Paraneoplastic neuropathies

Jean-Christophe Antoine and Jean-Philippe Camdessanche

Purpose of review
To review recent advances in paraneoplastic neuropathies with emphasis on their definition, different forms and therapeutic development.

Recent findings
A strict definition of definite paraneoplastic neuropathies is necessary to avoid confusion. With carcinoma, seronegative sensory neuronopathies and neuronopathies and anti-Hu and anti-CV2/CRMP5 antibodies are the most frequent. With lymphomas, most neuropathies occur with monoclonal gammopathy including AL amyloidosis, POEMS syndrome, type I cryoglobulinemia and antimyelin-associated glycoprotein (MAG) neuropathies and Waldenström’s disease. Neuropathies improving with tumor treatment are occasional, occur with a variety of cancer and include motor neuron disease, chronic inflammatory demyelinating neuropathy and nerve vasculitis. If antibodies toward intracellular antigens are well characterized, it is not the case for antibodies toward cell membrane proteins. Contactin-associated protein-2 antibodies occur with neuromyotonia and thymoma with the Morvan’s syndrome in addition to Netrin 1 receptor antibodies but may not be responsible for peripheral nerve hyperexcitability. The treatment of AL amyloidosis, POEMS syndrome, anti-MAG neuropathy and cryoglobulinemia is now relatively well established. It is not the case with onconeural antibodies for which the rarity of the disorders and a short therapeutic window are limiting factors for the development of clinical trials.

Summary
A strict definition of paraneoplastic neuropathies helps their identification and is necessary to allow an early diagnosis of the underlying tumor.

Keywords
antibodies, lymphoma, monoclonal gammopathy, neuromyotonia, sensory neuronopathy

INTRODUCTION
Since their definition by Boudin [1] in 1961, paraneoplastic peripheral neuropathies include disorders developing prior or during a cancer due to a remote effect of the tumor independently from neoplastic infiltration, cancer treatment, infectious and metabolic complications, or other well-known causes of neuropathy. Paraneoplastic disorders affect less than 1% of patients with cancer. As cancer and neuropathy are frequent disorders, they may coexist by chance in a substantial number of patients and strict criteria are necessary for their identification.

CLASSIFICATION OF PARANEOPLASTIC NEUROPATHIES
The 2004 recommended criteria of the PNS-Euro-network consortium for paraneoplastic neurological disorders are still valid [2] but need to be adapted for neuropathies. Definite paraneoplastic neuropathies (Table 1) include [1] disorders for which a direct pathogenic link between the tumor and neuropathy is demonstrated, [2] well-established paraneoplastic neurological syndrome but no identified antibodies, which mostly corresponds to seronegative sensory neuronopathies (SNNs) with cancer, and [3] neuropathies unequivocally improved by tumor treatment provided that the neuropathy has no spontaneous tendency to recovery. Any other neuropathy occurring within 2 years of a cancer is a possible paraneoplastic disorder (Table 1).

The identified mechanisms of paraneoplastic disorders mostly involve components of the immune system. With carcinoma, the expression by the tumor of a self-antigen present on the nervous
changes (POEMS) syndrome, the pathogenic factor is not the immunoglobulin (Ig) but probably cytokines produced by the tumor [8,9].

**KEY POINTS**

- As cancer and neuropathies are frequent disorders, paraneoplastic neuropathies need to be strictly defined. Definite paraneoplastic neuropathies include sensory neuropathy and disorders for which a link is demonstrated between the tumor and neuropathy.

- If antibodies toward intracellular antigens are well characterized in paraneoplastic neuropathies, it is not the case for antibodies toward cell membrane proteins and Caspr2 antibodies are probably not responsible for neuro-myotonia.

- The therapeutic window for disorders targeting the neuron cell body is very short.

- Treatment of POEMS syndrome, AL amyloidosis and cryoglobulinemia is relatively well established. Further data are necessary with anti-MAG-neuropathy.

system leads to a breakdown of immune tolerance, production of onconural autoantibodies (Abs) and activation of cytotoxic T-lymphocytes [3]. With thymoma, the mechanism probably involves liberation by the tumor of autoreactive regulatory T cells and tumoral epithelial cells self-antigen expression [4]. Two categories of antigens are now distinguished, namely intracellular and membrane antigens [5,6]. This may have important consequences as Abs toward intracellular antigens probably do not have access to their target and T cells are the main effectors while with cell surface antigens, Abs may reach their target, modulate their expression or damage the cell membrane through complement activation [5,7]. HuD and CV2/Contactin Response Mediator Protein 5 (CRMP5) are the most frequently recognized intracellular antigens with neuropathies, whereas contactin-associated protein-2 (Casp2) is on the axonal membrane. Another difference is that a tumor is almost universal with intracellular antigens and not with cell membrane antigens.

