BRITISH JOURNAL OF HOSPITAL MEDICINE

REVIEW

Autoantibodies in the diagnostic work-up of neuropathy: clinically useful or purely academic?

Nitin Sahi[1]

Majid Ghasemi[1]

Yusuf A Rajabally[1,2]

Author details can be found at the end of this article

Correspondence to:
Yusuf A Rajabally;
y.rajabally@aston.ac.uk

Abstract

The search for autoantibodies in patients with acute and chronic neuropathies has become widespread in neurological practice. These tests are more routinely available and therefore are more commonly requested in larger hospitals with neuroscience centres, although they are now also regularly requested from district general hospital settings, including by non-neurologists. However, the clinical value of these frequently expensive tests is often unclear and their impact on management not always obviously beneficial. This article reviews the main immunological tests used to search for specific autoantibodies in the setting of neuropathy and discusses their potential diagnostic importance, together with the eventual therapeutic implications of results obtained.

Key words: Autoantibodies; Dysimmune; Inflammatory; Neuropathy

Submitted: 3 March 2020; accepted after double-blind peer review: 21 April 2020

Introduction

Dysimmune forms of neuropathy are important to recognise as they are treatable. The first step in the evaluation of an individual with neuropathy is to find the pattern of involvement, based on clinical and electrophysiological findings, including sensory or motor, small fibre or large fibre involvement, symmetric or asymmetric, proximal or distal predominant, and axonal or demyelinating. The next step is to evaluate for causes based on the pattern of neuropathy. After routine evaluation, a search for autoantibodies has become increasingly common. This article discusses their clinical value for management.

Monoclonal gammopathy and neuropathy

Monoclonal gammopathy is characterised by the production of excessive homogenous immunoglobulin or paraprotein as a result of abnormal monoclonal proliferation of plasma cells. This may be pre-malignant, such as monoclonal gammopathy of undetermined significance, or associated with underlying malignancy, as in multiple myeloma and Waldenström's macroglobulinaemia.

The association of neuropathy and monoclonal gammopathy is common. Around 10% of patients with neuropathy of unknown cause have a monoclonal protein. Monoclonal gammopathy of undetermined significance occurs in up to 1% of normal subjects over the age of 50 years, up to 1.7% above the age of 70 years and 6% above 90 years. Including all immunoglobulin subclasses, the incidence of polyneuropathy among patients with immunoglobulin M (IgM) monoclonal gammopathy can be as high as 50%, suggesting that 50% of patients with IgM monoclonal gammopathy of undetermined significance may have or develop peripheral neuropathy (Dalakas, 2018).

Malignant monoclonal gammopathy is differentiated from monoclonal gammopathy of undetermined significance by the level of plasma cell proliferation and presence of osteolytic bone lesions, lymphadenopathy or organomegaly. In patients identified with Waldenström's macroglobulinaemia and multiple myeloma the priority is systemic treatment of the underlying haematological malignancy.

Monoclonal gammopathy of undetermined significance can be further categorised dependent on the monoclonal protein secreted, risk and pattern of progression into three groups:

1. IgM monoclonal gammopathy of undetermined significance

How to cite this article:
Sahi N, Ghasemi M, Rajabally YA. Autoantibodies in the diagnostic work-up of neuropathy: clinically useful or purely academic? Br J Hosp Med. 2020. https://doi.org/10.12968/hmed.2020.0085

2. Non-IgM monoclonal gammopathy of undetermined significance (consisting of IgG monoclonal gammopathy of undetermined significance and IgA monoclonal gammopathy of undetermined significance)
3. Light-chain monoclonal gammopathy of undetermined significance.

