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Antibodies in Autoimmune Neuropathies

What to Test, How to Test, Why to Test

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Abstract

Autoimmune neuropathies are a heterogeneous group of immune-mediated disorders of the peripheral nerves. Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) are the archetypal acute and chronic forms. Over the past few decades, pathogenic antibodies targeting antigens of the peripheral nervous system and driving peripheral nerve damage in selected patients have been described. Moreover, the detection of these antibodies has diagnostic and therapeutic implications that have prompted a modification of the GBS and CIDP diagnostic algorithms. GBS diagnosis is based in clinical criteria, and systematic testing of anti-ganglioside antibodies is not required. Nonetheless, a positive anti-ganglioside antibody test may support the clinical suspicion when diagnosis of GBS (GM1 IgG), Miller Fisher (GQ1b IgG), or acute sensory-ataxic (GD1b IgG) syndromes is uncertain. Anti–myelin-associated glycoprotein (MAG) IgM and anti-disialosyl IgM antibodies are key in the diagnosis of anti-MAG neuropathy and chronic ataxic neuropathy, ophthalmoplegia, M-protein, cold agglutinins, and disialosyl antibodies spectrum neuropathies, respectively, and help differentiating these conditions from CIDP. Recently, the field has been boosted by the discovery of pathogenic antibodies targeting proteins of the node of Ranvier contactin-1, contactin-associated protein 1, and nodal and paranodal isoforms of neurofascin (NF140, NF186, or NF155). These antibodies define subgroups of patients with specific clinical (most importantly poor or partial response to conventional therapies and excellent response to anti-CD20 therapy) and pathologic (node of Ranvier disruption in the absence of inflammation) features that led to the definition of the "autoimmune nodopathy" diagnostic category and to the incorporation of nodal/paranodal antibodies to clinical routine testing. The purpose of this review was to provide a practical vision for the general neurologist of the use of antibodies in the clinical assessment of autoimmune neuropathies.

Introduction

Autoimmune neuropathies (ANs) are a group of rare diseases of the peripheral nerves (PNs). Immune mechanisms mediating these disorders are not well understood. However, the detection of antibodies against PN structures in patients with AN has contributed to a better understanding of the heterogeneous pathogenesis of these diseases. Although the discovery of autoantibodies has been a research topic for 4 decades, the recent description of pathogenic antibodies targeting cell adhesion molecules of the node of Ranvier has boosted the interest in the field. Antibodies have become a useful tool in the diagnosis of patients with AN because they help classifying patients with AN in subgroups based on the underlying disease mechanisms and optimizing the therapeutic strategy to improve prognosis.

Antibody testing does not substitute the formal diagnostic process of AN, but when used appropriately and, very importantly, with the appropriate techniques, can optimize this process.

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Glossary

AGO = argonaute; **AN** = autoimmune neuropathy; **ASAN** = acute sensory ataxic neuropathy; **CANDA** = chronic ataxic neuropathy with anti-disialosyl antibodies; **CANOMAD** = chronic ataxic neuropathy ophthalmoplegia, M-protein, cold agglutinins, and disialosyl antibodies; **Caspr1** = contactin-associated protein 1; **CBA** = cell-based assay; **CIDP** = chronic inflammatory demyelinating polyneuropathy; **CNTN1** = contactin-1; **CRMP5** = collapsin response-mediator protein-5; **EIA** = enzyme immunoassay; **FGFR3** = fibroblast growth factor receptor 3; **GBS** = Guillain-Barré syndrome; **Ig** = immunoglobulin; **LMNS** = lower motor neuron syndrome; **MAG** = myelin-associated glycoprotein; **MFS** = Miller Fisher syndrome; **MGUS** = monoclonal gammopathy of undetermined significance; **MMN** = multifocal motor neuropathy; **NF155** = neurofascin 155; **pan-NF** = pan-neurofascin; **PCB** = pharyngeal-cervical-brachial; **PN** = peripheral nerve; **RCF** = reversible conduction failure.

However, the clinical course, phenotype, and electrophysiologic findings still are the triggers prompting autoantibody testing in patients in which AN is suspected. In this study, we will review WHAT antibodies are associated with each clinical phenotype in AN, HOW to develop the best diagnostic and technical testing strategy for these antibodies, and finally we discuss WHY is it necessary to test these antibodies and to try to discover novel antigens to improve the management of patients with AN.

What to Test

A systematic approach can be used to classify AN according to their clinical presentation. First, based on the time course of disease onset, neuropathies are (1) acute (less than 4 weeks), (2) subacute (between 4 and 8 weeks), or (3) chronic (more than 8 weeks). Second, based on the presenting symptoms, neuropathies are mainly (1) sensory or sensory-ataxic, (2) motor, or (3) sensory-motor. Third, according to electrophysiologic studies, neuropathies classically can be divided into (1) demyelinating or (2) axonal. Recently, a new category of "nodo-paranodopathies" was proposed for neuropathies in which the dysfunction of the node of Ranvier results in reversible conduction failure (RCF), with or without concomitant axonal degeneration.[1] We will detail which antibodies are associated with some of these phenotypic categories and which testing process do we follow in patients in whom AN is suspected (Figure 1).

