Paraneoplastic neuropathies

Jean-Christophe Antoine and Jean-Philippe Camdessanché

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-Euronetwork 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

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Curr Opin Neurol 2017, 30:000–000
DOI:10.1097/WCO.0000000000000475

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KEY POINTS

- As cancer and neuropathies are frequent disorders, paraneoplastic neuropathies need to be strictly defined. Definite paraneoplastic neuropathies include sensory neuronopathy 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 neuromyotonia.
- 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 onconeural 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 (Caspr2) 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 changes (POEMS) syndrome, the pathogenic factor is not the immunoglobulin (Ig) but probably cytokines produced by the tumor [8,9].

NEUROPATHIES AND INTRACELLULAR ANTIGENS

Subacute sensory neuronopathy and the anti-Hu antibody syndrome

Subacute sensory neuropathy (SSN) is the most frequent paraneoplastic neurological syndrome [10]. It is probably T-cell mediated and targets sensory neurons in dorsal root ganglia [11,12]. The onset is subacute or rapidly progressive but indolent and protracted courses occur [13]. Sensory loss is frequently multifocal or asymmetrical, and as a rule, involved the upper limbs in a nonlength-dependent distribution. The face, chest or trunk may also be concerned [14▪▪]. Although large and small sensory neurons are simultaneously affected, in some cases, predominance of lesions on one type of neurons results in a mostly ataxic or small fiber painful neuropathy [15]. The electrodiagnostic (EDX) hallmark of SNN is a severe and diffuse alteration of sensory nerve action potentials. Motor conduction velocity is classically normal but mildly alterations may lead to inappropriate diagnosis [16,17]. CSF usually shows elevated protein concentration, pleocytosis and oligoclonal bands. In 70–80% of cases, SSN occurs with small cell lung cancer (SCLC). Most patients have anti-Hu Abs. Antiamphyphisin or CV2/CRMP5 Abs may occur with or without anti-Hu Abs and in about 10% of patients, no onconeural antibody is found. These patients usually have another type of tumor including breast cancer or Hodgkin's disease [18]. Diagnosis may be difficult in the first stages of the disease. For this, a simple and sensitive score has been proposed [19,18]. In our personal series, paraneoplatic SSNs represent about 20% of all SNNs so that a diagnostic strategy is necessary to identify them early [20]. Patients with rapid evolution must be investigated for cancer particularly when pain, abnormal CSF and mild motor nerve conduction abnormalities are present.

Other PNS disorders occur with anti-Hu Abs due to the involvement of lower motor or autonomic neurons [13]. In 10% of cases, dysautonomia manifests as orthostatic hypotension, arrhythmia or digestive pseudo-obstruction [13]. In one study, up to 20% of patients have ganglionic acetylcholine receptor Abs, which are not specific of a paraneoplastic origin [21]. Lower motor neurons involvement induces motor deficit, amyotrophy and fasciculations [13]. As patients usually have concomitant

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Table 1. Classification of definite paraneoplastic neuropathies

Neuropathy	Cancer	Reported case number	Abs and other biomarkers	Other criteria for definite paraneoplastic	Comments
Neuronopathies					
Sensory neuronopathy	SCLC 80% – HL and other carcinoma	>500	Hu, CV2/CRMP5, other onconeural		One case with Ma2 Abs and NHL
Lower motor neuron disease	SCLC-HL-carcinoma	<20 cases	Hu with SCLC only	Some improved with tumor treatment	Rare cases Ma2 Abs
Mixed sensory and motor	SCLC-70%	>200	Hu		According to presentation, may be confused with different forms of axonal sensory motor neuropathy
Autonomic neuropathy	SCLC 70% – HL and other carcinoma	SCLC<200 – other <10	Hu, (ganglionic AChR)	Some with HL improved with immunotherapy	Frequently associated with SSN and anti-Hu Abs
Sensory-motor neuropathies without gammopathy					
Axonal	Carcinoma and HL	Rare	Usually none	Some improved with tumor treatment	Rare cases with Yo or Ma2 Abs
Axonal and demyelinating	SCLC and thymoma	<50 with CV2/CRMP5 AB	CV2/CRMP5		Frequently associated with CNS involvement with CV2/CRMP5 Abs
Demyalinating (CIDP)	Carcinoma and NHL	<50	Rarely CV2/CRMP5	Some improved with tumor treatment	With NHL, neurolymphomatosis is the differential diagnosis
vasculitic neuropathy	SCLC, NHL, and other carcinoma	<50	Rarely Hu	Some improved with tumor treatment	
Sensory-motor neuropathies with gammopathy					
Axonal sensory and painful	AL amyloidosis and myeloma	>500	free light chains		multisystemic organ involvement
Démyelinating	Waldenströem	>500	anti-MAG IgM k		mostly sensory and distal, tremor
	NHL	<10	antiganglioside IgM		CANOMAD or motor neuropathy according to Abs activity
	Osteosclerotic myeloma and plasmocytoma (POEMS)	>400	IgG l VEGF		multisystemic organ involvement
Vasculitic neuropathy	type I cryoglobulinemia lymphopathy	>200	Cryoglobulin and low complement level		Mostly sensory and multisystemic organ involvement
Neuromyotonia	Thymoma (SCLC and NHL) 30%	<100	Caspr2 and Netrin 1 receptor		Insomnia, delirium with Morvan syndrome. Myasthenia gravis frequent

