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Antibody Testing in Peripheral Neuropathies

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Causes of peripheral neuropathy (PN) include a wide range of genetic, toxic, metabolic, and inflammatory disorders. Several PNs have an autoimmune basis, either as a consequence of systemic autoimmune disease, an autoimmune disorder specifically targeting peripheral nerve or ganglia, or a remote effect of malignancy. Several clinical presentations are distinctive for the autoimmune neuropathies. Subacute progression, asymmetric or multifocal deficits, and selective involvement of motor, sensory, or autonomic nerves are clues suggesting an autoimmune, inflammatory cause. The clinical presentation, however, may be indistinguishable from other forms of chronic length-dependent sensorimotor PN.

Antibodies against specific glycolipids or glycoproteins, such as anti-GM1 and anti–myelin-associated glycoprotein (MAG), are associated with inflammatory (often demyelinating) peripheral nerve syndromes. In some cases, these antibodies identify motor or sensory neuropathies that are responsive to immunotherapy [1–3] or those with a different prognosis [4,5]. Antineuronal nuclear and cytoplasmic antibodies (such as anti-Hu and CRMP-5) help identify patients who have paraneoplastic neuropathy resulting from remote immunologic effects of malignancy [6,7]. Various other serologic tests, although less specific, can be used to provide clues about the presence of systemic autoimmune disease that can affect the nerves. These include serologic markers for Sjögren's syndrome (SS), rheumatoid arthritis, celiac disease, and systemic vasculitides (such as Churg-Strauss syndrome) [8,9].

Because the cause of acquired neuropathies often is obscure, autoantibody testing can be of great diagnostic value in identifying autoimmune

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neuropathy. There currently are many available antibody tests to consider when evaluating PNs. Some tests are important and specific in the appropriate clinical settings, whereas the significance of other antibodies remains unknown. As an added complication, antibody assay techniques vary among laboratories, as do the sensitivity and specificity of the serologic testing. The role of these autoantibodies in the pathogenesis of PN remains largely unproved and debated [10–12]. Nevertheless, several mechanisms recently have been elucidated by which antiganglioside antibody binding to axons or Schwann cells may exert a pathogenic effect. These include alteration of ion flux causing partial conduction block and triggering leukocyte responses resulting in cytotoxicity, cytokine production, phagocytosis, and degranulation. Furthermore, animal models that mimic sensory ataxic and motor axonal neuropathies in humans have been generated in rabbits immunized with GD1b and GM1 [13,14] Antibody results in individual patients must be correlated with clinical findings to determine the significance of the findings. Whenever possible, autoantibody tests should be selected according to the clinical presentation to enhance usefulness and cost-effectiveness.

Antibodies against glycosylated nerve components

Peripheral nerve contains many glycoprotein and glycolipid components. Gangliosides are complex acidic glycosphingolipids containing the lipid ceramide, glucose, galactose, and one or more sialic acid residues [15]. The ceramide moiety anchors the glycolipid to the nerve cell membrane. In the nomenclature, the first letter, G, stands for ganglioside, and the second letter corresponds to the number of sialic acid residues (M = 1, D = 2, T = 3, and Q = 4). The numeral represents the number of complete tetrasaccharide chains (usually 1 in humans), and the final lower-case letter (a or b) denotes the isomeric position of the sialic acid residue. At least a dozen different gangliosides are present in peripheral nerve [10]. Several glycolipids are sulfated, the most common being sulfatide (sulfated galactosylceramide). Although these gangliosides represent only a small fraction of the total glycolipid content of peripheral nerve, they typically are exposed on the surface of the nerve or myelin membrane and, therefore, are potential antigenic targets for circulating components of the immune system. Furthermore, the glycolipid structure of the nervous system is unique compared with other tissues. In theory, this could lead to an autoimmune process that is organ specific. Antibodies against glycolipids are believed an important part of the immune response against microbial carbohydrate antigens. Thus, molecular mimicry may explain the pathophysiology of postinfectious inflammatory neuropathies [16]. Lipopolysaccharide from *Campylobacter jejuni* strains that are associated closely with Guillain-Barré syndrome (GBS) or Miller Fisher syndrome (MFS) more often contain GM1 or GQ1b mimics than those bacterial strains that cause only enteritis [17]. Ganglioside and other glycolipid

antibodies may be useful serologic markers of inflammatory PN (Table 1) but also may be found in a variety of other disease states and in normal healthy individuals.