Acute-Onset Autoimmune Neuropathies

Acute-onset ANs are usually included in Guillain-Barré syndrome (GBS). GBS has a monophasic course that develops over days to weeks reaching nadir within 4 weeks (over 90% of patients in the first 2 weeks) that is followed by a recovery phase that can take weeks to months. GBS includes different clinical variants and electrophysiologic patterns. Anti-ganglioside antibodies are found in between 40% and 60% of patients with GBS, although the reported prevalences vary significantly, likely because of diversity of detection methods.[2,3] A polyclonal immune response mediates the production of IgG and IgM antibodies against specific gangliosides that are associated with diverse GBS variants. Gangliosides are glycosphingolipids that contain 1 or more sialic acid residues linked to the oligosaccharide core. They are highly abundant in the nervous system, especially in neuronal membranes, where they participate in cell signaling and cell-to-cell communication. In PN, the main gangliosides are GM1, GM2, GD1b, GD1a, GT1a, and GQ1b. Anti-ganglioside titers reach their peak in the acute phase of the disease and subsequently decrease during follow-up, supporting their role in the pathogenesis of the disease. In addition, experimental data support the pathogenicity of anti-ganglioside antibodies in GBS.

Anti-ganglioside antibodies can also be detected in chronic neuropathies such as multifocal motor neuropathy (MMN) and chronic ataxic neuropathies with anti-disialosyl antibodies. Unlike GBS, in which immunoglobulin (Ig) M and IgG isotypes are detected, supporting the presence of a normal class-switch phenomenon, class switch from IgM to IgG does not occur in autoantibodies associated with chronic neuropathies with anti-ganglioside antibodies and anti–myelin-associated glycoprotein (MAG). The reason why this occurs is unknown but probably related to the fact that these IgM antibodies target glycosylated epitopes, a frequent type of target antigen in natural autoantibodies, that typically do not undergo class switching.[4]

GBS diagnosis relies on clinical and electrophysiologic criteria, and guidelines do not recommend testing anti-gangliosides antibodies in most patients with typical sensory-motor GBS because of their moderate diagnostic sensitivity and delay in result obtention.[5] From a therapeutic perspective, identifying these antibodies in typical GBS cases does not change the therapeutic strategy because treatment selection is independent of antibody positivity. However, testing for these antibodies may be beneficial in atypical cases in which diagnostic doubts arise.

Antibodies Associated With Acute Ataxic Neuropathies

Autoimmune acute ataxic neuropathies include acute sensory-ataxic neuropathy (ASAN) and Miller Fisher syndrome (MFS). ASAN is characterized by a sensory neuropathy with profound sensory ataxia. It associates with IgG antibodies targeting gangliosides bearing disialosyl epitopes, mainly GD1b and, less frequently, GQ1b.[6] In fact, experimental ASAN is induced in rabbits by sensitization to GD1b ganglioside, which is enriched in dorsal root ganglion neurons.[7] Testing anti-GD1b IgG antibodies is crucially important in cases in which an acute sensory-ataxic neuropathy develops.

The differential diagnosis may include toxic, paraneoplastic, systemic, or vitamin-deficiency neuropathies, and thus, a confirmatory anti-GD1b test would lead to a significantly different therapeutic approach in these patients because they would confirm the autoimmune origin and monophasic nature of the ataxic neuropathy.

MFS is a variant of GBS characterized by ophthalmoplegia, ataxia, and lower limb areflexia. In addition, pupillary abnormalities (mydriasis), facial and bulbar palsy, sensory disturbances, weakness, or autonomic symptoms may appear.[8] Most of these patients have an antecedent infectious illness up to 4 weeks before the onset of the neurologic symptoms. Most common triggers include upper respiratory infections, gastrointestinal symptoms, or fever.[8] Anti-GQ1b IgG antibodies are detected in up to 90% of patients with MFS.[9] GQ1b is enriched in the oculomotor cranial nerves (but not in other cranial nerves or nerve roots) and in the motor endplates of extraocular muscles. Anti-GQ1b antibodies bind to paranodal myelin and motor nerve terminals of the oculomotor, trochlear, and abducens cranial nerve. Furthermore, MFS may present with cerebellar-like ataxia due to a selective dysfunction of the muscle spindle afferents to the spinocerebellar nucleus mediated by anti-GQ1b antibodies. Anti-GQ1b antibodies cross-react with the structurally similar ganglioside GT1a. Both are likely triggered by molecular mimicry after a Campylobacter jejuni infection.[10] Anti-GQ1b IgG are also present in more than two-thirds of cases with Bickerstaff brainstem encephalitis[11] that overlaps with MFS and includes disturbances of consciousness and, occasionally, tetraparesis and extensor plantar response that suggest CNS involvement. The mechanisms underlying CNS involvement remain unknown. In addition, pure ataxic GBS and isolated acute ophthalmoplegia may also be associated with anti-GQ1b IgG and are included in the "anti-GQ1b IgG syndrome" spectrum.[12] These disorders have a better prognosis compared with typical GBS because they usually show spontaneous recovery.

The diagnostic performance of anti-GQ1b antibodies granted them a testing recommendation in the recent GBS guidelines.[5] In fact, because anti-GQ1b antibodies are very frequent in MFS, a negative anti-GQ1b IgG test, especially when atypical features appear, should raise concerns regarding the MFS diagnosis and should prompt clinicians to consider other possibilities (Wernicke encephalopathy, mitochondrial disorders, toxic neuropathies). On the contrary, a clearly positive test, in the context of a full or partial syndrome (pure acute ophthalmoplegia or acute ataxia without ophthalmoplegia) helps reassure the diagnosis.