Abs, antibodies; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; POEMS polyneuropathy-organomegaly-endocrinopathy-M component-skin changes; SCLC, small cell lung cancer; VEGF, vascular endothelial growth factor.

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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 antiamphiphysin 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 hyperexcitablity (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

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classification. However, rare cases of motor neuron disease [50,51], vasculitis [52] or CIDP [53] which improved with the tumor treatment can be considered as definite paraneoplastic neuropathies.

A similar spectrum of neuropathies has been reported with Hodgkin and non-Hodgkin lymphomas [54]. With non-Hodgkin lymphomas, the main concern is to differentiate them from neoplastic infiltration. In a series of 32 cases, only five could be considered as paraneoplastic (two CIDP, one SNN and one nerve vasculitis), whereas in the others neurolymphomatosis was demonstrated or highly suspected including in cases corresponding to definite CIDP [55].

NEUROPATHIES WITH MALIGNANT MONOCLONAL 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 withllight chains. Neuropathy reveals amyloidosis in 25% of cases and is characteristically painful and 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 ophtalmoplegia [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.

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Table 2. Main orientations for searching a tumor in a patient with neuropathy

When to search for a tumor in a patient with neuropathy?	
With sensory neuronopathy	Particularly if subacute, painful, abnormal CSF and mild abnormal motor conduction
With neuromyotonia	
With onconeural antibody	
With monoclonal gammopathy	The gammopathy may not be detected in the serum with solitary plasmocytoma or cryoglobulinemia
When the central and autonomic nervous system are simultaneously involved	Particularly if subacute evolution
When the CSF is inflammatory	After exclusion of infectious diseases
When the neuropathy has an unusual evolution	Unexpected poor response to treatment, severe and rapid evolution with axonal loss and very unusual presentation

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 plamocytoma [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▪▪,97,98].

CONCLUSION

A strict definition of paraneoplastic neuropathies helps identifying patients for whom an underlying cancer should be suspected (Table 2). With carcinoma, SNN and neuronopathies with onconeural Abs are the most frequent. With lymphomas, most neuropathies occur with monoclonal gammopathy. Neuropathies improving with tumor treatment are occasional and heterogeneous. If antibodies toward intracellular antigens are well characterized, it is not the case for antibodies toward cell membrane proteins and Caspr2 Abs are probably not responsible for neuromyotonia. Despite a lack of control studies, treatment of AL amyloidosis, POEMS syndrome, anti-MAG neuropathy and cryoglobulinemia is 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.

Acknowledgements

None.

Financial support and sponsorship

J.-C. A. receives royalties from patents for the use of CRMP5 as autoantibody test.