Monitoring is required because there is a risk of malignant transformation of up to 1% each year (Go and Rajkumar, 2018). In suspected cases, serum immunofixation is recommended to identify a monoclonal protein, as this is more sensitive than serum protein electrophoresis; the latter misses 17% of all monoclonal proteins and 30% of all IgM monoclonal gammopathies identified with immunofixation (Kahn and Bina, 1988). The next step after identifying monoclonal protein is to determine whether the monoclonal gammopathy may be the cause of neuropathy or whether it is a coincidental finding. The likelihood of a causal relationship is far higher with IgM than with other monoclonal proteins. Anti-myelin associated glycoprotein (MAG) antibodies are detected in approximately 50% of patients with IgM monoclonal protein related neuropathy. Anti-MAG has been reported almost invariably in the context of IgM monoclonal gammopathy, but almost 6% of patients with a chronic inflammatory demyelinating polyneuropathy phenotype are positive for this antibody without having detectable monoclonal gammopathy (Pascual-Goñi et al, 2019).

The relationship between other, non-IgM monoclonal gammopathies is unproven. For that reason, forms of chronic inflammatory demyelinating polyneuropathy associated with such monoclonal proteins are treated as any chronic inflammatory demyelinating polyneuropathy. Similarly, the management of axonal length-dependent neuropathies associated with such monoclonal proteins does not differ from that of chronic idiopathic axonal polyneuropathy.

Polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes (POEMS) syndrome and amyloid light-chain amyloidosis (seen very rarely) are specific situations where the overall approach and management is different. POEMS syndrome is a rare paraneoplastic disorder. The predominant features are polyneuropathy with underlying clonal plasma cell disorder, usually with IgG/IgA monoclonal protein and almost exclusively lambda light chains. The neuropathy in POEMS often precedes the bone lesions, which are osteosclerotic, in contrast to the osteolytic lesions in multiple myeloma. It is often mistaken for chronic inflammatory demyelinating polyneuropathy, but typically presents with severe neuropathic pain, early axonal loss and resulting distal atrophy. Elevated serum vascular endothelial growth factor (VEGF) levels have become a very useful diagnostic tool. The treatment of POEMS includes local radiotherapy, chemotherapy and autologous stem cell transplantation (Dispenzieri, 2019).

Vasculitic neuropathy

Vasculitic neuropathies are an important and prevalent group of dysimmune neuropathies, divided in two major groups – systemic and non-systemic – based on the involvement of other organs besides the peripheral nerves. Antineutrophil cytoplasmic antibody (ANCA) has an established association with vasculitic neuropathy (Bischof et al, 2019). A review reported >95% specificity of ANCAs for systemic vasculitic neuropathy (Collins et al, 2019). The presence of ANCA is accepted as an exclusionary criterion for non-systemic vasculitic neuropathy (Hadden et al, 2017), with management implications.

Sjögren's syndrome

Neurological symptoms are often the first manifestation of Sjögren's syndrome and can precede sicca symptoms (dry eyes and dry mouth). Neuropathy is associated with 5–15% of cases of Sjögren's syndrome, although the reported prevalence ranges vary greatly (Berkowitz and Samuels, 2014). Neurological symptoms are predominantly sensory; most frequently sensory ataxic ganglionopathy, painful small fibre neuropathy and length dependent axonal neuropathy. Sensorimotor polyneuropathy, autonomic neuropathy, cranial neuropathies and multiple mononeuropathies are less common.

Neuropathy is often the reason to perform serological testing for antibodies to extractable nuclear antigens anti-Ro/SSA and anti-La/SSB. These are hallmark antibodies,

found in 60–70% of people with Sjögren's syndrome and included in classification criteria. While both antibodies can be found concomitantly, anti-La/SSB is rarely found in isolation. Seropositivity may identify more 'active' patients associated with earlier disease onset, glandular dysfunction and extraglandular manifestations, although this is not useful as a biomarker in treatment response to B cell depletion (Hernández-Molina et al, 2011). Seropositivity for anti-Ro/SSA and/or anti-La/SSB is 10–55% in people with Sjögren's syndrome with neuropathy and lower in those with small-fibre or non-ataxic subtypes. Lip minor salivary gland biopsy and other objective tests for Sjögren's syndrome should be considered in patients with seronegative neuropathy of unclear aetiology.

Paraneoplastic syndromes and anti-neuronal antibodies

Paraneoplastic neuropathies are disorders of peripheral nerves occurring before or after diagnosis of cancer as a result of a remote effect of malignancy independently from neoplastic infiltration.