Antibodies Associated With Acute Motor Neuropathies

In 50% of patients with acute motor neuropathies, anti-GM1 and anti-GD1a IgG antibodies are detected. GM1 and GD1a are expressed in both motor and sensory roots, but antibodies against GM1/GD1a preferentially bind motor fibers, explaining the relative disproportion on the motor involvement in these disorders.[13] GM1 is expressed on both axonal and Schwann cell membranes, especially in the nodes of Ranvier, where anti-GM1 IgG induces glial injury, followed by secondary axonal degeneration through nanoruptures in the axonal membrane.[14] Studies on animal models demonstrated complement-dependent pathogenicity of anti-GM1 IgG causing RCF and/or axonal degeneration.[14] Many motor GBS cases report diarrhea in the days preceding disease onset because a molecular mimicry mechanism is responsible for the development of anti-GM1/GD1a autoantibodies. Best example is *Campylobacter jejuni* infection, in which strains expressing a GM1 and GD1a-like lipo-oligosaccharide on their bacterial wall lead to the production of anti-GM1/GD1a antibodies.

Despite clear evidence associating anti-GM1 antibodies with pure motor GBS, a systematic testing of anti-ganglioside antibodies for diagnostic purposes is not recommended.[5] However, a positive anti-GM1 IgG test is reassuring to validate the clinical suspicion when diagnostic doubts arise. Anti-GM1 antibodies may also be useful for prognosis because high baseline and persistent high levels of anti-GM1 IgG titers are associated with poor outcomes.[15]

Antibodies Associated With Acute Sensory-Motor Neuropathies

Acute sensory-motor neuropathy is the most frequent variant of GBS. Most patients are seronegative for anti-ganglioside antibodies despite antibody and complement deposits being detected on the surface of Schwann cells in GBS nerve biopsies. Anti-GM1 IgG antibodies, nonetheless, are detected in a small proportion of these patients.[15] In addition, anti-GM2 IgM antibodies are detected in sensory-motor GBS after cytomegalovirus infection[16] associating with younger age and an aggressive course that includes cranial nerve involvement, respiratory support need, and severe sensory loss. Recently, antibodies targeting the node of Ranvier were reported in a small subset of patients with acute-onset sensory-motor neuropathies mimicking GBS.[17] Very few have a monophasic course; the majority progress to chronicity requiring chronic therapeutic strategies. Accordingly, in acute sensory-motor neuropathies, particularly when specific features appear (see Antibodies Associated With Chronic Symmetric Sensory-Motor Neuropathies), testing anti-ganglioside antibodies and nodal/paranodal antibodies may be crucial to, on the one hand, exclude an autoimmune nodopathy (that has a very different prognostic and therapeutic profile) and, on the other hand, help confirm GBS diagnosis if anti-GM1 IgG antibodies are positive.

Antibodies Associated With Pharyngeal-Cervical-Brachial Palsy

The pharyngeal-cervical-brachial (PCB) variant of GBS consists of an acute-onset bulbar paralysis and cervicobrachial weakness associated with areflexia in the upper limbs.[18,19] The neurophysiologic findings in PCB are axonal rather than demyelinating. Some patients may associate ophthalmoplegia and ataxia, indicating overlap with MFS. Most cases have a

history of infection such as upper respiratory tract or gastrointestinal infections, and serologic evidence of Campylobacter jejuni was reported in 30%.[20] Half of PCB patients carry anti-GT1a IgG antibodies, which preferentially bind to the lower glossopharyngeal and vagal nerves.[21] GT1a is structurally similar to GQ1b, and thus, antibodies targeting both molecules cross-react. In addition, IgG antibodies to GM1, GM1b, GD1a, or GalNAc-GD1a are detected in a quarter of these patients.[20] Testing antigangliosides may be particularly useful in partial forms of the disease, for example, in acute bulbar palsy, in which a positive anti-GT1a tests may clarify what it can otherwise be a broad differential diagnosis.

Subacute and Chronic Neuropathies

Subacute and chronic-onset inflammatory neuropathies include chronic inflammatory demyelinating polyneuropathy (CIDP), autoimmune nodopathies, neuropathies associated with IgM monoclonal gammopathy of undetermined significance (MGUS), and MMN. In these disorders, the immune attack is primarily directed against PN; antibodies against gangliosides, MAG, or proteins of the node of Ranvier play a key role in their development. There is another group of AN in which the immune response is not directed primarily against the PN and may associate with involvement of other target organs. This group includes vasculitic neuropathies, neuropathies associated with systemic autoimmune diseases, and paraneoplastic neuropathies. In many of them, specific antibodies are also useful for their diagnosis.