With lymphoma, the tumor itself produces factors that are responsible for the neuropathy. Usually, this factor is a monoclonal component. Monoclonal IgM can behave as Abs reacting with a membrane antigen as myelin-associated glycoprotein (MAG) or gangliosides. These Abs are likely responsible for the neuropathy and more frequently occur with monoclonal gammopathy of unknown significance-MGUS than with Waldenström's disease [7]. In other circumstances, the physicochemical properties of the M component lead to the formation of amyloid deposits (AL amyloidosis) or cryoglobulinemia. Finally, with Polyneuropathy-Organomegaly-Endocrinopathy-M component-Skin system leads to a breakdown of immune tolerance, production of onconural autoantibodies (Abs) and activation of cytotoxic T-lymphocytes [3]. With thymoma, the mechanism probably involves liberation by the tumor of autoreactive regulatory T cells and tumoral epithelial cells self-antigen expression [4]. Two categories of antigens are now distinguished, namely intracellular and membrane antigens [5,6]. This may have important consequences as Abs toward intracellular antigens probably do not have access to their target and T cells are the main effectors while with cell surface antigens, Abs may reach their target, modulate their expression or damage the cell membrane through complement activation [5,7]. HuD and CV2/Contactin Response Mediator Protein 5 (CRMP5) are the most frequently recognized intracellular antigens with neuropathies, whereas contactin-associated protein-2 (Casp2) is on the axonal membrane. Another difference is that a tumor is almost universal with intracellular antigens and not with cell membrane antigens.

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### Table 1. Classification of definite paraneoplastic neuropathies

<table>
<thead>
<tr>
<th>Neuropathy</th>
<th>Cancer</th>
<th>Reported case number</th>
<th>Abs and other biomarkers</th>
<th>Other criteria for definite paraneoplastic</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory neuronopathy</td>
<td>SCLC 80% – HL and other carcinoma</td>
<td>&gt;500</td>
<td>Hu, CV2/CRMP5, other onconeural</td>
<td></td>
<td>One case with Ma2 Abs and NHL</td>
</tr>
<tr>
<td>Lower motor neuron disease</td>
<td>SCLC-HL-carcinoma</td>
<td>&lt;20 cases</td>
<td>Hu with SCLC only</td>
<td>Some improved with tumor treatment</td>
<td>Rare cases Ma2 Abs</td>
</tr>
<tr>
<td>Mixed sensory and motor</td>
<td>SCLC-70%</td>
<td>&gt;200</td>
<td>Hu</td>
<td></td>
<td>According to presentation, may be confused with different forms of axonal sensory motor neuropathy</td>
</tr>
<tr>
<td>Autonomic neuropathy</td>
<td>SCLC 70% – HL and other carcinoma</td>
<td>SCLC&lt;200 – other &lt;10</td>
<td>Hu, (ganglionic AChR)</td>
<td>Some with HL improved with immunotherapy</td>
<td>Frequently associated with SSN and antiHu Abs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sensory-motor neuropathies without gammopathy</th>
<th>Cancer</th>
<th>Reported case number</th>
<th>Abs and other biomarkers</th>
<th>Other criteria for definite paraneoplastic</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axonal</td>
<td>Carcinoma and HL</td>
<td>Rare</td>
<td>Usually none</td>
<td>Some improved with tumor treatment</td>
<td>Rare cases with Yo or Ma2 Abs</td>
</tr>
<tr>
<td>Axonal and demyelinating</td>
<td>SCLC and thymoma</td>
<td>&lt;50 with CV2/CRMP5 AB</td>
<td>CV2/CRMP5</td>
<td></td>
<td>Frequently associated with CNS involvement with CV2/CRMP5 Abs</td>
</tr>
<tr>
<td>Demyelinating (CIDP)</td>
<td>Carcinoma and NHL</td>
<td>&lt;50</td>
<td>Rarely CV2/CRMP5</td>
<td>Some improved with tumor treatment</td>
<td>With NHL, neurolymphomatosis is the differential diagnosis</td>
</tr>
<tr>
<td>Vasculitic neuropathy</td>
<td>SCIC, NHL, and other carcinoma</td>
<td>&lt;50</td>
<td>Rarely Hu</td>
<td>Some improved with tumor treatment</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sensory-motor neuropathies with gammopathy</th>
<th>Cancer</th>
<th>Reported case number</th>
<th>Abs and other biomarkers</th>
<th>Other criteria for definite paraneoplastic</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axonal sensory and painful</td>
<td>AL amyloidosis and myeloma</td>
<td>&gt;500</td>
<td>free light chains</td>
<td></td>
<td>multisystemic organ involvement</td>
</tr>
<tr>
<td>Déméyelinating</td>
<td>Waldenströem</td>
<td>&gt;500</td>
<td>antiMAG IgM k</td>
<td>mostly sensory and distal, tremor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NHL</td>
<td>&lt;10</td>
<td>antiganglioside IgM</td>
<td>CANOMAD or motor neuropathy according to Abs activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Osteosclerotic myeloma and plasmocytoma</td>
<td>&gt;400</td>
<td>IgG I VEGF</td>
<td>multisystemic organ involvement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(POEMS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasculitic neuropathy</td>
<td>type I cryoglobulinemia</td>
<td>&gt;200</td>
<td>Cryoglobulin and low complement level</td>
<td>Mostly sensory and multisystemic organ involvement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>lymphopathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuromyotonia</td>
<td>Thymoma (SCLC and NHL) 30%</td>
<td>&lt;100</td>
<td>Caspr2 and Nettin 1 receptor</td>
<td>Insomnia, delirium with Morvan syndrome. Myasthenia gravis frequent</td>
<td></td>
</tr>
</tbody>
</table>

