, NSW, Australia

Diphtheria is now an uncommon cause of peripheral neuropathy, however recent reports have related to pharyngeal infection¹. Here we report a rare case of a sensorimotor neuropathy, initially resembling immunotherapy-resistant Guillain-Barre syndrome, following a highly toxigenic cutaneous diphtheria infection.

A 66-year-old Australian man, a frequent world traveller, presented in March 2018 with progressive sensorimotor neuropathy with neuropathic pain, maximal in the left foot (initial ONLS-Overall Neuropathy Limitations Scale-6). He had a resolving ulcer on the second left toe, present since January in Vanuatu, and treated with antibiotics; and recent Rhinovirus. Nerve conduction studies (NCS) suggested demyelination; lumbar puncture showed elevated protein-1.27g/L, normal cells. Intravenous immunoglobulin (IVIg) (2g/kg) and pregabalin induced minimal improvement.

Despite plasmapheresis (x5), pulsed methylprednisolone (Week 3), then oral steroid (1g/kg), and further IVIg, the patient progressed. Mild diplopia, facial weakness/paraesthesia, dysphonia, dysphagia, and moderate pulmonary restriction developed (Wk2-4). By Wk6 he had marked quadriparesis/proprioceptive loss (ONLS-11), and Raynaud-like fluctuating left foot cyanosis.

Autoimmune/serological investigations including ganglioside/paranodal antibodies were unremarkable apart from positive Ro60/52. MRI spine (Wk5) showed patchy cauda equina enhancement. Neurophysiology (Wk5) showed lower limb (LL) denervation, and somatosensory evoked potentials (SSEPs) were absent/delayed(LL/UL). Initial toe swab culture/PCR review showed a highly toxigenic strain of Corynebacterium diphtheriae, expressing A/B toxin beta subunits. IVIg was ceased due to deep vein thrombosis and likely diphtheritic neuropathy. Steroids were weaned during rehabilitation (Wk8-16), and there was dramatic functional improvement: ONLS-Wk10-9/Wk16-5/Wk24-2. Sural nerve/muscle biopsies (Wk7) showed a chronic active axonal neuropathy, and VEGF was normal. Neurophysiologically, improvement was mild by 5 months; substantial by 11 months.

This is the first report of generalised neuropathy related to cutaneous diphtheria infection since 1946²³. The axonal loss is atypical, with diphtheria usually associated with demyelinating neuropathy⁴. It is unclear whether timing, distal infection, antitoxin non-use, or organism strain affected the pathology.


Keywords: Inflammatory, Pain, Axonal Regeneration, Other

Grant Support: Nil
Electrophysiological findings in axonal-demyelinating polyneuropathy in diabetes

Anna Potulsk-Chromik¹, Marta Lipowska¹, Małgorzata Lukawska¹, Andrzej Seroka¹, Anna Kostera-Pruszczyk²

¹Department of Neurology, Medical University of Warsaw, Warsaw, Poland, ²Department of Neurology, Medical University of Warsaw, Warsaw, Poland

Introduction

DM affects about 9% of the general population and 26% in persons 65 years or older. Half of patients with DM have some form of neuropathy, more than 80% of these are diabetic peripheral neuropathy (DPN). The increasing prevalence of diabetes creates need to improve identification of potentially treatable neuropathies, such as chronic inflammatory demyelinating neuropathy (CIDP).

Patients and methods

Retrospective analysis of nerve conduction study (NCS) data included 12 patients aged 14-65 y.o. with the diabetes (including 3 with DM1) and at least partially treatment responded demyelinating polyneuropathy (9 male and 3 female).

Results

NCS analysis of all patients data revealed motor-sensory neuropathy.

Analysis of only motor nerves focused on typical demyelinating parameters CV, DML due to PNS/EFNS criteria of definite CIDP was fulfilled in all patients.

Distal CMAP duration was longer than 9ms in at least one of the four motor nerves in 6/12 patients, however abnormal DCMAP duration according to EFNS/PNS criteria were found in 10/12.

Typical partial motor conduction block >50% accompanying with abnormal DCMAP duration in these nerves was observed in 5/13 whereas in one patient conduction block was observed in 7 nerves with normal DCMAP duration.

According to Lotan criteria the scores of DM patients ranged from 8 to 16. The histological parameters and ancillary studies proposed by Lotan was not taken under consideration.

Conclusion

Coexistence of typical demyelinating changes in patients with DM should be always analyzed due to clinical and electrophysiological CIDP criteria. It is a challenge to identify CIDP in a diabetic population due to concomitant axonal damage. Patients with CIDP and DM may respond to treatment, that’s why there is a need to differentiate CIDP from DPN accurately.

Keywords: Diabetes, Inflammatory, Other

Grant Support: none
Aging of the neuromuscular system dramatically increases vulnerability to debilitating conditions, including peripheral neuropathy, neurodegeneration, and sarcopenia. As a result, clinical interventions for age-related diseases require treatments that ameliorate both the nervous and muscular systems. Previously, we reported that muscle-derived stem/progenitor cells (MDSPCs) have the capacity for multipotent differentiation, including the ability to adopt neuronal and glial phenotypes in vitro. Local transplantation of undifferentiated MDSPCs into a critical-size sciatic nerve defect in mice promotes complete peripheral nerve regeneration, restores functional gait, and reverses muscle atrophy. Furthermore, systemic transplantation of young MDSPCs into a murine model of human progeria (a condition marked by accelerated aging) remarkably delays the onset of aging-related diseases and significantly extends lifespan. In this study, we investigated the efficacy of systemic MDSPC transplantation as a novel method to ameliorate structural and functional changes associated with age-related neuromuscular decline. Neuromuscular tissues from 22-month-old C57bl/6 mice were evaluated one to two months post-intraperitoneal transplantation of young MDSPCs (NA-IP) or PBS (NA) and compared with 6-month-old mice (6mo) as healthy controls. Compared to NA, NA-IP mice exhibited a significant increase in AChR density in muscle and decreased muscle atrophy, shown by an increase in muscle mass. Additionally, systemic transplantation of MDSPCs significantly increased median cross-sectional area of both the axon and myelinated fiber of the sciatic nerves by >25% compared to NA mice. Interestingly, myelinated fiber area was not significantly different between the NA-IP and 6mo mice, providing evidence that young MDSPC transplantation improves aged neuromuscular tissues. Finally, NA-IP mice displayed an ability to run longer at higher speeds with significantly improved gait parameters including stride length and variance, indicating that MDSPC transplantation increases endurance and physical stamina of naturally aged mice. These results demonstrate the therapeutic potential of MDSPCs to restore structure and function of aging neuromuscular tissues.


Keywords: Axonal Regeneration, Axonal Biology

Grant Support: None.
Antibodies directed against peripheral neurons, Schwann cells and myelin are frequently found in Zika-exposed subjects

Simon Rinaldi¹, Alexander Davies¹, Cinta Lleixà², Ana Siles², Carolina Ramírez Santana³, Juan-Manuel Anaya³, Claudia Romero-Vivas⁴, Andrew Falconar⁵, Lyda Osorio⁶, Beatriz Parra⁶, Carlos Pardo⁷, Susan Halstead⁸, Hugh Willison⁸, Luis Querol²

¹University of Oxford, Oxford, United Kingdom of Great Britain and Northern Ireland, ²Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, ³Universidad del Rosario, Bogota, Colombia, ⁴clromero@uninorte.edu.co, Barranquilla, Colombia, ⁵London School of Health and Tropical Medicine, London, United Kingdom of Great Britain and Northern Ireland, ⁶Universidad del Valle, Cali, Colombia, ⁷Johns Hopkins, Baltimore, MD, USA, ⁸University of Glasgow, Glasgow, United Kingdom of Great Britain and Northern Ireland

Introduction: Following the Zika outbreak in French Polynesia, a spike in Guillain-Barré syndrome (GBS) diagnoses was observed in the region. By the time the epidemic reached South America, it had been established that 1 excess GBS case occurred for every 4000 people infected. Whether Zika-GBS results from autoimmunity or direct viral toxicity remains unclear. This is important to establish, however, not only to aid diagnosis and direct appropriate treatment of this complication, but also for the development of safe Zika virus vaccines.

Methods: Serum samples were obtained within Colombia from 53 patients who developed a neurological syndrome following Zika infection (43 GBS, 10 other), 74 subjects with uncomplicated Zika, and 38 non-Zika exposed controls. Some samples were collected several months after the acute event. Sera were tested for IgG and IgM reactivity against human-induced-pluripotent-stem-cell derived peripheral myelinating co-cultures, primary Schwann cells and dorsal root ganglion (DRG) neurons. The antigen target(s) of sera with distinct binding patterns were then sought using immunoprecipitation and mass spectrometry, with potential candidates further evaluated by ELISA and/or transfected-cell-based assays. Co-cultures were also used to assess the ability of selected sera to induce demyelination. Results: Overall, 16 /43 (37.2%) patients with Zika-GBS reacted moderately or strongly against primary DRG or Schwann cells, whereas only 2 (2.7%) uncomplicated Zika subjects and 4 (10.5%) controls reacted moderately. These differences were statistically significant. IgM binding to myelinating co-cultures was frequently detected with both Zika-GBS and infectious control sera. IgG reactivity was infrequent, but significantly more common with Zika-GBS patients’ sera compared to controls. Reactivity against the abaxonal membrane of myelinating Schwann cells was particularly notable. Serum from one uncomplicated Zika subject with this pattern of reactivity induced complement-dependent demyelination on exposure to the co-culture.

Conclusion: Antibodies targeting peripheral nerve structures are common after Zika infection and can induce demyelination.

References: None.

Keywords: Inflammatory, Schwann Cell, Other

Grant Support: None.
Immunomodulatory effects of bortezomib in experimental autoimmune neuritis in lewis rats.

Rafael Klimas1, Melissa Sgodzai1, Nuwin Mohamad1, Xiomara Pedreiturria1, Jeremias Motte1, Min-Suk Yoon2, Ralf Gold1, Kalliopi Pitarokoili1

1Ruhr-University Bochum, St. Joseph University Hospital Bochum, Bochum, Germany, 2Ruhr-University Bochum, Ev. Augusta Hospital Hattingen, Hattingen, Germany

Introduction: In a case series of ten treatment refractory chronic inflammatory demyelinating polyradiculopathy (CIDP) patients Bortezomib (BTZ) was able to stop disease progression when administered subcutaneously 1.3 mg/m2 KOF at day 1, 4, 7 and 10. The exact mechanisms of action remain unknown while the dose-limiting side-effect of Bortezomib is an axonal polyneuropathy. Methods: To determine the minimum concentration inducing polyneuropathy we treated female Lewis rats with BTZ (0.05, 0.2 mg/kg) intraperitoneally (i.p.) and the control group with 5% DMSO. Subsequently, EAN was induced in 6 weeks old rats by P2-peptide (n=12/group). One group was treated with 0.05mg/kg BTZ i.p, onother group was treated with 0.1mg/kg BTZ i.p. A control group received 5% DMSO at day 9, 13, 17 and 21. Von Frey hair-(vFH) and hot plate test were performed at day 10, 14, 18 and 22. Clinical score and weight were assessed daily. Electrophysiological analyses of sciatic nerve were performed at day 0 and 23. At day 23, we performed flow cytometric analyses of the immune cells in spleen, lymph nodes, blood, and bone marrow . Subsequently, sciatic nerve and bone marrow tissue were analyzed by immunofluorescence stainings. Analyses of mRNA expression were performed on sciatic nerve. Results: Treatment with 0.05 mg/kg BTZ i.p. improved EAN significantly, reduced inflammatory infiltrates and demyelination in the sciatic nerves and ameliorated electrophysiological neuritis signs without inducing axonal neuropathy. Furthermore, BTZ improved vFH and hot plate test. Flow cytometric analyses showed a reduction of CD4+, CD11b+, IgK+ cell populations in several lymphoid organs. Conclusions: We revealed for the first time the immunomodulatory effects of bortezomib in EAN. It improves clinical EAN score, electrophysiological signs of large myelinated axons and small-fiber function in vFH test, without causing neuropathy as a side-effect. The proposed relevant immunological mechanism is the modification of dendritic and B-cell populations.


Keywords: Inflammatory, Axonal Regeneration, Small Fibers

Grant Support: -holder of scholarship of the `University structured doctoral program, FoRUM` -holfer of scholarship of the RUB Research School "Project.International", PR.INT
Introduction

Polyneuropathy in POEMS syndrome (Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin change) has been rarely described in detail. Here, we describe the characteristics of neuropathy in a large series of patients, and try to identify prognostic factors.

Methods

In this monocentric retrospective study, we analyzed the clinical and neurophysiological characteristics (at diagnosis, 6 months and 1 year follow-up) of patients with POEMS syndrome diagnosed in our University Hospital between 1980 and 2017. The primary end-point was the Modified Rankin Scale (mRS) score.

Results

36 patients (mean age at diagnosis: 54 years; 58% male) with POEMS syndrome were analyzed. Hematologic diagnosis was monoclonal gammapathy of unknown significance (MGUS) in 28% of cases, solitary plasmocytoma (25%), myeloma (19%), and multiple plasmocytoma (14%). Diagnosis was delayed up to 12 months after symptom onset in 75% of cases. The mean mRS at diagnosis was 2.61 +/- 1.13. The neuropathy was clinically and electrically sensorimotor, length-dependent and severe (56% of patients had mRS ≥ 3). Nerve conduction studies showed a mixed axonal and demyelinating pattern (44% of cases), a pure axonal pattern (25%), or pure demyelinating features (28%). 39% (n=14) of patients were treated with autologous stem-cell transplantation (ASCT) and 33% had radiotherapy. At 1 year follow-up, 33% of patients had improved, 36% were stabilized, and 14% worsened. Age over 65 years and weight loss were of poor prognosis (p=0,0483 and p=0,0383). Patients treated with ASCT improved in 54% of cases whereas patients treated with radiotherapy improved in 33% of cases. ASCT was associated with good prognosis (OR=7, IC95 1,14-42,97, p=0,0253).

Conclusion

POEMS syndrome polyneuropathy is severe, rapidly progressing, length-dependent, with both axonal and demyelinating electrophysiological features in a majority of cases. Age over 65, weight loss are of poor prognosis whereas ASCT is associated with a good outcome.


Keywords: Axonal Regeneration, Schwann Cell, Pain

Grant Support: None.
Poster 104

Outcomes after single-cycle rituximab in patients with anti-MAG polyneuropathy: an average eleven years follow-up analysis

Martina Garnero1, Diego Franciotta2, Chiara Briani3, Chiara Demichelis4, Marina Grandis4, Valeria Prada4, Angelo Schenone4, Luana Benedetti4

1Neurology Department, Ospedale Sanremo, ASL 1, Sanremo, Italy, 2Neuroimmunology Laboratory, IRCCS Mondino Foundation, Pavia, Pavia, Italy, 3Department of Neurosciences, University of Padova, Padova, Padova, Italy, 4DiNOGMI, University of Genova, IRCCS, Policlinico San Martino, Genova, Genova, Italy

Introduction. Several studies make rituximab the most efficacious drug in anti-myelin-associated glycoprotein (MAG) polyneuropathy.

Open questions still remain about the duration of the benefit of a single treatment course and how to repeat therapy in responsive patients.

We studied twenty-one patients (mean age, 74.7 years) with anti-MAG polyneuropathy, who improved after rituximab (375 mg/m², 4 consecutive weekly intravenous infusions), prospectively followed-up for an average of 11.2 years to assess the duration of clinical benefit and the best timing for retreatment.

Patients and Methods. We empirically decided not to perform maintenance therapies, but to treat the patients upon relapse, defined as a worsening by one point in at least two of the three scales (INCAT, MRC, ISS).

Duration of clinical benefit was related with the following parameters: age, sex, disease duration, scores of the clinical scales, anti-MAG antibody titres, and serum B-cell-activating factor (BAFF) levels pre-therapy.

Results. Clinical improvement after the first rituximab cycles lasted on average 6 years (range 2-12) and significantly correlated with pre-therapy lower scores of both the INCAT and ISS scales, lower serum anti-MAG antibody and BAFF levels. When the cohort of patients was split between those who relapsed after 2-3 years (1017.0 ± 117.2 pg/mL) vs those at 4 year, or later (627.9 ± 70.5 pg/mL) ROC curve analysis showed an AUC of 0.937 (95% CI, 0.810-1.065; p = 0.01), and a cut-off of 860 pg/mL (likelihood ratio, 12.0).

In conclusion our data indicate that, after an initial rituximab cycle, clinical improvements can last for on average 6 years. One of the most interesting pre-therapy predictors of clinical response is lower serum BAFF level; the cut-off value of 860 pg/mL might be useful to identify patients with poor response to treatment. Further studies on larger series of patients are needed to validate our findings and cut-off.

References: None.

Keywords: Inflammatory

Grant Support: None.
Poster 105

Difference of Clinical and Paraclinical Patterns in anti-FGFR3-Positive Sensory Neuronopathy Cases from Brazil and Europe

Yannick Tholance¹, Yannick Tholance¹, Carole Rosier², Alberto Martinez³, Christian Moritz⁴, François Lassablière⁴, Karine Ferraud⁵, Marcondes França Jr³, Jean-Philippe Camdessanché², Jean-Christophe Antoine²

¹Synaptopathies and Autoantibodies (INMG), Department of Biochemistry in University hospital of Saint-Etienne, Saint-Etienne, France, ²Synaptopathies and Autoantibodies (INMG), Department of Neurology in University hospital of Saint-Etienne, Saint-etienne, France, ³Department of Neurology, University of Campinas (UNICAMP), Campinas, Brazil, ⁴Synaptopathies and Autoantibodies (INMG), Saint-Etienne, France, ⁵Department of Neurology in University hospital of Saint-Etienne, Saint-Etienne, France

Sensory neuronopathies (SNN) are rare diseases of the peripheral nerve system. Although being often classified as idiopathic, many cases are associated with immune-mediated diseases, suggesting an active involvement of the immune system. Indeed, we have reported that an antibody reacting with the intracellular domain of the Fibroblast Growth Factor Receptor 3 (FGFR3) identifies a subgroup of patients with SNN. Here we report the results of a prospective, multicentric and international study in which 42 anti-FGFR3-positive SNN patients were identified in one Brazilian center and in 35 European centers. The incidence of the anti-FGFR3 antibodies was higher in SNN Brazilian patients than in European ones (15/42 (35.7%) vs 27/211 (12.8%), p = 0.0003). When we compared the clinical and paraclinical patterns of the anti-FGFR3-positive SNN cases from Brazil and Europe, we found that Brazilian cases were younger at the onset of the neuropathy (median age 44 (39-50) vs. 61 (50-68), p=0.0006) and were more frequently associated with other autoimmune diseases than in the European cases, particularly regarding the frequency of Sjögren syndrome (46.7% vs. 3.8%, p=0.001). The distribution of sensory symptoms among the Brazilian anti-FGFR3-positive patients was more frequently asymmetrical (93% vs. 24%, p<0.0001; odd ratio 169, 3.4-8424 95% confident interval, p=0.01), proximal (73% vs. 26%, p=0.003), and affecting the upper limbs (100% vs. 52%; p=0.001). After several years of evolution, paresthesia (100% vs. 67%, p=0.01), ataxia in upper limbs (73% vs. 30%, p=0.0001), global areflexia (80% vs. 26%, p=0.001) and dysautonomia (67% vs. 9%, p=0.0002) were more frequent in Brazilians than in Europeans. Overall, our prospective and international study identified a striking difference in the prevalence of anti-FGFR3 antibodies and in the clinical and paraclinical pattern of anti-FGFR3-positive SNN patients from Brazil and Europe which suggests that environmental or genetic factors may lead to an autoimmune reaction against FGFR3.


Keywords: Inflammatory, Clinical Trials, Other, Other

Grant Support: None.
Poster 106

Holistic Characterization of the Repertoire of Targeted Autoantigens of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

Christian Moritz¹, Oda Stoevesandt², Yannick Tholance³, Carole Rosier⁴, Karine Ferraud⁴, Jean-Philippe Camdessanche³, Jean-Christophe Antoine³

¹Institut NeuroMyoGene INSERM U1217/CNRS UMR 5310 at the University of Lyon, Saint-Étienne, France, ²Cambridge Protein Arrays Ltd., Cambridge, United Kingdom of Great Britain and Northern Ireland, ³University Hospital of Saint-Étienne, Institut NeuroMyoGene INSERM U1217/CNRS UMR of the University of Lyon, Saint-Étienne, France, ⁴Institut NeuroMyoGene INSERM U1217/CNRS UMR of the University of Lyon, Saint-Étienne, France

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare disease of the peripheral nervous system. Patients suffer from progressively increasing limb weakness, ataxia, absent or diminished tendon reflexes, and paresthesia. The disease is considered as having an autoimmune background, hence the identification of autoantibodies has been a focus of research in recent years. Identifying corresponding autoantigens would improve the diagnosis, treatment, and understanding of the disease, but, recent studies failed to identify an antigen for the majority of classical CIDP patients. We screened sera from 50 CIDP patients with an improved immunoblotting-based technique.¹ Based on the resulting immunological fingerprints, the sera from 22 classical CIDP patients were selected and their set of targeted autoantigens profiled via protein arrays, containing about 16,000 different bait proteins. As controls, 12 other neurological diseases and 9 healthy controls were profiled in parallel. A patient with Sjögren syndrome manifesting the known autoantibodies anti-Ro/SSA/Trove2 and anti-SS-B, as well as an autoimmune hepatitis patient manifesting anti-SLA/SEPSECS, served successfully as positive controls. Rather than addressing single antigens, we have developed a novel idea of studying the total repertoire of antigens in a more holistic way. The size of the antigen repertoire appears to depend on the clinical situation; e.g. CIDP patients responsive to intravenous immunoglobulin therapy targeted three times more autoantigens than non-responders. Bioinformatic analyses of the repertoires as a whole revealed that a significant part of the autoantibody set specifically targets neuronal disease-related antigens as well as proteins involved in glycoprotein metabolic processes. Our project helps to understand the role of autoantibodies in CIDP patients by addressing the set of autoantigens holistically.


Keywords: Inflammatory, Pain

Grant Support: German Research Foundation (DFG; MO 3240/1-1:1), CSL Behring (Fonds de dotation)
Misdiagnosis and Diagnostic Pitfalls of CIDP

Merel Broers¹, Carina Bunschoten¹, Tiago Beck¹, Hester Lingsma², Jeffrey Allen³, Richard Lewis⁴, Esther Brusse¹, Judith Drenthen⁵, Pieter van Doom¹, Bart Jacobs⁶

¹Department of Neurology, Erasmus MC, University Medical Center Rotterdam, The Netherlands, Rotterdam, Netherlands, ²Department of Public Health, Erasmus MC, University Medical Center Rotterdam, The Netherlands, Rotterdam, Netherlands, ³Department of Neurology, University of Minnesota, Minneapolis, Minneapolis, MN, USA, ⁴Department of Neurology, Cedars-Sinai Medical Center, Los Angeles, Los Angeles, CA, USA, ⁵Department of Clinical Neurophysiology, Erasmus MC, University Medical Center Rotterdam, The Netherlands, Rotterdam, Netherlands, ⁶Department of Neurology and Immunology, Erasmus MC, University Medical Center Rotterdam, The Netherlands, Rotterdam, Netherlands

Purpose: The diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is challenged by the disease rarity, heterogeneity and differential diagnosis. Misdiagnosis of CIDP is a common problem in the United States of America. We aim to determine the extent of misdiagnosis, including over- and underdiagnosis, and to identify pitfalls in the diagnosis of CIDP in the Netherlands.

Methods: We retrospectively included all tertiary patient referrals to our university hospital between April 2011 and March 2017 with CIDP, or another initial diagnosis that we revised into CIDP. Final diagnosis in all patients was made after an extensive discussion in consensus meetings. Overdiagnosis was defined as initial incorrectly diagnosed with CIDP. Underdiagnosis was defined as initial missed CIDP diagnosis.

Results: Of 297 patients screened, 113 patients met the inclusion criteria. Preliminary results are based on the first 38 patients, including 33 patients initially diagnosed with CIDP and 5 patients with another initial diagnosis revised into CIDP. Overdiagnosis was observed in 10/33 (30%) patients, of whom 5 received immunomodulatory treatment before referral. The diagnosis was changed to axonal polyneuropathy (n=4), IgM anti-MAG neuropathy (n=1), CANOMAD (n=1), anti-Hu related polyneuropathy (n=1), hereditary polyneuropathy (n=1), sensory neuropathy (n=1) or polyneuropathy not demonstrated (n=1). Identified pitfalls were absence of proximal weakness, cytoalbuminologic dissociation, presence of serum antibodies associated with polyneuropathy, and NCS classified as axonal polyneuropathy. Underdiagnosed patients (5/28) were referred with possible entrapment neuropathy (n=1), Guillain-Barré syndrome (n=1), spinal muscular atrophy (n=1), paraproteinemic polyneuropathy (n=1) or polyneuropathy not further specified (n=1). The diagnostic pitfall in the underdiagnosis group was an atypical clinical presentation.

Conclusion: Based on these preliminary results, misdiagnosis of CIDP is also common in the Netherlands and includes both over- and underdiagnosis. The results of the full cohort (n=113), will be

References: None.

Keywords: Inflammatory

Grant Support: This study is funded by the Dutch Prinses Beatrix Spierfonds (grant application number: W.OR16–18).
One year closer to clinical trials with a new antigen specific treatment for anti-MAG neuropathy

Pascal Hänggi¹, Butrint Aliu¹, Lijuan Pang¹, Delphine Demeestere¹, Andreas Steck², Beat Ernst¹, Ruben Herrendorff³

¹University of Basel, Basel, Switzerland, ²University Hospital Basel, Basel, Switzerland, ³Polyneuron Pharmaceuticals AG, Basel, Switzerland

Anti-myelin-associated glycoprotein (MAG) neuropathy is a rare and disabling autoimmune disorder affecting the peripheral nervous system. The pathogenicity of anti-MAG IgM autoantibodies that target the HNK-1 glycoepitope is well established. Patients suffer from severe symptoms including sensorimotor deficits, ataxia, paraesthesia and tremor. Nowadays, there are only off-label treatments with limited efficacy available. We have previously shown that the new antigen-specific drug candidate PPSGG efficiently depletes pathogenic anti-MAG IgM in vivo and abrogates the reactivity of patients' antibodies to MAG on sciatic nerves ex vivo.