Paraneoplastic neuropathy typically occurs before diagnosis or at early stages of malignancy. Therefore, early recognition and treatment of a paraneoplastic disorder is likely to prevent progression or even regress the neuropathy, in addition to improving the prognosis of cancer.

In order to differentiate paraneoplastic neuropathy some clinical features may help, including subacute onset and rapidly progressive course, early upper limb involvement, coexistent CNS involvement, presence of risk factors for cancer, and constitutional symptoms. Several patterns of peripheral nerve involvement are recognised in paraneoplastic disorders, including neuronopathy (sensory or motor), axonal neuropathy (sensory and motor, autonomic), demyelinating neuropathy, vasculitic neuropathy and neuromyotonia (Antoine and Camdessanche, 2017).

Two types of antigens are identified: intracellular and membrane antigens. In general, antibodies towards intracellular antigens are not pathogenic. The most important recognised paraneoplastic antibodies related to neuropathy include anti Hu (also known as ANNA-1; anti-neuron specific cell nuclear antibodies), anti CV2/CRMP5, anti Caspr2 (contactin-associated protein-like 2), and anti-MAG IgM. In suspected paraneoplastic neuropathy, seropositivity for these antibodies should prompt a search for an underlying malignancy. If initial screening is negative, surveillance screening may discover a malignancy several months or years later. However, paraneoplastic antibodies are not detected in every affected individual, so seronegativity does not exclude the diagnosis.

Subacute sensory neuronopathy is a classical paraneoplastic neurological syndrome resulting from immune-mediated attack of sensory neurons in the dorsal root ganglia. Subacute sensory neuronopathy is the most common paraneoplastic neuropathy. It may occur in isolation or as part of a paraneoplastic encephalomyelitis and is associated with small cell lung cancer in 80% of cases (Graus et al, 2001). Most cases are associated with anti-Hu antibodies in serum and CSF with high specificity and sensitivity, although up to 20% of paraneoplastic sensory neuropathies may be seronegative (Molinuevo et al, 1998). Other antibodies have been described with subacute sensory neuronopathy, most commonly anti-CV2/CRMP5 antibodies, which may occur with or without anti-Hu and are more likely to be associated with other cancers such as breast adenocarcinoma. The clinical presentation of subacute sensory neuronopathy is usually of subacute multifocal or asymmetric sensory loss with sensory ataxia and areflexia. Face and trunk involvement may be affected in somatotopic regions reflective of neuronopathy. Evaluation of CSF commonly shows elevated protein, pleocytosis and oligoclonal bands.

In addition to subacute sensory neuronopathy, involvement of lower motor neurons (weakness, atrophy, fasciculation) and autonomic neurons (orthostatic hypotension, arrhythmia or gastric dysmotility) may also occur with anti-Hu antibodies. Since these patients usually have simultaneous subacute sensory neuronopathy, their clinical picture might lead to misdiagnosis of multiple mononeuropathy, polyradiculopathy, or Guillain–Barré-like syndrome.

More than 10% of patients with paraneoplastic anti-Hu antibodies present with only gastrointestinal dysmotility and 5–10% of patients with chronic pseudo-obstruction have anti-ganglionic AchR antibodies (Winston and Vernino, 2010). Both antibodies are also associated with the less common autoimmune autonomic ganglionopathy, which often presents with orthostatic hypotension, arrhythmia or gastric dysmotility.

Paraneoplastic sensory and motor neuropathies usually are seronegative. However, patients with both anti-Hu and anti-CV2/CRMP5 antibodies may have subacute sensory neuronopathy superimposed on demyelinating sensory and motor neuropathy. The demyelinating neuropathy with anti-CV2/CRMP5 antibodies may be slowly progressive (Samarasekera and Rajabally, 2011) and mimic chronic inflammatory demyelinating polyneuropathy (Antoine et al, 2001). Melanoma is the second most common neoplasia associated with chronic inflammatory demyelinating polyneuropathy and half of reported cases displayed anti-ganglioside antibodies (Rajabally and Attarian, 2018).