Abs, antibodies; HL, Hodgkin’s lymphoma; NHL, non-Hodgkin’s lymphoma; POEMS polyneuropathy-organomegaly-endocrinopathy-M component-skin changes; SCIC, small cell lung cancer; VEGF, vascular endothelial growth factor.
Nerve, neuromuscular junction and motor neuron diseases

SSN, the resulting presentation may be confused with mononeuropathy multiplex, polyradiculopathy or Guillain–Barré syndrome. Nerve vasculitis [22] and demyelinating changes [23] rarely occur with anti-Hu Abs.

PNS disorders with anti-CV2/CRMP5 and other onconeural antibodies

Neuropathy occurs in 57% of patients with anti-CV2/CRMP5 Abs frequently with cerebellar ataxia, limbic encephalitis, ocular involvement or Lambert Eaton myasthenic syndrome. SCLC and thymoma are the usual tumors [24]. The neuropathy is mostly sensory or sensory-motor. EDX shows axonal or mixed axonal and demyelinating pattern [25] which may mimic chronic inflammatory demyelinating polyneuropathies (CIDPs) [26] in keeping with the fact that CRMP5 is expressed in Schwann cells and involved in myelination [27]. Neuropathy occurs only occasionally with other onconeural Abs. Anecdotal cases of sensory neuropathy have been reported with anti-Yo Abs [28], mononeuritis multiplex with Ma2 Abs [29] and sensorimotor neuropathy with anti-antiampiphysin Abs [30]. Immunoreactivities against bIV spectrin [31], gangliosides [32] or Inositol 1,4,5-trisphosphate receptor type 1 [33] reported in the setting of cancer and neuropathy needs confirmation.

Motor neuron diseases with onconeural antibodies

Amyotrophic lateral sclerosis is not a paraneoplastic disorder [34] and pure lower motor neuron disease is very rare with onconeural antibodies. It has been reported with anti-Hu Abs [35], including with autopsy confirmation [21] sometimes as a delayed relapse of a first paraneoplastic syndrome [36]. Some patients with anti-Ma2 Abs develop a lower motor neuron disorder of the cervical spinal cord with snake eyes-like changes on MRI [37].