We recently performed a more in-depth assessment of PPSGG addressing the selectivity of anti-MAG IgM binding, the characteristics of the drug-antibody interaction, as well as the pharmacokinetic and metabolic properties. These studies enabled first dosing assumptions for clinical trials. Moving forward to its clinical evaluation, we performed safety pharmacology studies in rats and dogs with PPSGG.

Consistent with the data from a mouse model, we showed that PPSGG and the anti-MAG IgM:PPSGG complex was taken up actively into human macrophages (THP-1 cell line) and other cell types of the human mononuclear phagocyte system by phagocytosis. We demonstrated a 1:1 or 1:2 stoichiometry of the PPSGG:anti-MAG IgM binding by analytical ultra-centrifugation and size exclusion chromatography. In the dose assumption study, we determined the dose of PPSGG that is required to deplete specific anti-MAG IgM levels. The extrapolation indicates that a single dose of 5 mg/kg PPSGG is expected to remove a significant proportion of anti-MAG IgM in patients. In a dose range finding toxicity study, PPSGG showed a favorable safety profile, even at elevated dose levels. In dogs, multiple dosing of 200 mg/kg did not cause any drug related side effects.

Taken together, we are convinced that PPSGG is a very promising drug candidate and will be further developed for clinical trials in anti-MAG neuropathy.


Keywords: Inflammatory, Clinical Trials, Other

Grant Support: None.
Poster 109

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) Associated With Sarcoidosis Or Connective Tissue Disease.

Clément Vialatte de Pémille¹, Nicolas Noël², David Adams³, Cécile Cauquil³
Introduction:

CIDP are heterogeneous pathologies. Diagnosis can be challenging because of atypical presentations (CIDP-chameleons) and differential diagnoses (CIDP-mimicking) to exclude. Neurosarcoidosis (NS) and connective tissue diseases (CTD) are rarely associated with CIDP. We analysed the presentations of CIDP associated with these diseases and highlight the helpful “red flags”.

Methods:

We performed a retrospective study by analysing patients with NS (group S) and CTD (group C) fulfilling EFNS-PNS CIDP diagnosis criteria and compared them with patients with idiopathic CIDP (group I). Zajicek criteria were used for NS diagnosis and ACR criteria for CTD.

Results:

Forty-four patients were included (median age 60 yo, 23 women): 17 in group I, 16 in group S and 11 in group C. NS diagnosis, according to Zajicek criteria, was definite in 9 cases (granuloma within peripheral nerve tissue), probable in 6 cases and possible in 1 case. Among CTD diagnosis there were 7 Gougerot-Sjogren syndrome (GSS), 1 systemic lupus erythematosus (SLE), 2 SLE with GGS and 2 mixed connective tissue diseases. CIDP diagnosis was definite in 57.1% in group S and 54.5% in group C. General status was significantly (p<0.05) altered in both groups, C and S, when compared to group I. Subacute onset (78.6% vs 5.9%) and unresponsiveness to treatment by Intravenous Immunoglobulins (IVIg) (14.3% vs 82.4%) were significantly observed in group S when compared to group I. Interestingly, there were more motor conduction blocs in group S compared to group I (46.6% and 83.3% respectively, p=0.12). CSF and histological analyses showed no differences except for the presence of granulomas.

Discussion:

Our results confirm and enhance the red flags of CIDP diagnosis. Altered general status, subacute onset or unresponsiveness to IVIG are observed in patients with CIDP and NS or CTD. Motor conduction blocs can be found in peripheral NS mimicking CIDP.

References: None.
Keywords: Inflammatory

Grant Support: None.

Poster 110

Incidence of antibodies against the node of Ranvier in a prospective cohort of 1000 CIDP

Emilien Delmont¹, Alexandre Brodovitch¹, Shahram Attarian¹, Jose Boucraut²

¹Referral centre for neuromuscular diseases and ALS, APHM, Marseille, France, ²Immunology department, APHM, Marseille, France

IgG4 antibodies against proteins of the node of Ranvier have been recently described in severe CIDP resistant to intravenous immunoglobulins treatment (IVIg). Their incidence varies from 4% to 16% in sera banks of CIDP patients analyzed retrospectively.

Our objective was to determine the incidence of IgG4 antibodies against proteins of the node of Ranvier in a multicenter, prospective cohort of 1000 consecutive CIDP.

IgG4 antibodies against neurofascin 155 (NF155), neurofascin 186 (NF186), contactin 1 (CNTN1), contactin associated protein 1 (Caspr1) were tested with a flow cytometry technique using HEK cells transfected with the plasmid of the proteins of interest.

IgG4 antibodies against proteins of the node of Ranvier were detected in 19 patients (incidence 1.9%): 10 anti-NF155, 8 anti-CNTN1 and 1 anti-Caspr1. These patients had subacute onset (29%), marked sensory ataxia (94%), postural tremor (59%) and were resistant to IVIg treatment (73%). Half of the patients with antibodies against CNTN1 also had membranous glomerulonephritis. The patient with antibodies against Caspr1 did not have painful paraesthesia.

Incidence of antibodies against the node of Ranvier was lower than previously described. It could be explained by several hypotheses. First, other studies have retrospectively analyzed sera banks of CIDP patients, while we have prospectively analyzed sera sent for routine detection of antibodies against nodal and paranodal proteins. Secondly, only IgG4 antibody isotype were considered as positive samples. We confirmed the clinical features previously described namely the resistance to IgIV treatment. Unlike the 2 previously reported cases, the patient with anti-Caspr1 antibodies did not express excessive pain. Renal involvement seems frequent in patients with anti-CNTN1 antibodies.

Antibodies against the proteins of the node of Ranvier are uncommon in CIDP patient but they are clinically relevant

References: None.

Keywords: Inflammatory, Node

Grant Support: None.
Secondary Endpoints (PATH Extension Study): Long-term Outcomes of Subcutaneous Immunoglobulin IgPro20 in CIDP Maintenance Treatment

Ivo van Schaik1, Orell Mielke2, Vera Bri3, Hans-Peter Hartung4, Richard Lewis5, Gen Sobue6, John-Philip Lawo7, Michaela Praus7, Billie Durn7, David Cornblath8, Ingemar Merkies9

1University of Amsterdam, Amsterdam, Netherlands, 2CSL Behring, Marburg, Germany, 3University of Toronto, Imam Abdulrahman Bin Faisal University, Toronto, Canada, 4Heinrich Heine University, Düsseldorf, Germany, 5Cedars-Sinai Medical Center, Los Angeles, CA, USA, 6Nagoya University Graduate School of Medicine, Nagoya, Japan, 7CSL Behring, King of Prussia, PA, USA, 8Johns Hopkins University School of Medicine, Baltimore, MD, USA, 9Maastricht University Medical Center, St Elisabeth Hospital, Maastricht, Netherlands

Introduction: Subcutaneous immunoglobulin (SCIG) IgPro20 (Hizentra®, CSL Behring) was efficacious in chronic inflammatory demyelinating polyneuropathy (CIDP) in the PATH study. A 48-week open-label extension study to the PATH study, explored long-term outcomes of IgPro20 (0.2 g/kg and 0.4 g/kg) in CIDP.

Methods: Subjects started with 0.4 g/kg weekly IgPro20 and switched to 0.2 g/kg weekly after 24 weeks. In case of CIDP relapse, 0.4 g/kg was re-initiated. After a study amendment, subjects started on 0.2 g/kg weekly with dose increase at relapse. The primary endpoint was relapse rate (≥1 point deterioration in total adjusted INCAT [Inflammatory Neuropathy Cause and Treatment] score versus baseline). Secondary endpoints included change in INCAT, I-RODS (Inflammatory Rasch-built Overall Disability) centile score, Medical Research Council (MRC) sum score, mean grip strength, and patient treatment preference.

Results: Eighty-two subjects were enrolled, most received both doses. Relapse rates were 10% (during treatment with 0.4 g/kg, n=72) and 48% (during treatment with 0.2 g/kg [n=73]; 89% of whom recovered within 4 weeks upon switching to 0.4 g/kg). At baseline, both dose groups had similar median scores on all secondary endpoints. All scores showed deterioration at relapse, both on 0.2 g/kg (change from baseline: INCAT, +1 point; I-RODS, -8.0 points; MRC, -3 points; grip strength, -6.3 kPa) and 0.4 g/kg (+1, -13, -8, -12, respectively) with improvement at recovery after dose increase in the 0.2 g/kg group. For non-relapsers, endpoints generally remained unchanged. Most patients (≥80%) kept preferring SCIG over previous treatment during this long-term follow-up study.

Discussion: Secondary endpoints confirm efficacy of IgPro20 in long-term maintenance treatment of CIDP. IgPro20 0.4 g/kg was more efficacious than 0.2 g/kg. However, many subjects didn’t relapse on 0.2 g/kg, and most who did deteriorate improved after dose increase. Patient preference for SCIG over previous treatment remained high during long-term follow-up.

References: None.

Keywords: Inflammatory

Grant Support: This study was supported by CSL Behring.
Poster 112

The overlapping spectrum of Chronic Inflammatory Demyelinating Polyradiculoneuropathy and anti-MAG neuropathy
Giuseppe Liberatore1, Claudia Giannotta1, Dario Cocito2, Fiore Manganelli3, Raffaella Fazio4, Chiara Briani5, Massimiliano Filosto6, Luana Benedetti7, Anna Mazzeo8, Girolama Marfia9, Andrea Cortese10, Giuseppe Cosentino11, Stefano Jann12, Angelo Clerici13, Marinella Carpo14, Angelo Schenone15, Marco Luigetti16, Giuseppe Lauria17, Giovanni Antonini18, Tiziana Rosso19, Gabriele Siciliano20, Guido Cavalett21, Pietro Doneddu1, Lucio Santoro2, Erdita Peci2, Stefano Tronci2, Marta Ruiz2, Stefano Cotti Piccinelli22, Antonio Toscano8, Giorgia Mataluni9, Luca Leonardi18, Mario Sabatelli23, Eduardo Nobile Orazio1

1Neuromuscular and Neuroimmunology Service, Humanitas Clinical and Research Institute – IRCCS –, Rozzano, Milan, Italy, 2Presidio Sanitario Major, Istituti Clinici Scientifici Maugeri, Turin, Italy, 3Department of Neuroscience, Reproductive Sciences and Odontostomatology, University of Naples ‘Federico II’, Naples, Italy, 4Department of Neurology, Institute of Experimental Neurology (INSPE), San Raffaele Scientific Institute, Milan, Italy, 5Neurology Unit, Department of Neuroscience, University of Padova, Padova, Italy, 6Center for Neuromuscular Diseases and Neuropathies, ASST ‘Spedali Civili’, University of Brescia, Brescia, Italy, 7Neurology Unit, Sant’Andrea Hospital, La Spezia, Italy, 8Department of Clinical and Experimental Medicine, Unit of Neurology, University of Messina, Messina, Italy, 9Dysimmune Neuropathies Unit, Department of Systems Medicine, Tor Vergata University of Rome, Rome, Italy, 10IRCCS Foundation C. Mondino National Neurological Institute, Pavia, Italy, 11Department of Experimental BioMedicine and Clinical Neurosciences (BioNeC), University of Palermo, Palermo, Italy, 12Department of Neuroscience, Niguarda Ca’ Granda Hospital, Milan, Italy, 13Neurology Unit, Circolo & Macchi Foundation Hospital, Insubria University, DVBS, Varese, Italy, 14Neurology Unit, ASST Bergamo Ovest-Ospedale Treviglio, Treviglio, Italy, 15Department of Neuroscience, Rehabilitation, University of Genoa and IRCCS AOU San Martino-IST, Genoa, Italy, 16Fondazione Policlinico Universitario A. Gemelli IRCCS, UOC Neurologia, Catholic University of Sacred Heart, Rome, Italy, 17Unit of Neuroalgology, IRCCS Foundation ‘Carlo Besta’ Neurological Institute, Milan, Italy, 18Unit of Neuromuscular Diseases, ‘Sapienza’ University of Rome, Sant’Andrea Hospital, Rome, Italy, 19ULSS2 Marco Trevidiana, UOC Neurologia-Castelfranco Veneto, Treviso, Italy, 20Neurology University, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, 21School of Medicine and Surgery and Experimental Neurology Unit, University of Milano-Bicocca, Monza, Italy, 22Center for Neuromuscular Diseases and Neuropathies, ASST ‘Spedali Civili’, University of Brescia, Brescia, Italy, 23NeuroMuscular Omnicentre (NEMO)- Pol. A. Gemelli, Catholic University of Sacred Heart, Rome, Italy
**Objective:** diagnosis of Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) can be challenging and one of the possible pitfalls is the possible presence of the neuropathy associated with anti-myelin-associated-glycoprotein (MAG) IgM monoclonal gammopathy.

**Methods:** We implemented a multicentric web-based database to collect data from patients with CIDP followed throughout Italy. In order to exclude anti-MAG neuropathy we tested our patients for anti-MAG protein on ELISA (Buhlmann method). We considered as positive a titer >7000 Buhlmann.

**Results:** By February 2019 we tested for anti-MAG protein 267 of the 530 included patients with a diagnosis of typical or atypical CIDP. Eighteen patients (6.7%) had high anti-MAG IgM antibodies (mean titer 45,500, range 9,300-125,000). Twelve patients had a diagnosis of typical CIDP (67%), 5 of DADS (28%) and one of sensory CIDP. Compared to patients without antibodies (249), patients with anti-MAG IgM had an older mean age of disease onset (61 vs 48.8 years) and a shorter disease course (5.5 vs 8.8 years). Patients with and without antibodies had a similar frequency of cramps, ataxia, fatigue at onset, relapsing course (50% in both groups) and increased CSF proteins (about 70%). On nerve conduction studies, patients with anti-MAG antibodies had a more frequent presence of sensory abnormalities compatible with demyelination (50% vs 30%) and of increased distal latency (50% vs 19%). Patients with anti-MAG antibodies had an overall similar response to therapy compared with CIDP patients, but a less frequent response to IVIg (61% vs 72%) and a similar response to steroids (50% vs 51%).

**Discussion:** Some patients with the clinical features of CIDP may have anti-MAG antibodies with a similar clinical and electrophysiological spectrum and response to immunotherapy compared to patients without antibodies. Even if these patients are currently excluded from the diagnosis of CIDP they share the same clinical and therapeutic features of CIDP.

**References:** None.

**Keywords:** Inflammatory

**Grant Support:** None.
International Validation of the modified Erasmus GBS Outcome Score (mEGOS) for Guillain-Barré Syndrome

Alex Doets1, Hester Lingsma1, Christa Walgaard1, Badrul Islam2, Amy Davidson3, Yuko Yamagishi4, Susumu Kusunoki4, Mazen Dimachkie5, Kenneth Gorson6, Bart Jacobs1, the IGOS Consortium7

1Erasmus MC University Medical Center Rotterdam, Rotterdam, Netherlands, 2The International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), Dhaka, Bangladesh, 3University of Glasgow, Glasgow, United Kingdom of Great Britain and Northern Ireland, 4Kindai University Faculty of Medicine, Osaka-Sayama, Japan, 5University of Kansas Medical Center, Kansas City, USA, 6St. Elizabeth’s Medical Center, Tufts University School of Medicine, Boston, USA, 7n.a., n.a., Unknown or unspecified country

Introduction. The modified Erasmus GBS Outcome Score (mEGOS) estimates the probability of being unable to walk independently (GBS disability score >2) in individual patients with Guillain-Barré syndrome (GBS), based on age, preceding diarrhoea and limb strength. The mEGOS was based on Dutch patients and has been validated in a Japanese cohort. The aim of this study was to validate mEGOS in the International GBS Outcome Study (IGOS) cohort.

Methods. The study was based on data from patients included in the IGOS-1300 cohort that were aged over 6 years and were unable to walk. Patients from Bangladesh were excluded. Model performance was assessed regarding discrimination (area under the receiver operating characteristic curve, AUC) and calibration, in separate regions. Outcome was inability to walk at 4, 13 and 26 weeks. Missing values were imputed using single imputation.

Results. For validation of mEGOS at admission 606 patients were eligible (Europe n=394, North-America n=116, Asia n=52), and 517 for validation of mEGOS at week 1 (Europe n=353, North-America n=78, Asia n=49). For the full IGOS cohort and for patients from Europe, discriminative ability of mEGOS was good at all three time points, with AUC-values equal to or higher than 0.7. Model calibration was suboptimal in these subgroups, with observed percentages of poor prognosis exceeding predicted probabilities (e.g. mEGOS at admission, week 4, observed percentage poor prognosis/predicted probability poor prognosis: full cohort 63%/55%, Europe 65%/55%). Similar performance of mEGOS was found for patients from North-America and Asia, but 95% confidence intervals around AUC-values and calibration curves were wide.

Conclusion. The mEGOS is a promising tool for the prediction of poor prognosis in GBS worldwide. Recalibration is required to further improve model performance and enable region-specificity. Larger sample sizes are required for North-America and Asia to increase reliability and create a region-specific model.

References: None.

Keywords: Inflammatory, Other

Grant Support: This study is funded by GBS-CIDP Foundation International, gain, Erasmus MC University Medical Centre Rotterdam, University of Glasgow, CSL Behring, Grifols and Annexon.
The impact of eculizumab on neurological improvement in Guillain–Barré syndrome: Subanalysis of JET-GBS study

Sonoko Misawa¹, Satoshi Kuwabara¹, Yukari Sekiguchi¹, Hiroshi Amino¹, Tomoki Suichi¹, Susumu Kusunoki²

¹Department of Neurology, Chiba University Graduate School of Medicine, Chiba, Japan, Chiba, Japan,
²Department of Neurology, Faculty of Medicine, Kindai University, Osaka-Sayama, Japan

Japanese eculizumab trial for Guillain–Barré syndrome (JET-GBS) study has shown that eculizumab could facilitate neurological improvement, and increase the probability to regain full muscle strength in patients with severe Guillain–Barré syndrome. This study aimed to determine impact of eculizumab on neurological improvement in GBS. We analyzed changes in manual muscle testing score (sum of the scores from 13 muscles, full score = 65) and calculated mEGOS score and probability unable to walk at week 24 in 34 GBS patients (23 in the eculizumab group and 11 in the placebo group) who participated in JET-GBS study. Most patients were severely affected and 87% of the eculizumab group and 91% of the placebo group were graded as functional grade 4 or 5. Intravenous immunoglobulin plus either eculizumab (900 mg) or placebo were administrated for 4 weeks. The proportion of patients who achieved full recovery of manual muscle testing score was 60.9% in the eculizumab group and 27.3% in the placebo group (p=0.141). The mEGOS at hospital admission score was similar for the eculizumab (median 4.5, range 1 – 9; at week 1, 5, 1 - 12) and placebo (5.5, 3 – 8; 5, 1 - 11) groups. However, eculizumab substantially shifted the curve in the predicted probability unable to walk at 24 weeks to the right (more favorable direction). These sub-analysis results suggest that eculizumab could substantially contribute to almost complete recovery of motor function in GBS and mEGOS can be useful to determine indication of eculizumab.

References: None.

Keywords: Clinical Trials, Inflammatory

Grant Support: None.
A Dose Response RCT Of IV immunoglobulin In Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)/DRIP Study

Krista Kuitwaard¹, Esther Brusse², Alexander Vrancken³, Filip Eftimov¹, Nicolette Notermans³, Anneke van der Kool⁶, Ingemar Merkies⁵, Hester Lingsma², Bart Jacobs², Pieter van Doorn⁶

¹Erasmus MC University Medical Center, Albert Schweitzer Hospital, Rotterdam, Dordrecht, Netherlands, ²Erasmus MC, University Medical Center, Rotterdam, Netherlands, ³Brain Center Rudolf Magnus University Medical Center Utrecht, Utrecht, Netherlands, ⁴Academic Medical Center Amsterdam, Netherlands, ⁵School of Mental Health and Neuroscience, Maastricht, Netherlands, ⁶Erasmus MC. University Medical Center, Rotterdam, Netherlands

Maintenance IVIg treatment regimens vary largely between CIDP patients and the best strategy to find the optimal dosage and interval is unknown. Guidelines on how to dose IVIg more effectively and efficiently are needed. High peak serum IgG levels may not be needed in IVIg maintenance treatment and these might be responsible for side effects. More frequent lower dosing of IVIg is likely to result in more stable and higher trough levels of IgG which might improve the efficacy. The DRIP study is a double-blind randomised placebo-controlled cross-over study. The main objective is to investigate whether more frequent low dosage IVIg treatment is more effective than less frequent high dosage IVIg treatment. Secondary objectives are to investigate whether more frequent lower dosing leads to fewer side effects. CIDP patients proven to be IVIg dependent receiving an individually established stable dosage and interval of IVIg treatment are included. The intervention group (A) was treated with half their normal dosage of IVIg at half their interval; the contrast group (B) with their normal dosage and interval of IVIg followed by a placebo infusion at half their normal interval (total IVIg dosage remained the same over time). After a wash-out phase patients cross-over. Hand grip strength (Martin Vigorimeter) was used as the primary outcome measurement. A difference of > 8 kPa in the mean of the four Vigorimeter changes from baseline in favor of the group treated with half the dosage and interval was considered a relevant improvement. Secondary outcome measures were changes in the R-ODS, R-FSS, and SF-36 and the occurrence of side effects. Twenty-five patients have been included, of which 22 patients completed both treatment periods. Three patients did not receive the second treatment due to clinical worsening. The trial is completed and data entry almost finished. Results will be presented.

References: None.

Keywords: Inflammatory, Clinical Trials, Other

Grant Support: Baxalta/Shire
Title: Intravenous Immunoglobulin Overtreatment in Chronic Inflammatory Demyelinating Polyneuropathy: Double-Blind Randomized Controlled Non-Inferiority Trial (IOC-TRIAL)

Max Adrichem¹, Ilse Lucke², Alexander Vrancken³, Luuk Wieske¹, Rob de Haan¹, Marcel Dijkgraaf¹, Nicol Voermans⁴, Leo Visser⁵, Catharina Faber⁶, Krista Kuitwaard⁷, Pieter van Doorn⁸, Ingemar Merkies⁶, Ivo van Schaik², Filip Eftimov², Nicolette Notermans³

¹Amsterdam UMC - University of Amsterdam, Amsterdam, Netherlands, ²Amsterdam UMC - University of Amsterdam, Amsterdam, Netherlands, ³University Medical Center, Utrecht, Netherlands, ⁴Radboud University Medical Center, Nijmegen, Netherlands, ⁵Elisabeth-Tweesteden Hospital, Tilburg, Netherlands, ⁶Maastricht Academic Medical Center, Maastricht, Netherlands, ⁷Albert Schweitzer Hospital, Dordrecht, Netherlands, ⁸Erasmus Medical Center, Rotterdam, Netherlands
RECIPE: a phase II randomized controlled trial of rituximab for refractory CIDP with IgG4 autoantibodies

Masahiro Iijima1, Shinobu Shimizu1, Yuki Fukamii2, Ryoji Nishi3, Yuichi Kawagashira3, Haruki Koike3, Hidenori Ogata4, Jun-ichi Kira5, Ken-ichi Kaida6, Michiaki Koga7, Takashi Kanda8, Masahiro Mori9, Satoshi Kuwabara9, Masahisa Katsuno3

1Department of Advanced Medicine, Nagoya University Hospital, Nagoya, Japan, 2Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya, Japan, 3Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya, Japan, 4Department of Neurology, Kyushu University Hospital, Fukuoka, Japan, 5Department of Neurology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, 6Department of Neurology, National Defense Medical College, Tokorozawa, Japan, 7Department of Neurology and Clinical Neuroscience, Yamaguchi University Graduate School of Medicine, Yamaguchi, Japan, 8Department of Neurology and Clinical Neuroscience, Yamaguchi University Graduate School of Medicine, Ube, Japan, 9Department of Neurology, Graduate School of Medicine, Chiba University, Chiba, Japan

Introduction: Potential efficacy for rituximab is indicated for refractory CIDP, especially IgG4 autoantibodies positive cases.

Methods: To evaluate the efficacy and safety of rituximab intravenously administered to CIDP patients with positive or negative IgG4 autoantibody, we are going to perform a multicenter, placebo-controlled, randomized, partially blind, parallel-group, comparative study. A total of 15 CIDP patients with positive IgG4 autoantibody (contactin-1 or neurofascin-155) will be divided into 10 in the rituximab group and 5 in the placebo group. On the other hand, a total of 10 refractory CIDP patients with negative IgG4 autoantibody will be administered by rituximab. The primary endpoint is the adjusted INCAT Disability Scale, and the analysis will compare the score evaluated prior to treatment and at each timepoint after week 26, 38, and 52 to calculate the proportion and its 95% confidence interval of patients who achieve one or more points improvement from the baseline with positive IgG4 autoantibody in the rituximab group and 5 in the placebo group. On the other hand, a total of 10 refractory CIDP patients with negative IgG4 autoantibody will be administered by rituximab. The primary endpoint is the adjusted INCAT Disability Scale, and the analysis will compare the score evaluated prior to treatment and at each timepoint after week 26, 38, and 52 to calculate the proportion and its 95% confidence interval of patients who achieve one or more points improvement from the baseline with positive IgG4 autoantibody in the rituximab group and 5 in the placebo group. Scores at each timepoint and differences between scores between prior to treatment and at each timepoint are summarized as mean, standard deviation, median, minimum and maximum values in patients with positive IgG4 autoantibody (rituximab and placebo groups) and those with negative IgG4 autoantibody. The secondary endpoints include grip strength, R-ODS, MRC sum score, indices in nerve conduction study, CSF protein, B cell counts, expression of human anti-chimeric antibodies to rituximab, serum rituximab level, serum titers of IgG4 antibodies (anti-contactin-1 and anti-neurofascin-155) and those IgG subclasses.