Antibodies Associated With Chronic Sensory-Ataxic Neuropathies

Several autoimmune disorders may cause chronic sensory-ataxic neuropathies, and their identification has therapeutic implications. First, demyelinating neuropathies associated with IgM-MGUS have a characteristic phenotype with a slowly progressive course, with predominantly sensory disturbances, ataxia, and tremor.[22] Patients may also present with distal weakness in the lower limbs. More than 50% of these patients have IgM antibodies against MAG[23] while a small percentage (5%) have anti-sulfatide IgM antibodies.[24] MAG is a glycoprotein expressed on the membrane of Schwann cells. Anti-MAG IgM deposits in the outer layers of myelin, particularly in the paranodal regions and Schmidt-Lanterman incisures. Widely spaced myelin lamellae, caused by IgM deposition between compact myelin layers, are typically observed in nerve biopsies of anti-MAG patients.[25] Nerve conduction studies usually show a length-dependent pattern with preferential involvement of the distal nerve segments, most prominently prolonged distal motor latencies, and sensory potentials are usually absent. Anti-MAG antibodies are pathogenic in animal models, and consequently, patients might benefit from B-cell depletion therapies. A recent retrospective analysis demonstrated that a decrease in anti-MAG levels is associated with treatment response.[26] Rituximab remains the preferred treatment choice, despite 2 randomized controlled trials that failed to meet their primary end points, likely because clinical scores were not sensitive enough to capture treatment effect, plus the fact that only 1 treatment course was administered. Findings from uncontrolled studies indicate that between 30% and 50% of patients may potentially experience benefit with rituximab.[27] Plasma cell inhibition with novel Bruton tyrosine kinase inhibitors could represent a therapeutic alternative in anti-MAG neuropathy, although positive clinical trials supporting their use are needed. Thus, detecting anti-MAG antibodies in the context of MGUS, even if the polyneuropathy is not purely demyelinating (because of secondary axonal loss or involvement limited to sensory nerves), it is important to identify those patients with an MGUS-associated polyneuropathy that may be candidate for immunomodulatory treatment.

Another subset of IgM-mediated neuropathy is chronic ataxic neuropathy with anti-disialosyl antibodies (CANDA), in which anti-GD1b and antibodies targeting disialosyl-bearing gangliosides are detected, associated or not with IgM-MGUS.[28] Some of these patients have CANOMAD syndrome: chronic ataxic neuropathy, ophthalmoplegia, M-protein, cold agglutinins, and disialosyl antibodies (GD1b and GQ1b among others).[29] Electrophysiologic studies demonstrate sensory axonal or demyelinating neuropathy with motor conduction abnormalities that can be found even in the absence of clinical motor involvement. Generally, these disorders respond to IVIg or rituximab. Because the differential diagnosis of chronic sensory-ataxic neuropathies is broad, including toxic, metabolic, mitochondrial disorders or vitamin deficiencies, a positive anti-GD1b test, even in the absence of MGUS, is critical to detect these treatable neuropathies.

Paraneoplastic and systemic autoimmune diseases can also present with neuropathy. Anti-Hu antibodies associate with sensory neuronopathy with subacute or chronic onset. Their early detection is key because these antibodies usually precede lung cancer. Sjögren-associated sensory neuronopathies must also be taken into account in the differential diagnosis because they can be the first manifestation of Sjögren syndrome. Anti-Ro and anti-La antibodies should be tested if this syndrome is suspected, although a negative result does not exclude the diagnosis, and in cases of high suspicion, a salivary gland biopsy should be performed. Sjögren syndrome–associated neuronopathies may have an aggressive course, and their prompt recognition and early start of immunotherapy can improve their prognosis.

Recently, antibodies to the fibroblast growth factor receptor 3 (FGFR3)[30] were reported in a subset of patients with sensory neuronopathy, in the context (or not) of a systemic autoimmune disease (such as systemic lupus erythematosus or Sjögren syndrome). Anti-FGFR3 IgG epitope is intracellular, and its pathogenicity remains unknown. Additional studies have linked anti-FGFR3 antibodies to a broader range of neuropathies, including a subset of small fiber neuropathy where a recent IVIg clinical trial yielded negative results.[31] Given these uncertainties, the clinical significance of these antibodies and the optimal diagnostic test require clarification

before incorporating anti-FGFR3 antibody testing into routine clinical practice. IgG antibodies against argonaute (AGO) were also reported in a cohort of patients with sensory neuronopathy.[32] However, the association of anti-AGO antibodies with sensory neuronopathies needs to be investigated because they were also detected in a small proportion of patients without neuropathy.

In summary, despite some of the antigens described in sensory neuropathies still need validation, etiologic diagnosis is crucial because it has important therapeutic and follow-up implications (including cancer screening). In this process, testing the specific autoantibodies is critical considering the relative clinical and electrophysiologic similarities of these diseases.

Antibodies Associated With Chronic Motor Neuropathies

MMN is the most frequent chronic pure motor AN. Less commonly, a chronic pure motor CIDP variant has also been described. MMN is characterized by asymmetric and predominantly distal weakness of the limbs (usually arms are affected first) and conduction blocks in the motor nerves with relatively spared sensory nerves. These patients respond well to IVIg and may deteriorate with steroids. Anti-GM1 IgM antibodies are detected in around 50% of patients with MMN. By contrast, specific antibodies have not been associated with pure motor CIDP. The importance of testing anti-GM1 IgM antibodies relies mainly on the differential diagnosis of MMN that includes several other untreatable lower motor neuron syndromes (LMNSs), including amyotrophic lateral sclerosis. For example, anti-GM1 antibody detection can be useful in patients with LMNS who do not meet the diagnostic criteria for MMN because conduction blocks are absent. High anti-GM1 IgM titers in the context of a LMNS should encourage physicians to consider additional tests confirming the autoimmune nature of the syndrome or even a therapeutic trial with IVIg. However, low titers of anti-GM1 IgM antibodies need to be interpreted cautiously because they may appear in a broader range of neuropathies.