Disorders associated with anti-ganglioside antibodies

Gangliosides are sialic acid-containing glycosphingolipids that accumulate to form groups on the surfaces of neuronal membranes. High titres of various anti-ganglioside antibodies have been described in patients with axonal forms of Guillain–Barré syndrome, in particular the pure motor form known as acute motor axonal neuropathy.

Various infectious agents have been associated with Guillain–Barré syndrome but the association of acute motor axonal neuropathy with antecedent *Campylobacter jejuni* is the most well established (Rees et al, 1995). A similar immune process is seen in Miller–Fisher syndrome, where the antigenic GQ1b ganglioside, also involved in Bickerstaff's brainstem encephalitis, is targeted (Shahrizaila and Yuki, 2013) (Table 1). The pharyngo-cervico-brachial variant of Guillain–Barré syndrome is associated

Table 1. Variants of Guillain–Barré syndrome associated with antiganglioside antibodies

Clinical syndrome	Clinical features	Gangliosides
Acute inflammatory demyelinating polyneuropathy	Segmental multifocal demyelination	No strong antibody association
	Decreased motor conduction velocity and conduction block, and temporal dispersion	
	Autonomic involvement	
	Cranial nerve palsy	
	Sensory loss common	
Acute motor axonal neuropathy	Cranial nerve involvement rare	GM1 GD1a GA1NAc-GM1b
	Reduced compound muscle action potentials, may have transient conduction block	
Acute motor sensory axonal neuropathy	Sensory and motor involvement	
	More severe and prolonged than acute motor axonal neuropathy	
Miller–Fisher syndrome	Triad of ophthalmoplegia, ataxia and areflexia	GQ1b GD1a GD1b GM1 GT1a
Bickerstaff's brainstem encephalitis	Alteration in consciousness, ataxia, and ophthalmoparesis with preserved reflexes	GQ1b GD1a GD1b GM1
Acute ataxic neuropathy	Ataxia without ophthalmoplegia or Rombergism	GQ1b
Acute sensory ataxic neuropathy	Ataxia without ophthalmoplegia but with Rombergism	GD1b
Acute ophthalmoparesis	Rarely facial or bulbar weakness	GQ1b
Pharyngeal-cervical-brachial	Facial, oropharyngeal, cervical, and upper limb weakness without lower limb involvement	GT1a, GQ1b, GD1a

with anti-GT1a antibodies in about 50% of cases, which may cross react with GQ1b (Wakerley and Yuki, 2014).

Antiganglioside antibodies are also present in at least 40% of patients with multifocal motor neuropathy. Multifocal motor neuropathy is a rare but treatable disease presenting with slowly progressive asymmetrical distal weakness with little or no sensory involvement. Symptoms usually start in the upper limb and follow distribution of individual nerves (Yeh et al, 2020). Rarely there is cranial nerve or respiratory involvement, but upper motor neuron signs, bulbar weakness or sphincter disturbance suggest alternative diagnoses. The characteristic electrophysiological finding of persistent conduction block is often key to confirming multifocal motor neuropathy. There is a good response to high-dose intravenous immunoglobulin, which remains the only treatment with proven efficacy (Eftimov and Van Schaik, 2011).

Finally, antiganglioside antibodies are present in 'chronic ataxic neuropathy with ophthalmoplegia, M-protein and disiaosyl antibodies' (CANOMAD). CANOMAD is a syndrome characterised by ataxic neuropathy, ophthalmoplegia, monoclonal gammopathy, cold agglutinins and disialosyl antibodies. It is an IgM antibody-associated neuropathy, against disialylated and polysialylated gangliosides – GD1b, GD3, GT1b, and GQ1b (Willison et al, 2001). The overall clinical and laboratory pattern is similar to Miller–Fisher syndrome, but the antibody response in Miller–Fisher syndrome is in the form of IgG against GQ1b and GT1a, in contrast to CANOMAD, which has an IgM response. In terms of clinical course, CANOMAD is a chronic disorder extending over several years.