Results: Registration of the initial trial participant will be scheduled from 1Q to 2Q in 2019.

Conclusions: The RECIPE Trial aims to clarify the efficacy of rituximab from IgG4 autoantibodies positive CIDP and refractory patients who are resistant to conservative therapies.

References: None.

Keywords: Clinical Trials, Inflammatory, Node

Grant Support: Japan Agency for Medical Research and Development (AMED)
Restabilization after intravenous immunoglobulins (IVIg) withdrawal in patients with chronic inflammatory demyelinating polyneuropathy (CIDP)

Ilse Lucke¹, Max Adrichem¹, Alexander Vrancken², Ivo van Schaik¹, Filip Eftimov¹

¹Amsterdam UMC - university of Amsterdam, Amsterdam, Netherlands, ²University Medical Center Utrecht, Utrecht, Netherlands

Background: As biomarkers for disease activity in CIDP are lacking, IVIg withdrawal attempts are advocated to assess whether the disease is active. Patients and physicians can be reluctant to stop treatment, as it might lead to an increase in disability. Our objective was to assess the effectiveness of IVIg restabilization in patients deteriorating after IVIg withdrawal.

Methods: Patients randomized into the withdrawal arm of the double-blind controlled non-inferiority IOC-trial (registration number: ISRCTN1363769) were eligible for this prospective follow-up study if they deteriorated. Patients who were randomized for IVIg continuation and remained stable during the trial, could enter a withdrawal attempt after the trial. All patients who deteriorated were included. The withdrawal protocol consisted of infusions of 75%, 50% and 25% of the individual maintenance dose, followed by placebo. The restabilization protocol consisted of a loading dose of 2g/kg followed by patient’s individual maintenance dose. After the trial, the withdrawal and restabilization protocols were recommended, but final decision was at discretion of the physician.

Primary outcome was the proportion of patients who restabilized at 12 weeks. Restabilization was defined as no change on a 5-point patient global impression scale and/or a change less than the MCID on i-RODS compared to baseline. Disability and impairment were scored using i-RODS, MRC-sum score and grip strength.

Results: A total of 28 patients were included. All patients were considered restabilized at 12 weeks. IVIg was restarted according to the restabilization protocol in 19 patients (68%), of which 14 patients (74%) recovered within three weeks. Nine patients received an extra dose of their previous maintenance dose or were restarted on therapy without a loading dose. All nine patients recovered within 12 weeks.

Conclusion: All patients restabilized within 12 weeks after restart of IVIg. The 3-step withdrawal schedule did not lead to any long-term disability or impairment.

References: None.

Keywords: Clinical Trials, Inflammatory

Grant Support: None.
Second IVlg Course in Guillain-Barré Syndrome Patients with Poor Prognosis (SID-GBS); Double-blind Randomized Controlled Trial.

Christa Walgaard¹, Bart Jacobs¹, Hester Lingsma¹, Ewout Steyerberg², David Cornblath³, Pieter van Doorn¹

¹Erasmus Medical Center, Rotterdam, Netherlands, ²Erasmus Medical Center, LUMC, Rotterdam, Leiden, Netherlands, ³Johns Hopkins University, Baltimore, MD, USA

Introduction

Guillain-Barré syndrome (GBS) has a variable clinical severity and outcome and the standard treatment with IVlg (0.4 g/kg for 5 days) is insufficient for patients with the severest forms. In this RCT the additional value of a second IVlg course is investigated in GBS patients with a predicted poor outcome according to the modified Erasmus GBS Outcome Score (mEGOS). The SID-GBS study (NTR 2224) currently is the only large RCT in GBS worldwide.

Methods

Included were patients with GBS (age ≥12 years) and an indication to start standard IVlg treatment. One week after start of IVlg, patients with a poor prognosis predicted by the mEGOS model (score 6-12) were randomized to receive a second IVlg course of 0.4 g/kg for 5 days or placebo (double-blind). Primary endpoint: GBS disability score (range 0-6) at 4 weeks is compared between the treatment groups using a proportional odds model and pre-specified covariate adjustment to correct for known prognostic factors at baseline. Secondary endpoints included GBS disability score at 8, 12 and 26 weeks, MRC sum score and Overall Neuropathy Limitations Scale at 4, 8, 12 and 26 weeks and safety. Also nerve conduction study data and serial serum IgG levels are available. In total 59 hospitals in The Netherlands participated in this trial.

Results

Of the 339 included patients, 93 patients with a predicted poor prognosis were randomized. Recently the half year follow-up of the last included patient was completed. The database will be locked in February 2019. The results of this RCT will be presented at the congress.

Conclusion

This RCT potentially will change the treatment and perspective of GBS patients with a poor prognosis. It hopefully opens the way for a more individualized and better treatment of this severe disease.

References: None.

Keywords: Clinical Trials, Inflammatory

Grant Support: Prinses Beatrix Spierfonds, Grant / Award Number: WAR07-28
Poster 120

A Randomized, Single-Blinded, Non-Inferiority Cross-Over Trial of Facilitated Subcutaneous Immunoglobulin in Multifocal Motor Neuropathy

Ali Al-Zuhairy¹, Johannes Jakobsen², Henning Andersen³, Søren Sindrup⁴, Lars Markvardsen⁵

¹Department of Neurology, Neuroscience Center, Copenhagen University Hospital (Rigshospitalet), Copenhagen, Denmark, ²Department of Neurology, Copenhagen University Hospital (Rigshospitalet), Copenhagen, Denmark, ³Department of Neurology, Aarhus University Hospital, Aarhus, Denmark, ⁴Department of Neurology, Odense University Hospital, Odense, Denmark, ⁵Department of Neurology, Aarhus University Hospital, Aarhus, Denmark

Purpose: To optimize subcutaneous therapy with immunoglobulins we compared large volume infusion of IgG facilitated by pretreatment with hyaluronidase (fSCIG) to conventional infusion of multiple small dosages (cSCIG) in 20 patients with multifocal motor neuropathy (MMN).

Methods: A randomized, non-inferiority, cross-over and observer-blinded design was applied with a treatment period of 24 weeks at each therapy. The primary study parameter was isometric strength. Secondary study parameters were the scores of the following tests: The Overall Disability Sum Score, Medical Research Council, grip strength using a hand-held dynamometer, 9 Hole Peg Test, Six Spot Step Test and EQ-5D-5L Index Value and VAS.

Results: In 18 patients fSCIG was feasible, 2 patients leaving the study due to side-effects. The results for the primary and secondary parameters will be presented at the meeting. - Mild and short-lasting generalized side-effects were similar in the two groups, whereas the relative frequency of localized side-effects at the injection site was increased after fSCIG (0.63 (95% CI: 0.23 – 1.00) vs 0.09 (95% CI: 0.00 – 0.22), P =0.005). The preference of the patients favoured fSCIG for 2 out of 5 VAS-scores as well as the total mean score of all preferences (P =0.03).

Conclusion: fSCIG seems feasible and safe. In addition, it is preferred by patients but is accompanied by a higher frequency of short lasting localized side-effects.

Clinicaltrials.gov: NCT02556437

European Clinical Trials Database: 2015-003453-18

References: None.

Keywords: Clinical Trials, Inflammatory

Grant Support: The study was supported by a research grant from Baxter/Baxalta, now part of Shire covering the expenses for a PhD-study, without providing personal benefits to any of the authors.
**Poster 121**

**Guillain-Barré Syndrome in the United States, 2009–2015**

James Sejvar, Jessica Leung, Jesus Soares, Tatiana Lanzieri

*Centers for Disease Control and Prevention, Atlanta, GA, USA*

Introduction: To describe the incidence and clinical characteristics of Guillain-Barré Syndrome (GBS) in the United States during 2009–2015. Methods: We analyzed medical claims from IBM Watson MarketScan® Commercial Claims and Encounters databases. We defined a GBS patient as an enrollee with an inpatient claim with GBS as the principal diagnosis code, based on ICD-9 or ICD-10 codes, and at least 1 claim for any of the following procedures: lumbar puncture, EMG/nerve conduction study, IV immunoglobulin, or plasmapheresis. We assessed hospitalization in the intensive care unit (ICU), intubation, dysautonomia, death, and infections within 60 days prior to GBS onset. Results: We identified 3,532 GBS patients, corresponding to an annual incidence of 1.1 to 1.3/100,000 persons during 2009–2015. GBS incidence was higher in males (1.2/100,000) than females (0.9/100,000) (p=0.006) and increased with age, from 0.4/100,000 in persons 0–17 years old to 2.1/100,000 in persons ≥65 years old (p<0.001). Half of GBS patients were hospitalized in the ICU, 8% were intubated, 1% died, and 2% developed dysautonomia. Half of the GBS patients had an antecedent infectious illness, but only 125 (3.5%) had an infectious pathogen identified (influenza, Epstein-Barr virus, cytomegalovirus, campylobacter, Mycoplasma pneumoniae, or hepatitis E). Conclusions: The incidence of GBS using a large national claims database was comparable to that reported in the literature. Cases in this series appeared to be less severe than typically reported, possibly due to less enrollment of elderly patients. Half of GBS patients reported a prior infectious illness, but only a minority had a specific pathogen identified.

**References:** None.

**Keywords:** Inflammatory, Other

**Grant Support:** None.
A Case of Peripheral Sensory Ataxia Causing Recurrent Falls

Wei Min James Tung¹, Genevieve Lynn Yu², Jasmine Shimin Koh², Thirugnanam Umapathi²

¹Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore, ²National Neuroscience Institute, Singapore, Singapore

A previously healthy elderly man presented with a 2-month history of subacute, progressive numbness of hands and feet, associated with unsteady gait and frequent falls. Neurologic examination revealed diffuse hyporeflexia, mild proximal limb weakness with severe proprioceptive and vibration loss in both legs. Gait was very ataxic. Babinski sign was absent. There was no bladder, bowel impairment, cerebellar signs or cranial nerve signs. Pupils were of normal size and reacted well to light. Initial clinical diagnosis was chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), with a differential diagnosis of sensory neuronopathy. Nerve conduction studies (NCS) showed normal sensory nerve action potentials with no conduction slowing. Differential diagnosis list was revised. Spinal imaging and blood tests (vitamin B12, folate, copper levels; HIV and syphilis serology) did not indicate dorsal spinal column pathology. Spinal tap showed raised protein with normal cells. Tibial somatosensory evoked potentials (SSEP) suggested proximal conduction defect. Median SSEP was normal. A diagnosis of chronic immune sensory polyradiculopathy (CISP) was made. Patient was started on intravenous methylprednisolone 1g daily for 5 days followed by oral prednisolone at 1mg/kg with improvement in symptoms. The plan is to add a steroid-sparing agent, namely azathioprine. If the recovery is suboptimal, the treatment will be switched to intravenous immunoglobulin. CISP is an uncommon, probably under-recognized, treatable condition that is believed to lie within the CIDP spectrum. We highlight this important cause of peripheral sensory ataxia with normal routine NCS. A high index of suspicion, prompting further assessment with SSEP, spinal tap and imaging of the proximal nerve roots, will help clinch the diagnosis.

References: None.

Keywords: Inflammatory

Grant Support: None.
Anti-GM1 complex antibodies in patients with different electrophysiological subtypes of Guillain-Barré syndrome

Min Wang¹, Yan Song¹, Baojun Qiao¹, Hugh Willison², Bart Jacobs³, Yuzhong Wang¹

¹Affiliated Hospital of Jining Medical University, Jining, China, ²University of Glasgow, Glasgow, United Kingdom of Great Britain and Northern Ireland, ³Erasmus University Medical Centre, Rotterdam, Netherlands

Introduction: Auto-antibodies binding to myelin and axon followed by complement deposition results in nerve damage in Guillain-Barré syndrome (GBS). IgG antibodies against GM1, expressed by both axon and myelin, and complex composed of GM1 and other glycolipids expressed by myelin only were detected. This study is aimed to investigate the difference in frequency of anti-GM1 complex including GM1:galactocerebroside(GalC) and GM1:sulfatide IgG antibodies in patients with different electrophysiological subtypes.

Methods: Thirty patients with GBS who finished with serial nerve conduction studies within 4 weeks after onset were participants of International GBS outcome study from November 2016 to November 2018 in our center. The final electrophysiological classification was made according to Uncini’s criteria (2017). The serum samples were diluted at 1/500 to detect the antibodies against GM1, GM1:GalC (1:1), and GM1:sulfatide (1:1) complex. Fisher’s Exact Test was used to compare the difference in the frequency of anti-GM1 complex antibodies in patients with axonal, demyelinating and equivocal subtypes.

Results: The median age of the patients was 55 (ranging from 24-81). The ratio of male to female was 2. Of the 30 patients, 8 (26.7%) showed demyelinating subtype, 11 (36.7%) showed axonal subtype, 9 (30.0%) showed equivocal subtype and 2 (6.7%) were normal. None of the patients with demyelinating and equivocal subtypes had antibodies against GM1 or GM1 complexes. Of the axonal patients, 54.5% (6/11) had antibodies against GM1 or GM1 complexes, of which, 5 had antibodies against both GM1:GalC and GM1:sulfatide while 1 patient had antibodies against GM1:sulfatide only. The frequency of anti-GM1 complex antibodies in patients with axonal subtype was higher than those with demyelinating (p=0.018) and equivocal subtypes (p=0.014).

Conclusions: Antibodies against GM1: GalC and GM1:sulfatide complexes seem not pathogenic in patients with demyelinating GBS, which deserves further confirmation in large cohorts study.

References: None.

Keywords: Inflammatory

Grant Support: None.
Predictive Modelling for Acute Inflammatory Demyelinating Polyneuropathy

Cheng-Yin Tan¹, Yukari Sekiguchi², Khean-Jin Goh¹, Satoshi Kuwabara², Nortina Shahrizaila¹

¹Department of Medicine, University of Malaya, Kuala Lumpur, Malaysia, ²Graduate School of Medicine, Chiba University, Chiba, Japan

Introduction: Electrophysiology of Guillain-Barré syndrome (GBS) is dynamic. Serial studies may provide understanding of the GBS pathophysiology. However, it is important to achieve the highest accuracy of GBS electrodiagnosis at the first study. The current study aims to develop a model that would predict the probabilities of acute inflammatory demyelinating polyneuropathy (AIDP) from other GBS electrodiagnostic subtypes. Methods: The derivation cohort was derived from existing GBS patients with two sets of electrophysiological data. The electrodiagnosis of AIDP was made based on the two-study criteria. Predictive electrophysiological parameters of AIDP were identified from the derivation cohort. Potential predictors of AIDP were considered in multivariate logistic regression models and a predictive model was developed. This model is currently being validated in an independent cohort of GBS patients. Results: Between 2010 and 2018, 108 patients with GBS were recruited. In this derivation cohort, 56 (51.9%) patients were AIDP and 52 (48.1%) were non-AIDP. Median and ulnar distal motor latencies (DML) (p = 0.003; p = 0.014, respectively) at first study (1-20 days) and median DML (p = 0.043) and conduction velocity (p = 0.011) at second study (3-8 weeks) were independently associated with AIDP. Both predictive models displayed good discrimination of AIDP with the area under the curve (AUC) of 0.86. Scores of the predictive model at first study ranged from 0-6 and 0-5 at second study. Based on these scores, the probabilities of AIDP ranged from 13 to 100% and 29 to 99% in the first and second study, respectively. Conclusion: A prognostic model was developed and showed good performance in predicting the probability of AIDP based on a single electrophysiological study.


Keywords: Inflammatory

Grant Support: Dr. CY Tan receives research grant from the University of Malaya (BK074-2017).
Impairment of reflex sensory pathway in multifocal motor neuropathy (MMN): an electrophysiological demonstration

Eglė Sukockienė, Ruxandra Iancu Ferfoglia, Agustina M. Lascano, André Truffert

Division of Neurology, Department of Clinical Neurosciences, Geneva University Hospitals, Geneva, Switzerland

Introduction We report a case of multifocal motor neuropathy (MMN) with bilateral patellar areflexia but normal strength and no amyotrophy of quadriceps muscles. Methods The medical history and clinical examination were completed by electrophysiological tests: motor evoked potentials (MEPs) after transcranial magnetic stimulation (TMS) and patellar T response recordings. Results. The patient has a 13-year history of weakness and tremor of both upper limbs, and nerve conduction studies fulfilling MMN criteria. Lower limbs were asymptomatic but patellar tendon reflexes were absent. The femoral nerve compound muscle action potentials (CMAPs) and the MEPs were of normal amplitudes and latencies, in contrast with T responses which were virtually absent. Conclusions. Our findings demonstrate reflex afferent pathway subtotal interruption in this particular patient, raising the question of proximal sensory fibers involvement in MMN. Further investigations are needed to determine the frequency and significance of this sign.

References: None.

Keywords: Inflammatory

Grant Support: None.
Japanese Nationwide Epidemiologic Survey of POEMS syndrome

Tomoki Suichi¹, Sonoko Miasawa¹, Minako Beppu¹, Sho Takahashi², Yukari Sekiguchi¹, Kazumoto Shibuya¹, Hiroshi Amino¹, Astuko Tsuneyama¹, Yo-ichi Suzuki¹, Keigo Nakamura¹, Yasunori Sato³, Satoshi Kuwabara¹

¹Chiba University, Chiba, Japan, ²Jikei University School of Medicine, Tokyo, Japan, ³Keio University, Tokyo, Japan

Polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes (POEMS) syndrome is a rare cause of demyelinating polyneuropathy associated with plasma cell dyscrasia and overproduction of vascular endothelial growth factor. We conducted a nationwide survey in 2015, using an established epidemiologic analysis. Data processing sheets were sent to all neurology and hematology specialist departments throughout Japan to identify patients with POEMS syndrome who were seen between April 2012 and March 2015. Primary survey aimed to estimate the number of patients, and secondary survey aimed to obtain clinical information. The estimated number of patients with POEMS syndrome in Japan was 392 (95% confidence interval [CI], 320-464), and the prevalence was calculated as 0.3 per 100,000 people. Details of clinical information were available in 167 patients. Median onset age was 54 years (range, 21-84 years) and the ratio of male to female was 1.5. All patients showed polyneuropathy, and 89% had monoclonal plasma cell proliferative disorder. Other common features were skin changes (84%), edema/effusion (81%), and organomegaly (76%). Patients were treated with any of radiation, corticosteroids, melphalan, thalidomide, lenalidomide, bortezomib and/or autologous stem cell transplantation. Primary therapeutic options were thalidomide (n=86) and autologous stem cell transplantation (n=71). The 10-year overall survival was 93% (95% CI, 86-96%). This study showed current epidemiological and clinical status of POEMS syndrome in Japan. Compared with previous studies, the results suggested that the prognosis of POEMS has been improved by myeloma treatment such as autologous stem cell transplantation and immunomodulatory drugs.

References: None.

Keywords: Other

Grant Support: None.
Different distributions of nerve conduction slowing/block in typical and atypical chronic inflammatory demyelinating polyneuropathy

Kazumoto Shibuya, Atsuko Tsuneyama, Sonoko Misawa, Yukari Sekiguchi, Hiroshi Amino, Yo-ichi Suzuki, Tomoki Suichi, Keigo Nakamura, Satoshi Kuwabara

Department of Neurology Graduate School of Medicine Chiba University, Chiba, Japan

Introduction: Chronic inflammatory demyelinating polyneuropathy (CIDP) is clinically classified into 'typical' and 'atypical' subtypes, such as multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) and distal acquired demyelinating symmetric neuropathy (DADS). Our previous studies have shown different treatment response among those subtypes. To reveal pathophysiological differences, we investigated distributions of demyelinating nerve conduction abnormalities in CIDP subtypes. Methods: Seventy-nine CIDP patients were retrospectively analyzed. Depending on nerve conduction studies, conduction slowing and abnormal compound muscle action potential amplitude reduction (>30%) were assessed in the median and ulnar nerves, in which the nerve segments were divided into the 4 and 5 portions from root/plexus to distal axons, respectively. Results: Patients had typical CIDP (n=53), MADSAM (n=21), or DADS (n=5) subtypes. Conduction slowing was prominent at the plexus/root and distal portions of the both nerves in all clinical subtypes, but conduction slowing was more prominent in typical CIDP, compared with MADSAM (p < 0.05). Abnormal amplitude reduction in the nerve trunk were more frequent in MADSAM, compared with typical CIDP (p < 0.05). Conclusions: Typical CIDP preferentially affects the plexus/root and distal portions, whereas the nerve trunk is prominently impaired in MADSAM. The blood-nerve barrier is anatomically deficient at the distal nerve terminals and roots, and antibody-mediated demyelination occurs in typical CIDP, whereas cellular immunity with blood-nerve barrier breakdown is likely to be major mechanism in MADSAM. These pathophysiological differences may result in different treatment responses among CIDP subtypes.


Keywords: Inflammatory

Grant Support: None.
Introduction: Frequent fasciculations and muscle atrophy are observed in multifocal motor neuropathy (MMN) which often mimics amyotrophic lateral sclerosis (ALS). Widespread pattern of fasciculations in ALS have been demonstrated by using needle-electromyography and muscle ultrasound methods. However, the distribution of fasciculations in MMN has not been well explored. Objective: The aim of this study is to elucidate the difference in the distribution of fasciculations between MMN and ALS by using muscle ultrasound. Method: This study included 5 patients with MMN (4 definite MMN and 1 possible MMN based on EFNS/PNS guideline) and 15 patients with ALS (5 definite ALS, 9 probable ALS and 1 possible ALS based on the revised El Escorial criteria). Muscle ultrasound was performed in 41 muscles (the tongue muscle and 40 muscles of the trunk and limbs on both sides) in patients with MMN. In ALS the tongue muscle and 20 muscles on the side of the onset were examined. Ultrasound recording was performed at 1 site in each muscle for 60 seconds to judge the presence of fasciculations. Result: The fasciculations detection rates on the onset side was significantly higher in ALS patients (45.8 ± 5.1 %, mean ± SD) than in MMN patients (21.9 ± 8.8 %) (p < 0.05). In MMN patients, no fasciculation was detected in the tongue and the muscles of the thoracic segment. There was no difference in the fasciculations detection rate between the onset and non-onset sides and between the upper and lower limbs in MMN. Conclusion: In MMN, fasciculations were detected extensively in the limbs by muscle ultrasound. However, the detection rate in MMN was lower than in ALS. Furthermore, no detection of the fasciculations in the tongue and truncal muscles could be the key point to differentiate MMN from ALS.


Keywords: Inflammatory

Grant Support: No grant support.
Evaluation of complement proteins and cleavage fragments in CSF samples from Guillain-Barre syndrome patients

Sethu Sankaranarayanan¹, Poojan Suri¹, Haiyan Qiu², Vidhu Mathur², Israt Jahan³, Zhahirul Islam³, Ted Yednock²

¹Annexon Biosciences, South San Francisco, CA, USA, ²Annexon Biosciences, South San Francisco, USA, ³ICDDRb, Dhaka, Bangladesh

Guillain-Barre syndrome (GBS) is an acute antibody-mediated autoimmune disease involving rapidly progressive muscle weakness and impaired mobility, as well as respiratory distress in a subset of patients. GBS is characterized by autoantibody binding to peripheral nerve components, followed by C1q recruitment and classical complement cascade activation. Soluble complement activation products recruit immune cells into the nerve (C3a and C5a), activation products deposited onto nerve surface direct immune cell attack (C1q, C4d and C3d) and assembly of the terminal lytic complex (C5b-C9) causes membrane damage. Disruption of the blood brain barrier at peripheral nerve roots in GBS has been reported, so evaluated both antibody levels and complement activation products in CSF as a reflection of changes in the nerve root compartment. Previous studies have shown modest increases of terminal complement components (C5a and C5b-9). We developed specific and sensitive assays for early complement cascade components, including C1q, C4, C2, and C3, as well as activation products C2b, C3a, C3d, C5a and C5b-9. A significant increase in the levels of complement proteins, C1q, C4, C2, and C3 were observed in CSF of GBS subjects compared to controls. Much of these increases could be accounted for by damage to the blood brain barrier with increased permeability to serum proteins, as evidenced by an ~6-fold elevation in CSF serum albumin compared to controls. In addition, there was a 35-fold increase in IgG and a 90-fold increase in IgM levels in CSF, suggesting that high levels of pathogenic antibodies in nerve roots could drive complement activation. Consistent with this idea there was a disproportionate increase in the complement activation product C2b compared to C2 in the CSF. These results support measurement of complement activation products within the CSF of GBS patients as a way of monitoring classical complement cascade activity and its role in pathology.

References: None.