Anti–myelin-associated glycoprotein antibodies

In addition to gangliosides, peripheral nerve also contains several glycoproteins, including MAG, myelin protein zero, and peripheral myelin protein 22. In 1980, Latov and colleagues [18] described a patient who had a demyelinating neuropathy and an IgM-κ gammopathy. The patient improved with immunosuppressive therapy. MAG later was identified as the target antigen for the IgM-κ monoclonal antibody. It also was determined that monoclonal proteins with and without anti-MAG activity would bind to peripheral nerve gangliosides [19]. As a result of these observations, glycoproteins and gangliosides were proposed as potential autoantigens in PN. Subsequent reports confirmed that approximately 50% of patients who have neuropathy and IgM gammopathy have IgM autoantibodies to MAG [20]. Anti-MAG autoantibodies often cross-react with other peripheral nerve glycolipids, including 3-sulfated glucuronyl paragloboside (SGPG) and sulfated glucuronyl lactosaminylparagloboside, which share an antigenic carbohydrate determinant with MAG [21].

The typical clinical presentation of the neuropathy associated with anti-MAG antibodies is a slowly progressive, distal, symmetric, predominantly sensory or sensorimotor PN [20–22]. Most patients are male. The neuropathy begins with sensory symptoms, and approximately 75% of patients

Table 1
Ganglioside autoantibodies and neuropathy syndromes

Autoantibody	Main immunoglobulin classes	Clinical syndromes
SGPG/MAG	IgM, monoclonal	Demyelinating neuropathy with IgM gammopathy [20,21]
GM1/asialo GM1	IgM > IgG	MMN [1,2,30]
	IgG or IgM	ALS/MND [30,31]
	IgG > IgM	GBS [4,5]
	IgG	AMAN
	IgG or IgM	Lower motor neuron syndromes [3]
GD1b	IgM,[a] monoclonal	Sensory PN [19,35,36]
	IgM[b]	MND [37]
	IgG > IgM[b]	GBS
GQ1b	IgG > IgM	MFS [43]
Sulfatide	IgM > IgG	Chronic sensory PN [22,47]
GALOP	IgM, monoclonal	Ataxic sensory neuropathy

Abbreviations: AMAN, acute motor axonal neuropathy; GBS, Guillain-Barre syndrome; MFS, Miller-Fisher syndrome; MND, motor neuron disease; MMN, multifocal motor neuropathy.

[a] IgM cross-reacts with other gangliosides sharing disialosyl configurations.

[b] Immunoglobulin often cross-reacts with GM1 and other gangliosides.

present with paresthesias [20]. Large-fiber sensory deficits can be severe. Gait ataxia presents a major disability in one third of patients, and hand tremor commonly is observed. Over time, the majority of patients develop motor nerve involvement with primarily distal weakness. The legs usually are affected more than the arms. Deep tendon reflexes usually are reduced or absent.

On laboratory testing, an IgM paraprotein is found in approximately 50% of cases on serum protein electrophoresis (SPEP) and immunofixation (IFE) studies, typically with a κ light chain. Nerve conduction studies demonstrate demyelination in a majority of patients [20–22]. Prolonged distal motor latencies are the most reliable finding, seen in 90% of patients. Neuropathy associated with IgM gammopathy but no anti-MAG activity may be clinically indistinguishable from the anti-MAG neuropathy [23].

A positive anti-MAG assay confirmed by Western blot is strongly suggestive of an immune-mediated PN, usually associated with an IgM paraprotein. Some patients fulfill diagnostic criteria for CIDP and should be treated appropriately. Immunotherapy regimens should be attempted in patients who have significant neurologic impairment, although the treatment response often is disappointing. The presence of an IgM paraprotein should prompt a workup for an underlying plasma cell dyscrasia.

Anti-GM1 antibodies

In 1984, Freddo and coworkers described a lower motor neuron syndrome with monoclonal IgM reactive to GM1 and gangliosides GD1b and asialo GM1 [24]. Polyclonal autoantibodies to GM1 subsequently were reported in patients who had multifocal motor neuropathy (MMN) [2]. Since then, the presence of anti-GM1 antibodies has been described in a variety of motor neuron disorders and motor-predominant neuropathies, including amyotrophic lateral sclerosis (ALS) and GBS (see Table 1).