New antibodies in dysimmune neuropathies

Chronic inflammatory demyelinating polyneuropathy is a chronic progressive or relapsing remitting neuropathy characterised by symmetrical weakness, sensory involvement and diminished reflexes with immune-mediated demyelination. Various subtypes are described (Van den Bergh et al, 2010). Most patients respond well to conventional immunotherapy in the form of steroids and plasma exchange. A number of antibodies against nodal and paranodal antigens have been reported in a minority of patients with chronic inflammatory demyelinating polyneuropathy (Querol et al, 2017). The discovery of antigenic targets at the nodes of Ranvier in patients with chronic inflammatory demyelinating polyneuropathy has provided impetus in the understanding of pathogenesis and treatment options.

Numerous studies have consistently reported association of anti-NF155 antibody and chronic inflammatory demyelinating polyneuropathy with a frequency of <10% and, importantly, high specificity. Several studies have described a specific clinical phenotype, consisting of younger age of onset, more subacute and severe onset, disabling tremor, ataxia, significantly higher CSF protein, distal dominant weakness, and good response to rituximab but not intravenous immunoglobulin (Querol et al, 2015).

Anti-contactin (CNTN1) antibodies have similarly been found in <10% of patients with chronic inflammatory demyelinating polyneuropathy. Anti-CNTN1 is associated with a phenotype with older age of onset, aggressive subacute weakness, sensory ataxia and early axonal involvement, and poor response to intravenous immunoglobulin (Querol et al, 2017).

Anti-CASPR1 antibodies were initially described in one patient with Guillain–Barré syndrome and one patient with chronic inflammatory demyelinating polyneuropathy, who both presented with severe neuropathic pain. Anti-CASPR1 is the rarest of the paranodal antibodies with only two other patients reported, although antibodies may also occur against a CNTN1/CASPR1 complex.

Antibodies to nodal targets NF186, NF140 and gliomedin appear rarer than their paranodal counterparts. Patients had more severe and subacute onset, more common sensory ataxia and were older at onset. Importantly, response to intravenous immunoglobulin was better than anti-NF155 seropositive patients.

Anti-FGFR3 antibodies have been associated with various types of predominantly sensory neuropathy, after initial description in sensory ganglionopathy (Antoine et al, 2015). Anti-FGFR3 antibodies were described in 15% of cases of sensory neuropathy

at large in a multicentre European/Brazilian study. Positive cases included subjects with small fibre neuropathy. The frequency of anti-FGFR3 antibodies was significantly higher in Brazil than in Europe (36% vs 13%; $P<0.001$), suggesting possible roles of genetic and environmental factors (Tholance et al, 2020).

Discussion

The use of antibody testing has become more widespread in the management of patients with neuropathy. Electrophoresis and immunofixation of serum proteins in all patients, as well as testing for ANCA in selected patients with suspected vasculitic neuropathy, is of direct relevance to clinical management. In the former case, the potential for identification of a haematological malignancy or, more commonly, of a monoclonal gammopathy of undetermined significance requiring long-term monitoring, clearly provide the justification. This is supported by the importance of identifying IgM monoclonal gammopathies which may be associated with anti-MAG antibodies or, for example, in a clinically-suggestive case scenario, the presence of a low-level IgG or IgA paraprotein and lambda light chain, raising the possibility of a treatable but otherwise fatal POEMS syndrome. Anti-MAG antibodies are associated with a separate entity (anti-MAG neuropathy) that needs to be differentiated from chronic inflammatory demyelinating polyneuropathy, given the very different treatment modalities to be considered. ANCA testing is also diagnostically helpful, particularly in the absence of definite pathological confirmation of vasculitis, in the absence of systemic involvement and to justify escalation of immunosuppressant treatment. Extractable nuclear antigens allow identification of Sjögren's syndrome, of which neurological manifestations are frequently the first presentation.

Antiganglioside antibody testing has become widely available in clinical practice. The presence of these antibodies, consistent with specific forms of Guillain–Barré syndrome and Miller–Fisher syndrome in particular, does have potential diagnostic utility but does not, in general, have management implications. In subacute ocular and bulbar presentations, however, it may help separate Miller–Fisher syndrome from neuromuscular junction disease, such as myasthenia gravis. Initial therapeutic decisions are made before results become known to the clinician and, importantly, treatment is similar for Guillain–Barré syndrome and Miller–Fisher syndrome, irrespective of antiganglioside antibody status. This is different in the chronic setting. In multifocal motor neuropathy, presence of anti-GM1 antibodies can be useful, particularly in the absence of electrophysiological motor conduction blocks. In CANOMAD, the presence of the disalosyl antibodies is essential for the diagnosis, and may justify long-term treatment. The possibility of antiganglioside positivity in a context of malignancy rather than preceding *C. jejuni* enteritis in chronic inflammatory demyelinating polyneuropathy, although rare, may also be of interest in considering more detailed assessment, in particular for melanoma.