Keywords: Inflammatory, Pre-clinical Studies

Grant Support: None.
Poster 130

Multicentre Study Investigating Association of GBS with Flaviviruses and other Arboviruses in Asia - Patient Characteristics

Lai Lim Yip Ivy¹, Joy Agustin Sherwin¹, Umapathi N Thirugnanam¹, Gee Jin Ng¹, Thashi Thashi Chang ², Ohnmar Ohnmar³, Monica Saini¹, Lisa Ng⁴, Hugh Willison⁵, Neelika Malavige⁶, Terrence Terrence⁷, Surat Tanprawate Tanprawate⁸, Hoang Nghia⁹, Sara Khan¹⁰, Say Saysavath¹¹, Somchit Vorachit¹², Moe Moe Zaw Zaw¹³, Meenakshi Bhattacharya¹⁴, Prafulla Shembalkar¹⁵
The primary objective is to study if flaviviruses and other arboviruses are important pathogens in the development of Guillain-Barré syndrome (GBS) in South and South-East Asia (S SEA). This is a multicentre study involving hospitals in Singapore, Myanmar, Laos, Vietnam, Thailand, Pakistan, Sri Lanka, and India. It has cooperative affiliations with ZIKA-IGOS (ZIKA-International Guillain-Barré syndrome Outcome Study). The methodology involves examining GBS patients, hospital and community controls for evidence of recent arbovirus infections, using various microbiologic assays that account for confounding cross and co-infections. From December 2018 to February 2019 we have recruited a total of 87 patients from Singapore, Sri Lanka, and Myanmar. Median age was 48 years and range 13-87 years. The male-female ratio was 2.25:2. With regards to antecedent infections, the majority, 35 reported respiratory symptoms. Only 8 patients reported diarrhea. This is consistent with anecdotal reports from local doctors that diarrhea associated GBS in uncommon in this region. Two patients in Sri Lanka and one in Myanmar were clinically diagnosed to have Dengue infection prior to the onset of GBS. In Singapore, Miller–Fisher syndrome (MFS) was the predominant GBS subtype, accounting for half the cases. In Sri Lanka and Myanmar, MFS accounted for only a few cases, while the large majority were patients with limb weakness. In terms of electrodiagnostic classification, 5 out of 25, 13 out of 46 and 12 out of 16 were AMAN cases respectively in Singapore, Sri Lanka, and the Myanmar cohort. Over the next few months, more centers will start active recruitment and we hope to have enough data to compare with international databases like ZIKA-IGOS and IGOS.


Keywords: Inflammatory, Schwann Cell

Grant Support: CIDP GBS International Grant
The variety of peripheral neuropathies in eosinophilic granulomatosis with polyangiitis

Makoto Samukawa 1, Hanami Sakata 1, Yoshiko Taniguchi 1, Miyuki Morikawa Morikawa 1, Yuko Yamagishi Yamagishi 1, Shigeru Kawai 1, Yukihiro Hamada 2, Motoi Kuwahara 1, Hiroki Takeuchi Takeuchi 3, Yoshiyuki Mitsui Mitsui 1, Nobuyuki Oka 4, Susumu Kusunoki 1

1 Kindai University Faculty of Medicine, Osakasayama, Japan, 2 Izumi City General Hospital, Izumi, Japan, 3 National Hospital Organization, Minami-Kyoto Hospital, Joyo, Japan, 4 Kyoto Konoe Rehabilitation Hospital, Kyoto, Japan

Background

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare systemic necrotizing vasculitis. Peripheral neuropathy occurs in 68-98% of the patients with EGPA; mononeuropathy multiplex (MNM) with axonal damage is the most characteristic feature. However, polynueuropathy and/or demyelinating findings were rarely observed on nerve conduction study (NCS). Corticosteroids are typically effective but sometimes intractable, especially for peripheral nerve involvement.

Methods

We collected eight patients [male:female=1:7, age: 53 (28-83)] with EGPA and peripheral neuropathy, and assessed their clinical features.

Results

Axonal MNM was observed on NCS in seven patients. We considered the pathogenesis of neuropathy in these patients as vasculitis. In contrast, the remaining case showed demyelinating polyneuropathy on NCS and no evidence of vasculitis on microscopic examination of sural nerve. Serum anti-glycolipid antibody assay showed antibody activities to several gangliosides; 2+ to GM1, GM2, GT1b and GQ1b, 3+ to GD1a, GD1b, GD3, each added with phosphatidic acid in the patient with demyelinating polyneuropathy. These findings of this patient suggested immune-mediated mechanisms. Two of the seven patients with MNM had good response to corticosteroids. Corticosteroids were ineffective in the other five patients with MNM and in the patient with demyelinating polyneuropathy, whereas intravenous immunoglobulin (IVIg) was effective for those patients.

Conclusion

MNM was the most frequent pattern in peripheral neuropathies in EGPA although some patients could develop immune-mediated demyelinating polyneuropathy. IVIg was effective for the cases with refractoriness to corticosteroids in EGPA.

References: None.

Keywords: Inflammatory

Grant Support: None.
Neuropathy by B-cell chronic lymphocytic leukemia involvement of the central nervous system: a case report

Tiziana Rosso¹, Stefania Lelli², Ercole De Biasi³

¹UOC Neurologia Castelfranco Veneto-Dipartimento di Medicina Clinica-Distretto di Asolo-AULSS2 Marca Trevigiana, Castelfranco Veneto, Italy, ²UOC Neurologia Castelfranco Veneto-Dipartimento di Medicina Clinica-Distretto Asolo-AULSS2 Marca Trevigiana, Castelfranco Veneto, Italy, ³UOC Ematologia Camposampiero-AULSS6 Euganea, Camposampiero, Italy

B-cell chronic lymphocytic leukemia (B-CLL) is a chronic and slowly developing leukemia.

Neurologic complications by direct leukemic involvement of the central nervous system (CNS) have been rarely reported. A 67 y.o. man was diagnosed in 2012 with a monoclonal B Lymphocitosis (MBL) which developed in B-CLL (CD5+CD19+) in 2016, according to a second peripheral blood typing. In the summertime 2018 he complained pain and paresthesias without motor symptoms and underwent a first neurophysiological study that revealed a mild asymmetric neuropathy. Complete blood count showed a moderate lymphocytosis. Serum protein electrophoresis was normal; antibodies against gangliosides, MAG and neuronal antigens were negative. A lumbar puncture, showed 87 mg/ml proteins and 124/ml mononuclear cells that were lymphocytes at the cytological examination. A second electrodiagnostic study was stable. In November he began worsening. A third neurophysiological study was unmodified. A second lumbar puncture revealed 74 mg/ml proteins and 70 cells: immunophenotyping of cerebrospinal fluid and peripheral blood lymphocytes detected the same clonal lambda B cell population. In January 2019, patient complained scattered bone pain, but X-rays were negative for osteolytic lesions. A fourth electrodiagnostic study showed deterioration of the nerve conductions consistent with the asymmetric worsening symptoms. He underwent a second neurological and haematological opinions, including molecular analyses on circulating CLL cells, mutational status of variable region of immunoglobulin heavy chain, mutation of TP 53 gene and chromosomal analyses using fluorescent in situ hybridization. A gadolinium-MRI of the spine showed enhancement at the spinal roots level and meninges.

Nowadays the prognosis in CLL has been defined with the added value of new immunological and genetic tests. Central nervous system involvement (CNSi) is a rare complication in CLL. A diagnostic “gold standard” of CNS involvement in CLL is CSF cytology, but implementation of CSF-FCI as a routine diagnostic tool may be of a greater importance.

References: None.

Keywords: Inflammatory, Pain, Other, Human Genetics

Grant Support: None.
Reversible conduction failure of sensory in acute axonal subtypes of Guillain Barré syndrome

Shuo Yang¹, Hua Pan², Na Chen², Lei Zhang², Ying Wang², Lin Chen², Hengheng Wang², Fan Jian², Songtao Niu², Mingsheng Liu³, Zaiqiang Zhang², Liying Cui³, Kimura Jun⁴

¹Beijing Tiantan Hospital, China National Clinical Research Center for Neurological Diseases, Beijing, China, ²Beijing Tiantan Hospital, China National Clinical Research Center for Neurological Diseases, Beijing, China, ³Peking Union Medical College Hospital, Chinese Academy of Medical Science, Beijing, China, ⁴College of Medicine, University of Iowa, Iowa, USA

Introduction Acute motor axonal neuropathy (AMAN) generally manifests as purely motor involvement. One serial electrophysiological research has recorded amplitude increase of sensory nerve action potential (SNAP) in AMAN.¹ The aim of this study is to investigate whether reversible conduction failure (RCF) of sensory occurred in AMAN as well as acute motor and sensory axonal neuropathy (AMSAN).

Methods We recruited 16 AMAN and 11 AMSAN patients based on Uncini’s criteria.² All subjects underwent at least two times clinical and electrophysiological evaluations within 8 weeks. Compared the variation of SNAP amplitude in serial recordings. Results The average time from onset of symptoms to baseline electrophysiological examination in AMAN and AMSAN groups were 16 days (range 4-30 days) and 14 days (range 5-26 days). We recorded increase of SNAP amplitude in nine AMAN and seven AMSAN patients through serial electrophysiological tests. In AMAN group, SNAP amplitude improved 144% (range 107%-271%) for median nerves in digit I and 163% (range 61%-312%) in digit III, 100% (range 85%-115%) for ulnar nerves, 185% (range 64%-395%) for tibial nerves, and 67% (range 60%-73%) for sural nerves. In AMSAN group, the corresponding values presented 126% (range 71%-226%), 60% (range 53%-71%), 111% (range 63%-158%), 100%, 149% (range 61%-245%). A total of four AMAN and six AMSAN patients met the criteria of sensory RCF. Seven of them accompanied by limbs numbness, which relieved apparently as well as weakness after IVIg treatment. Three AMSAN patients returned to normal SNAP in the reexamination. Conclusions Although SNAPs of most AMAN usually show normal, a significant increase in amplitudes can be seen in serial evaluations, which meet the criteria of sensory RCF as well as AMSAN. In addition, some AMSAN patients can return to normal SNAP after treatment, suggesting that AMAN and AMSAN may be two continuums in axonal Guillain-Barré syndrome.


Keywords: Clinical Trials, Node, Axonal Biology

Grant Support: None
Repeater F-waves in demyelinating and axonal polyneuropathies

Dimitra Veltsista¹, Angeliki Gerardou¹, Elisabeth Chroni²

¹University of Patras, Medical School, Patras, Greece, ²University of Patras, Medical School, Patras, Greece

Introduction: Repeater F-waves (Freps) are F-waves identical in latency, size and shape. Freps are rarely evaluated in routine studies, primarily because of difficulty in recognizing them by visual inspection. The purpose of this study was to investigate the presence of Freps in demyelinating (PN-D) and axonal (PN-A) polyneuropathies, using a specially designed computer program for the automated identification of Freps (F Wave Analyzer).

Methods: F-waves were recorded following forty consecutive supramaximal stimuli to the ulnar nerve in 17 patients with PN-D, 13 patients with PN-A and 29 healthy subjects as controls. The F Wave Analyzer automatically identifies Freps based on predefined selection criteria and groups them. Parameters of Freps and non repeater F-waves (Fnonreps) were studied and compared. Results: In both patient groups, the total number of different F waveforms that appeared more than once in a series, called repeating neurons (RNs), Freps persistence (100xFreps/40stimuli) and Index Freps (100xFreps/total number of F-waves) were significantly higher than the control group (all P values < 0.05). No significant differences in Freps indices were identified between the PN-D and PN-A group. A negative correlation between F persistence and Index Freps was demonstrated in the PN-D group (P= 0.077). Famp mean/M(%) and Famp max/M (%) values in Fnonreps of PN-A patients were significantly higher compared to healthy subjects (P<0.05), and tended to be higher than the PN-D group (P=0.07). RNs with 5 or more repetitions were present in 64.7% and 76.9% of the PN-D and PN-A patients respectively, but in none of the healthy subjects. Conclusion: Indexes of Freps and RNs could be used as additional electrodiagnostic estimates, since they were significantly increased in demyelinating and axonal polyneuropathies, compared to healthy subjects. The automated analyzing system provides fast, effortless and accurate identification of Freps, making it suitable for clinical settings.

References: None.

Keywords: Other

Grant Support: None
Poster 135

Exposure-Response of Serum IgG Levels and INCAT Scores in CIDP Patients Receiving Subcutaneous Immunoglobulin (IgPro20)

Theresa Yuraszeck¹, Richard Lewis², David Cornblath³, Xuewen Ma¹, Orell Mielke⁴, Vera Bril⁵, Hans-Peter Hartung⁶, Gen Sobue⁷, John-Phillip Lawo¹, Billie Durn¹, Ingemar Merkies⁸, Ivo van Schaik⁹, Michael Tortorici¹

¹CSL Behring, King of Prussia, PA, USA, ²Cedars-Sinai Medical Center, Los Angeles, CA, USA, ³Johns Hopkins University School of Medicine, Baltimore, MD, USA, ⁴CSL Behring, Marburg, Germany, ⁵University of Toronto, Imam Abdulrahman Bin Faisal University, Toronto, Canada, ⁶Heinrich Heine University, Düsseldorf, Germany, ⁷Nagoya University Graduate School of Medicine, Nagoya, Japan, ⁸Maastricht University Medical Center, St Elisabeth Hospital, Maastricht, Netherlands, ⁹University of Amsterdam, Amsterdam, Netherlands

Introduction: The relationship between chronic inflammatory demyelinating polyneuropathy (CIDP) disease activity and serum IgG levels in patients treated with immunoglobulins is critical for dose determination. We investigated the exposure-response of serum IgG levels and disease activity and developed a population pharmacokinetic/pharmacodynamic (PK/PD) model characterising the relationship between serum IgG exposure and disease severity using data from the PATH study.

Methods: PK/PD data from 171 subjects who received either 0.2 or 0.4 g/kg subcutaneous immunoglobulin (IgPro20; Hizentra®, CSL Behring, King of Prussia, PA, USA) or placebo in the PATH study (NCT01545076) were included in the analysis. Total IgG concentrations at baseline and after subcutaneous infusion were summarised. IgG PK parameters from a previous population PK model were used to predict individual PK profiles. The relationship between exogenous IgG (defined as total serum IgG at INCAT [Inflammatory Neuropathy Cause and Treatment] score assessment minus baseline IgG levels before intravenous immunoglobulin restabilisation) and last measured INCAT score was investigated. A PK/PD model consisting of baseline and drug effects with inter-individual variability was developed to quantify the link between exogenous IgG and INCAT score.

Results: The mean values of total IgG concentration change from baseline in the 0.4 g/kg group were always higher than those in other groups. A relationship between time-matched exogenous IgG and INCAT score was demonstrated; the percentage of patients experiencing stability/improvement increased from 59% to 88% when the exogenous concentrations increased from 0–2 to >8 g/L. The model predicted that the probability of INCAT improvement/stability increases with higher exogenous IgG concentration.

Conclusions: This analysis demonstrates a quantitative link between serum IgG level and INCAT score in CIDP patients. The role of exogenous IgG levels as a potential biomarker to predict treatment response in CIDP should be investigated further.

References: None.

Keywords: Inflammatory

Grant Support: This study was supported by CSL Behring.
Introduction Intravenous immunoglobulin (IVIg) and plasma exchange (PE) are proven effective treatments in Guillain-Barré syndrome (GBS) but it is undefined when and how these treatments are used in clinical practice. The aim of the study was to describe the current treatment practice of GBS. The study was based on prospective observational data from the first 1300 patients included in the International GBS Outcome Study (IGOS). We described the treatment practice of GBS in general, and for (1) severe forms (unable to walk independently), (2) no recovery after initial treatment, (3) treatment-related fluctuations, (4) mild forms (able to walk independently), and (5) variant forms including Miller Fisher syndrome, taking patient characteristics and hospital type into account. Results We excluded 88 (7%) patients because of insufficient data, protocol violation or alternative diagnosis. Patients from Bangladesh (n=189, 15%) were described separately because 83% were not treated. Intravenous immunoglobulin (IVIg), plasma exchange (PE) or other immunotherapy was provided in 941 (92%) of the remaining 1023 patients, including patients with severe GBS (724/743, 97%), mild GBS (126/168, 75%), Miller Fisher syndrome (53/70, 76%) and other variants (33/40, 83%). Of 235 (32%) patients who did not improve after their initial treatment, 82 (35%) received a second immune modulatory treatment. A treatment-related fluctuation was observed in 53 (5%) of 1023 patients, of whom 36 (68%) were re-treated with IVIg or PE. Those who were re-treated, were more often admitted to university hospitals (n=31/39, 79%) than to non-university hospitals (n=5/14, 36%, p=0.01). Conclusions In current practice, patients with mild and variant forms of GBS, or with treatment-related fluctuations and treatment failures are frequently treated, even in absence of trial data to support this choice. The variability in treatment practice can be explained in part by the lack of evidence and guidelines for effective treatment in these situations.

References: None.

Keywords: Other

Grant Support: None.
IgM anti-MAG(+) peripheral Neuropathy: from proper assessment to trial needs (IMAGiNe study)

Mariëlle Pruppers1, Ingemar Merkies2, Catharina Faber2, Alexander Vrancken3, David Cornblath4, Luis Querol5, Stojan Peric6, Michael Lunn7, Yusuf Rajabally8, Rob Hadden9, Eduardo Nobile-Orazio10, Chiara Briani11, Juliette Svahn12, Thomas Harbo13, Hans-Peter Hartung14, Peter van den Bergh15, Richard Lewis16, Amanda Pettier17, Jeffrey Allen18, Yessar Hussain19, Amro Stino20, Nicolette Notermans3

1Maastricht University Medical Center, University Medical Center Utrecht, Maastricht, Netherlands, 2Maastricht University Medical Center, Maastricht, Netherlands, 3University Medical Center Utrecht, Utrecht, Netherlands, 4Johns Hopkins Hospital, Baltimore, USA, 5Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, 6Clinical Center of Serbia, University of Belgrade, Belgrade, Serbia, 7Centre for Neuromuscular disease, National Hospital for Neurology and Neurosurgery, London, United Kingdom of Great Britain and Northern Ireland, 8University Hospitals Birmingham, Queen Elizabeth Hospital Birmingham, Birmingham, United Kingdom of Great Britain and Northern Ireland, 9King’s College Hospital, London, United Kingdom of Great Britain and Northern Ireland, 10Humanitas Clinical Institute, Rozzano, Italy, 11Università di Padova, Padua, Italy, 12Hospices Civils de Lyon, Lyon, France, 13Aarhus University Hospital, Aarhus, Denmark, 14Heinrich Heine Universität Düsseldorf, Düsseldorf, Germany, 15Neuromuscular Reference Center UCL St-Luc, Brussels, Belgium, 16Cedars-Sinai Medical Center, Los Angeles, USA, 17University Vanderbilt, Nashville, USA, 18University of Minnesota, Minnesota, USA, 19Austin Neuromuscular Center, Austin, USA, 20Ohio State University, Ohio, USA

IgM peripheral neuropathy is a late-onset, male predominance, slowly progressive, symmetric, predominantly sensory ataxic neuropathy with relatively mild or no weakness. Neuropathic pain and a prominent tremor can occur as well. International consensus regarding assessment and treatment of patients with IgM peripheral neuropathy is lacking. This has multifactorial origins with most of the problems leading back to flawed study designs. This includes short follow-up periods, examining relatively low numbers of patients, differences in the definition of ‘a responder’ and the use of inappropriate, often ordinal and non-responsive, outcome measures. During the 230th ENMC meeting in 2017, these subjects were discussed and it was concluded that the IMAGiNe study would serve as a platform for a collaborative effort in resolving the current problems. The IMAGiNe study is an international, multi-center, prospective, observational cohort study, aiming for an unique collection of a large number of prospectively collected and highly standardized clinical data of well-defined patients with IgM peripheral neuropathy. Several study parameters measuring weakness, sensation, activity and participation, ataxia, pain, and quality of life are of interest. The main objectives are (1) to describe in detail the variation in clinical subtypes, clinical disease course, past and current practice of treatment, and antibody titers and (2) to develop IgM-specific outcome measures that are simple, valid, reliable and particularly responsive. The latter is pivotal to capture relevant changes over time. To date, 117 patients were included in centers in the Netherlands, Italy, the USA, Serbia and Spain and multiple other centers are preparing to include patients as well. As the first study result, the IgM-specific Rasch-built Overall Disability Scale (IgM-RODS) will be developed in 2019. In order to develop the IgM-RODS, around 30 non-European patients are still needed. During the PNS 2019, an update will be given on the current state of the study.

References: None.

Keywords: Inflammatory

Grant Support: Mazawey Fellowship from the GBS/CIDP Foundation International
Poster 138

Different Clinical Findings Between Anti-GQ1b Antibody-Positive And -Negative Bickerstaff Brainstem Encephalitis

Keisuke Yoshikawa

Department of Neurology, Kindai University Faculty of Medicine, Osaka, Japan

Bickerstaff brainstem encephalitis (BBE) is characterized by acute self-limited consciousness disturbance, ophthalmoplegia, and ataxia. Anti-GQ1b antibody is frequently present in the acute-phase sera from patients with BBE. Up to date, only few clinical studies of BBE have been reported because it is a rare disease. Recent nationwide survey in Japanese population proposed the diagnostic criteria of BBE and reported that definite BBE showed different clinical findings compared with probable BBE. However, it remains unclear whether clinical findings differ between BBE with and without anti-GQ1b antibody. In the present study, we compared 73 anti-GQ1b antibody-positive BBE cases with 10 antibody-negative cases. All cases fulfilled the above diagnostic criteria and those clinical information and sera were collected from various hospitals throughout Japan between 2014 and 2017. Anti-GQ1b antibody was examined in each serum by enzyme-linked immunosorbent assay (ELISA). We identified the distinctive findings of anti-GQ1b antibody-positive BBE compared with the antibody-negative cases; (a) Upper respiratory infection and sensory disturbance were more common (70% vs 20% and 56% vs 10%, p<0.01, respectively), (b) cell count or protein concentration in the cerebrospinal fluid were lower (12.5/μl vs 75.9/μl, p<0.01 and 63.5 mg/dl vs 159mg/dl, p<0.01, respectively), (c) abnormal findings on brain MRI were less (8% vs 50%, p<0.01), and (d) consciousness disturbance improved earlier (10 days vs 23 days, p=0.015). Furthermore, IVIG was more frequently administered in BBE with anti-GQ1b antibody (86% vs 50%, p<0.05). In conclusion, our findings indicate that BBE with anti-GQ1b antibody shows distinct clinical features and has homogeneous pathogenetic mechanisms similar to Miller Fisher syndrome.

References: None.

Keywords: Inflammatory

Grant Support: None.
The purpose of this study is to investigate the unique clinical and serological features of Guillain-Barré syndrome (GBS) and related diseases (GBSRD; GBS, Fisher syndrome [FS] and Bickerstaff brainstem encephalitis [BBE]) after influenza virus infection (GBSRD-I). We collected clinical information of 63 consecutive patients with GBSRD-I whose serum samples were sent to our laboratory from multiple hospitals in Japan between October 2009 and February 2017 for the examination of anti-glycolipid antibodies. IgG antibodies against 11 glycolipids (GM1, GM2, GM3, GD1a, GD1b, GD3, GT1b, GT1a, GQ1b, GalNAc-GD1a, and galactocerebroside) were examined in all patients. We compared the clinical and serological features between 63 GBSRD-I patients and 82 patients with GBSRD after Campylobacter jejuni infection (GBSRD-C). Among the anti-glycolipid antibodies, anti-GQ1b antibody and anti-GT1a antibody were the most frequently detected antibody in GBSRD-I (15/63, 24%) whereas anti-GM1 antibody in GBSRD-C (24/82, 29%). In accord with this, FS was more frequent in GBSRD-I than in GBSRD-C (22% vs 9%, p=0.02). In the 48 patients with GBS after influenza virus infection (GBS-I), cranial nerve deficits, sensory disturbance, and ataxia were more frequently observed than in those with GBS after C. jejuni infection (GBS-C) (46% vs 15%, 75% vs 46%, and 29% vs 4%, p<0.01 for each symptom). The results of nerve conduction studies (assessed by Ho’s criteria) exhibited acute inflammatory demyelinating polyneuropathy more frequently in GBS-I than in GBS-C (60% vs 25%, p<0.01). In conclusion, in GBSRD-I, anti-GQ1b and anti-GT1a antibodies are the most frequently detected anti-glycolipid antibodies and FS is frequent. GBS-I is characterized by frequent AIDP, cranial nerve deficits, sensory disturbances, and ataxia.

References: None.

Keywords: Inflammatory

Grant Support: None.
Neurophysiological and Imaging Features can Differentiate between GBS with Treatment-Related Fluctuations and Acute-Onset CIDP

Tsun Haw Toh¹, Nortina Shahrizaila², Mohd Azly Yahya¹, Khean Jin Goh², Cheng Yin Tan²

¹University of Malaya Medical Centre, Kuala Lumpur, Malaysia, ²University of Malaya, Kuala Lumpur, Malaysia

Introduction: Distinguishing acute-onset chronic inflammatory demyelinating polyneuropathy (A-CIDP) from Guillain-Barré syndrome (GBS) with treatment-related fluctuations (TRF) can be challenging. In this study, we investigated the clinical, neurophysiological and nerve ultrasound parameters of patients with GBS-TRF and A-CIDP to identify features that might differentiate between the two diagnoses.

Methods: Patients with GBS-TRF and A-CIDP were identified from an existing cohort of GBS patients presenting to our centre from 2011 to 2018. The clinical, neurophysiological and nerve ultrasound data were compared.

Results: Three GBS-TRF (mean age 58±3 years old) and four A-CIDP (mean age 68±4 years old) patients were included. The mean time to first neurological deterioration was significantly longer in the A-CIDP patients compared to GBS-TRF (12 vs 5 weeks; p=0.04). Based on two studies, both GBS-TRF and A-CIDP patients fulfilled the electrodiagnostic criteria for demyelination. At first study, patients with A-CIDP had significantly prolonged F wave latencies compared to GBS-TRF (41 vs 27 ms; p=0.046). The sural nerve action potentials were significantly reduced in amplitude in A-CIDP compared to GBS-TRF patients at first study (4.9 vs 19.1 µV; p<0.001). At second study, the sural potentials were present in GBS-TRF patients but unrecordable in the A-CIDP patients. On nerve ultrasound, there was significantly larger cross-sectional area of the ulnar nerve at the elbow (12 vs 6 mm2; p=0.039) and peroneal nerve at the knee (15 vs 8 mm2; p=0.004) in the A-CIDP patients.