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

1. Boudin G. Degenerative peripheral neuropathies and myeloma. Bull Soc méd Hôp Paris 1961–1962; 77:490–500.
2. Graus F, Delattre JY, Antoine JC, *et al.* Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry 2004; 75:1135–1140.
3. Antoine JC. Peripheral neuropathies associated with antibodies directed to intracellular neural antigens. Rev Neurol (Paris) 2014; 170:570–576.
4. Shelly S, Agmon-Levin N, Altman A, Shoenfeld Y. Thymoma and autoimmunity. Cell Mol Immunol 2011; 8:199–202.
5. Didelot A, Honnorat J. Paraneoplastic disorders of the central and peripheral nervous systems. Handb Clin Neurol 2014; 121:1159–1179.
6. Graus F, Titulaer MJ, Balu R, *et al.* A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol 2016; 15:391–404.
7. Kyle RA, Rajkumar SV. Monoclonal gammopathies of undetermined significance: a review. Immunol Rev 2003; 194:112–139.

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8. Gherardi RK, Belec L, Soubrier M, *et al.* Overproduction of proinflammatory cytokines imbalanced by their antagonists in POEMS syndrome. Blood 1996; 87:1458–1465.
9. Watanabe O, Maruyama I, Arimura K, *et al.* Overproduction of vascular endothelial growth factor/vascular permeability factor is causative in Crow-Fukase (POEMS) syndrome. Muscle Nerve 1998; 21:1390–1397.
10. Giometto B, Grisold W, Vitaliani R, *et al.* Paraneoplastic neurologic syndrome in the PNS Euronetwork database: a European study from 20 centers. Arch Neurol 2010; 67:330–335.
11. Graus F, Ribalta T, Campo E, *et al.* Immunohistochemical analysis of the immune reaction in the nervous system in paraneoplastic encephalomyelitis. Neurology 1990; 40:219–222.
12. Dalmau J, Furneaux HM, Rosenblum MK, *et al.* Detection of the anti-Hu antibody in specific regions of the nervous system and tumor from patients with paraneoplastic encephalomyelitis/sensory neuronopathy. Neurology 1991; 41:1757–1764.
13. Graus F, Keime-Guibert F, Rene R, *et al.* Anti-Hu-associated paraneoplastic encephalomyelitis: analysis of 200 patients. Brain 2001; 124:1138–1148.
14. Gwathmey KG. Sensory neuronopathies. Muscle Nerve 2016; 53:8–19.

■■ A recent and exhaustive overview of sensory neuronopathies.