Importantly, the detection of antineuronal antibodies in subjects with a suspicion of paraneoplastic neuropathy can lead to greater vigilance and consequent early identification of occult malignancy, although this may require prolonged surveillance. Patients with subacute sensory neuronopathy or painful neuropathy, in particular, should be assessed for paraneoplastic antibody status. However, as seronegativity does not exclude paraneoplastic neuropathy, it may be argued that surveillance and therapeutic decisions should be similar irrespective of antibody status, as absence of these antibodies does not exclude paraneoplastic disease. Antibody testing, although part of the advisable work-up, should therefore not replace thorough clinical assessment and proper use of imaging including computed tomography, magnetic resonance imaging and especially positron emission tomography.

The discoveries of antiparanodal and nodal antibodies in patients with chronic inflammatory neuropathies have opened the debate further regarding immunological tests for patients with dysimmune neuropathy. This new knowledge has certainly improved the understanding of pathophysiological mechanisms involved in this subset of patients. That positive patients display resistance to usual first-line treatments for chronic inflammatory demyelinating polyneuropathy but reported improvement with rituximab (Querol et al, 2015), while displaying typical, marked demyelinating physiology (Kouton et al, 2020), is of interest.

Key points

- Serum protein electrophoresis with immunofixation should be performed in all patients with polyneuropathy and may potentially identify treatable haematological malignancy.
- Antineutrophil cytoplasmic antibody (ANCA) seropositivity is not only of diagnostic utility in vasculitic neuropathy but can help justify escalation of immunosuppressant treatment.
- A finding of antiganglioside antibodies in patients with Guillain–Barré syndrome is largely academic because their presence does not alter treatment decisions, but they can be helpful in diagnosis of multifocal motor neuropathy and CANOMAD (chronic ataxic neuropathy with ophthalmoplegia, M-protein and disiaosyl antibodies).
- Detection of paraneoplastic antibodies may lead to early diagnosis of occult malignancy but seronegativity does not exclude paraneoplastic neuropathy.
- Novel nodal and paranodal antibodies may confer better understanding of pathogenesis and treatment escalation in chronic inflammatory demyelinating polyneuropathy, such as using rituximab.
- Antibody testing should not be a substitute for careful clinical evaluation, use of other diagnostic tools or logical thought.

Availability of testing to antiparanodal antibodies is presently mostly limited to research bases but is increasingly accessible. Rituximab is not routinely commissioned, depending on centres, but applications for use of this drug may be more successful in patients with treatment-resistant chronic inflammatory demyelinating polyneuropathy or Guillain–Barré syndrome when these antibodies are detected. Although this may be understandable, the growing number of reports of rituximab response in patients with antiparanodal antibody-negative chronic inflammatory demyelinating polyneuropathy, and a trial starting in Japan (Shimizu et al, 2020), as well as the authors' experience, suggest wider consideration, including in antibody-negative patients, would be appropriate in refractory disease. Suspected antiparanodal antibody-positive cases should be referred to a neuroscience centre to consider testing and therapeutic escalation. However, an important factor to bear in mind is the low prevalence of these antibodies, reportedly present in less than 10% of cases, and in the authors' experience less than 5%, of subjects with chronic inflammatory demyelinating polyneuropathy, an already rare disease.

Conclusions

Although of considerable research interest in larger centres treating neuropathy, the majority of antibodies tested for in clinical practice do not provide the basis for major alteration of management plans. In addition, the issue of overreliance on results which may lead to delayed, or frankly inappropriate decisions, such as not escalating treatment in cases of progressive suspected vasculitic neuropathy or suspected paranodal dysimmunity, should not be overlooked. This, together with the cost implications of widespread testing, requires careful consideration. As for any investigation in any area of medicine, availability should not necessarily justify systematic implementation nor override careful clinical evaluation, use of other diagnostic tools or logical thought.