Conclusion: Despite the small number of patients, we found that electrophysiological and nerve imaging parameters can be useful in distinguishing between GBS-TRF and A-CIDP.

References: None.

Keywords: Inflammatory

Grant Support: None.
Guillain-Barre syndrome as an initial manifestation of antiphospholipid syndrome

Sung-Yeon Sohn¹, Byung-Nam Yoon², Jung-Joon Sung³

¹Department of Neurology, Eulji University Medical Center, Daejeon, Korea (Republic of), ²Department of Neurology, Seoul Paik Hospital, Inje University College of Medicine, Seoul, Korea (Republic of), ³Department of Neurology, Seoul National University Hospital, Seoul, Korea (Republic of)

Detection of antiphospholipid antibodies (aPL) in sera from patients with Guillain-Barre syndrome (GBS) have long been recognized since the 1980s. However, earlier researches on the association between antiphospholipid syndrome (APS) and GBS have yielded conflicting results, partly owing to the fact that APS is a “clinically defined syndrome”. We describe a GBS patient who fulfilled the revised Sydney criteria for the clinical diagnosis of APS, and discuss whether GBS should be considered as an uncommon neurological manifestation of APS or a mere coincidence. A 75-year-old man was referred to our hospital due to acute paraplegia of both lower extremities and aggravating dyspnea for two days. After admission, intravenous immunoglobulin was administered at once since the patient’s condition rapidly deteriorated (Grade 4 based on GBS disability scale by Hughes et al.). Laboratory findings showed elevated D-dimer, fibrin degradation products (FDP) level, and testing for lupus anticoagulant, IgG antibodies to β2-glycoprotein 1 and cardiolipin yielded positive results. Computed tomography scan for the evaluation of dyspnea revealed pulmonary artery thromboembolism and deep vein thrombosis in the left popliteal vein. Oral anticoagulant was added. He began to gradually recover two weeks after admission. Repeated blood tests for aPL after twelve weeks still showed elevated levels, confirming the diagnosis of APS.

References: None.

Keywords: Inflammatory

Grant Support: None.
Poster 142

Is testosterone a potential agent for patients with delayed recovery from Guillain- Barre syndrome?

Anomali Vidanagamage, Lakitha Weerathunga, Dinusha DHarmaratne, Lakmal Samarasinghe, Asfir Lebbe, Gamini Pathirana, Kamal Gunaratne, Arjuna Fernando

National Hospital, Colombo, Sri Lanka

Introduction

Management of Guillain- Barre syndrome is challenging when there is delayed recovery.

Case report

A 32 years old man presented with ascending paralysis with a preceding diarrheal illness.
On examination, there was bilateral symmetrical proximal predominant weakness with areflexia. On the 6th day of weakness, he was intubated secondary to respiratory paralysis.

The nerve conduction showed Acute inflammatory demyelinating polyneuropathy and the CSF showed cytoprotein dissociation compatible with Guillain – Barre syndrome (GBS). He was treated with IV immunoglobulin at diagnosis.

Due to delayed recovery, he received a second cycle of IV immunoglobulin commencing on the 15th day and therapeutic plasma exchange on the 31st day.

As he had a very long ICU stay without clinical improvement the 2nd round of plasma exchange was commenced on Day 51.

Still, his recovery was poor and was ventilator dependent.

The long illness was complicated with the syndrome of inappropriate ADH release (SIADH), autonomic instability and 4 episodes of sepsis while in the ICU.

His repeat nerve conduction study on day 71 showed a critical illness myopathy and polyneuropathy on top of previous demyelinating changes.

At the same time, his serum testosterone level was low, although the serum DHEA level was normal.

On anecdotal evidence he was given intramuscular testosterone 300 mg weekly for three weeks, commencing on day 74.

Within the first week, there was a marked increase in the VC and he could be weaned off from the ventilator by day 83. The improvement of limb power was gradual.

Repeat nerve conduction done on day 101 showed a significant improvement in comparison to previous study and the previously noted myopathic changes were not seen and only recovering neurogenic changes were noted.

Conclusion

The role of testosterone in demyelinating peripheral neuropathies need to be further evaluated considering the potential therapeutic benefits.

References: None.

Keywords: Inflammatory

Grant Support: None.
Temporal-Spatial Activation of Spinal Microglia after Peripheral Nerve Injury

Hauke Wüstenberg, Philip Röth, Ines Muke, Michael Schroeter, Helmar Lehmann

University Hospital Cologne, Cologne, Germany

It is well known that peripheral nerve damage evokes a microglia activation in the spinal cord. However, the underlying mechanisms, the temporal-spatial activation pattern and the functional consequences of this unique interaction between immune effectors of central and peripheral nervous system are largely unknown. The aim of this study was to characterize the temporal-spatial activation pattern of spinal microglia after peripheral nerve injury.

We used male and female 6 weeks old C57BL/6 mice and subjected them to a crush of the peroneal nerve, a branch of the sciatic nerve. Activation and polarization/differentiation of microglia in the spinal cord was assessed by immunohistochemistry and qPCR at day 7, day 14, and day 21 after nerve crush. Alteration of spinal microglia was induced by feeding mice with chow containing PLX3397, a colony stimulating factor 1 receptor (CSF-R1) inhibitor.

Increased numbers of microglia could be detected in the ventral and dorsal horn of the spinal cord ipsilateral to the crushed nerve. Microglia co-localized with the cell nuclei of crushed nerves mostly at the L4 segment of the spinal cord, as confirmed via tracer injections. Microglia numbers peaked at day 7, polarization and differentiation of microglia occurred until day 21, where most pro-inflammatory microglia were observed. Microglia depletion via PLX3397-containing chow caused a partial reduction in microglia numbers in the spinal cord.

Our data indicate that peripheral nerve damage elicits a persistent accumulation of rather pro-inflammatory microglia in the associated spinal cord segment. This accumulation can be prevented by systemic inhibition of CSF-R1.

References: None.

Keywords: Inflammatory, Other

Grant Support: None.
Poster 144

BENDAMUSTINE–RITUXIMAB (BR) COMBINED THERAPY FOR TREATMENT OF IMMUNO-MEDIATED NEUROPATHIES ASSOCIATED TO HEMATOLOGICAL DISORDERS

Angela Zuppa1, Federico Massa2, Chiara Demichelis2, Chiara Briani3, Sergio Ferrari4, Angelo Schenone2, Luana Benedetti2

1Department of Neuroscience, DINOGMI, University of Genoa, Genoa, Italy, 2DINOGMI, University of Genoa, Genoa, Italy, 3Department of Neurosciences, University of Padova, Padova, Italy, 4Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Verona, Italy

Rituximab is a therapeutic choice in anti-MAG polynuropathy (AMPN) but its usefulness in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) associated with hematological diseases (HD) is still controversial. Moreover to date one case-report described long-term efficacy of combined Bendamustine-Rituximab (BR) in AMPN refractory to Rituximab. Herein we described a six-months combined BR treatment in two patients affected by CIDP and one by AMPN associated to HD. Case1 (69 years old, F) and Case2 (50 years old, F) developed a severe CIDP in the context of splenic marginal non-Hodgkin lymphoma and Chronic lymphocytic leukemia (CLL), respectively. Case3 (80-year-old, F) was affected by severe AMPN associated to Waldenström's macroglobulinemia with high level anti-MAG antibodies. In Case1 and Case3 BR was the first-line therapy because of HD severity, while in Case2 BR followed an unsuccessful 18-months attempt with conventional treatments. All patients had a progressive clinical improvement - defined by at least 2 points in INCAT scale - during therapy (Case1) or two months after the last course (Case2 and Case3). Moreover in Case2 the most impressive improvement concerned attitudinal and intentional tremor. In Case3 anti-MAG antibodies significantly declined already two months from the last treatment (178.531 to 112.641 BTU). Case1 and Case3 were progression-free during a mean follow up of ten months. In Case2, after three years of sustained stability, a clinical relapse occurred along with CLL reactivation. Six-months Rituximab therapy was administered but Rituximab alone allowed a shorter disease remission (1 year) compared to the previous combination of BR. To our knowledge to date only one case-report described long-term efficacy of BR in AMPN refractory to Rituximab. In our three cases combination of BR was a valid option in immune-mediated neuropathies associated to HD. Moreover BR schedule led to a longer sustained improvement than Rituximab alone in relapsing CIDP associated to CLL.


Keywords: Inflammatory

Grant Support: None.
Including Sensory Nerve Conduction Studies in a Modified Electrodiagnostic Criteria for Guillain-Barré Syndrome

Wei Ting Wang¹, Jonathan Jia Jing Pong¹, Joshua Ian Lim¹, Jasmine Shimin Koh², Genevieve Lynn Yu², Christen Sheng Jie Lim³, Thirugnanam Umapathi²

¹National University of Singapore, Yong Loo Lin School of Medicine, Singapore, Singapore, ²National Neuroscience Institute, Department of Neurology, Singapore, Singapore, ³National University Hospital, University Medicine Cluster, Singapore, Singapore

The emphasis of electrodiagnostic (EDX) criteria for Guillain-Barré Syndrome (GBS) has traditionally been on differentiating GBS subtypes over the accurate diagnosis of GBS itself. Sensory studies, including the sural-sparing pattern, are generally excluded, despite studies showing its utility in differentiating GBS from mimics. We studied the utility of a simplified EDX criteria, incorporating sensory nerve conduction studies (NCS), that affords a graded level of diagnostic certainty. We analysed the NCS of 136 Singaporean GBS patients. Motor and sensory NCS findings were compared against age and height-adjusted normal values rather than set cuts-offs such as 120% of the upper limit of F-wave latency. The EDX certainty of GBS was categorized into:

**Definite:** two abnormal motor nerves and the sural-sparing pattern of sensory abnormality. **Probable:** (i) one abnormal motor nerve and the sural-sparing pattern of sensory abnormality or (ii) two abnormal motor nerves. **Possible:** (i) Normal NCS, (ii) single motor nerve abnormality with or without sensory nerve abnormalities, or (iii) normal motor NCS with either diffuse sensory nerve abnormalities or the sural-sparing pattern. Using this criteria, 47 (34.6%), 57 (41.9%) and 32 (23.5%) of GBS patients were classified as “definite”, “probable” or “possible” GBS respectively, whereas traditional EDX criteria only diagnosed 69 (50.7%) of cases. 14 (22.9%), 21 (34.4%) and 26 (42.6%) of 61 Miller-Fisher Syndrome patients were grouped into “definite”, “probable” or “possible” categories, respectively. Traditional criteria only detected 14.7% of cases. The improvement in sensitivity was largely due to simplification of the motor NCS criteria. We expect the addition of sural-sparing pattern to increase the criteria’s diagnostic certainty by discriminating GBS from its mimics. We are currently validating the utility of this criterion, particularly its specificity, by prospectively applying it to patients presenting with acute flaccid paralysis.

References: None.

Keywords: Inflammatory, Other

Grant Support: None.
Antecedent infection spectrum in patients with Guillain-Barré syndrome: a single center, prospective study

Yuzhong Wang¹, Weifang Wang², Bart Jacobs³, Baojun Qiao², Daiqiang Liu², Xungang Feng², Yanlei Hao²

¹Department of Neurology, Affiliated Hospital of Jining Medical University, Jining, Shandong Province, China, Jining, China, ²Department of Neurology, Affiliated Hospital of Jining Medical University, Jining, China, ³Department of Neurology and Immunology, Erasmus University Medical Centre, Rotterdam, Netherlands

Infection agents bearing a series of antigenic molecules triggering the autoimmune response against the peripheral nerve may result in the variety of clinical manifestations in Guillain-Barré syndrome (GBS). This study includes a total of 150 consecutive patients fulfilled the diagnostic criteria for GBS and its variants from Affiliated Hospital of Jining Medical University (October 2013 to June 2017) and aimed to investigate the antecedent infection spectrum in GBS in local region. According to the previous reports and unpublished data from Chinese Centre for Disease Control, 14 of infectious pathogens were selected. All of the infections were detected using the commercial ELISA kits. Serum samples of patients with other neurological diseases and healthy donors from the local biological sample bank were selected as the controls. Of the patients with GBS, a total of 53% (80/150) had positive serology for either C jejuni (n = 40, 27%), Influenza A (n = 26, 17%), Influenza B (n = 24, 16%), Hepatitis A virus (n = 7, 5%), Dengue virus (n = 4, 3%), Cytomegalovirus (n = 4, 3%), Epstein-Barr virus (n = 4, 3%), Mycoplasma pneumonia (n = 3, 2%), Herpes simplex virus (n = 3, 2%), Varicella-zoster virus (n = 2, 1%) and Rubella virus (n = 1, 0.7%). Of the patients, 26 (17%) had two or more than two of the infections. None of the patients had positive serology for Hepatitis E virus, Haemophilus influenza and Zika virus. There were significantly higher frequency of antecedent infection of C jejuni, Influenza A, Influenza B and Hepatitis A virus between the patients with GBS and the controls. The GBS in our region was related to antecedent infection of C jejuni, Influenza A, Influenza B and Hepatitis A virus. The relation between these infections and clinical features of the patients will be further presented.

References: None.

Keywords: Inflammatory

Grant Support: This work was supported by the National Natural Science Foundation of China (81771360, 81771298 and 81301072), Shandong Medical and Healthy Science Technology Development Plan (2016WS0184) and the Technology boosting new and old kinetic energy conversion projects of Jining City (2017SMNS002).
Electrophysiologic assessment of eculizumab efficacy in severe Guillain-Barré syndrome: A post-hoc analysis of JET-GBS study

Yukari Sekiguchi¹, Sonoko Misawa¹, Tomoki Suichi¹, Hiroshi Amino¹, Minako Beppu¹, Motoi Kuwahara ², Susumu Kusunoki², Satoshi Kuwabara³

¹Department of Neurology, Chiba University, Chiba, Japan, ²Department of Neurology, Faculty of Medicine, Kindai University, Osaka, Japan, ³Department of Neurology, Graduate school of Chiba university, Chiba, Japan

A previous clinical trial (Japanese eculizumab trial for Guillain–Barré syndrome [JET-GBS]) has suggested the efficacy of eculizumab for patients with Guillain–Barré syndrome (GBS). To further elucidate the mechanisms of efficacy, we investigated nerve conduction study (NCS) results of 34 patients who participated in JET-GBS. Antiganglioside IgG antibodies (GM1, GD1a, GalNAc-GD1a, GQ1b, GM1/GD1a and GM1/GalNAc-GD1a) were measured at entry. NCS were performed at entry, Weeks 4, 13 and 26. Amplitudes of compound muscle action potential (CMAP) were measured in the median, ulnar, peroneal and tibial nerves. Reversible conduction failure (RCF) was defined as increase in CMAP amplitudes at 4W >150% compared with the baseline.

One patient was excluded because discontinued the study before 4 weeks and could not follow the serial study. Of the 33 patients, 22 was given eculizumab and 11 placebo. The mean CMAP amplitudes at each point showed no significant difference between the eculizumab and placebo groups. RCF was present in 26% (35/132) of the nerves tested, and the frequency of RCF was higher in patients with antibodies than in those without antibodies (29% vs 5%, p<0.05). In the antibody-positive group (n=28), RCF occurred more frequently in the eculizumab group than in the placebo group (38% vs 15%, p<0.05). The rate of patients who reached functional grade 2 (able to walk independently) and ONLS arm grade ≤1 at 4 weeks were significantly higher in the patients with RCF than without RCF (91% vs 47% and 73% vs 29%, p<0.05).

Our results showed that in patients with antibodies to the above-mentioned gangliosides eculizumab could inhibit complement activation and thereby antibody-mediated axonal damage which would be underlying mechanisms of eculizumab effects, and therefore resulting in improved outcomes during the sub-acute phase of GBS. How eculizumab might affect patients without antiganglioside antibodies requires further investigation.

References: None.

Keywords: Inflammatory, Clinical Trials

Grant Support: None.
**Poster 148**

**Anti-glycolipid antibodies and clinical features in recurrent Guillain-Barre syndrome.**

Ayumi Uchibori, Atsuro Chiba

*Kyorin University, Tokyo, Japan*

**Purpose:** To reveal the clinical features of recurrent Guillain-Barré syndrome (R-GBS) as well as the profile of their antibodies.

**Method:** We retrospectively analyzed seven patients who were diagnosed with R-GBS among 1539 patients in whom anti-ganglioside antibodies were measured from January 2010 to April 2018. Anti-ganglioside antibodies were measured by ELISA using isolated antigens (GM1, GD1a, GD1b, GT1a, GT1b, GQ1b, asialo-GM1, GM2, GM3, GD3, GD2) and ganglioside complexes (GSCs, combinations of two of GA1, GM1, GD1b, GD1a, GT1a, GT1b and GQ1b), and clinical records of the patients were reviewed.

**Results:** Patients were five males and two females. The age of initial onset was 20-67 years old. Mean age was 35.1. The mean interval from initial onset to recurrence was 9.2 years. All seven patients presented ophthalmoplegia. In the first episode, four patients presented with Fisher syndrome (FS), one presented with GBS with ophthalmoplegia and the others presented with Bickerstaff brainstem encephalitis (BBE). Three of the four patients presenting with FS in the first episode developed BBE in the second or third episode. In all cases, antibodies to GQ1b or GSCs containing GQ1b were detected. In one patient, we analyzed chronological changes of antibodies. The antibody titers decreased in the recovery phase, and raised again in the recurrence. The number of antigens recognized increased recurrence by recurrence.

**Discussion:** It has been reported that R-GBS presents with similar clinical features. In this study, all patients presented disorders with FS-associated ophthalmoplegia, so it was considered that they presented with the same spectrum of disorders associated with anti-GQ1b antibodies. R-GBS tended to become more severe on recurrence. Chronological change of antibody titers and antigen specificities in one patient suggested that the variation of antigen fine specificity could change in each recurrence.

**References:** None.

**Keywords:** Other

**Grant Support:** None.
Prognosis and clinical features of acute motor axonal neuropathy with conduction block

Eun Hee Sohn, Sooyoung Kim, Hui-Jin Chang, Juyoun Lee, Ae Young Lee

Department of Neurology, Chungnam University Hospital, Daejeon, Korea (Republic of)

Introduction: Acute motor axonal neuropathy (AMAN) and AMAN with conduction block (CB) are the two subtypes of pure motor axonal Guillain-Barre syndrome (GBS). The outcome of AMAN with CB is expected to be better than AMAN because of the reversible CB. We conducted this study to compare the prognosis and clinical features of AMAN with CB with other types of GBS.

Methods: The patients who were diagnosed with GBS were enrolled retrospectively. The electrodiagnostic tests were conducted around 1 week, 2 weeks, and 1 month. We classified the patient into AMAN, AMAN with CB, and AIDP based on the serial changes of electrodiagnostic tests. Disabilities were evaluated with Hughes functional grading scale at the nadir, 1 month, and 6 months after onset. Clinical features, such as severe low back and delayed facial palsy, were collected.

Results: The final Hughes score was significantly lower in AMAN with CB compared with AMAN or AIDP. The degree of improvement of Hughes score within the 1st month from the onset was most distinct in AMAN with CB. Severe low back pain and delayed facial palsy were more frequent in AMAN with CB.

Conclusion: AMAN with CB showed relatively good prognosis compared with other subtypes of GBS. CB in AMAN indicated a better prognosis.

References: None.

Keywords: Inflammatory

Grant Support: None.
Difference in seasonality of CIDP research volume on google trends

Emanuele Spina¹, Antonietta Topa², Stefano Tozza¹, Raffaele Palladino¹, Rosa Iodice², Fiore Manganelli², Lucio Santoro¹

¹University of Naples Federico II, Naples, Italy, ²University of Naples "Federico II", Naples, Italy

Often patients with rare diseases acquire information about their health status, disease course, and possible treatments from web search engine e.g. Google or similar. Every search is stored in large databases, available for analysis through tools as Google Trends, which provides annual, monthly, and seasonal trends about specific queries. Analysis of these queries could reveal the moment of greatest incidence of diseases. There is a growing body of evidence demonstrating seasonality for neurological disorders such as Guillan-Barré Syndrome or Multiple Sclerosis. To our knowledge this is the first study assessing seasonality of chronic inflammatory demyelinating polyneuropathy (CIDP).

In this study we analysed google trends for “cidp” “chronic inflammatory neuropathy” and their translation and relative translation. Data were automatically normalized by Google Trends, presented as relative search volumes (0-100), and compared across nations and time period. Data were analysed for nations with at least 10 million of inhabitants and acceptable search volumes, in a time frame from January 2010 to December 2018, employing multilevel Poisson generalized linear model.

Overall world analysis showed us an higher incidence of research in Spring [p>0.00; research volume 8% higher, with March and May with most researches) and Autumn [p>0.00; research volume 15% higher, mostly in October] as compared with lowest search volume in Winter (January). Northern Emisphere showed same results, otherwise in Southern Emisphere only in Autumn vs Winter we found different trends. Further analysis conducted on trends for each single state confirmed previous observation.

We can conclude that the increased research in Spring and Autumn (commonly considered the most stressfull seasons for the immune system) could reflect the higher incidence of infective diseases (e.g. respiratory or gastrointestinal viral infection) that may be implicated in triggering a pathogenic immune response.

References: None.

Keywords: Inflammatory, Other

Grant Support: None.
Predicting IVIg Treatment Response In CIDP – A Substudy Of INCbase

Luuk Wieske

department of Neurology, Amsterdam Neuroscience, Amsterdam UMC, Amsterdam, Netherlands

Introduction

Intravenous immunoglobulin (IVIg) is effective treatment for most but not all patients with CIDP. There is no reliable evidence that can predict if patients will respond to IVIg. In case a patient does respond to IVIg, it is unknown for how long IVIg treatment should be continued. As CIDP can run a monophasic, relapsing-remitting or progressive course, current guidelines propose to periodically taper IVIg to determine disease activity. This may lead to both redundant IVIg withdrawal and deterioration in some patients or unnecessary continuing IVIg in others.

A prediction model developed from large high-quality prospective cohorts can provide reliable individualized data to support decisions on what treatment to start and how long to continue. Within INCbase, a prospective international CIDP registry, one of the key goals is to develop a prediction model of IVIg treatment response based on clinical and diagnostic features and to determine predictors for long-term maintenance treatment.

Methods

From INCbase, newly diagnosed patients fulfilling the EFNS/PNS criteria for CIDP will be selected. Baseline variables for the prediction model will include data on phenotype and diagnostic results. Follow-up will be according the INCbase core module, including disability (iRODS), grip strength and current treatment data. Treatment response will be defined using minimal clinical important difference on I-RODS and/or increase of 8 kPa in grip strength at 6 months. Using baseline variables, a prediction model will be developed and externally validated in an independent cohort. To study predictors for long-term outcome and need for maintenance treatment, the association between baseline variables, initial treatment response and disability and treatment dependency at 2-year follow-up will be analysed. The goal is to include at least 500 patients.

References: The prediction model study is supported by Takeda Pharmaceutical Company and Kedrion Biopharma.

Keywords: Inflammatory

Grant Support: None.
Poster 152

MRI of neuralgic amyotrophy in the subacute phase.

Paolo Ripellino¹, Elisa Ventura¹, Darryl Sneag², Giorgia Melli¹, Alessandro Cianfoni¹, Claudio Gobbi¹

¹Neurocenter of Southern Switzerland, Lugano, Switzerland, ²Hospital for Special Surgery, New York, Switzerland
Background

Neurolgic Amyotrophy (NA) is a potentially disabling disease that can be misdiagnosed in the early stages of onset due to overlapping symptoms with other conditions. There is a need for objective testing to confirm its diagnosis in the subacute phase, since available data are limited to isolated case reports.

Aims

To describe MRI findings of NA in the subacute phase.

Methods

We retrospectively reviewed MRI exams of 14 NA patients that underwent brachial plexus MRI within 8 weeks from disease onset. Images were reviewed independently and blindly by two radiologists. NA was diagnosed by two neuromuscular experts, with support of EMG data and extensive serological screening. Each patient underwent 3T cervical and brachial plexus MRI using multiplanar T1- and T2- weighted fat suppressed, 3D-SPACE STIR, 3D T1-VIBE (after gadolinium administration) sequences.

Results

Mean age was 47 years. Six patients developed NA in the context of acute hepatitis E, two following zoster reactivation, and four were idiopathic. In all cases, cervical MRI excluded abnormality to explain symptoms. In 5 cases cervical root (C6 or C7) on the affected side appeared hyperintense and enlarged in the 3D SPACE STIR with MIP reconstructions, without Gd-enhancement. In 4 cases constrictions of nerves (suprascapular, axillary) were identified. Denervation edema (increased T2-weighted intensity) was observed in the clinically affected muscles in 8 cases, i.e. trapezius, deltoid, supraspinatus, infraspinatus, biceps. In 3 cases these muscles showed also gadolinium- enhancement. In two cases the denervation pattern was patchy, involving only a portion of the muscle (e.g. the anterior part of the deltoid). Bilateral muscle denervation edema was observed only in HEV+ cases.

Conclusion

MRI seems helpful to confirm the clinical suspect of NA, showing muscle denervation edema (sometimes with patchy distribution) and nerve pathology (cervical roots enlargement, nerve constrictions). Bilateral involvement seems peculiar of acute HEV infection.


Keywords: Inflammatory, Other, Axonal Biology

Grant Support: ABREOC 2016 (Ente Ospedaliero Cantonale)
Three Cases of Early Tremor in the Course of Guillain-Barré Syndrome

Susanne Ten Holter¹, Maartje Louter¹, Filip Eftimov², Joke Dijk³

¹Haaglanden Medical Centre, The Hague, Netherlands, ²Amsterdam University Medical Centre, Amsterdam, Netherlands, ³Amsterdam University Medical Centre, Amsterdam, Netherlands

Objective: To report 3 cases of patients developing tremor in the course of Guillain-Barré Syndrome (GBS).