15. Oki Y, Koike H, Iijima M, *et al.* Ataxic vs painful form of paraneoplastic neuropathy. Neurology 2007; 69:564–572.
16. Oh SJ, Gurtekin Y, Dropcho EJ, *et al.* Anti-Hu antibody neuropathy: a clinical, electrophysiological, and pathological study. Clin Neurophysiol 2005; 116:28–34.
17. Camdessanche JP, Antoine JC, Honnorat J, *et al.* Paraneoplastic peripheral neuropathy associated with anti-Hu antibodies. A clinical and electrophysiological study of 20 patients. Brain 2002; 125:166–175.
18. Antoine JC, Robert-Varvat F, Maisonobe T, *et al.* Testing the validity of a set of diagnostic criteria for sensory neuronopathies: a francophone collaborative study J Neurol 2014; 261:2093–2100.
19. Camdessanche JP, Jousserand G, Ferraud K, *et al.* The pattern and diagnostic criteria of sensory neuronopathy: a case-control study. Brain 2009; 132:1723–1733.
20. Camdessanche JP, Jousserand G, Franques J, *et al.* A clinical pattern-based etiological diagnostic strategy for sensory neuronopathies: a French collaborative study. J Peripher Nerv Syst 2012; 17:331–340.
21. Vernino S, Adamski J, Kryzer TJ, *et al.* Neuronal nicotinic ACh receptor antibody in subacute autonomic neuropathy and cancer-related syndromes. Neurology 1998; 50:1806–1813.
22. Younger DS, Dalmau J, Inghirami G, *et al.* Anti-Hu-associated peripheral nerve and muscle microvasculitis. Neurology 1994; 44:181–183.
23. Antoine JC, Mosnier JF, Honnorat J, *et al.* Paraneoplastic demyelinating neuropathy, subacute sensory neuropathy, and anti-Hu antibodies: clinicopathological study of an autopsy case. Muscle Nerve 1998; 21:850–857.
24. Honnorat J, Cartalat-Carel S, Ricard D, *et al.* Onco-neural antibodies and tumour type determine survival and neurological symptoms in paraneoplastic neurological syndromes with Hu or CV2/CRMP5 antibodies. J Neurol Neurosurg Psychiatry 2009; 80:412–416.
25. Antoine JC, Honnorat J, Camdessanche JP, *et al.* Paraneoplastic anti-CV2 antibodies react with peripheral nerve and are associated with a mixed axonal and demyelinating peripheral neuropathy. Ann Neurol 2001; 49:214–221.
26. Samarasekera S, Rajabally YA. Demyelinating neuropathy with anti-CRMP5 antibodies predating diagnosis of breast carcinoma: favorable outcome after cancer therapy. Muscle Nerve 2011; 43:764–766.
27. Camdessanche JP, Ferraud K, Boutahar N, *et al.* The collapsin response mediator protein 5 onconeural protein is expressed in Schwann cells under axonal signals and regulates axon-Schwann cell interactions. J Neuropathol Exp Neurol 2012; 71:298–311.
28. Taieb G, Renard D, Deverdal M, *et al.* Pure monomelic sensory neuronopathy associated with antiyo antibodies. Muscle Nerve 2012; 45: 297–298.
29. Ayrignac X, Castelnovo G, Landrault E, *et al.* Ma2 antibody and multiple mononeuropathies. Rev Neurol (Paris) 2008; 164:608–611.
30. Coppens T, Van den Bergh P, Duprez TJ, *et al.* Paraneoplastic rhombencephalitis and brachial plexopathy in two cases of amphiphysin auto-immunity. Eur Neurol 2006; 55:80–83.
31. Berghs S, Ferracci F, Maksimova E, *et al.* Autoimmunity to beta IV spectrin in paraneoplastic lower motor neuron syndrome. Proc Natl Acad Sci U S A 2001; 98:6945–6950.
32. Weiss MD, Luciano CA, Semino-Mora C, *et al.* Molecular mimicry in chronic inflammatory demyelinating polyneuropathy and melanoma. Neurology 1998; 51:1738–1741.
33. Jarius S, Ringelstein M, Haas J, *et al.* Inositol 1,4,5-trisphosphate receptor type 1 autoantibodies in paraneoplastic and nonparaneoplastic peripheral neuropathy. J Neuroinflammation 2016; 13:278.
34. Corcia P, Gordon PH, Camdessanche JP. Is there a paraneoplastic ALS?

■ Amyotroph Lateral Scler Frontotemporal Degener 2015; 16:252–257. A review of the problematic of cancer and ALS.

35. Forsyth PA, Dalmau J, Graus F, *et al.* Motor neuron syndromes in cancer patients. Ann Neurol 1997; 41:722–730.
36. Ducray F, Graus F, Vigliani MC, *et al.* Delayed onset of a second paraneoplastic neurological syndrome in eight patients. J Neurol Neurosurg Psychiatry 2010; 81:937–939.
37. Waragai M, Chiba A, Uchibori A, *et al.* Anti-Ma2 associated paraneoplastic neurological syndrome presenting as encephalitis and progressive muscular atrophy. J Neurol Neurosurg Psychiatry 2006; 77:111–113.
38. Huijbers MG, Querol LA, Niks EH, *et al.* The expanding field of IgG4-mediated

■■ neurological autoimmune disorders. Eur J Neurol 2015; 22:1151–1161. A unifying view of a group of disorders mediated by IgG4 in which the antibody possibly interacts with the functioning of their target protein without activating complement.

39. Hart IK, Maddison P, Newsom-Davis J, *et al.* Phenotypic variants of autoimmune peripheral nerve hyperexcitability. Brain 2002; 125:1887–1895.
40. Maddison P, Mills KR, Newsom-Davis J. Clinical electrophysiological characterization of the acquired neuromyotonia phenotype of autoimmune peripheral nerve hyperexcitability. Muscle Nerve 2006; 33:801–808.
41. Joubert B, Saint-Martin M, Noraz N, *et al.* Characterization of a subtype of

■■ autoimmune encephalitis with anti-contactin-associated protein-like 2 antibodies in the cerebrospinal fluid, prominent limbic symptoms, and seizures. JAMA Neurol 2016; 73:1115–1124. This article highlights the different significations 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 detected in the serum with Morvan's syndrome.