MMN with conduction block is a potentially treatable neuropathy characterized by asymmetric, painless, slowly progressive weakness most commonly affecting the distal upper limbs [2,25]. Because of the asymmetric, distal weakness, sensory sparing, and occasional atrophy and fasciculations, MMN may resemble ALS. Upper motor neuron signs, however, are not a feature of MMN. Motor nerve conduction studies demonstrating conduction block outside of common compression sites are associated strongly with MMN and help distinguish it from MND [25,26]. There also are some patients who have clinical features of MMN without conduction block that respond to immunotherapy [27].

High-titer, anti-GM1 IgM antibodies are present in 50% to 60% of patients who have MMN [11,28]. The sensitivity of IgM anti-GM1 antibodies in MMN may be increased to 85% by complexing the GM1 antigen with secondary amino groups (co-GM1 antibody test) [29]. Because of the incomplete sensitivity, anti-GM1 antibody should not be considered a requirement

for the diagnosis of MMN. Large studies of patients who had PN and MND suggest that high titers of IgM anti-GM1 antibodies are specific for immune-mediated motor-predominant neuropathies [28,30]. Lower titers of GM1 antibodies are hard to interpret, as they may be found in ALS, other PNs [1,31], or normal controls.

Anti-GM1 antibodies, predominantly of the IgG class, also are reported in a variety of acute motor neuropathies, including GBS [4,5]. Seropositivity for GM1 and related gangliosides in GBS is associated closely with evidence of *C jejuni* infection. Several GBS studies find that anti-GM1 antibodies are associated with a more severe neuropathy with widespread axonal degeneration and worse recovery [4,5], although this association is not absolute. *C jejuni* infection and anti-GM1 antibodies commonly are found in patients who have the classic, demyelinating form of GBS. Thus, the value of anti-GM1 testing in individual patients who have GBS is limited, and a positive result has no clear implication for patient management.

In addition to GM1, antibodies to a variety of other gangliosides are found in GBS, including GD1a, GD1b, and GM2. Overall, high-titer anti-ganglioside antibodies are detected in approximately 40% of GBS sera [32]. Some studies show that IgM anti-GM2 antibodies are found in approximately 50% of GBS associated with cytomegalovirus (CMV) infection, a frequency significantly higher than for other forms of GBS [33]. Another study, however, fails to find a close association between these antibodies and GBS, as anti-GM2 antibodies were found occasionally in normal subjects and also seen in acute CMV infection whether or not GBS was present [34].

Anti-GD1b and anti-GD1a antibodies

Clinical correlates for anti-GD1b antibodies are varied, including sensory and sensorimotor PN syndromes similar to those associated with antisulfatide antibodies [19,35,36], MND [37], and GBS [38]. In most settings, the antibody is of the IgM class and cross-reacts with other disialosyl-bearing gangliosides, including GD2, GD3, GT1b, and GQ1b. Although serologic testing for anti-GD1b antibodies is available through commercial laboratories, the role of this antibody in the diagnosis and treatment of neuropathy remains unclear.

Anti-GD1a antibodies are reported in several cases of axonal GBS [38]. In a recent study using a Chinese population [39], IgG anti-GD1a antibodies were detected in a high proportion (60%) of patients who had acute motor axonal neuropathy (AMAN). Only 4% of patients who had the demyelinating form of GBS harbored these antibodies. Although IgG anti-GM1 antibodies also were found frequently in the AMAN population, they were not as specific or sensitive as IgG anti-GD1a antibodies. No relationship between antiganglioside antibodies and *C jejuni* infection was found. The investigators concluded that reactivity to a GD1a-related epitope may be important in the pathogenesis of axonal GBS. The role of anti-GD1a antibodies in clinical practice, however, remains unresolved.