Background: GBS is a monophasic neuropathy causing weakness and/or impaired sensation and sometimes pain. Tremor is known to be a manifestation of chronic inflammatory demyelinating neuropathy (CIDP),¹² but has rarely been reported in GBS.³⁻⁵

Methods: We describe three male patients at the age of 25, 29 and 39 years, who were seen on the movement disorder outpatient clinic of our tertiary referral centre.

Results: The three patients had developed GBS symptoms 12 months, 13 months and 13 years earlier. Two patients had sensory and motor involvement, one patient had a pure motor GBS. In all patients, tremor had developed several days after debut of the GBS symptoms. Two patients were treated with intravenous immunoglobulins. Tremor persisted despite full recovery of strength and sensory impairment. On examination, a postural and intention tremor was observed in the hands in all patients. In two patients, tremor was also present in the feet and tremor was present in the tongue in one patient. Besides high frequency rhythmic movements with small amplitude, irregular jerky movements were seen. Tremor analysis in one patient showed a 8-9 Hz tremor in action. Results of the tremor analysis of the other patients follow and will be described. In all patients the tremor had remained stable over time. In one patient, tremor caused impairment in daily life for which propranolol was tried but not tolerated.

Conclusions: Tremor may develop early in the course of GBS and may persist up to years after recovery of motor and sensory symptoms.


Keywords: Other

Grant Support: None.
Poster 154

Vasculitic neuropathy associated with IgA vasculitis (Henoch-Schönlein purpura) as an unusual manifestation: Clinicopathological analysis

Kazuma Sugie¹, Masatoshi Omoto², Nobuyuki Eura¹, Tomo Shiot¹, Hideaki Nishihara², Takao Kiriyama¹, Hiroshi Kataoka¹, Takashi Kanda²

¹Department of Neurology, Nara Medical University, Kashihara, Japan, ²Department of Neurology, Yamaguchi University, Ube, Japan

Background

IgA vasculitis (IgAV: formerly Henoch-Schönlein purpura) is systemic vasculitis affecting small vessels, characterized by palpable purpura, arthralgia, acute enteritis, and glomerulonephritis. Peripheral nerve system dysfunction rarely occurs in IgAV. Here, to assess the clinicopathological features of the peripheral nervous system in IgAV, we evaluated a group of patients with neuropathy associated with IgAV.

Patients and Methods

Among Japanese 175 patients with peripheral neuropathy who underwent a sural nerve biopsy, we identified three patients who had neuropathy with IgAV. We evaluated the clinical features and the detailed pathological findings of the nerve biopsy specimens.

Results

The three patients who had neuropathy associated with IgAV were 43-, 55-, and 67-year-old women. All patients had mononeuropathy multiplex with severe paresthesia in the distal-dominant lower limbs. SNAPs of the sural nerve were not evoked in any patient. Corticosteroid therapy improved the paresthesia effectively in all patients. Examination of sural nerve specimens consistently revealed obvious axonal changes and marked loss of myelinated fibers. The degree of loss of myelinated fibers differed at each fascicle. Unmyelinated fibers were nearly normal. Immunohistochemical analysis showed the presence of IgA deposits and C3 complement in the perineurium and the vessel wall of the endoneurium in all patients. Our findings suggested that IgA deposits in the perineurium might be associated with nerve-blood barrier involvement.

Conclusion

To our knowledge, this is the first detailed report to document the clinicopathological features of patients with neuropathy associated with IgAV. We suggest that peripheral nerve system dysfunction may rarely be attributed directly to IgAV with involvement of complement.

References: None.

Keywords: Inflammatory

Grant Support: None.
Poster 155

Suspected paraneoplastic Guillain-Barre syndrome with anti-CASPR2 antibodies

Phuongthao Quan, Xiao Weng, Glynnis Zieman, Erik Ortega
Objective:
To present a rare case of Guillain-Barre syndrome (GBS) associated with contactin-associated-protein-like 2 (CASPR2) antibodies in a patient with chronic myeloid leukemia (CML).

Introduction:
GBS is an immune-mediated neurological disease that targets the peripheral nervous system, resulting in acute ascending paralysis and hypo- or areflexia [1]. CASPR2 is a surface membrane protein that plays an essential role in the clustering of the voltage-gated potassium channels in the juxtaparanodal region [2]. To our knowledge, there have only been three reported cases of CASPR2-associated GBS, only one of which was associated with malignancy [3,4].

Case report:
Patient was a 21-year-old male who presented with progressive paresthesia and weakness. He had been diagnosed with CML three months prior. On presentation, he had quadriparesis and areflexia.

MR imaging of his neuroaxis showed equivocal enhancement of the descending nerve roots. Lumbar puncture was not obtained due to thrombocytopenia. EMG showed evidence of demyelination. Ganglioside antibodies were negative, but CASPR2 antibody was positive.

Renal biopsy was performed, prompted by oliguria and global proteinuria, and revealed findings of acute tubular necrosis with early membranous glomerulonephritis. Skin biopsy was suggestive of bullous pemphigoid or paraneoplastic pemphigus.

The patient was initially treated with plasmapheresis without improvement, and was later started on rituximab. He remained bed-bound and ventilator-dependent and was eventually discharged to a nursing facility. He subsequently passed away a few months later, prior to follow-up, from complications of CML.

Conclusion:
To our knowledge, this is a second case of CASPR2-related GBS in a patient with malignancy. The presence of a severe treatment-resistant GBS phenotype along with multisystem failure suggests an underlying paraneoplastic process. Although paraneoplastic processes are more frequently encountered in the elderly population, our case demonstrates the need to consider malignancy workup regardless of age for patients presenting with severe treatment-resistant GBS with other non-neurologic symptoms.

Keywords: Inflammatory

Grant Support: None.
A severe case of neuro-Sjögren's syndrome induced by pembrolizumab

Alex Vicino, Ghosn Jacqueline, Michel Obeid, Thierry Kuntzer

Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland

BACKGROUND:

The prevalence of connective tissue disease (CTD) induced by immune checkpoint inhibitors (CPIs) in the absence of pre-existing autoimmunity is unknown.

CASE PRESENTATION:

We report the case of a melanoma patient treated for 8 months with pembrolizumab, who developed a subacute ataxic sensory neuronopathy (SNN), including a right trigeminal neuropathy. Salivary gland biopsy showed inflammatory changes suggestive of Sjögren's syndrome, while brain MRI revealed enhancement of the right trigeminal ganglia. A high level of protein and pleocytosis was found in the cerebrospinal fluid, with negative cultures. Nerve conduction studies revealed the absence of sensory nerve action potentials in the upper and lower limbs and reduced motor responses in the upper limbs, fulfilling criteria for SNN. Blood tests revealed an important inflammatory syndrome, hemolytic anemia, elevation of total IgG levels and the presence of ANA autoantibodies specific to anti-SSA (52 and 60 kd). All these elements were absent before the initiation of the treatment with pembrolizumab. Initially, there was a clinical response following intravenous frontline methylprednisone, but the subacute relapse required the introduction of second-line treatment with intravenous immunoglobulins and then rituximab, which led to a quick clinical improvement.

CONCLUSIONS:

Herein, we describe the first case of a patient who developed a typical SNN as a complication of severe neuro-Sjögren's syndrome induced by pembrolizumab treatment.

References: None.

Keywords: Inflammatory

Grant Support: None.
Modification of the I-RODS to Assess Outcome of Guillain-Barré Syndrome Using the IGOS Cohort

Melissa Mandarakas¹, Alex Doets¹, Julie Pallant², Pieter van Doorn¹, Ingemar SJ Merkies³, Bart Jacobs⁴, On behalf of the IGOS Consortium⁵

¹Department of Neurology, Erasmus MC University Medical Center, Rotterdam, Netherlands, ²Department of Rural Health, University of Melbourne, Melbourne, Victoria, Australia, ³Department of Neurology, Maastricht University Medical Centre, Maastricht, Netherlands, ⁴Departments of Neurology and Immunology, Erasmus MC University Medical Center, Rotterdam, Netherlands, ⁵Not Applicable, Not applicable, Unknown or unspecified country

INTRODUCTION. I-RODS is a patient-reported outcome measure of disability for GBS, used in interventional and observational studies including the International GBS Outcome Study (IGOS). Previous work by our group found that the cultural applicability of I-RODS for a GBS-specific population was limited, with multidimensionality and mis-fitting items identified. We aimed to validate the I-RODS with IGOS data to improve scoring for international use in GBS.

METHODS. Item, factor and Rasch analysis determined appropriate items to develop a modified outcome measure, IGOS-RODS, using the IGOS-1300 cohort. Discriminative ability was determined by comparing Rasch-derived scores to measures of disease severity: muscle strength [Medical Research Council (MRC) sum-score] and disability level [GBS Disability Score (GBSDDS)].

RESULTS. Data were available from 604 patients at Week 4 follow-up (mean age 52±17.5, 40% female) representing the disability spectrum. Item analysis directed the removal of 4 items (n=3 items >20% 'not applicable' responses, n=1 redundancy). Factor analysis divided items into two domains: Gross Motor Subscale (GM-Subscale) and Self-Care Subscale (SC-Subscale) for Rasch analysis. The GM-Subscale comprised 9 items, with no modifications required to fit the Rasch model. The 11-item SC-Subscale was reduced to 7 items, addressing item misfit and local dependency. Total scores were converted to Rasch-derived scores ranging 0-100 for the GM-Subscale (mean score 44.0±34.5; scores indicate increasing ability level) and the SC-Subscale (mean score=67.0±31.3). IGOS-RODS scores discriminated between patients with mild (GM-Subscale mean score=67.0, SC-Subscale median score=86.5) and severe GBS (GM-Subscale mean score=11.0, SC-Subscale mean score=39.0) (p<0.001). IGOS-RODS scores were correlated with MRC sum-scores (r=0.6 for GM-Subscale, r=0.8 for SC-Subscale, p=0.01).

CONCLUSION. The new IGOS-RODS subscales are useful to analyze international GBS data and may discriminate between disease severity levels. Studies to develop a new outcome measure of disability for international GBS patients, with a focus on cultural applicability, sensitivity and responsiveness are recommended.

References: None.

Keywords: Inflammatory

Grant Support: None.
Poster 158

**Ex vivo modulation of Schwann cell differentiation by neuritogenic T cells**

Alicia Wang, Maher Almahfoud, Bernice Walter, Christoph Kleinschnitz, Fabian Szepanowski, Anne-Kathrin Mausberg, Mark Stettner

*Department of Neurology, University Medicine Essen, University Duisburg-Essen, Essen, Germany, Essen, Germany*

Although the heterogeneous pathogenesis of inflammatory demyelinating neuropathies remains a matter of debate and active research, the contribution of innate and adaptive immune responses has been well defined and the beneficial effects of immunomodulatory therapies in both GBS and CIDP further support the idea of an immune-mediated pathogenesis. Nevertheless, demyelination does not appear to be an exclusive result of direct immune-mediated nerve damage, but the establishment of an inflammatory milieu via the secretion of cytokines from T cells and their effector cells is likely to propagate Schwann cell dedifferentiation. Recent studies suggest that Schwann cell dedifferentiation may indeed play a central role in inflammatory neuropathies, and may therefore significantly contribute to demyelination. However, the molecular and cellular mechanisms underlying the interaction of immune and glial cells under neuroinflammatory conditions are barely understood. Therefore, we aimed to establish an ex vivo model to closely track and better understand these cellular interactions.

Dorsal root ganglia (DRG) explanted from E15 rat embryos served as an ex vivo model of peripheral nervous system myelination. Neuritogenic T cells were isolated from Lewis rats following induction of experimental autoimmune neuritis; T cells from healthy rats served as control. Myelinated DRG cultures were co-incubated with T cells for a period of 4-72 h. Subsequently, the expression of Schwann cell differentiation-related genes was examined using real-time PCR.

Following exposure of DRG cultures to neuritogenic T cells, we observed a time-dependent decrease in the expression of myelin basic protein and the differentiation-related gene Sox10.

These findings suggest that the proposed model may indeed be suitable to gain deeper insight into neuroinflammatory mechanisms propagating demyelination aside from mere cellular damage. Moreover, our results further strengthen the assumption that modulation of Schwann cell differentiation states by immune cells may be a critical step towards demyelination in inflammatory neuropathies.

**References:** None.

**Keywords:** Inflammatory, Schwann Cell

**Grant Support:** None.
Non-inflammatory Demyelinating Polyradiculoneuropathy associated with monospecific anti-GD1b IgM antibody: a case report

Matteo Tagliapietra, Tiziana Cavallaro, Gianluigi Zanusso, Riccardo Orlandi, Sergio Ferrari, Salvatore Monaco

Department of Neurosciences Biomedicine and Movement Sciences; University of Verona, Verona, Italy

BACKGROUND: The clinical picture of autoimmune neuropathies due to disialosyl antibodies depends both on the specific subcellular localization and expression of different gangliosides and on the diverse mechanisms inducing nerve dysfunction. Chronic ataxic neuropathy is a rare presentation that has been described in association with anti-GD1b IgM. We report clinicopathologic features in a patient with anti-GD1b IgM neuropathy.

CASE PRESENTATION: A 55-year-old man presented with sensory ataxia progressing in months to a severe form with dysautonomia and mild distal weakness. Nerve conduction studies revealed diffuse symmetric proximal conduction slowing with conduction blocks. Cerebrospinal fluid examination demonstrated albuminocytological dissociation. Serologic studies identified high titer anti-GD1b IgM (1:5120), and a concurrent diagnosis of B-cell Chronic Lymphocytic Leukemia was established.

Failure to respond to standard immunotherapy with intravenous immunoglobulin, plasma exchange or to rituximab-bendamustine prompted a sural nerve biopsy. The specimen had a normal density of myelinated fibers, with sparse intramyelinic oedema and ultrastructural finding of fissuring of the myelin sheaths. Immunohistological studies documented the absence of complement or immunoglobulin deposits, and excluded lymphoproliferative or inflammatory infiltration. Patient was started on subcutaneous immunoglobulin with clinical response.

CONCLUSION: Anti-GD1b IgM antibodies nerve impairment seems to be related to a non-inflammatory disruption of the myelin sheath, possibly due to antibody-mediated loss of GD1b function in lipid rafts.

References: None.

Keywords: Inflammatory, Other

Grant Support: None.
Impact of lysophosphatidic acid signaling on Schwann cell differentiation in experimental autoimmune neuritis

Fabian Szepanowski, Maximilian Winkelhausen, Leon-Phillip Szepanowski, Christoph Kleinschnitz, Anne Mausberg, Mark Stettner

Department of Neurology, University Medicine Essen, Essen, Germany

Lysophosphatidic acid (LPA) is a pleiotropic lipid messenger that addresses at least six specific G-protein coupled receptors. While LPA receptor signaling has been demonstrated to be critically important for normal embryonic development, in adults LPA has been implicated in a variety of pathophysiological processes. Most notable among these may be its role as an inflammatory mediator and its presumed contribution to neuropathic pain and demyelination. Accumulating evidence points to a significant involvement of LPA in the regulation of immune functions as well as Schwann cell physiology, with potential relevance for the pathophysiology of peripheral neuroinflammation. However, while the clinical efficacy of specific LPA receptor antagonists is currently being investigated in autoimmune diseases such as systemic sclerosis, the role of LPA signaling in inflammatory neuropathies has remained completely undefined.

We have recently demonstrated that LPA is required for Schwann cell dedifferentiation and activation following mechanical nerve injury. Given the broad expression of LPA receptors on both Schwann cells and cells of the innate and adaptive immune system, we hypothesized that inhibition of LPA signaling may ameliorate the course of disease in experimental autoimmune neuritis.

To this end, Lewis rats received an orally available LPA receptor antagonist named AM095, specifically targeting the LPA1 receptor subtype. AM095 was administered via a therapeutic treatment regime, starting with first clinical signs approximately 10 days post-immunization.

Lewis rats treated with AM095 displayed a significant improvement in clinical scores, most notably during the remission phase. Furthermore, immunohistochemical analysis of sciatic nerves revealed a reduction in the number of Schwann cells expressing the dedifferentiation marker Sox2.

These findings suggest that interference with LPA1 signaling might constitute a novel therapeutic target for the treatment of inflammatory neuropathies, potentially affecting regenerative responses in the peripheral nerve by modulating Schwann cell differentiation.

References: None.

Keywords: Schwann Cell, Inflammatory

Grant Support: None.
Poster 161

Rat neuron / human Schwann cell co-cultures to assess demyelinating properties of patient-derived serum factors

Leon-Phillip Szepanowski, Anne Mausberg, Christoph Kleinschnitz, Fabian Szepanowski, Mark Stettner

Department of Neurology, University Medicine Essen, Essen, Germany

In the ever evolving field of inflammatory neuropathies, new tools for elucidating the underlying pathomechanisms of these diseases are urgently required. These tools include cell cultures closely resembling the actual human organism. Unfortunately, human neurons are a scarce resource and induced pluripotent stem cell derived neurons require extensive maintenance. However, recent research indicates that IPSC-sensory neurons of human origin and rat Schwann cells are able to interact and capable of forming a functioning unit. These co-cultures expressed typical markers of proper myelination and no morphological alterations were detectable. Based on these findings, the association of purified rat neurons and primary human Schwann cells might result in an easy-to-use cell culture model to study demyelinating factors derived from neuropathy patients.

Our approach utilizes dorsal root ganglia sensory neurons extracted from E15 Lewis rat embryos, purified by immunopanning and subsequent elimination of remaining glial cells by antimitotic agents. After a week of neurite sprouting, primary Schwann cells of human origin are seeded onto the neurons and allowed a period of alignment, after which myelination is initiated. A variety of Schwann cell-differentiating compounds will be tested for optimized myelination capacity. The resulting myelinated co-cultures are then analyzed for the number of formed internodes and different markers of orderly myelination.

This co-culture model might be especially suitable to gain deeper insight into the molecular and cellular mechanisms of myelin destruction as observed in immune-mediated demyelinating neuropathies. Serum and immune cells extracted from patients suffering from this heterogeneous group diseases could be applied to this culture system in order to detect and further analyze destructive factors and their impact on Schwann cell physiology and myelin integrity.

References: None.

Keywords: Schwann Cell, Inflammatory

Grant Support: None.
Distribution of Natural Killer cells in the peripheral nerve in experimental autoimmune neuritis

Bernice Walter, Anne Mausberg, Christoph Kleinschnitz, Fabian Szepanowski, Mark Stettner

Department of Neurology, University Medicine Essen, Essen, Germany

The Guillain-Barré-Syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) are autoimmune-mediated diseases of the peripheral nervous system, characterized by the infiltration of various subsets of innate and adaptive immune cells, propagating demyelination and/or axonal damage and finally leading to disability. Natural Killer (NK) cells are part of the innate immune system and play an important role in the initial defense against viral pathogens as well as tumor cells. However, NK cells also have important regulatory functions and may be involved in several autoimmune diseases, although their role as positive or negative regulators of autoimmunity has remained controversial and may substantially differ between disease models.

The contribution of NK cells to inflammatory neuropathies is largely unknown. This prompted us to investigate the time course of NK cell infiltration into the peripheral nervous system in experimental autoimmune neuritis.

Sciatic nerve samples are taken from Lewis rats at three different stages of disease: onset of disease with first clinical signs, peak of disease and the remission phase. Antibodies against markers such as CD56, NKG2D and CD335 will be used to identify NK cells via immunohistochemistry. CD3 staining will be performed to distinguish NK cells from T-lymphocytes and NKT cells.

A better understanding of the kinetics and distribution of NK cell infiltration might set the basis for future investigations aiming to decipher potentially beneficial regulatory or detrimental effector functions of NK cells in inflammatory neuropathies.

References: None.

Keywords: Inflammatory

Grant Support: None.
Guillain-Barré Syndrome and Autoimmune Hemolytic Anemia Following an Allogeneic Bone Marrow Transplantation.

Marta Ruiz¹, Andrea Visentin², Francesca Castellani¹, Federica Lessi², Silvia Imbergamo², Marta Campagnolo¹, Alessandro Salvalaggio¹, Chiara Brianì³

¹University of Padova, Department of Neurosciences, Padova, Italy, ²Hematology and Clinical Immunology Unit, Department of Medicine, University of Padova, Padova, Italy, ³University of Padua, Department of Neurosciences, Padova, Italy

Guillain-Barré syndrome (GBS) is the most frequent cause of flaccid paralysis worldwide. Although there is evidence of an immune-mediated pathogenesis, GBS in immunocompromised patients has been described. We report on a patient diagnosed with GBS after allogeneic stem cell transplantation (ASCT) for acute myeloid leukemia (AML). A 69-year-old woman, diagnosed with AML in July 2017. After achieving complete remission with standard chemotherapy (idarubicin and cytosine arabinoside) she underwent ASCT in March 2018 conditioning therapy including treosulfan and fludarabine. Subsequently the patient received immunosuppressive therapy with cyclosporine to prevent graft versus host disease (GVHD). In October 2018 the patient developed a rapid progressive symmetrical ascending motor weakness with distal paresthesias, areflexia. Neurophysiology revealed a diffuse sensory-motor demyelinating polyneuropathy. Cerebrospinal fluid (CSF) analysis showed albumino-cytological dissociation (protein 1.76 g/L, WBC 1/µL). Laboratory test ruled out infectious diseases. CSF immunophenotyping ruled out AML relapse. No clinical or laboratory signs of Graft Versus Host Disease (GVHD) were observed. Concurrently, the patient presented autoimmune hemolytic anemia. She underwent intravenous immunoglobulins (IVIg) (2g/Kg for 5 days) and high dose steroid therapy (prednisolone 1 mg/kg) for the anemia. Two weeks after onset, significant clinical worsening with respiratory involvement occurred, and a second cycle of IVIg (1g/Ke for 2 days) was administered, with progressive improvement. After one month, when the patient was transferred to a neurorehabilitation facility, she was able to stand and walk for a few steps with bilateral support. GBS is a rare complication of ASCT, more commonly as a GVHD-related or post-infectious event. A direct neurotoxic effect of cyclosporine on the peripheral nervous system has never been proven. Allogeneic ASCT could represent a risk factor for GBS and other immune-mediated diseases, suggesting a possible underlying derangement effect on both humoral and cell-mediated immunity, especially in the first year after ASCT.

References: None.

Keywords: Inflammatory

Grant Support: None.
Poster 164

Predictors Of Respiratory Failure In Guillain-Barré Syndrome In Children.

Joyce Roodbol¹, Rudolf Korinthenberg², Esmee Venema³, Hester Lingsma³, Marie-Claire de Wit¹, Bart Jacobs⁴

¹Erasmus MC – Sophia Children’s Hospital, University Medical Center Rotterdam, Rotterdam, Netherlands, ²University Hospital Freiburg, Freiburg, Germany, ³Erasmus MC, University Medical Center Rotterdam, Rotterdam, Netherlands, ⁴Erasmus MC University Medical Center Rotterdam, Rotterdam, Netherlands

Guillain-Barré syndrome (GBS) has a highly variable clinical course and prediction models have been developed to predict the risk of respiratory failure, including the Erasmus GBS Respiratory Insufficiency Score (EGRIS). The clinical course of GBS in children is different from adults and the current prediction models may not apply to children. In this study we determined the predictors of respiratory failure in two independent European cohorts of children with GBS. One cohort from German speaking countries, included 265 children (median age 6 years, IQR 3-10 years), and one cohort from the Netherlands, included 156 children (median age 6 years, IQR 3-13 years). Clinical information regarding preceding infection, presenting symptoms, results of cerebrospinal fluid and nerve conduction studies were collected. Univariable and multivariable regression analysis were performed on the combined cohort as a basis for the EGRIS-kids model.

The combined cohort consisted of 421 children (age 0-17 years), 229 were male (54%). The median duration between the onset of neurological symptoms and hospital admission was 5 days (IQR 3-9, range 62 days). 79 children (19%) required mechanical ventilation at nadir and one patient died. Multivariate regression analysis showed that older age, the presence of cranial nerve involvement, presence of autonomic dysfunction, a higher GBS disability score, a shorter period in days between onset of symptoms and hospital admission and a higher protein level in CSF increased the probability of developing respiratory failure. A model was developed to predict respiratory failure based on information available at admission including age, cranial nerve involvement and GBS disability score. The apparent AUC was 0.74.

In conclusion, EGRIS-Kids provides the opportunity to predict at admission in children with GBS the risk of respiratory failure. Further validation in independent cohorts of children is required to use the model in clinical practice.

References: None.

Keywords: Inflammatory

Grant Support: Prinses Beatrix Spierfonds
Poster 165

Comparison of high-frequency and ultra-high-frequency probes in chronic inflammatory demyelinating polyneuropathy

Angela Puma, Nicolae Grecu, Luisa Villa, Sabrina Sacconi

Université Côte d’Azur, Peripheral Nervous System, Muscle and ALS Department, CHU Nice, France, Nice, France

Objectives: In patients with chronic inflammatory demyelinating polyneuropathy (CIDP) high-resolution ultrasound (HFUS, 18-20 MHz) shows focal enlargement, particularly in the proximal segments of upper arm motor nerves (1-3). Ultra-high frequency ultrasound (UHFUS, 50-70 MHz) has a higher spatial resolution and may aid to better characterize nerve structure (4). The aim of this study was to compare the two ultrasound probes in the evaluation of motor nerve characteristics in CIDP patients.

Methods: Eleven patients with definite or probable CIDP underwent US evaluation of median and ulnar nerves, bilaterally. Nerve and fascicle cross-sectional area (CSA), vascularization, and echogenicity were assessed.

Results: Nerve and fascicle CSA were increased in the proximal segments, especially in the median nerve, in 9/11 patients at the HF evaluation and in 10/11 patients at the UHF one. A statistically significant difference between CSA values obtained with the two probes was found only for fascicle values. UHFUS allowed a more precise estimation of fascicle size and number. We were able to identify nerve vascularization in 4/11 patients examined only with the UHF probe.