Antibodies Associated With Chronic Asymmetric Sensory-Motor Neuropathies

The chronic asymmetric sensory-motor phenotype can appear in the context of a primary AN within the CIDP spectrum or secondary to a mononeuritis multiplex. On the one hand, multifocal CIDP (also referred to as the Lewis-Sumner syndrome) presents with asymmetric sensory-motor symptoms affecting the upper and/or lower extremities. Anti-GM1 IgM antibodies may be detected in a subset of these patients, as they may be neuropathies of the MMN spectrum with more prominent sensory symptoms.[33] Neurophysiologic studies demonstrate reduced sensory nerve action potentials and motor conduction blocks. However, vasculitic mononeuritis multiplex, including anti-neutrophil cytoplasmic antibody–associated vasculitis with anti-proteinase-3 or anti-myeloperoxidase antibodies, cryoglobulinemic vasculitis, or anti-C1q vasculitis, should be considered in the differential diagnosis of chronic sensory-motor asymmetric neuropathies. Unlike multifocal CIDP, neurophysiologic studies in mononeuritis multiplex may show asymmetric sensory-motor axonal involvement. Identifying these disorders is critical because it can reveal a systemic disease involving other organs.

Antibodies Associated With Chronic Symmetric Sensory-Motor Neuropathies

Demyelinating chronic symmetric sensory-motor neuropathies are included within the diagnostic category of typical CIDP. Although anatomopathological evidence of Ig deposits on the surface of Schwann cells in nerve biopsies from patients with CIDP and a good response to IVIg suggest the role of autoantibodies in the pathogenesis of these disorders,[34] many previous studies failed to detect autoantibodies in typical CIDP. This is probably because typical CIDP includes diverse AN with different pathogenic mechanisms, involving humoral and cellular processes. Antibody testing may help excluding CIDP mimics in patients with clinical suspicion of CIDP.[35] It is of importance that anti-MAG antibodies must be tested in patients with IgM MGUS. Furthermore, anti-MAG antibodies can be rarely detected in patients meeting CIDP diagnostic criteria in the absence of IgM-paraprotein.[22] For this reason, guidelines recommend to repeat IgM paraprotein testing by immunofixation periodically in these cases (and if IgM-paraprotein appears, anti-MAG testing is obliged). Direct anti-MAG antibody testing may be considered in patients with a distal CIDP variant even if they do not have detectable IgM-paraprotein because their diagnosis and therapeutic approach are different from typical CIDP.[36]

Paraneoplastic neuropathy with anti-CRMP5 or amphiphysin antibodies may present with a polyradiculoneuropathy pattern mimicking CIDP, and in most cases, the symptoms of neuropathy precede the diagnosis of cancer.[37] Therefore, its diagnosis is important because of its implications in the treatment of these patients.

CIDP guidelines also recommend testing nodal/paranodal antibodies in patients with clinical suspicion of CIDP because they allow the diagnosis of patients who will benefit from a therapeutic approach different from that used for CIDP. For this reason, the new guidelines created a new category of AN named "autoimmune nodopathies"[38] that includes these new entities and differentiates them from CIDP.

Antibodies Defining Autoimmune Nodopathies

In the past decade, antibodies against proteins of the axoglial junctions in the nodes of Ranvier including contactin 1 (CNTN1), contactin-associated protein 1 (Caspr1), neurofascin 155 (NF155), and nodal neurofascin and pan-neurofoascin (pan-NF) were reported in 5%–10% of patients with CIDP (Figure 2). Despite their frequency in the general population of AN being low, their description has been crucial to identify disease subtypes and to understand the immunopathologic mechanisms that underlie these disorders.

Figure 1 Antibodies in Autoimmune Neuropathies: Associated Clinical Syndromes and Diagnostic Categories, Clinical Use, Pathogenicity, and Diagnostic Tests