Author details

[1]Regional Neuromuscular Service, Queen Elizabeth Hospital, University Hospitals Birmingham, UK

[2]Aston Medical School, Aston University, Birmingham, UK

Conflicts of interest

The authors declare no conflicts of interest.

References

Antoine JC, Honnorat J, Camdessanch 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(2):214–221. https://doi.org/10.1002/1531-8249(20010201)49:2<214::AID-ANA41>3.0.CO;2-W

Antoine JC, Boutahar N, Lassabliere F et al. Antifibroblast growth factor receptor 3 antibodies identify a subgroup of patients with sensory neuropathy. J Neurol Neurosurg Psychiatr. 2015;86(12):1347–1355. https://doi.org/10.1136/jnnp-2014-309730

Antoine JC, Camdessanche JP. Paraneoplastic neuropathies. Curr Opin Neurol. 2017;30(5):513–520. https://doi.org/10.1097/WCO.0000000000000475

Berkowitz AL, Samuels MA. The neurology of Sjögren's syndrome and the rheumatology of peripheral neuropathy and myelitis. Pract Neurol. 2014;14(1):14–22. https://doi.org/10.1136/practneurol-2013-000651

Bischof A, Jaeger VK, Hadden RD et al. Peripheral neuropathy in antineutrophil cytoplasmic antibody-associated vasculitides: insights from the DCVAS study. Neurol Neuroimmunol Neuroinflamm. 2019;6(6):e615. https://doi.org/10.1212/NXI.0000000000000615

Collins MP, Dyck PJB, Hadden RD. Update on classification, epidemiology, clinical phenotype and imaging of the nonsystemic vasculitic neuropathies. Curr Opin Neurol. 2019;32(5):684–695. https://doi.org/10.1097/WCO.0000000000000727

Dalakas MC. Advances in the diagnosis, immunopathogenesis and therapies of IgM-anti-MAG antibody-mediated neuropathies. Ther Adv Neurol Disord. 2018;11:175628561774664. https://doi.org/10.1177/1756285617746640

Dispenzieri A. POEMS Syndrome: 2019. Update on diagnosis, risk-stratification, and management. Am J Hematol. 2019;94(7):812–827. https://doi.org/10.1002/ajh.25495

Eftimov F, Van Schaik IN. Immunotherapy of multifocal motor neuropathy. Expert Opin Biol Ther. 2011;11(3):329–342. https://doi.org/10.1517/14712598.2011.548798

Go RS, Rajkumar SV. How I manage monoclonal gammopathy of undetermined significance. Blood. 2018;131(2):163–173. https://doi.org/10.1182/blood-2017-09-807560

Graus F, Keime-Guibert F, Rene R et al. Anti-Hu-associated paraneoplastic encephalomyelitis: analysis of 200 patients. Brain. 2001;124(6):1138–1148. https://doi.org/10.1093/brain/124.6.1138

Hadden RD, Collins MP, Živković SA et al. Vasculitic peripheral neuropathy: case definition and guidelines for collection, analysis, and presentation of immunisation safety data. Vaccine. 2017;35(11):1567–1578. https://doi.org/10.1016/j.vaccine.2015.11.047

Hernández-Molina G, Leal-Alegre G, Michel-Peregrina M. The meaning of anti-Ro and anti-La antibodies in primary Sjögren's syndrome. Autoimmun Rev. 2011;10(3):123–125. https://doi.org/10.1016/j.autrev.2010.09.001

Kahn SN, Bina M. Sensitivity of immunofixation electrophoresis for detecting IgM paraproteins in serum. Clin Chem. 1988;34(8):1633–1635. https://doi.org/10.1093/clinchem/34.8.1633

Kouton L, Boucraut J, Devaux J et al. Electrophysiological features of chronic inflammatory demyelinating polyradiculoneuropathy associated with IgG4 antibodies targeting neurofascin 155 or contactin 1 glycoproteins. Clin Neurophysiol. 2020;131(4):921–927. https://doi.org/10.1016/j.clinph.2020.01.013