NEUROMYOTONIA AND CONTACTIN-ASSOCIATED PROTEIN-2 ANTIBODIES

Acquired neuromyotonia, peripheral nerve hyperexcitability (PNH) and Isaacs’ syndrome are different designations of a disorder marked by abnormal muscle activities with cramps, stiffness, twitching, spasms and abnormal relaxation [38**]. Weakness, paresthesias and hyperhidrosis can also occur. Sleep disruption, mood changes and hallucinations characterize the Morvan’s syndrome [39]. Diagnosis relies on recording of fibrillation and fasciculation potentials, myokimia organized in doublets, triplets or multiplets, myokimic, neuromyotonic and posteffort or poststimulation discharges [40]. Neuromyotonia occurs with thymoma in 15–20% of cases, rarely with SCLC or lymphoma [39]. Thymoma incidence is higher with Morvan’s syndrome explaining that myasthenia gravis is particularly frequent in this context sometimes years before or after the onset of PNH [41**,42**]. Interestingly, some patients with Morvan’s syndrome develop small fiber neuropathy [43*]. Antivoltage-gated potassium channel antibodies have initially been thought to be responsible for this disorder [44,45], but it is now established that Caspr2, a membrane protein of the juxta-paranodal region, is the actual target of Abs [46]. As Caspr2 Abs also occur with limbic encephalitis, their role in PNH remains unclear. Joubert et al. [41**] reported that detection of Caspr2 Abs in the CSF was associated with limbic encephalitis. PNH occurred in 11% of these cases. In contrast with the Morvan syndrome, Caspr2 Abs were only detected in the serum and thymoma was present in 75% of patients [41**]. Interestingly, CSF Abs in patients with limbic encephalitis were constantly IgG4 and recognized the discoidin and laminin G1 domains of Caspr2, whereas in patients with PHN Abs reacted with different epitopes. As Caspr2 is associated with potassium channels, one may expect that IgG4 antibodies, which have no proinflammatory activity, may interfere with their target functioning [38**] and modify axonal excitability. However, this has not yet been demonstrated. In one experiment, anti-Caspr2 Abs did not have access to the juxta-paranaodal region after intraneural injection [47]. In addition, as most patients with isolated PNH do not have Caspr2 Abs [42**], other yet unknown antibodies are probably responsible for PNH.

Recently, Netrin 1 receptor antibodies have been identified as predictive of thymoma in patients with PNH and myasthenia gravis, frequently in association with Caspr2 Abs [42**]. Interestingly, in this study, Caspr2 and Netrin 1 receptor were expressed by thymoma epithelial cells suggesting that autoreactive T cells may be primed and selected in the tumor similarly to what may occur with CRMP5 [48].

NEUROPATHIES IMPROVING WITH TUMOR TREATMENT

A variety of neuropathies have been reported as paraneoplastic with carcinoma and no onconeural antibodies including motor neuron disease, plexopathy, sensory neuropathy, Guillain–Barré syndrome, CIDP, vasculitic neuropathies and autonomic neuropathies [49]. Most correspond to possible paraneoplastic disorders according to the aforementioned
NEUROPATHIES WITH MALIGNANT MONOCYTONAL GAMMOPATHY

Diagnosis criteria of POEMS syndrome include polyneuropathy and monoclonal plasma cell disorder with monoclonal IgG or IgA (mostly λ isotype) and at least one major criterion (Castleman’s disease, sclerotic bone lesions or vascular endothelial growth factor elevation) and one minor criterion (organomegaly, edema, endocrinopathy, skin changes, papilledema, thrombocytosis or polycythemia) [56]. Clonal plasma cell bone marrow infiltration occurs in majority of cases, but solitary plasmacytoma represents up to 30% of patients [57]. The neuropathy is usually severe, distal, sensorimotor and demyelinating with early axonal loss [58]. In a recent study, patients with POEMS syndrome and Castleman’s disease had less severe neuropathy than with POEMS syndrome alone whereas with Castleman’s disease alone, it was usually mild and sensory [59**]. Neuropathies with nonosteosclerotic myeloma are heterogeneous [60]. Most of them depend on amyloidosis, whereas others are associated with cryoglobulinemia or endoneurial IgG deposits.

AL amyloidosis occurs in 20–40% of patients with multiple myeloma particularly with light chains. Neuropathy reveals amyloidosis in 25% of cases and is characteristically painful or sensory or sensory-motor mainly affecting small fibers [61,62]. Carpal tunnel syndrome, macroglossia, purpura, nephrotic syndrome, congestive heart failure and orthostatic hypotension are typical [63]. About 70% of patients have at least two organ involvements at presentation. Sometimes, the neuropathy mimics CIDP [64]. A rare presentation with lymphoplasmocytic lymphoma is amyloidomas of roots and plexus [65].

Waldenström’s macroglobulinemia occurs with a large spectrum of neuropathy including axonal neuropathy, amyloidosis and vasculitis [66] but in about 50% of cases, the IgM reacts with MAG [67,68]. The neuropathy is similar to that of MGUS, typically chronic, distal and mostly sensory with predominantly distal demyelinating pattern on EDX [69]. Up to 30% of patients with IgM, MGUS evolve to Waldenström’s disease [70]. Other reactivity is fairly rare. Antidisialosyl gangliosides reactivity has been reported with predominantly sensory neuropathy and ophthalmoplegia [71,72] and anti-GM1 reactivity with multifocal motor neuropathy [73,74].