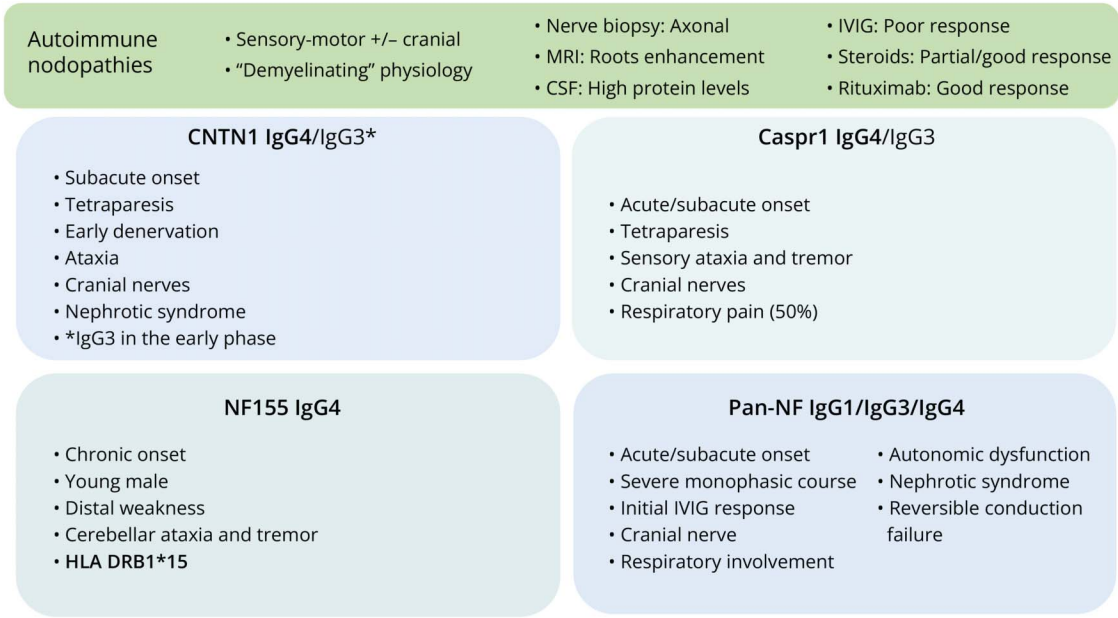
Onset	Syndrome	Category	Antibody	Clinical use	Pathogenicity	Diagnostic tests
Acute	Sensory-ataxic	ASAN	Disialosyl IgG	Diagnostic	Likely pathogenic	ELISA/TLC
	Pure motor	AMAN/AMSAN	GM1/GD1a – GalGalNAc IgG	Diagnostic	Likely pathogenic	ELISA/TLC
	Sensory-motor	AIDP	GalGalNAc IgG	Diagnostic	Likely pathogenic	ELISA/TLC
		Acute onset nodopathies	Pan-NF, Caspr1, CNTN1, NF155	Diagnostic, monitoring	Pan-NF, Caspr1 → Likely pathogenic CNTN1, NF155 → Pathogenic	CBA, ELISA, teased nerve fibers IF
	Pharingo-cervical	PCB palsy	GT1a IgG	Diagnostic	Likely pathogenic	ELISA/TLC
	Ataxia ophth-almoparesis	MFS spectrum	GQ1b-GT1a IgG	Diagnostic	Likely pathogenic	ELISA/TLC
Subacute/chronic	Sensory-ataxic	IgM MGUSP	MAG IgM, sulfatides IgM	Diagnostic, monitoring?	MAG → Pathogenic Sulfatides →Unknown	ELISA, nerve IF, HNK-1 CBA
		CANOMAD	Disialosyl IgM	Diagnostic	Likely pathogenic	ELISA/TLC
		Sensory neuronopathy	Para-neoplastic: Hu IgG, amphiphysin IgG	Diagnostic	Not pathogenic	Brain IF, blot
			Sjögren: Ro, La IgG	Diagnostic	Not pathogenic	EIA
	Pure motor	MMN	GM1/GalGalNAc IgM	Diagnostic	Likely pathogenic	ELISA/TLC
	Sensory-motor asymmetric	Multifocal CIDP	?			
		Mononeuritis multiplex	ANCA (MPO, PR3), cryoglobulins	Diagnostic, monitoring	MPO → Pathogenic; PR3 → Unknown Cryoglobulins → Unknown	ANCA →IF; MPO, PR3 →EIA Cryoglobulins →Cryoprecipitate quantification and immunofixation
	Sensory-motor symmetric	CIDP	Typical: ?			
			Distal: MAG IgM	Diagnostic, monitoring	Pathogenic	ELISA, nerve IF, HNK-1 CBA
		Autoimmune nodopathies	NF155, CNTN1 Caspr1, Pan-NF	Diagnostic, monitoring	NF155, CNTN1 → Pathogenic Caspr1, Pan-NF → Likely pathogenic	CBA, ELISA, teased nerve fibers IF
		Paraneoplastic	CRMP5, amphiphysin IgG	Diagnostic	Not pathogenic	Brain IF, blot

AIDP = acute inflammatory demyelinating polyneuropathy; AMAN = acute motor axonal neuropathy; AMSAN = acute motor-sensory axonal neuropathy; ANCA = anti-neutrophil cytoplasmic antibodies; ASAN = acute sensory ataxic neuropathy; CANOMAD = chronic ataxic neuropathy ophthalmoplegia, M-protein, cold agglutinins, and disialosyl antibodies; Caspr1 = contactin-associated protein 1; CBA = cell-based assay; CIDP = chronic inflammatory demyelinating polyneuropathy; CMV = cytomegalovirus; CNTN1 = contactin-1; CRMP5 = collapsin response-mediator protein-5; EIA = enzyme immunoassay; MAG = myelin-associated glycoprotein; MFS = Miller Fisher syndrome; MGUSP = polyneuropathy associated with monoclonal gammopathy of undetermined significance; MMN = multifocal motor neuropathy; MPO = myeloperoxidase; NF155 = neurofascin 155; PanNF = pan-neurofascin; PR3 = anti-proteinase-3; TLC = thin-layer chromatography.