Molinuevo JL, Graus F, Serrano C et al. Utility of anti-Hu antibodies in the diagnosis of paraneoplastic sensory neuropathy. Ann Neurol. 1998;44(6):976–980. https://doi.org/10.1002/ana.410440620

Pascual-Goñi E, Martín-Aguilar L, Lleixà C et al. Clinical and laboratory features of anti-MAG neuropathy without monoclonal gammopathy. Sci Rep. 2019;9(1):6155. https://doi.org/10.1038/s41598-019-42545-8

Querol L, Rojas-Garcia R, Diaz-Manera J et al. Rituximab in treatment-resistant CIDP with antibodies against paranodal proteins. Neurol Neuroimmunol Neuroinflamm. 2015;2(5):e149. https://doi.org/10.1212/NXI.0000000000000149

Querol L, Devaux J, Rojas-Garcia R, Illa I. Autoantibodies in chronic inflammatory neuropathies: diagnostic and therapeutic implications. Nat Rev Neurol. 2017;13(9):533–547. https://doi.org/10.1038/nrneurol.2017.84

Rajabally YA, Attarian S. Chronic inflammatory demyelinating polyneuropathy and malignancy: a systematic review. Muscle Nerve. 2018;57(6):875–883. https://doi.org/10.1002/mus.26028

Rees JH, Gregson NA, Hughes RA. Anti-ganglioside GM1 antibodies in Guillain-Barre syndrome and their relationship to Campylobacter jejuni infection. Ann Neurol. 1995;38(5):809–816. https://doi.org/10.1002/ana.410380516

Samarasekera S, Rajabally YA. Demyelinating neuropathy with anti-CRMP5 antibodies predating diagnosis of breast carcinoma: favorable outcome after cancer therapy. Muscle Nerve. 2011;43(5):764–766. https://doi.org/10.1002/mus.22036

Shahrizaila N, Yuki N. Bickerstaff brainstem encephalitis and Fisher syndrome: anti-GQ1b antibody syndrome. J Neurol Neurosurg Psychiatr. 2013;84(5):576–583. https://doi.org/10.1136/jnnp-2012-302824

Shimizu S, Iijima M, Fukami Y et al. Efficacy and Safety of Rituximab in Refractory CIDP With or Without IgG4 Autoantibodies (RECIPE): protocol for a double-blind, randomized, placebo-controlled clinical trial. JMIR Res Protoc. 2020;9(4):e17117. https://doi.org/10.2196/17117

Tholance Y, Moritz CP, Rosier C et al. Clinical characterisation of sensory neuropathy with anti-FGFR3 autoantibodies. J Neurol Neurosurg Psychiatr. 2020;91(1):49–57. https://doi.org/10.1136/jnnp-2019-321849

Van den Bergh PY, Hadden RD, Bouche P et al. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society - first revision. Eur J Neurol. 2010;17(3):356–363. https://doi.org/10.1111/j.1468-1331.2009.02930.x

Wakerley BR, Yuki N. Pharyngeal-cervical-brachial variant of Guillain-Barre syndrome. J Neurol Neurosurg Psychiatr. 2014;85(3):339–344. https://doi.org/10.1136/jnnp-2013-305397

Willison HJ, O'Leary CP, Veitch J et al. The clinical and laboratory features of chronic sensory ataxic neuropathy with anti-disialosyl IgM antibodies. Brain. 2001;124(10):1968–1977. https://doi.org/10.1093/brain/124.10.1968

Winston N, Vernino S. Recent advances in autoimmune autonomic ganglionopathy. Curr Opin Neurol. 2010;23(5):514–518. https://doi.org/10.1097/WCO.0b013e32833d4c7f

Yeh WZ, Dyck PJ, van den Berg LH, Kiernan MC, Taylor BV. Multifocal motor neuropathy: controversies and priorities. J Neurol Neurosurg Psychiatr. 2020;91(2):140–148. https://doi.org/10.1136/jnnp-2019-321532