Lymphoproliferative disorders occur in 90% with type I monoclonal cryoglobulinemia [75**] and occasionally with type II mixed cryoglobulinemia [76]. A predominantly distal sensory and axonal neuropathy characterize 24% of cases usually in association with systemic manifestations including purpura, ulcers, Reynaud’s phenomenon, arthralgia and renal manifestations [77]. Nerve biopsy shows necrotizing vasculitis or a perivascular lymphocytic reaction needing to exclude lymphomatous infiltration [55]. Endoneurial deposits of the monoclonal component have also been reported [78].

TREATMENT

Symptomatic treatment must not be neglected [79]. Pain may greatly benefit from tricyclic antidepressants, antiepileptic and sometimes morphinic drugs [80]. With neuromyotonia, carbamazepine, phenytoin, lamotrigine and sodium valproate are used alone or in combination [81].

The therapeutic window for SNN (and probably for paraneoplastic neurological syndromes targeting neuron cell bodies as a whole) does not exceed 2–3 months [82*]. Several studies have tried immunomodulatory or immunosuppressant treatments including high-dose steroids, intravenous IVIgs, plasma exchanges, cyclophosphamide, rituximab, sirolimus or a combination of them [83–88]. Some of these studies suggest slight improvement or stabilization but as a whole, their results are inconclusive and only provide class IV evidences [89]. In a retrospective study of a large number of patients with anti-Hu Abs, an early treatment of the tumor was the only factor significantly associated with stabilization of the neurological disorder [13].

With PNH, tumor treatment may permit disease control [90]. Clinical improvement, autoantibody titer lowering and reduction of electrical activities had been reported after plasma exchanges [45,90]. Despite the absence of large trials, IVIgs, prednisolone, azathioprine and methotrexate have been proposed as well [81]. More recently, Laurencin et al. [43*] highlighted the interest of rituximab in patients with severe Morvan’s syndrome.
As with carcinomas, high level of therapeutic evidences is rare with malignant monoclonal gammopathy and early tumor treatment is certainly the most efficient to improve or stabilize the neuropathy. Patients with POEMS syndrome [57] or IgM monoclonal gammopathy with antibody activities [91**] usually do not or only poorly respond to steroids, IVIg or plasma exchanges. With type I cryoglobulinemia, the treatment targets the underlying malignancy and may include rituximab [75**]. With vasculitis and type II cryoglobulinemia, protocols incorporating anti-CD20 antibodies may be efficient [92]. With anti-MAG IgM, a recent Cochrane review [91**] concluded that rituximab may reduce the level of both the monoclonal component and antibody activity and be beneficial on some outcome measures. With AL amyloidosis [93**], the Mayo Clinic group has advocated high-dose chemotherapy and stem cell transplantation in selected cases [57], whereas a French collaborative study reported the efficacy of conventional doses of melphalan and prednisone [94,95**]. With POEMS syndrome and systemic plasma cell proliferation, a treatment similar to that of amyloidosis is proposed, whereas local radiotherapy is recommended with solitary or dominant plasmocytoma [57,96**]. Thalidomide, lenalidomide and bortezomib are interesting drugs for both amyloidosis and POEMS syndrome, but their PNS neurotoxicity is to be taken into account [93**].

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Conflicts of interest
J.-P. C. declares no conflicts of interest or disclosure associated with this publication.

REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest

Paraneoplastic neuropathies Antoine and Camdessanche


49. This article highlights the different significances of Caspr2 antibodies. When detected in the CSF, they are usually of IgG4 isotype, react with a single epitope of the protein and occur with limbic encephalitis, whereas they are only identified in the serum with Morvan’s syndrome.


53. This article demonstrates that Caspr2 antibodies occur only in patients with Morvan’s syndrome and are usually absent with isolated neuropathies. With NTRK1 antibodies, they predict thymoma in a patient with myasthenia gravis.


55. A report of four well-studied patients with thymoma, Caspr2 antibodies, neuro-myotonia and small fiber neuropathy.


Nerve, neuromuscular junction and motor neuron diseases

92. A useful review of treatments in MAG neuropathies.
98. A review on AL amyloidosis.
100. A review of the Mayo Clinic experience showing that an initial aggressive treatment of POEMS syndrome is associated with long-term good results.