In most cases, these antibodies are predominantly of the IgG4 subclass, which confers them pathogenic peculiarities: a high antigenic affinity and an inability to fix complement or bind to Ig receptors, which may explain why these patients do not respond to IVIg. However, as with other IgG4-mediated diseases, most patients respond well to B-cell depletion.[39] Of interest, these neuropathies show electrophysiologic demyelinating features without demyelinating pathology. Ultrastructurally, anti-CNTN1 and anti-NF155 patients show injury limited to the paranode, where antibodies disrupt axoglial junctions leading to paranodal loop detachment, while true de-remyelination and inflammatory changes are absent.[40] In addition, patients with anti-nodal-NF autoimmune nodopathy show pathology restricted to the node with the disappearance of the nodal microvilli of the Schwann cell that were replaced by elongated cytoplasmic extensions that occluded the nodal gap.[41] Both electrophysiologically and pathologically, these disorders are consistent with the original nodo-paranodopathy description.[1]

Anti-CNTN1 autoimmune nodopathy is characterized by a subacute-onset, predominantly motor, demyelinating neuropathy with poor response to IVIg.[42] Patients may also have ataxia and can associate cranial nerve involvement and respiratory failure. Anti-CNTN1+ AN often associates with nephrotic syndrome because of deposition of CNTN1 immune complexes in the glomeruli.[43] Nerve conduction studies show evidence of slow nerve conduction, but also early axonal involvement and early acute denervation is frequent. Anti-CNTN1 IgG4 antibodies demonstrated their pathogenicity in animal models[44]: After intraneural injection, IgG4 anti-CNTN1 diffused into the paranode and induced progressive deterioration of the animal model. Recent studies demonstrated that anti-CNTN1 IgG4 are, most frequently, bispecific and, thus, functionally monovalent antibodies are pathogenic.[45] In addition, anti-CNTN1 IgG3 antibodies can be detected during the early phases and may explain why a few patients show initial response to IVIg.[46] Anti-CNTN1 antibodies decrease (or become negative)

Figure 2 Autoimmune Nodopathies: Key Features That Should Prompt Testing for Nodal/Paranodal Antibodies



Caspr1 = contactin-associated protein 1; CNTN1 = contactin-1; IVIg = IV immunoglobulin; NF155 = neurofascin 155; PanNF = pan-neurofascin.

almost always after anti-CD20 therapy and are a good biomarker to monitor disease resolution and recurrence.

Anti-Caspr1 autoimmune nodopathy is characterized by an acute or subacute onset (that may lead to an initial misdiagnosis of GBS) with tetraparesis; sensory disturbances; ataxia, tremor, cranial nerve involvement including ophthalmoparesis and facial weakness; and respiratory failure.[2] CSF protein levels are highly elevated, and nerve conduction studies demonstrate slow conduction velocities associated with early axonal involvement. Anti-Caspr1 antibodies are mainly of the IgG4 subclass, but IgG3 antibodies are also detected during the early phase and in a few patients with GBS. Rarely, antibodies targeting both CNTN1 and Caspr1 can be detected.[17] In vitro and in vivo studies demonstrated that anti-Caspr1 IgG4 penetrated the borders of the paranodes and disrupted the interaction between NF155 and CNTN1/Caspr1 supporting their pathogenicity, but in vivo model studies are required to further elucidate their pathogenic mechanisms.[47] Anti-Caspr1 antibodies become negative in most patients upon successful treatment and are also useful to monitor disease course and recurrence in these patients.[48]

Anti-NF155 IgG4 is detected in 5%–10% of patients in which CIDP is suspected.[49] Anti-NF155 positive autoimmune nodopathy frequently occurs in young men and presents with predominantly distal motor involvement, ataxia, and cerebellar-like tremor. Head and vocal tremor or facial weakness was also reported. CSF protein levels are markedly elevated, and neurophysiologic studies demonstrate acquired demyelination. Most patients with anti-NF155+ autoimmune nodopathy carry the HLA DRB1*15 allele.[50] The pathogenicity of anti-NF155 IgG4 was demonstrated in animal models[51]: Anti-NF155 IgG4 caused NF155 depletion and prevented paranode formation during neonatal development. In adult rats, intrathecal infusion induced demyelinating polyradiculopathy with weakness and ataxia. Unlike anti-CNTN1 antibodies, bivalency was crucial for the pathogenicity of anti-NF155 antibodies and Fab-arm exchange, yielding functionally monovalent antibodies, decreased their pathogenicity.[52] Anti-NF155 antibodies titers are also useful to monitor these patients, and recent studies demonstrated their correlation with clinical scales and with serum neurofilament levels.[53]

Antibodies against nodal-NF and pan-NF are associated with an acute or subacute-onset severe phenotype, including tetraplegia, cranial nerve involvement, dysautonomia, respiratory failure, and nephrotic syndrome.[54] Cases with severe but monophasic course (even without B-cell depleting therapy) were reported. Some patients show an initial response to IVIg, followed by severe clinical deterioration. Anti-nodal-NF antibodies target the nodal isoforms of NF140 and NF186 while anti-pan-NF antibodies target an Ig domain found in the 3 NF isoforms (NF140, NF155, and NF186) located in the node and paranode. Electrophysiologic studies show conduction blocks and decreased motor nerve amplitudes that resolved after clinical remission. These findings suggest an RCF typical of nodopathies. Recent in vitro studies demonstrated that anti-pan-NF antibodies impaired the formation of the node of Ranvier supporting their pathogenicity.[55] However, animal model studies to unravel pathogenic mechanisms of these antibodies are pending.

Antibodies targeting the juxtaparanodal protein Caspr2 were reported in patients with neuromyotonia or neuropathic pain, generally associated with CNS involvement. However, a few patients can present with isolated neuropathic pain.[56] In addition, juxtaparanodal antibodies against leucine-rich repeat LGI family member 4 were recently reported in a Japanese cohort of patients with CIDP.[57] These antibodies associated with subacute-onset CIDP with high CSF protein levels and partial response to IVIg. These antibodies await validation in other cohorts.