Anti-GQ1b antibodies

In contrast to the limited specificity of other antiganglioside antibodies, anti-GQ1b antibodies are linked closely to MFS. MFS is considered a variant of GBS characterized by the triad of ophthalmoplegia, ataxia, and areflexia. Formes frustes of MFS typically present as acute cranial motor neuropathies with ataxia [40]. GQ1b is expressed abundantly in paranodal regions of the oculomotor, trochlear, and abducens nerves [41], providing a rationale for the ophthalmoplegia common to patients who have anti-GQ1b antibodies. Several studies confirm that high titers of anti-GQ1b IgG antibodies are present in 80% to 100% of patients who have MFS [42,43]. Anti-GQ1b IgG antibodies also are reported in GBS patients who have ophthalmoplegia or ataxia [41,44] and with other neurologic disorders that bear clinical similarities to MFS, such as Bickerstaff's encephalitis [45], and acute ophthalmoparesis [46]. GQ1b epitopes are present in certain strains of *C jejuni* that are associated with antecedent infections in patients who have MFS [4,16]. As with "classic" forms of GBS, patients who have MFS respond to plasma exchange, with a corresponding reduction in anti-GQ1b antibody titers [42]. Other antiganglioside antibodies that are associated with MFS and ataxic neuropathy are anti-GT1a, anti-GD3, and anti-GD1b [40].

Antisulfatide antibodies

The discovery of cross-reactivity of anti-MAG antibodies to sulfated glycolipids encouraged researchers to investigate whether or not autoantibodies to other common sulfated glycolipids could be found in patients who have PN. Two initial studies demonstrated autoantibodies to sulfatide in approximately 25% of patients who had predominantly sensory PN that otherwise would have been classified as idiopathic [22,47]. Later studies, however, failed to show a high frequency of antisulfatide antibodies in patients who had this common clinical presentation [28,48]. The predicted frequency of IgM antisulfatide antibodies in idiopathic PN later was estimated at only 0.7% [49].

Patients who have PN and who have sulfatide antibodies tend to present with chronic, axonal, predominantly sensory PN. Sensory loss is symmetric, distal, and slowly progressive over a period of years, eventually impairing small- and large-fiber function. Pain is the predominant symptom in approximately one half of patients. Distal weakness is uncommon [50] and tends to be mild. Higher titers of antisulfatide antibodies are relatively specific for chronic, sensory-predominant PN. Monoclonal gammopathies are present in up to 50% of those cases. Low titers are found in a variety of neuropathic and non-neuropathic conditions (including idiopathic thrombocytopenic purpura, autoimmune hepatitis, and human immunodeficiency virus).

A subgroup of patients who has *g*ait disorder, *a*ntibody, *l*ate-age–*o*nset *p*olyneuropathy (GALOP) syndrome has been reported. These patients commonly have a monoclonal IgM and have antibodies to sulfatide and other

antigens, including a central myelin GALOP antigen [51]. Testing for GALOP antibodies is available but the significance is not established fully.

Paraneoplastic peripheral neuropathy

Paraneoplastic neurologic disorders (PND) are immunologic disorders of the nervous system in patients who have malignancy. PND may affect any part of the nervous system. PN is encountered commonly in cancer patients, in many cases attributable to metabolic derangements or toxic effects of chemotherapeutic agents. An inflammatory/autoimmune PN can occur as a remote effect of cancer, usually preceding any systemic symptoms or diagnosis of cancer. It is believed that the most common presentation of paraneoplastic PN is a length-dependent sensorimotor axonal neuropathy indistinguishable from those of nonparaneoplastic causes. One study estimates that 4.5% of patients who have unexplained adult-onset axonal sensorimotor neuropathy have a malignancy [52]. A few clinical features may increase the suspicion of PND. The onset of paraneoplastic neuropathy tends to be more rapid with progression of symptoms, signs, and electrophysiologic changes over weeks or months. Pain is typical, and there may be unusual manifestations (such as intense itching reported in association with breast cancer) [53]. On electrophysiologic studies, there may be evidence of more widespread nerve involvement affecting nerve roots and peripheral nerves. Analysis of cerebrospinal fluid may show elevated protein or mild lymphocytic pleocytosis.

Paraneoplastic PN is associated with several cancers (small cell and non–small cell lung cancer, breast cancer, and thymoma) and with several autoantibody markers (Table 2), notably type-1 antineuronal nuclear antibodies (ANNA-1), CRMP-5, and N-type calcium channel antibodies. Antibody studies, however, can be negative in many patients who have paraneoplastic PN [52]. Typically, the neurologic syndrome precedes the diagnosis of cancer, and the detection of cancer often is delayed despite close surveillance.