Conclusion: The UHF probe gives more detailed information on changes in the internal nerve structure in patients with CIDP. In particular, it allows to better characterize fascicle size and morphology and to have a precise estimation of their number. Its frequency range also allows to evaluate nerve vascularization.

Significance: Ultrasound evaluation could become an adjunctive diagnostic tool for CIDP. Further studies are needed to validate the examined parameters as biomarkers for the evaluation and follow-up of CIDP patients.


Keywords: Inflammatory, Other

Grant Support: None.
Mechanism of Action and Long-term Safety of Hyaluronidase-Facilitated Subcutaneous Immunoglobulin 10% in Primary Immunodeficiency Disease

Leman Yel, Pauline Ellerbroek, Pieter van Paassen, Leif Hanitsch, Alessandro Plebani, Reinhold Schmidt, P.M. van Hagen, Ping Wang, Katharina Fielhauer, Heinz Leibl

1Baxalta US Inc., a Takeda company, Cambridge, MA, USA, 2Department of Internal Medicine and Infectious Diseases, University Medical Centre, Utrecht, Netherlands, 3Academisch Ziekenhuis Maastricht, Maastricht, Netherlands, 4Institut für Medizinische Immunologie Charité Universitätsmedizin Berlin, Berlin, Germany, 5Pediatric Clinics, University of Brescia and ASST Spedali Civili di Brescia, Brescia, Italy, 6Klinik für Immunologie und Rheumatologie, Medizinische Hochschule Hannover, Hannover, Germany, 7Erasmus University Medical Center, Department of Internal Medicine., Rotterdam, Netherlands, 8Baxalta Innovations GmbH, a Takeda company, Vienna, Austria

Purpose: Infusion volume of subcutaneous immunoglobulin (SCIG) is limited by hyaluronan, an extracellular matrix component that causes resistance to bulk-fluid flow. Recombinant human hyaluronidase (rHuPH20)-facilitated subcutaneous immunoglobulin (fSCIG) 10% replacement therapy is a novel therapy that utilizes rHuPH20 to increase subcutaneous tissue permeability to facilitate infusion volumes up to 600 mL. fSCIG can be self-infused at rates, volumes, and frequencies similar to intravenous immunoglobulin (IVIG), with a safety profile similar to SCIG. We will describe the mechanism of action of fSCIG, report long-term safety data on fSCIG, and assess prescribed treatment regimens and administration parameters in patients with primary immunodeficiency disease (PID).

Methods: This ongoing prospective, noninterventional, open-label, uncontrolled, multicenter study includes patients aged ≥18 years with PID who are receiving or were prescribed fSCIG (EUPAS5812).

Results: As of March 15, 2018, of 111 enrolled patients, 101 received ≥1 dose of fSCIG and were included in the safety analysis population; mean (SD) fSCIG exposure duration was 1.72 (0.92) years. The incidence of nonserious adverse events (treatment-related and unrelated, excluding infections) in the safety population (n=101) was 2.45 events per person-year; 426 events were observed in 70 patients. During initial treatment with fSCIG (n=92), the median infusion duration was 3.0 hours (range: 2.0–4.0), the median maximum infusion rate was 240 mL/hour (range: 80–400), and the median number of infusion sites was 1 (range: 1–2). The median IgG dose administered was 77.7 mg/kg body weight/week (range: 2.3–275).

Conclusions: These prospectively collected data of fSCIG in routine clinical practice suggest that fSCIG is tolerated in PID. The infusion characteristics and attributes of fSCIG make it an attractive candidate for study in diseases that require high-dose immunoglobulin, such as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), in which IVIG is the mainstay treatment. A phase 3 trial in CIDP is ongoing (NCT02549170).

References: None.

Keywords: Inflammatory

Grant Support: None.
Poster 167

High-Dose Therapy and Autologous Transplant for POEMS Syndrome: Effective, but how to optimise?
Stephen Keddie, Oliver Tomkins, Shirley D'Sa, Michael Lunn

1MRC Centre for Neuromuscular Diseases, National Hospital for Neurology and Neurosurgery, London, United Kingdom of Great Britain and Northern Ireland, 2UCLH Centre for POEMS, Cancer Division, University College London Hospitals NHS Trust, London, United Kingdom of Great Britain and Northern Ireland, 3UCLH Centre for POEMS, Cancer Division, University College London Hospitals NHS Trust, London, London, United Kingdom of Great Britain and Northern Ireland, 4MRC Centre for Neuromuscular Diseases, National Hospital for Neurology and Neurosurgery, London, United Kingdom of Great Britain and Northern Ireland

Background: High dose melphalan-conditioned autologous stem cell transplantation (ASCT) is an effective therapy in POEMS syndrome. We have demonstrated superior overall and progression free survival from ASCT compared to other modalities of treatment.

Aims: To study the effectiveness of ASCT in POEMS syndrome, factors influencing the natural history and management of relapse.

Methods: We reviewed 42 patients who underwent ASCT from 1998 to 2018. Patient characteristics, previous lines of treatment, harvesting regimens, engraftment data, episodes of engraftment syndrome (ES) and transplant-related morbidity were recorded. Disease status at ASCT was used as the baseline. Response assessment was carried out at 3, 6 and 12 months and a tailored frequency thereafter. Time to maximal VEGF, haematological, radiological, clinical responses and the nature and management of progression events were recorded.

Results: Overall survival (OS) was 92.9% (mean follow up 62.6 months). One-year OS was 95.4% and progression-free survival (PFS) was 81.6%; 5-year OS 89.5% and PFS 76.9%. Three patients died without progression (1 peri-transplant, I unknown cause, 1 MDS). Three patients (16.7%) had ES. Haem CR or VGPR was achieved by 50%. Average VEGF levels improved from 4,959pg/mL to 489.5pg/mL at 6 months and 330pg/mL at 1 year (p<0.001). Significant neurological improvement was seen in all but 2 patients (median pre- to post-transplant Overall Neuropathy Limitation Scale score from 6 to 2 (p<0.01)). Six patients (14.3%) have relapsed to date. No patient who achieved haem CR has relapsed, compared to those with <CR (31.6% relapse rate (p=0.027).

Summary/Conclusion: This analysis confirms that ASCT is an effective treatment for POEMS and attainment of haem CR after ASCT is associated with a lower relapse rate. No patients who achieved clearance of bone marrow plasma cell clones and paraproteinaemia in our cohort have relapsed, compared to almost a third of those with a persistent clonal burden.

References: None.

Keywords: Inflammatory

Grant Support: Dr Keddie is funded by the ABN and Guarantors of Brain
Poster 168

Combined central and peripheral demyelination - new insight into clinical features and potential risk factors.

Łukasz Rzepiński, Sławomir Wawrzyniak

The 10th Military Research Hospital and Polyclinic, Bydgoszcz, Poland

Background: Combined central and peripheral demyelination (CCPD) is a spectrum of demyelinating disorders affecting both central and peripheral nervous system. So far, no separate diagnostic criteria have been created for this disease entity, and the cases described have not been uniform. Among the factors that may predispose to the disease, the most common is the preceding infection.

Purpose: To determine the clinical picture of CCPD and to identify other factors that could increase the risk of the disease.

Methods: Of the 10 patients with co-existence of polyneuropathy and demyelinating lesions in the central nervous system, only those who simultaneously fulfilled the criteria for the diagnosis of both multiple sclerosis (McDonald criteria, 2010) and chronic inflammatory demyelinating polyradiculoneuropathy (EFNS/PNS criteria, 2010) were selected. Conditions for inclusion in the study were met by 2 patients. We analyzed the clinical features, co-morbidities and selected laboratory tests in these patients. Case 1: an 22-year-old woman with ascending paresthesia, progressive quadriparesis, ataxic gait and sphincter dysfunction, evolving after a flu-like syndrome; past medical history of chronic hepatitis C. Case 2: an 47-year-old man with progressive sensory disturbances in lower limbs, binocular vision problems (not simultaneous) and ataxic gait for one year; past medical history of type 1 diabetes with complications including neuropathy, retinopathy and nephropathy.

Results: Neurological examination in both patients revealed flaccid quadriparesis, global areflexia, bilateral Babinski sign, sensory ataxia, reduced superficial, vibration and position sense of affected limbs. No oligoclonal IgG bands were found in the cerebrospinal fluid (CSF).

Conclusions: Simultaneous finding in the neurological examination of the polyneuropathic syndrome, pyramidal signs, in the absence of oligoclonal bands in the CSF, may suggest the diagnosis of CCPD. It is necessary to precisely define diagnostic criteria and search for co-morbidities that may increase the risk of CCPD development.


Keywords: Inflammatory, Diabetes, Other, Other, Other

Grant Support: no
Poster 169

Long-term Observation In A Cohort of IgM Associated Neuropathies.

James Triplet, Elie Naddaf, Maria Torres, Thapa Prabin, Michelle Mauermann

*Mayo Clinic, Rochester, MN, USA*
Introduction:

IgM neuropathies are heterogeneous with variable prognosis and treatment response. Natural history data is needed to develop appropriate outcome measures for clinical trials.

Methods:

We performed a retrospective review of patients with a classical DADS or CIDP variant IgM-associated neuropathy evaluated at our institution from 2004 to 2018.

Results:

104 patients (24 women) were included; median age at presentation was 68 (range 41-89 years). Clinical phenotype was DADS (n=88) or CIDP (n=16). Median time to diagnosis was 30 months (range 1-240). First noted symptom was numbness in 68 patients, pain or burning in 22 and weakness in 9. Onset was asymmetrical in 25 patients.

At presentation, 100 patients reported numbness, 50 pain, 37 weakness, and 23 required assistance walking. The median initial neuropathy impairment scores (NIS) were: NIS-Total 21 points, NIS-Weakness 4 points, NIS-Sensory 8 points. Quantitative sensory testing was abnormal in 29/43, with 27 having large-fiber involvement.

Nerve conduction studies at presentation demonstrated frequent loss or reduction of tibial (76/96) and peroneal (79/100) CMAP. Prolonged distal motor latencies were frequent (ulnar 63/100, median 29/36, tibial 29/73, and peroneal 35/67). Sensory responses were attenuated or absent in 77/97 sural, 52/84 ulnar and 73/88 median nerves. R1 blink latency was prolonged in 28/57 patients.

Abnormalities were seen on autonomic reflex screen in 35/57 and thermoregulatory sweat test in 20/29 patients. 21 nerve biopsies were performed revealing axonal degeneration (n=15), demyelination (n=19), and epineurial perivascular inflammatory collections (n=17).

In 64 patients with follow up (median 56.8 months) the last NIS-Total was 26 points; NIS-Weakness 7.5 points; NIS-Sensory 10 points.

Conclusions:

In our cohort, a length-dependent, demyelinating, sensory-predominant peripheral neuropathy was the most common clinical phenotype of IgM-associated neuropathies followed by a sensorimotor polyradiculoneuropathy. Detailed long-term outcomes, progression rate and treatment response data will be presented at the time of the conference.

References: None.

Keywords: Inflammatory, Other

Grant Support: None.
Guillain-Barré syndrome (GBS), one of the most common acute inflammatory neuropathies, is pathologically characterized by intense immune cells intrusion into endoneurium. Inflammatory cell trafficking across the blood-nerve barrier, a process guided by chemokines, is a pivotal step in the development of inflammatory neuropathies. Among those chemokines, CXCL10 is strongly implicated in the pathogenesis of this disorder. Dipeptidyl peptidase IV (DP4) is a post-proline dipeptidyl aminopeptidase capable of enzymatically modifying chemokines including CXCL10. The DP4 mediated post-translational CXCL10 cleavage adversely alters/reduces inflammatory cell chemotaxis induced by CXCL10 and its receptor CXCR3. The crucial role played by DP4 in regulating cellular trafficking prompted us to investigate the biological relevance of DP4 in the pathogenesis of GBS. We hypothesize that reduced DP4 expression might contribute to risk of developing GBS and severity of disease by increasing inflammatory cell trafficking to endoneurium and restoration of DP4 expression can ameliorate immune mediated nerve injury by limiting CXCL10-induced pathogenic inflammatory cell infiltration. Our preliminary study shows that the serum sDP4 levels and DP4 enzymatic activity are significantly decreased in the acute stage of both axonal and demyelinating GBS patients compared to healthy controls, supporting our hypothesis. Our findings raise the possibility that post-translational modification of chemokines as a treatment strategy, aiming at modulating immune cell trafficking, in inflammatory neuropathies. Further, these results support investigation of the functional role of DP4 in regulating inflammatory cell recruitment in animal models of immune/inflammatory nerve injury.

References: None.

Keywords: Inflammatory

Grant Support: None.
Poster 171

Multifocal motor neuropathy: a rare and complex disease - an university center's experience.

Camila Pupe¹, Caroline Medeiros², Luis Felipe Maia¹, Arthur Monfredinho¹, Ivan Abreu¹, Thiago Rodrigues¹, Vanessa Lessa¹, Viviane Carvalho¹, Osvaldo Nascimento¹

¹Universidade Federal Fluminense, Rio de Janeiro, Brazil, ²universidade Federal Fluminense, Rio de Janeiro, AA, Brazil

To analyze the profile of the patients diagnosed with multifocal motor neuropathy (MMN) in a center specialized in peripheral nervous system diseases.

The MMN is a rare disease, acquired immune-mediated, characterized by asymmetric progressive paresis and atrophy without expressive sensory impairment. The electroneuromyography alterations are needed to fulfill criteria, including those of the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS).

Forty-six medical charts were selected in a data basis, using the key words “CIDP” and “MMN”, from 1984 to 2018. Clinico-epidemiological data and complementary exams were analyzed and projected on a clinical evaluation card.

From the 46 medical charts, 8 fulfilled the ENFS/PNS for MMN. Fifty percent were women. The median of age at the beginning of the symptoms was 46. In 50% of the patients (4), the initial presentations were mono-symptomatic (motor or sensory/ upper or inferior limbs), of which 75% (3) were of motor symptoms on upper limbs and 25% (1), of sensory symptoms on upper limbs. Both motor and sensory symptoms on upper limbs occurred in 25% of the patients and motor on upper and inferior limbs, in the other 25%. The clinical grading score at the time of diagnosis was 1 in 62,5%, 2 in 25% and 3 in 12,5% of the patients. The median of the time between the beginning of the symptoms and the diagnosis was 24 months. The median of the time between the beginning of the symptoms and the diagnosis was too long.

MMN was defined in 62,5%, probable in 12,5% and possible in 25%.

There was no difference between sexes. The sensory symptoms were present in 37,5% of the cases. The median of the time between the beginning of the symptoms and the diagnosis was too long.

References: None.

Keywords: Inflammatory

Grant Support: None.
Chronic inflammatory demyelinating polyneuropathy (CIDP) is a heterogenous chronic neuropathic disorder with various phenotypic variants, suggesting that CIDP is rather a spectrum of conditions. The large clinical heterogeneity and the low prevalence of these different neuropathies are reasons for the very few clinical trials of high scientific standard offering therapeutic recommendations based on highest clinical evidence. This cohort study aims at improving clinical care and basic scientific research by better connecting medical centers with neuroimmunological focus in Germany.

Until February 2019, 93 patients were recruited from 2 specialized neuroimmunological clinics. Obligatory inclusion criteria were a possible diagnosis of an immune-mediated neuropathy. The following optional data are being assessed: sex, age, height and weight, patient history, physical examination including several scores such as INCAT and Hughes scale, electrophysiological studies, CSF analysis, treatment regimens involving the clinical course, response to treatment, laboratory values and results from biopsies. The database is associated with a biobank.

The study included 77% males and 23% females with a median age of 59 years. 76% of patients were diagnosed with CIDP, 11% with MGUS neuropathy, 8% had a possible CIDP and the remaining 5% were diagnosed with either MMN, possible MMN, MADSAM or residual GBS.

Awaiting final approval from the national ethics committee, further centers will be included in the near future and bio sampling will start to address further relevant questions. Larger numbers of patients will provide a detailed insight into the epidemiology of inflammatory neuropathies in Germany.


Keywords: Inflammatory, Schwann Cell

Grant Support: The study is financed by the Kompetenznetzwerk Peripherer Nerv e.V. (KKPNS)
Biomarker Profiling of Neuropathic Pain in Idiopathic Peripheral Neuropathy

Perry Van Doormaal¹, Simone Thomas², Senda Ajroud-Driss³, Mazen Dimachkie⁴, Roy Freeman⁵, David Simpson⁶, Robinson Singleton⁷, Gordon Smith⁸, Ahmet Höke²

¹Johns Hopkins University School of Medicine, Baltimore, MD, USA, ²Johns Hopkins University School of Medicine, Baltimore, USA, ³Northwestern University, Chicago, USA, ⁴Kansas University Medical Center, Kansas City, USA, ⁵Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA, ⁶Icahn School of Medicine at Mount Sinai, New York, USA, ⁷University of Utah, Salt Lake City, USA, ⁸Virginia Commonwealth University, Richmond, USA

Introduction: Neuropathic pain is a common symptom in idiopathic peripheral neuropathy that has a significant effect on quality of life. However, not all patients develop this symptom. The mechanisms responsible for the occurrence or absence of neuropathic pain in these patients have not been unraveled.

Methods: We collected blood samples from the Peripheral Neuropathy Research Registry (PNRR), a prospective multicenter cohort study from six tertiary neuromuscular referral centers in the United States, to construct a biomarker profile containing proteomics, lipidomics and metabolomics data. In total 60 idiopathic peripheral neuropathy patients were included, 30 patients with severe neuropathic pain and 30 patients without any pain symptoms or pain medication. Both groups were matched for age, gender and BMI. Biomarker profiling was performed at Johns Hopkins University School of Medicine, using liquid chromatography mass spectrometry.

Results: After multiple quality controls we included 476 proteomic variables, 618 lipidomic variables and 109 metabolomic variables (1203 variables in total) for analysis.

We will present the results from univariate logistic regression analysis, as well as more in-depth multivariable penalized regression modeling and co-expression analysis of these biomarker profiles in the two patient groups.

Conclusion: Using this extensive biomarker profiling approach, we aim to find new risk factors and pathways leading to neuropathic pain in patients with peripheral neuropathy. This information not only gives us more knowledge on the development of neuropathic pain, but also might provide us with new therapeutic targets to decrease the burden of neuropathic pain.

References: None.

Keywords: Pain, Other

Grant Support: None.
Poster 174

Rate of progression of Utah Early Neuropathy Scale (UENS) score in diabetic neuropathy

J. Robinson Singleton¹, Peter Hauer¹, Cathy Revere¹, Stormy Foster-Palmer¹, Adrienne Aperghis¹, A. Gordon Smith²

¹University of Utah, Salt Lake City, UT, USA, ²Virginia Commonwealth University, Richmond, VA, USA

The Utah Early Neuropathy Scale (UENS) is a brief, validated exam scale focused on injury to small diameter nociceptive fibers. Twenty-four of 42 possible points are related to measurement of length dependent loss of pin sensation in legs and feet. While the UENS has been accepted as a standard clinical measure for diagnosis of small fiber neuropathy, its utility as a primary outcome measure in clinical trials has not been evaluated. Here we report natural history progression of the UENS. In an NIDDK DP3 single center study, 190 patients with diabetes were screened for neuropathy using Toronto criteria, then 83 found to have neuropathy were followed longitudinally at 9 month intervals for up to 27 months using a variety of clinical and ancillary measures, including the UENS. Among those with neuropathy, baseline UENS score significantly correlated with scores of symptom questionnaires including the Norfolk Quality of Life-Diabetes Neuropathy (NQoL-DN) and the NTSS-6; with nerve conduction study measures including sural sensory amplitude, peroneal amplitude and proximal conduction velocity; with intraepidermal nerve fiber density (IENFD) from distal thigh and distal leg 3m punch skin biopsies; but not with confocal corneal microscopy measures of nerve fiber length and density. Overall, 75 participants were followed for 9 months, and 56 for at least 18 months for a total of 149 nine-month segments. UENS worsened (increased) 1.08 (+/- StDev 3.51) points per 9 month segment overall. For those followed at least 18 months, there was a 2.2 (+/-4.1) point increase over this period. Change in UENS significantly correlated with change in NQoL-DN and IENFD, among other measures. The UENS is an objective, responsive, validated clinical instrument for which a linear natural progression slope can be measured, and would be an appropriate primary endpoint in small fiber neuropathy clinical trials.

References: None.

Keywords: Small Fibers, Diabetes, Metabolic

Grant Support: None.
Hereditary transthyretin amyloidosis (hATTR) is a rare protein misfolding disorder that causes progressive and debilitating polyneuropathy. A randomized, placebo-controlled phase 3 trial (NEURO-TTR; NCT01737398) demonstrated efficacy and safety of inotersen in patients with hATTR polyneuropathy.1 Patients who completed NEURO-TTR were eligible to enroll in an ongoing open-label extension (OLE) study (NCT02175004). We report an update on the long-term efficacy and safety of inotersen in patients with hATTR polyneuropathy after 24 months in the OLE. Assessments included modified Neuropathy Impairment Score +7 neurophysiologic tests composite score (mNIS+7), Norfolk Quality of Life–Diabetic Neuropathy questionnaire total score (Norfolk QOL-DN), Short Form 36 Health Survey version 2 (SF-36v2) Physical Component Summary (PCS), and safety monitoring. Of 139 patients who completed NEURO-TTR, 135 (97.1%) enrolled in the OLE. As of 5/31/2018, some patients were ongoing but had not yet completed 24 months in the OLE, and the longest inotersen exposure in both studies was 5.2 years. Patients who switched from placebo to inotersen in the OLE demonstrated slowing of neurologic disease progression by mNIS+7 and Norfolk QOL-DN as early as 6 months after starting inotersen (mean change from OLE baseline to month 6/year 2: 6.22/5.08 in mNIS+7 and 0.54/2.26 in Norfolk QOL-DN). Patients who received inotersen for 39 months (15 months in NEURO-TTR + 24 months in OLE) continued to show benefit (mean change from OLE baseline to year 2: 11.18 in mNIS+7 and 5.22 in Norfolk QOL-DN). Patients who continued inotersen also showed stabilization of health-related quality of life as measured by SF-36v2 PCS. No evidence of increased risk of grade 4 thrombocytopenia or severe renal events has been observed with increased exposure duration; no new safety concerns have been identified. In the OLE, inotersen improved, halted, or slowed progression of hATTR polyneuropathy, with greater stabilization observed in patients who initiated inotersen earlier.


Keywords: Amyloidosis, Clinical Trials, Clinical Trials, Human Genetics

Grant Support: Sponsored by Akcea Therapeutics.
Autoantibodies and Pain: The Role of Leucine-Rich Glioma Inactivated 1 in Primary Sensory Neurons

John Dawes, Gregory Weir, Paddy Waters, Sarosh Irani, David Bennett

University of Oxford, Oxford, United Kingdom of Great Britain and Northern Ireland

A number of patients with autoantibodies directed against the voltage-gated potassium channel complex (VGKCC) have neuropathic pain which can be reduced with immunotherapy (Klein et al., 2012). Autoantibodies are not directed against the Kv1 channels themselves, but instead to proteins with which they interact. Recent work has shown that autoantibodies directed against one of these neuronal targets, CASPR2, are causal to pain, not through inflammation or neuronal damage, but instead by directly impacting on dorsal root ganglion (DRG) neuron excitability via Kv1 channel disruption (Dawes et al., 2018). LGI1 (Leucine-rich glioma inactivated 1) is another component of the VGKCC and also targeted by autoantibodies in neuropathic pain patients. Studies have focused on the role of LGI1 in the CNS; LGI1-autoantibodies (-Abs) are commonly associated with limbic encephalitis and LGI1 is genetically linked to the development of epilepsy. In terms of pain, LGI1-Abs might also target DRG neurons (similar to CASPR2-Abs); however the role of LGI1 in the peripheral nervous system is unclear. Using in situ hybridisation and immunohistochemistry, we find that LGI1 mRNA is highly expressed by a variety of mouse DRG neurons including nociceptors. Serum from LGI1-Ab patients with neuropathic pain show IgG binding to live mouse DRG neurons in vitro. LGI1 is a secreted molecule and studies have shown exogenous application can regulate neuronal excitability (Seagar et al., 2017). We find that LGI1-EGFP targets DRG neurons in vitro and regulates their function. In summary, LGI1 is highly expressed at the level of the DRG and therefore primary sensory neurons represent a plausible site of action for LGI1-Abs in neuropathic pain patients. Furthermore, exogenous application of LGI1 reduces the excitability of DRG neurons, suggesting that this molecule is important in regulating sensory neuron function and this approach represents a possible avenue to reduce their excitability in pathological pain states.


Keywords: Pain

Grant Support: Wellcome trust MRC
Effects of candesartan on mouse models of vincristine- and oxaliplatine-induced neuropathy

Hichem Bouchenaki, Flavien Bessaguet, Laurent Magy, Laurence Richard, Franck Sturtz, Alexis Desmoulière, Aurore Danigo, Claire Demiot

1EA 6309 - Myelin Maintenance & Peripheral Neuropathy, Faculties of Medicine and Pharmacy, University of Limoges, Limoges, France, 2Department of Neurology, Reference Center for Rare Peripheral Neuropathies, University Hospital of Limoges, Limoges, France

Background: Neuropathic pain is the major dose-limiting effect of frequently-used chemotherapeutic agents such as vincristine (VCR) or oxaliplatine (OXP). We recently demonstrated that candesartan, an angiotensin II type 1 receptor antagonist, was neuroprotective against resiniferatoxin-induced sensory neuropathy and that this effect is mediated by stimulation of the angiotensin II type 2 receptor (AT2R). Thus, we chose to evaluate the effect of a preventive treatment by candesartan on mouse models of sensory neuropathy induced by VCR or by OXP.