How to Test

The antibody screening and confirmation tests used depend on the antibody tested (Figure 1), laboratory availability, and expertise. It is recommended to use a second assay to confirm their specificity and avoid false positives. Although overall assay accuracy is important, special emphasis needs to be placed on specificity and positive predictive values. The rarity of these disorders could lead, in a context in which clinical similarities support a broad use of the autoantibody tests, to high numbers of false positives that can then be treated with strategies that are inappropriate or directly harmful. Careful analysis of the technical features of the tests needs to be considered when implementing a diagnostic test, as the ones described in this review, and always consider technical errors if the results are unexpected for the clinical phenotype.

Anti-ganglioside antibodies are usually tested with an ELISA[58] and confirmed with thin layer chromatography that allows a more precise definition of sera reactivities. Dot-blot techniques are widely used for routine screening detection of anti-ganglioside antibodies, but their sensitivity and specificity are lower and, in our experience, blind reliance on their results frequently associate with misdiagnosis.[59] Ganglioside microarrays have been used to screen large number of samples for anti-ganglioside antibodies for research purposes, but they are not widely available in clinical service laboratories.

Antibodies against CNTN1, Caspr1, NF155, and nodal-NF identify their target epitopes when they are expressed in their native conformation. Therefore, both cell-based assays (CBAs) and immunofluorescence with teased-nerve fibers preparations are the optimal techniques to detect these antibodies. ELISA is widely accepted for screening of nodal/paranodal antibodies, titration, and IgG subclass identification. In fact, ELISA has, for example, higher sensitivity than fixed Caspr1 CBA in the detection of anti-Caspr1 antibodies.[48] EAN/PNS guidelines[35] recommend to use a second confirmatory technique to confirm positive antibodies because a low rate of false positives have been reported by ELISA or CBA. If screening is performed with ELISA, CBA can be confirmatory and vice versa. Immunofluorescence with teased nerve fibers shows a nodal, paranodal, or combined staining pattern depending on the antibody tested and is a good confirmation technique but is not widely available for clinical routine. Based on our experience, alternative techniques such as Western blot should be avoided because they yield a high false-positive rate. The results of an interlaboratory validation study awaiting publication will define the gold standard techniques for screening and confirmation of antibodies against the node of Ranvier.

Anti-MAG and anti-sulfatide antibodies are usually tested with a commercial ELISA. In patients with low anti-MAG titer (between 1.000 and 7.000 Bühlmann titer units) or in patients with no detectable IgM paraprotein, it is recommended to confirm these antibodies with immunofluorescence using commercially available PN tissue. Recently, a new CBA demonstrated good diagnostic performance for anti-human natural killer-1 antibodies (the epitope that anti-MAG antibodies target).[60] Anti-sulfatide IgM antibodies are also tested by ELISA and confirmed with PN immunofluorescence. Onconeural antibodies are tested in most laboratories with a commercial immunoblot. Because the detection of these antibodies has serious implications and, in some cases, the immunoblot is not specific or sensitive enough, it is highly recommended to use a second technique, such as immunofluorescence with brain tissue, to avoid false negatives and false positives, particularly if patients present with a typical paraneoplastic syndrome such as sensory neuronopathy.

Why to Test

Antibodies are useful tools in the diagnostic process of AN. They allow the identification of patients who may benefit from immunomodulatory treatment. They also may help detect a systemic or underlying disease. Moreover, the description of antibodies in AN has helped understand the immunopathogenesis of specific subtypes of AN in depth, and they are key effector mechanisms in AN of diverse nature. Thus, research aiming to find the antigens that drive the immune responses of those AN in which specific autoantibodies have not been discovered yet should be encouraged and funded.

In summary, although guidelines do not advocate for systematic testing of anti-ganglioside antibodies for diagnostic purposes in GBS, testing for anti-GD1b IgG antibodies helps in the differential diagnosis of acute sensory-ataxic neuropathies, while the presence of anti-GQ1b IgG antibodies strengthens the diagnostic certainty in MFS. Conversely, a negative anti-GQ1b IgG test should trigger concerns about the MFS diagnosis. Similarly, a positive anti-GM1 IgG test provides reassurance and validation of clinical suspicion when uncertainties in diagnosis arise. For chronic sensory-ataxic neuropathies, the identification of anti-MAG IgM and anti-disialosyl IgM antibodies plays a crucial role in diagnosing and treating properly anti-MAG neuropathy and CANDA/CANOMAD spectrum neuropathies. These antibodies also help differentiating these conditions from CIDP associated with an IgM monoclonal gammopathy. Furthermore, high-titer anti-GM1 IgM antibodies identify MMN and patients with LMNS that respond to IVIg but can

worsen with steroids. Moreover, nodal/paranodal antibodies play a crucial role in diagnosing autoimmune nodopathies and have proved useful for detecting subclinical disease activity and anticipate clinical relapses: In our clinical experience, serial nodal/paranodal antibody testing helps with detecting a relapse earlier and helps with prescribing immunosuppressive treatment in a timely manner.

For all these reasons, disease-specific antibodies, tested following appropriate protocols, are critically useful biomarkers for the diagnosis, prognosis, monitoring, and treatment selection in patients with AN and should be available in the clinical routine of all neurologists and neuromuscular specialists.

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