42. Torres-Vega E, Mancheno N, Cebrian-Silla A, *et al.* Netrin-1 receptor anti-

■■ bodies in thymoma-associated neuromyotonia with myasthenia gravis. Neurology 2017; 88:1235–1242. This article demonstrates that Caspr2 antibodies occur only in patients with Morvan's syndrome and are usually absent with isolated neuromyotonia. With Netrin-1 antibodies, they predict thymoma in a patient with neuromyotonia.

43. Laurencin C, Andre-Obadia N, Camdessanche JP, *et al.* Peripheral small fiber

■ dysfunction and neuropathic pain in patients with Morvan syndrome. Neurology 2015; 85:2076–2078. A report of four well-studied patients with thymoma, Caspr2 antibodies, neuromyotonia and small fiber neuropathy.

44. Newsom-Davis J, Buckley C, Clover L, *et al.* Autoimmune disorders of neuronal potassium channels. Ann N Y Acad Sci 2003; 998:202–210.
45. Shillito P, Molenaar PC, Vincent A, *et al.* Acquired neuromyotonia: evidence for autoantibodies directed against K+ channels of peripheral nerves. Ann Neurol 1995; 38:714–722.
46. Lancaster E, Huijbers MG, Bar V, *et al.* Investigations of caspr2, an autoantigen of encephalitis and neuromyotonia. Ann Neurol 2011; 69:303–311.
47. Manso C, Querol L, Mekaouche M, *et al.* Contactin-1 IgG4 antibodies cause paranode dismantling and conduction defects. Brain 2016; 139:1700–1712.
48. Camdessanche JP, Lassabliere F, Meyronnet D, *et al.* Expression of the onconeural CV2/CRMP5 antigen in thymus and thymoma. J Neuroimmunol 2006; 174:168–173.
49. Graus F, Dalmau J. Paraneoplastic neuropathies. Curr Opin Neurol 2013; 26:489–495.
50. Gordon PH, Rowland LP, Younger DS, *et al.* Lymphoproliferative disorders and motor neuron disease: an update. Neurology 1997; 48:1671–1678.
51. Evans BK, Fagan C, Arnold T, *et al.* Paraneoplastic motor neuron disease and renal cell carcinoma: improvement after nephrectomy. Neurology 1990; 40:960–962.
52. Oh SJ, Slaughter R, Harrell L. Paraneoplastic vasculitic neuropathy: a treatable neuropathy. Muscle Nerve 1991; 14:152–156.
53. Antoine JC, Mosnier JF, Lapras J, *et al.* Chronic inflammatory demyelinating polyneuropathy associated with carcinoma. J Neurol Neurosurg Psychiatry 1996; 60:188–190.
54. Graus F, Arino H, Dalmau J. Paraneoplastic neurological syndromes in Hodgkin and non-Hodgkin lymphomas Blood 2014; 123:3230–3238.
55. Tomita M, Koike H, Kawagashira Y, *et al.* Clinicopathological features of neuropathy associated with lymphoma. Brain 2013; 136:2563–2578.
56. Dispenzieri A. POEMS syndrome: update on diagnosis, risk-stratification, and management. Am J Hematol 2012; 87:804–814.
57. Dispenzieri A. POEMS syndrome: 2011 update on diagnosis, risk-stratification, and management. Am J Hematol 2011; 86:591–601.
58. Cui RT, Huang XS, Liu JX, *et al.* Electrophysiological characteristics of polyneuropathy in POEMS syndrome: comparison with CIDP. J Clin Neurophysiol 2012; 29:345–348.
59. Naddaf E, Dispenzieri A, Mandrekar J, Mauermann ML. Clinical spectrum

■■ of Castleman disease-associated neuropathy. Neurology 2016; 87:2457–2462. A study from the Mayo Clinic group reporting a large series of patients with POEMS syndrome and highlighting differences in the neuropathy pattern according to the presence or absence of Castleman's disease.

60. Vital C, Vallat JM, Deminiere C, *et al.* Peripheral nerve damage during multiple myeloma and Waldenstrom's macroglobulinemia: an ultrastructural and immunopathologic study. Cancer 1982; 50:1491–1497.
61. Kelly JJ Jr, Kyle RA, O'Brien PC, Dyck PJ. The natural history of peripheral neuropathy in primary systemic amyloidosis. Ann Neurol 1979; 6:1–7.
62. Adams D, Lozeron P, Lacroix C. Amyloid neuropathies. Curr Opin Neurol 2012; 25:564–572.