Paraneoplastic sensory neuropathy

Progressive neuropathy that affects the sensory nerves exclusively is termed pure sensory neuropathy, sensory ganglionopathy, or sensory neuronopathy. Approximately 20% of cases of sensory neuronopathy are paraneoplastic; the remainder are associated with systemic autoimmune disease (notably SS) or toxin exposure or remain idiopathic. Paraneoplastic sensory neuronopathy is uncommon, affecting less than 1% of patients who have small cell lung carcinoma [54]. There is a female predominance with a median age of onset of approximately 60 years. The underlying neoplasm is small cell lung carcinoma in 80% to 90% of cases [7,55]. In nearly all patients, the neurologic syndrome and seropositivity precede diagnosis of the tumor. The pathologic correlate of paraneoplastic sensory neuronopathy is destruction of neurons and inflammation in the dorsal root ganglia.

Table 2
Neuronal paraneoplastic autoantibodies associated with peripheral neuropathy

Antibody	Usual tumor	Commonly associated syndromes
ANNA-1 (anti-Hu) [7]	SCLC	Limbic encephalitis, ataxia, sensory neuronopathy, autonomic and sensorimotor neuropathies
CRMP-5 (anti-CV2) [6]	SCLC or thymoma	Encephalomyelitis, chorea, neuropathy, optic neuritis
Amphiphysin	Lung or breast cancer	Encephalomyelitis, neuropathy, stiff-person syndrome
ANNA-2 (anti-Ri)	Lung or breast cancer	Ataxia, opsoclonus-myoclonus, neuropathy
ANNA-3	SCLC	Ataxia, limbic encephalitis and neuropathy
N-type calcium channel antibodies	Lung or breast cancer	PN and many other syndromes

Alternate nomenclature is indicated in parentheses.

Initial symptoms consist of distal pain, numbness, and paresthesias, which can be asymmetric. Clumsiness and gait unsteadiness develop as a result of marked loss of joint position sense. This sensory ataxia is distinct from ataxia because of a cerebellar disorder. Unlike cerebellar disorders, speech and eye movements are normal. Loss of balance and coordination become much worse with eyes closed, and slow wandering movements of the digits or limbs (pseudoathetosis) may be seen. Muscle stretch reflexes usually are absent. Often, paraneoplastic sensory neuropathy progresses relentlessly over weeks or months, leading to significant disability because of inability to walk or attend to basic needs. Because of marked insensitivity, patients may be unaware of serious injuries to the extremities. Nerve conduction studies show absent or low amplitude sensory responses with normal or minimally affected motor studies. The trigeminal blink reflex response usually is normal, perhaps because trigeminal sensory neurons are more centrally located than the dorsal root ganglia. Abnormalities of the trigeminal blink reflex should raise the possibility of a nonparaneoplastic inflammatory sensory neuropathy (as can be seen with SS) [55,56].

Paraneoplastic and autoimmune autonomic neuropathy

In some cases, autoimmunity can target the cells and axons of the autonomic nervous system specifically and spare the motor and sensory nerves. Autonomic dysfunction has many causes, but many cases of subacute autonomic failure have an autoimmune basis and some have an underlying malignancy. Common symptoms of autonomic neuropathy are syncope (resulting from orthostatic hypotension), heat intolerance (resulting from anhidrosis), dry mouth, severe constipation, and vomiting. The latter symptoms are the result of abnormalities of gastrointestinal motility. An

autoimmune, nonparaneoplastic form of autonomic neuropathy (autoimmune autonomic neuropathy) seems to be caused by antibodies against neuronal ganglionic acetylcholine receptor (the receptor that mediates synaptic transmission in autonomic ganglia) [57].

Paraneoplastic autonomic neuropathy can present as a subacute panautonomic neuropathy (indistinguishable from nonparaneoplastic autoimmune autonomic neuropathy). Limited presentations also may occur, most notably severe gastrointestinal dysmotility without other autonomic features (paraneoplastic enteric neuropathy). As with other paraneoplastic disorders, the symptoms usually precede the diagnosis of cancer, and the tumors, when found, are limited in stage or are only locally metastatic (regional lymph nodes). Hence, because patients have no symptoms directly referable to their tumor, their autonomic symptoms cannot be attributed to direct effects of the malignancy, nonspecific consequences of chronic illness, or chemotherapy-induced neuropathy.