Methods: VCR (100 µg/kg, intraperitoneally (i.p.)) was administered once per day for 7 days and OXP (15mg/kg, i.p.) was administered in male Swiss mice. Treatments with candesartan (0.5 mg/kg, i.p.) were started at day 1 before administration of the chemotherapeutic agent, then until day 7. Development of VCR/OXP-induced peripheral neuropathy and effect of treatments were evaluated by functional tests.

Results: Mice treated with VCR showed high mechanical allodynia but no modifications of motor performance or mechanical/thermal nociception. Mice treated with OXP showed mechanical allodynia and cold allodynia/hyperalgesia but no modifications of motor performance. While candesartan totally restored tactile sensitivity in VCR mice, it showed no effect on mechanical allodynia in OXP mice. Cold allodynia and cold hyperalgesia were partially prevented by candesartan in OXP mice during the first days following OXP injection.

Conclusion: Candesartan prevents mechanical allodynia induced by VCR but not mechanical allodynia induced by OXP. Moreover, candesartan seems to partially prevent cold allodynia and cold hyperalgesia induced by OXP. Our finding encourages evaluation of candesartan's therapeutic potential in neuropathies induced by chemotherapeutic agents. Further investigations of differential mechanisms of chemotherapy-induced neurotoxicity is required for the discovery of new targets to tackle chemotherapy-induced neuropathic pain.

References: None.

Keywords: Pain, Pre-clinical Studies, Other

Grant Support: Hichem Bouchenaki was financially supported by Pharnext SA.
Presence of red flags in Transthyretin familial amyloid polineuropathy (TTR-FAP) at the moment of diagnosis

Lorenzo Silva Hernández, Alejandro Horga Hernández, Antonio Guerrerro Sola, Rafael García Sáez, Vanesa Pytel, Lucía Galán Dávila

Hospital Clínico San Carlos, Madrid, Spain

Transthyretin familial amyloidosis (hATTR) is a rare, multisystemic and life-threatening disorder that usually affects peripheral nerve system and other organs.

On the other hand, as there is treatment against this disease, prompt diagnosis is a critical cue in the evolution of these patients. High level of suspicion is required, and normally, there is an important delay in its diagnosis due to phenotypic heterogeneity, and cause of that it is so important for all physicians to know the characteristic red flags that accompanied this entity. Nevertheless, it is also considered that these red flags are an uncommon finding and its use is less appropriate for non-endemic regions and late-onset cases.

We present a descriptive study of a series of 30 consecutive patients with TTR-FAP, recorded in our center in the past 10 years and analyzed the presence of classic red flags at the moment of diagnosis. All the patients were diagnosed of symmetric sensitive-motor polyneuropathy and classified according to Coutinho stages. We made a classification of patient based on the presence of Val30Met (60%;18/30) or non-Val30Met (40%;12/30) mutation and early-onset (<50y) 6/30 or late-onset (>50y) 24/30 of disease.

At the moment of diagnosis presence of red flags were: bilateral carpal tunnel syndrome (CTS) (50%;15/30), bilateral and unilateral CTS (56%;17/30), autonomic dysfunction (56%;17/30), gastrointestinal symptoms (46.6%;14/30), unexplained loss of weight (26.6%;8/30), cardiac disease (40%;12/30), renal disease (3.3%;1/30), vitreous opacities (0/30), familial neuropathy (70%;21/30), familial cardiopathy (50%;15/30), gastrointestinal family history (10%; 3/30). 24/30 (80%) patients had 3 or more red flags at diagnosis.

Results shown that red flags are common findings at the moment of diagnosis even in late-onset patients, and their presence in a patient with symmetric polyneuropathy should alert us and conduce the diagnosis throughout TTR-FAP until excluded it cause response to treatment is much better in early stages of disease.


Keywords: Amyloidosis, Small Fibers

Grant Support: None.
Chronic Pain Following Non Freezing Cold Injury is Caused by an Acquired Sensory Neuropathy

Thomas Vale\textsuperscript{1}, Andreas Themistocleous\textsuperscript{1}, Mkael Symmonds\textsuperscript{1}, Michael Polydefkis\textsuperscript{2}, Andrew Rice\textsuperscript{3}, David Bennett\textsuperscript{1}

\textsuperscript{1}University of Oxford, Oxford, United Kingdom of Great Britain and Northern Ireland, \textsuperscript{2}Johns Hopkins University School of Medicine, Baltimore, MD, USA, \textsuperscript{3}Imperial College, London, United Kingdom of Great Britain and Northern Ireland

Non-freezing cold injury (NFCI) develops after prolonged (hours to days) exposure to cold temperatures, sufficient to cause cooling, but not freezing, of soft tissues. This can result in persistent sensory disturbance of the distal extremities and chronic pain. For unknown reasons African and Caribbean individuals are significantly predisposed. We have previously shown that patients with chronic symptoms show evidence of an acquired sensory neuropathy. In a published cohort of 42 cases, through deep phenotyping including thorough clinical assessment, quantitative sensory testing (QST) and skin biopsy, we have shown that small fibres are selectively affected in up to 95% of participants. Significant losses of function were observed on QST for modalities transduced by small fibres, but also for large fibres, but in the absence of any abnormality on nerve conduction studies. Participants had significantly reduced intraepidermal nerve fibre densities compared to the published normative data. These original findings have been replicated as the cohort has increased to 81 cases. Whole genome sequencing of affected patients revealed the presence of a variant, R185H, in SCN9a, which encodes the sodium channel Nav1.7, in 10.9% of African participants, where the background frequency of this variant is just 2.8%. This particular variant has previously been implicated in patients with inherited small fibre neuropathy. Crucially, a group of control participants, matched for age and cold exposure, do not show the same evidence of neuropathy. In addition to measurement of intraepidermal nerve fibre density, analysis of sweat gland and blood vessel innervation has been undertaken. In conclusion, there is clear evidence that patients with chronic symptoms following NFCI have a sensory neuropathy. The mechanism of this injury remains unknown but clear predisposition in African and Caribbean individuals suggests a genetic component. The over-representation of the R185H variant in SCN9A warrants further investigation.

References: Vale, Symmonds, Polydefkis, Byrnes, Rice, Themistocleous, Bennett, Chronic non-freezing cold injury results in neuropathic pain due to a sensory neuropathy, Brain, 140, 2557, 2017

Keywords: Pain, Small Fibers, Human Genetics

Grant Support: UK Ministry of Defence The Wellcome Trust
Neurotrophic Strategy for Subacute Ophthalmic Herpetic Neuralgia at 6 months: Randomized, Single-center, Clinical trial Study

Gang Xu, Chao-Sheng Zhou, Wei-Zhen Tang, Xiu-Li Li

Affiliated Tenth People’s Hospital of Tongji University, Shanghai, China

Varicella zoster virus infection may affect the trigeminal nerve in 10% to 20% of cases, the ophthalmic branch is one of the most common sites of postherpetic neuralgia in the elderly. Patients with subacute ophthalmic herpetic neuralgia (SOHN) who are at least 50 years old are more likely to have severe pain and easily develop postherpetic neuralgia. Neural repairing strategy may be more effective and persistent. A single-center randomized controlled study was conducted to evaluate the long-term efficacy of local methylcobalamin injection in patients with SOHN. One hundred and five patients (>=50 years old, 65.1 ±6.1 years) with a pain score of 4 or greater were randomized to receive a combination of methylcobalamin (1000μg) and lidocaine (20mg) local injection (N=35), intramuscular (N=35) or oral methylcobalamin (N=35), plus subcutaneous 1.0% lidocaine injection for four weeks. Treatment efficacy was assessed on the basis of worst pain severity, global impression of change, and quality-of-life. Multilevel mixed modeling was employed to examine treatment responses. Results showed there was a significant difference in the tendency of pain score among 3 groups (p <0.001). Subjects in received local therapies group had significantly lower pain scores (2.8 ±1.4) and higher quality of life scores of EuroQoL (77.4 ±9.4) than those in received systemic treatment groups at endpoint (p<0.05), thirty-two subjects achieved pain reduction ≥ 30%, 19 perceived worst pain <3, 33 stopped using analgesics at endpoint. Furthermore, pain intensity decreased substantially following treatment and continued to decline until the endpoint of the follow-up period. A small number of subjects complained they remained SOHN-related discomforts; however, these discomforts didn’t aggravate during the 6-month follow-up. This study demonstrated that promoting the damaged nerve repair strategy based on local neurotrophic technique had a long-lasting analgesic effect on the painful region in patients with SOHN.

References: None.

Keywords: Clinical Trials, Pain, Other

Grant Support: This study was funded by the National Natural Science Foundation of China (81771209), Science and Technology Commission of Shanghai Municipality (16401934900), Shanghai Municipal Commission of Health and Family Planning (20134320), and Shanghai Chongming Sustainable Development Science and Technology Innovation Action Plan Project (CKY2018-33). The funders had no role in study design, data collection, data analysis, manuscript preparation, and publication decisions.
Clinical characteristics and nerve conduction study of the patients with carpal tunnel release; 261 cases.

Byung-Nam Yoon¹, Jun-Ku Lee², Ji-Eun Kim³, Sung-Yeon Sohn⁴, Jin-Ah Kim⁵, Ah Won Kim⁶, MinJu Cha⁷, Jung-Joon Sung⁸, Ahn Suk-Won⁷

¹Department of Neurology, Inje University Seoul Paik Hospital, Inje medical School, SEOUL, Korea (Republic of), ²Department of orthopedic surgery, Inje University Seoul Paik Hospital, Inje medical School, SEOUL, Korea (Republic of), ³Department of Neurology, Seoul Medical Center Hospital, SEOUL, Korea (Republic of), ⁴Department of Neurology, Eulji University Medical Center, Daejeon, Korea (Republic of), ⁵Department of Neurology, Seoul National University Hospital, SEOUL, Korea (Republic of), ⁶Department of Neurology, Seoul National University Hospital, Seoul National University College of Medicine, SEOUL, Korea (Republic of), ⁷Choong-Ang University Hospital, Seoul, Korea (Republic of)

Background: Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy. The most effective treatment is known as carpal tunnel release surgery. Several clinical features and examination can play an important role in determining surgery. A most common test used the nerve conduction study (NCS). We reviewed the NCS results of the patients who had undergone carpal tunnel release surgery.

Method: From January 2016 to December 2017, we consecutively enrolled patients who underwent carpal tunnel release surgery. All patients performed the physical examination about carpal tunnel syndrome such as tinel sign, Phalen test, nocturnal paresthesia, and thenar atrophy. Routine hematological investigations and NCS results including neurophysiological grade of CTS 0~VI (Bland 2000) were collected.

Results: Two hundred seventy-one patients with carpal tunnel release surgery were included. 10 patients were excluded because they did not have any improvement of a postoperative symptom. Of 261 patients, 72 (27.5%) had been operated on bilateral sides, 114 (43.6%) right side, and 75 (28.7%) left side. The mean age was 54.32 ± 11.18 years and the female: male ratio was 4.9: 1 (216/45). According to the neurophysiological grade of CTS, CTS grade I was 1.6%, II 8%, III 44.8%, IV 9.6% V 17.6% and VI 7.2%. 11.2% of patients had a CTS grade 0 which did not meet the neurophysiological CTS criteria. 8% of patients had worse CTS grade on the unoperated side. 52.4% of the patients had abnormalities on both sides, but only one side actually received surgery.

Conclusion: The patients who had undergone carpal tunnel release surgery had a tendency to concentrate on neurophysiological CTS grade III. Even if the patient is clinically CTS, the NCS could be normal (CTS grade 0). In our study, the CTS grades on NCS did not match the actual frequency of CTS surgery.

References: None.

Keywords: Other

Grant Support: None.
Responsiveness of Neuropathy Symptom and Change (NSC) Scores With Inotersen for Hereditary Transthyretin Amyloidosis Polyneuropathy

P. James Dyck¹, Teresa Coelho², Marcia Waddington Cruz³, Thomas Brannagan⁴, Sami Khella⁵, Chafic Karam⁶, John Berk⁷, Michael Polydefkis⁸, John Kincaid⁹, Janice Wiesman¹⁰, William Litchy¹, Michelle Mauermann¹, Elizabeth Ackermann¹¹, Brenda Baker¹², Shiangtung Jung¹², Spencer Guthrie¹¹, Michael Pollock¹¹, Peter Dyck¹

¹Mayo Clinic, Rochester, MN, USA, ²Centro Hospitalar do Porto, Porto, Portugal, ³Federal University of Rio de Janeiro, University Hospital, Rio de Janeiro, Brazil, ⁴Columbia University Medical Center, New York, NY, USA, ⁵University of Pennsylvania, Philadelphia, PA, USA, ⁶Oregon Health & Science University, Portland, OR, USA, ⁷Boston University, Boston, MA, USA, ⁸Johns Hopkins University, Baltimore, MD, USA, ⁹Indiana University, Indianapolis, IN, USA, ¹⁰New York University, New York, NY, USA, ¹¹Akcea Therapeutics, Cambridge, MA, USA, ¹²Ionis Pharmaceuticals Inc., Carlsbad, CA, USA

The modified Neuropathy Impairment Score +7 (mNIS+7) was developed from the NIS+7 to better represent neuropathic impairments in transthyretin amyloidosis polyneuropathy. In the 15-month phase 3 trial (NEURO-TTR; NCT01737398), inotersen, an antisense oligonucleotide inhibitor of transthyretin production, demonstrated a significant beneficial effect compared with placebo in the 2 primary outcomes of mNIS+7 and Norfolk Quality of Life—Diabetic Neuropathy questionnaire scores in patients with hereditary transthyretin amyloidosis (hATTR). The NIS is comprised of 3 major components (NIS-weakness, NIS-reflexes, and NIS-sensation loss), and the mNIS+7 is comprised of the NIS, along with 5 attributes of nerve conduction, somatotopic quantitative sensation testing of touch pressure and heat pain, and heart rate response to deep breathing (HRDB). In NEURO-TTR, 5 of the 7 main components of mNIS+7 showed statistically significant benefit by 15 months in patients receiving inotersen versus placebo. HRDB and touch pressure did not reach statistical significance; however, HRDB cannot be assessed in patients with active pacing or atrial fibrillation, which are common in patients with hATTR. In this analysis, we assessed the performance of the components of mNIS+7 by anatomic location (upper and lower limb) as well as the Lower Limb Function (LLF) test. The LLF test assesses 3 functional abilities: a patient’s ability to ambulate on toes, to ambulate on heels, and to arise from a kneeled position. All mNIS+7 components assessed by upper and lower limbs showed a statistically significant benefit in patients receiving inotersen versus placebo except NIS-reflexes (upper limb) and touch pressure (upper and lower limbs). Overall LLF score and each individual LLF test score showed statistically significant benefit by 15 months in patients receiving inotersen compared with placebo. These data support the beneficial effects of inotersen on muscle weakness, muscle stretch reflexes, sensation, attributes of nerve conduction of limb nerves, and lower limb function.

References: None.

Keywords: Amyloidosis, Axonal Biology, Clinical Trials, Human Genetics

Grant Support: Akcea Therapeutics
Introduction: Glial cells in the CNS play an important role in the development and maintenance of chronic pain. Accumulating evidence indicates that following peripheral nerve damage, spinal astrocytes release pro-inflammatory cytokines and chemokines to enhance and prolong persistent pain states. MSCs exhibit potent modulation of neuroinflammation, by inhibiting glial activation, and cytokine/chemokine production in the DRG and spinal cord.

Aim: We aimed to investigate the effect of co-cultured MSCs on astrocyte cells’ GFAP, glutamate transporter-1 (GLT-1) and glutamate-aspartate transporter (GLAST) gene expressions under inflammatory condition.

Methods: Primary mixed glial cultures were prepared from the cerebral cortices of 2-day-old rats and then astrocytes were isolated. MSCs were isolated from rat’s bone marrows and expanded. Astrocytes were co-cultured with MSCs by the inserts and LPS (200 and 400 ng/ml) was applied to culture wells. 48 h after incubation GFAP, GLT-1 and GLAST mRNA gene expressions of astrocytes were analysed by qRT-PCR using Taqman probes.

Results: Increased GFAP expression of LPS treated astrocytes was demonstrated by immunofluorescence staining. There was an increase in GFAP, GLT-1 and GLAST gene expressions in astrocytes depending on the concentration of LPS and a significant decrease in GFAP and GLT-1 gene expressions in astrocytes when co-cultured with MSC.

Conclusion: It was shown that the MSCs or conditioned medium decreased the expressions of inflammatory cytokines such as TNF-α, IL-1β and IL-6 in LPS-treated astrocyte cells. However, this is the first study which investigates the effects of MSCs on GFAP, GLT-1 and GLAST expressions in the astrocytes. In the context of neuropathic pain, astrocytes exhibit increased expression of GFAP in the spinal cord following nerve injury. GLT-1 and GLAST also have important roles in pain conditions. As the current treatment options for neuropathic pain are unsatisfactory, MSCs or secretoms may be considered as a new candidates for the treatment.

References: None.

Keywords: Inflammatory, Pre-clinical Studies, Other

Grant Support: We thank to Erciyes University Scientific Research Funding Commission.
Whole Exome Sequencing Study in Italian Families and Early-Onset Patients affected by Painful Peripheral Neuropathy

Silvia Santoro¹, Andrea Zauli¹, Margherita Marchi², Daniele Cazzato², Kaalindi Misra¹, Erika Salvi², Raffaella Lombardi², Giancarlo Comi³, Massimo Filippi⁴, Federica Esposito⁴, Filippo Martinelli Boneschi ⁵, Giuseppe Lauria⁶

¹San Raffaele Scientific Institute, Laboratory of Human Genetics of Neurological Disorders, INSPE, Milan, Italy, ²Fondazione IRCCS Istituto Neurologico “Carlo Besta”, Neuroalgology Unit, Milan, Italy, ³San Raffaele Scientific Institute, Lab of Human Genetics of Neurological Disorders, INSPE. Dept of Neurology, Milan, Italy, ⁴San Raffaele Scientific Institute, Department of Neurology, Milan, Italy, ⁵San Raffaele Scientific Inst. Univ of Milan, Dept of Biomedical Sciences for Health. Hosp San Donato Dept of Neurology, Milan, Italy, ⁶IRCCS Inst Neurologico “Besta”, Neuroalgology Unit. Univ of Milan, Dept of Biomedical and Clinical Sciences “Sacco”, Milan, Italy

Neuropathic pain is a frequent feature of peripheral neuropathy (PN) causing a significant impact on patients’ quality of life. Painful manifestations could be highly variable and it is not possible to predict high-risk subjects. Recent genetic studies suggested an etiological genetics basis of PN that involves voltage gated sodium channels (VGSCs) genes and open the discussion about the role of other pain-related genes.

We applied a whole exome sequencing (WES) study in Italian families and early-onset patients (EO) affected by PN to identify rare variants to better understand the genetic architecture and modulation of pain in PN.

Eight Italian families (22 patients and 9 controls) and 26 EO cases were recruited. DNA was enriched for coding genes and libraries were sequenced. Sequencing analysis was performed using an in-house bioinformatics pipeline. Variants were filtered according to depth, allele frequency in global-population databases (<5%) and in-house Italian controls cohort (<5%), evolutionary conservation, and computational predictors. Segregation models were applied to families and sharing models in EO patients.

Among the protein-coding genes covered by WES, ~4% of them were found mutated in at least 1 family, 1.65% of them were pain-related genes (hypergeometric test enrichment p value=0.018). ~21% of genes were mutated in at least 1 EO, and 1.54% of genes mutated in at least 2 EO were pain-related genes (hypergeometric test enrichment p value=0.006). Around 2.5% of mutated genes overlapped between families and EO and 5% of them were shared in at least 2 EO and segregating in at least 2 families. We found a different percentage of variants in VGSCs in EO compared to families.

Our data suggests a genetic heterogeneity of painful PN, in which VGSCs along with genes that impair the nervous signal transmission, transduction and maintenance of peripheral nerves structure are involved with disease onset and pain modulation.

References: None.

Keywords: Human Genetics, Pain, Small Fibers, Other

Grant Support: The study was funded by the European Union 7th Framework Programme (PROPANE STUDY grant n°602273)
Poster 185

Bioequivalency/Bioavailability Clinical Trials Of Neuropathic Pain Medications In Healthy Subjects

Zafer Sezer

Erciyes University, School of Medicine, Pharmacology Department, Hakan Çetinsaya GCP Center, Kayseri, Turkey

A bioequivalence study has become a necessity after pharmacological equivalent products have been shown not to provide equivalent therapeutic effects due to differences in pharmacokinetics. In addition to being effective, it reduces the cost of drugs, including drugs used in the treatment of neuropathic pain, and facilitates access to the medications. Bioequivalency/bioavailability (BE/BA) trials are necessary to control the safety and efficacy of generic medicines.

BE/BA trials have been conducting in our clinic, Erciyes University Medical Faculty Hakan Çetinsaya Good Clinical Practice (HC-GCP) Centre, Turkey, since 1999. We have been performed in 1255 clinical trials with healthy subjects until the end of 2018. Drugs used in the treatment of neuropathic pain such as pregabalin, duloxetine, and venlafaxine were also studied in our clinic. They were performed as an open-label, balanced, randomized, single/multiple doses, two/four period, crossover, fasting/fed condition studies. After the physical and laboratory examinations of healthy subjects, test or reference (innovator) study medications administered orally. All the subjects have a standardized meal during the hospitalization. Vital signs measurements and adverse events questioning were performed at certain times during trials. Blood samples were collected in certain time points and plasmas were stored until analysis. So that we compared the bioavailability of the medicines with the area under the plasma concentration-time curve (AUC0-t), maximum concentration (Cmax), and the time at which it occurred relative to the administered dose (Tmax) parameters. Mostly, test geometric mean is acceptable within the 80% to 125% limits for Cmax and AUC0-t. All subjects have physical and laboratory examinations at the end of study for their well-being.

References: None.

Keywords: Clinical Trials, Pain, Other

Grant Support: None.
CHEMOTHERAPY INDUCED PERIPHERAL NEUROTOXICITY: THE SEARCH FOR THE IDEAL OUTCOME MEASURE

PAOLA ALBERTI¹, DAVIDE BERNASCONI¹, CI-PERINOMS GROUP CI-PERINOMS GROUP²

¹UNIVERSITY OF MILANO-BICOCCA, MONZA, Italy, ²CI-PERINOMS GROUP, MONZA, Italy

PURPOSE. Chemotherapy Induced Peripheral Neurotoxicity (CIPN) is a common and long-lasting adverse event of anticancer drugs. No clearly effective treatments exist. This is in part caused by the absence of a gold-standard outcome measure. In the present study we longitudinally monitored a cohort of patients to explore this unmet need.

METHODS. Data from a cohort of 155 subjects were analyzed; they had no neuropathy at study entry. Neurological assessment was formalized with clinical Total Neuropathy Score© (TNSc©) and the "nurse" version(TNSn©). FACT-GOG-Ntx questionnaire (items 29-39 of the whole FACT-GOG scale) was also used. Assessments were performed at base line and at chemotherapy completion.

RESULTS. Female sex was prevalent in the cohort (85%). Taxanes were administered to 50%, platinum-drugs to 28% and a combination of both to 22%. At end of treatment, TNSc© showed a grade I neuropathy in 68% and a grade II in 20%. TNSc© score deterioration was associated with some FACT-GOG-Ntx items: 29 30, 31, 32, 37, 38 (p<0.001). When considering both TNSc© and TNSn© a direct relationship was observed between their scores and FACT-GOG-Ntx median number of pathological items (<0.001 each).

CONCLUSION. Our study supports showed CIPN development in a relevant proportion of patients. As stated by Huang et al. 2007, we also observed the first 4 FACT-GOG-Ntx items (29 [numbness/tingling in hands]), 30 [numbness/tingling in feet], 31[discomfort in hands], 32[discomfort in hands]) detect QoL alterations that match neurological deterioration. We observed the same for 2 more items: 37 (trouble in feeling small objects) and 38 (troubles in walking). Another novelty of our analysis is that the TNSn© scale showed a similar pattern of association to FACT-GOG-Ntx, suggesting this scale should also be implemented. Our findings might guide future trial design and interpretation.


Keywords: Pain, Other

Grant Support: None.
Acute pain is prevalent following burn injury and can transition to chronic pain in over 50% of patients. Prolonged acute pain is an important component that leads to chronic pain and there is little preclinical/clinical research to address this problem. Our research investigates burn injury-related pain and searches for risk factors that influence transitions from acute to chronic pain. We previously reported that mice fed a high-fat diet develop mechanical allodynia, but this dietary intervention did not alter the severity or duration of thermal or mechanical hypersensitivity due to a 2° burn of the hindpaw over 21 days. The further understand whether genetic background or pre-injury stress affects thermal and mechanical hypersensitivity associated with burn. A/J mice were exposed to repeated foot shock stress or sham foot shock for 10 continuous days and then underwent burn injury or sham burn injury of the plantar surface of the hindpaw. Under Avertin anesthesia, (200 µL/10g body weight), the hindpaw of the mouse was placed on a metal block with a controlled surface temperature of 65°C for 15 seconds. A 5-g weighted pouch was placed on the dorsum of the hind paw to maintain pressure between the heel and the heat source. Mechanical and thermal thresholds were assessed at baseline, during the foot shock protocol and at 1, 3, 7, 14, 21, 28, 33, 41, 48, and 55 days post-burn injury. Our results reveal that mice which undergo a burn develop significant ipsilateral thermal hypersensitivity and mechanical allodynia. The mechanical sensitivity data indicates per-stress mice took longer time to recover to its baseline compared to non-stress mice in both burn and non-burn group. Further, thermal sensitivity, weight change, and epidermal mast cells degranulation rate were also analyzed. Results from these studies will be presented and compared to previous findings associated with dietary interventions.

References: None.

Keywords: Pain, Metabolic

Grant Support: R01NS043314 (DEW), COBRE grant P20GM104936, IDeA grant P20GM103418, and Core support from IDDRC grant P30HD002528