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63. Kyle RA, Bayrd ED. Amyloidosis: review of 236 cases. Medicine (Baltimore) 1975; 54:271–299.

64. Mathis S, Magy L, Diallo L, *et al.* Amyloid neuropathy mimicking chronic inflammatory demyelinating polyneuropathy. Muscle Nerve 2012; 45: 26–31.

65. Ladha SS, Dyck PJ, Spinner RJ, *et al.* Isolated amyloidosis presenting with lumbosacral radiculoplexopathy: description of two cases and pathogenic review. J Peripher Nerv Syst 2006; 11:346–352.

66. Viala K, Stojkovic T, Doncker AV, *et al.* Heterogeneous spectrum of neuropathies in Waldenstrom's macroglobulinemia: a diagnostic strategy to optimize their management. J Peripher Nerv Syst 2012; 17:90–101.

67. Levine T, Pestronk A, Florence J, *et al.* Peripheral neuropathies in Waldenstrom's macroglobulinaemia. J Neurol Neurosurg Psychiatry 2006; 77:224–228.

68. Baldini L, Nobile-Orazio E, Guffanti A, *et al.* Peripheral neuropathy in IgM monoclonal gammopathy and Waldenstrom's macroglobulinemia: a frequent complication in elderly males with low MAG-reactive serum monoclonal component. Am J Hematol 1994; 45:25–31.

69. Attarian S, Azulay JP, Boucraut J, *et al.* Terminal latency index and modified F ratio in distinction of chronic demyelinating neuropathies. Clin Neurophysiol 2001; 112:457–463.

70. Nobile-Orazio E, Francomano E, Daverio R, *et al.* Antimyelin-associated glycoprotein IgM antibody titers in neuropathy associated with macroglobulinemia. Ann Neurol 1989; 26:543–550.

71. Kobayashi M, Kato K, Funakoshi K, *et al.* Neuropathology of paraneoplastic neuropathy with antidisialosyl antibody. Muscle Nerve 2005; 32: 216–222.

72. Willison HJ, O'Leary CP, Veitch J, *et al.* The clinical and laboratory features of chronic sensory ataxic neuropathy with antidisialosyl IgM antibodies. Brain 2001; 124:1968–1977.

73. Vallat JM, De Mascarel HA, Bordessoule D, *et al.* Non-Hodgkin malignant lymphomas and peripheral neuropathies: 13 cases. Brain 1995; 118(Pt 5):1233–1245.

74. Noguchi M, Mori K, Yamazaki S, *et al.* Multifocal motor neuropathy caused by a B-cell lymphoma producing a monoclonal IgM autoantibody against peripheral nerve myelin glycolipids GM1 and GD1b. Br J Haematol 2003; 123:600–605.

75. ■■ Sidana S, Rajkumar SV, Dispenzieri A, *et al.* Clinical presentation and outcomes of patients with type 1 monoclonal cryoglobulinemia. Am J Hematol 2017. doi:10.1002/ajh.24745.

A large series of patients with type I cryoglobulinemia.

76. Choudhry M, Rao N, Juneja R. Successful treatment of cryoglobulinaemia with rituximab. Case Rep Nephrol Urol 2012; 2:72–77.

77. Nemni R, Corbo M, Fazio R, *et al.* Cryoglobulinaemic neuropathy. A clinical, morphological and immunocytochemical study of 8 cases. Brain 1988; 111(Pt 3):541–552.

78. Vallat JM, Desproges-Gotteron R, Leboutet MJ, *et al.* Cryoglobulinemic neuropathy: a pathological study. Ann Neurol 1980; 8:179–185.

79. Antoine JC, Camdessanché JP. Treatment options in paraneoplastic disorders of the peripheral nervous system. Curr Treat Options Neurol 2013; 15:210–223.

80. Attal N, Cruccu G, Baron R, *et al.* EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol 2010; 17:e1113–e1188.

81. Skeie GO, Apostolski S, Evoli A, *et al.* Guidelines for treatment of autoimmune neuromuscular transmission disorders. Eur J Neurol 2010; 17: 893–902.