Paraneoplastic autonomic neuropathy commonly is associated with small cell lung cancer and anti-Hu (also known as ANNA-1) antibodies. Many patients who have paraneoplastic neuropathy have evidence of additional neurologic impairment, including limbic encephalitis, cerebellar ataxia, brainstem involvement, or myelitis [55]. Paraneoplastic gastrointestinal dysmotility is especially common and may be the presenting feature [7].

Paraneoplastic autoantibodies

The use and interpretation of antibody testing in suspected paraneoplastic neurologic disease (PND) is an area of much confusion because of the growing number of antibodies and their varied clinical associations. Antibodies that are associated with PN syndromes are presented in Table 2. The majority of paraneoplastic antibodies are directed against intracellular antigens in the nucleus or cytoplasm of neurons. In some cases, the protein antigen has been identified definitively, and testing using Western blot against recombinant protein is available. In other cases, the antibody is defined descriptively based on the pattern of immunohistochemical staining of brain sections. Many of the antibodies are shown to recognize antigens in nerve and in tumor cells. These antibodies are important as surrogate markers of a specific immune response to cancer. Each of the paraneoplastic neuronal nuclear and cytoplasmic antibodies can be associated with several different neurologic syndromes but typically are highly specific for the presence of cancer and predictive of the cancer type.

No single individual neuronal paraneoplastic antibody is a very sensitive diagnostic tool. Even when the most complete battery of paraneoplastic antibodies is obtained, many patients who have a subacute neurologic syndrome and proved cancer have no paraneoplastic antibody detected [58,59]. Thus, negative antibody tests cannot exclude a paraneoplastic cause of neuropathy, but seropositivity for a paraneoplastic antibody should mandate a thorough

evaluation for occult malignancy and close oncologic follow-up if cancer is not detected on the initial search. Anti-Hu (ANNA-1) and CRMP-5 (anti-CV2) antibodies deserve special attention because of their frequent association with PN. Several other uncommon paraneoplastic antibodies, including amphyiphysin, ANNA-2 (anti-Ri) and ANNA-3 also are associated with paraneoplastic neuropathy, usually lung or breast carcinoma. Patients who have these cancers also may produce antibodies against N-type voltage-gated calcium channels. These calcium channel antibodies are different from the P/Q-type calcium channel antibodies associated with Lambert-Eaton syndrome and may be associated with several paraneoplastic syndromes, including neuropathy.

Anti-Hu (ANNA-1) antibodies

Anti-Hu antibodies (ANNA-1) bind to a family of 35–40 kd proteins expressed in the nuclei of neurons of the central nervous system, dorsal root ganglia, and myenteric plexus. These antigens also are expressed in certain tumor cells, most notably small cell lung carcinoma. Low titers of anti-Hu IgG antibodies are detected in the serum of approximately 15% of patients who have small cell lung carcinoma without a paraneoplastic syndrome [60]. Higher titers are associated with a wide variety of neurologic syndromes, ranging from limbic encephalitis to neuropathy. PN is the most common initial manifestation, occurring in 70% to 80% of patients who have anti-Hu antibody [7]. Half of these paraneoplastic neuropathies are sensory. Approximately 25% of patients who have anti-Hu have some features of gastrointestinal dysmotility.

On detection of a positive serology, patients should be screened aggressively for an underlying malignancy, beginning with chest CT if routine chest radiographs are negative. Nearly 90% of adult patients who have anti-Hu antibodies have cancer, usually small cell lung carcinoma [61]. Bronchoscopy, mediastinoscopy, or thoracotomy may identify occult tumors when radiologic studies are negative [7]. Metabolic imaging with fluorodeoxyglucose positron emission tomography scan recently has been shown to be the most sensitive test for detecting occult small cell cancer in patients who have paraneoplastic disorders [62]. There are rare reports of anti-Hu positive patients who do not develop cancer after 4 or more years. One possibility is that the vigorous immune response leads to a spontaneous cancer remission [63]. In other cases, the small cell cancer may evade detection until a patient dies of neurologic complications. If a chest malignancy is not found, the search should be widened to include other tumors, especially neuroblastoma or small cell carcinomas arising in other organs. Periodic follow-up imaging every few months is recommended if initial screening is unremarkable.

As with most paraneoplastic antibodies, a pathogenic role for anti-Hu antibodies seems unlikely as passive transfer of anti-Hu antibodies or

immunization with the HuD antigen has failed to reproduce disease in animals, despite the development of high anti-Hu titers [12].