82. ■ Antoine JC, Robert-Varvat F, Maisonobe T, *et al.* Identifying a therapeutic window in acute and subacute inflammatory sensory neuronopathies J Neurol Sci 2016; 361:187–191.

A study on the cinetic of sensory potential in acute and subacute sensory neuronopathies showing that they stop their fall after two months.

83. Graus F, Vega F, Delattre JY, *et al.* Plasmapheresis and antineoplastic treatment in CNS paraneoplastic syndromes with antineuronal autoantibodies. Neurology 1992; 42:536–540.

84. Uchuya M, Graus F, Vega F, *et al.* Intravenous immunoglobulin treatment in paraneoplastic neurological syndromes with antineuronal autoantibodies. J Neurol Neurosurg Psychiatry 1996; 60:388–392.

85. Oh SJ, Dropcho EJ, Claussen GC. Anti-Hu-associated paraneoplastic sensory neuropathy responding to early aggressive immunotherapy: report of two cases and review of literature. Muscle Nerve 1997; 20:1576–1582.

86. Keime-Guibert F, Graus F, Fleury A, *et al.* Treatment of paraneoplastic neurological syndromes with antineuronal antibodies (anti-Hu, anti-Yo) with a combination of immunoglobulins, cyclophosphamide, and methylprednisolone. J Neurol Neurosurg Psychiatry 2000; 68:479–482.

87. Shams'ili S, de Beukelaar J, Gratama JW, *et al.* An uncontrolled trial of rituximab for antibody associated paraneoplastic neurological syndromes. J Neurol 2006; 253:16–20.

88. de Jongste AH, de Graaf MT, Martinuzzi E, *et al.* Three sensitive assays do not provide evidence for circulating HuD-specific T cells in the blood of patients with paraneoplastic neurological syndromes with anti-Hu antibodies. Neuro Oncol 2012; 14:841–848.

89. Giometto B, Vitaliani R, Lindeck-Pozza E, *et al.* Treatment for paraneoplastic neuropathies. Cochrane Database Syst Rev 2012; 12:CD007625.

90. Newsom-Davis J, Mills KR. Immunological associations of acquired neuromyotonia (Isaacs' syndrome). Report of five cases and literature review. Brain 1993; 116(Pt 2):453–469.

91. ■■ Lunn MP, Nobile-Orazio E. Immunotherapy for IgM antimyelin-associated glycoprotein paraprotein-associated peripheral neuropathies. Cochrane Database Syst Rev 2016; 10:CD002827.

A usefull review of treatments in MAG neuropathies.

92. De Vita S, Quartuccio L, Isola M, *et al.* A randomized controlled trial of rituximab for the treatment of severe cryoglobulinemic vasculitis. Arthritis Rheum 2012; 64:843–853.

93. ■■ Dispenzieri A, Buadi F, Kumar SK, *et al.* Treatment of immunoglobulin light chain amyloidosis: Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus statement. Mayo Clin Proc 2015; 90:1054–1081.

An update of the treatment of AL amyloidosis.

94. Gertz MA, Lacy MQ, Dispenzieri A, *et al.* Stem cell transplantation for the management of primary systemic amyloidosis. Am J Med 2002; 113:549–555.

95. ■■ Gertz MA. Immunoglobulin light chain amyloidosis: 2016 update on diagnosis, prognosis, and treatment. Am J Hematol 2016; 91:947–956.

A review on AL amyloidosis.

96. ■■ Kourelis TV, Buadi FK, Kumar SK, *et al.* Long-term outcome of patients with POEMS syndrome: an update of the Mayo Clinic experience. Am J Hematol 2016; 91:585–589.

A review of the Mayo Clinic experience showing that an initial aggressive treatment of POEMS syndrome is associated with long-term good results.

97. Misawa S, Sato Y, Katayama K, *et al.* Safety and efficacy of thalidomide in patients with POEMS syndrome: a multicentre, randomised, double-blind, placebo-controlled trial. Lancet Neurol 2016; 15:1129–1137.

98. Sidana S, Narkhede M, Elson P, *et al.* Neuropathy and efficacy of once weekly subcutaneous bortezomib in multiple myeloma and light chain (AL) amyloidosis. PLoS One 2017; 12:e0172996.

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