CRMP-5 (anti-CV2) antibodies

Approximately 10 years ago, in 1996, a novel paraneoplastic antibody was described, and designated anti-CV2, which recognized collapsin response-mediator proteins (CRMPs), specifically CRMP-3, and was associated with a variety of paraneoplastic syndromes [64]. More recently, another paraneoplastic antibody was characterized in more than 100 patients, which specifically recognized a 62-kd antigen that proved to be CRMP-5 [6]. CRMP-5 is a neuronal cytoplasmic protein present in adult central and peripheral neurons, and in small cell lung carcinomas. Given the similarities between CV2 and CRMP-5 antibodies, it is possible that these two paraneoplastic antibodies actually are one and the same. CRMP-5 antibodies are proving to be one of the most common markers of PND. The antibody often coexists with other paraneoplastic antibodies and is second in frequency only to anti-Hu (ANNA-1) as a marker of SCLC [6,61].

The associated neurologic syndromes are diverse (much like those associated with anti-Hu antibodies) and include PN, limbic encephalitis, ataxia, and recently recognized paraneoplastic syndromes of chorea and optic neuritis. PN, usually axonal sensorimotor type, is present in approximately one half of patients [6]. Autonomic neuropathy occurs in approximately one third. Lung carcinoma (small cell type) eventually is found in nearly 80% of seropositive patients. CRMP-5 antibodies also can be found in patients who have thymoma, with or without neurologic symptoms [6,65].

Neuropathy associated with systemic autoimmune diseases

Peripheral nerve vasculitis

In systemic vasculitis (most notably Churg-Strauss, polyarteritis nodosa, and Wegener's granulomatosis), PN occurs in 40% to 50% of patients. The neuropathy classically presents as painful mononeuritis multiplex, involvement of multiple individual nerves. Radial and peroneal nerves often are involved. A presentation with painful distal symmetric axonal neuropathy is not uncommon, however. Typically, if vasculitis affecting peripheral nerve is suspected, definitive diagnosis is obtained by biopsy of nerve (or other affected organs). Antibody tests can be useful in the initial evaluation to help raise the suspicion. These include antiproteinase 3 antibodies, antineutrophilic cytoplasmic antibodies (c-ANCA), which are found in many patients who have Wegener's granulomatosis and antimyeloperoxidase antibodies (p-ANCA), which are associated with Churg-Strauss and polyarteritis

nodosa. Antinuclear antibodies (ANA) and rheumatoid factor (RF) also are associated with these vasculitides.

PN is found commonly in patients who have rheumatoid arthritis. Severe painful neuropathy or mononeuritis multiplex occurs when there is an associated vasculitis. High levels of RF and ANA may be found in patients who have vasculitic neuropathy even if joint manifestations are not evident. Patients who do not have systemic vasculitis that have had typical rheumatoid arthritis for many years often develop a mild symmetric PN.

In all cases, aggressive treatment of the underlying vasculitis with corticosteroids and other immunosuppression is the mainstay of therapy. Isolated peripheral nerve vasculitis also can occur but generally is not associated with any serologic antibody markers.

Neuropathy with Sjögren's and sicca syndromes

The exact frequency of neuropathy associated with primary SS is unknown but estimated to be approximately 10% [66]. A variety of neuropathies can be encountered, and neuropathy may be the initial presentation of the autoimmune disease. Similar patterns of neuropathy may be encountered in patients who have sicca syndrome (dry eyes and dry mouth) that do not fulfill diagnostic criteria for SS [8]. Sensory neuropathy is the most common presentation, usually a painful distal small-fiber neuropathy. Sensory ganglionopathy with sensory ataxia and trigeminal sensory loss is a distinctive but uncommon presentation. The involvement of the trigeminal sensory nerve helps distinguish this form of sensory ganglionopathy from the paraneoplastic sensory neuronopathy [56]. Autonomic features often are present in neuropathic presentations, characterized by sweating abnormalities and constipation. In a minority of cases, tonic unresponsive pupils can occur. Preliminary studies suggest that antibodies against the muscarinic acetylcholine receptor (AChR) may be associated with the autonomic neuropathy of SS [67]. Other less common neuropathic presentations include trigeminal sensory neuropathy, multiple cranial neuropathies, or vasculitis with mononeuritis multiplex. Central nervous system manifestations also can be associated with SS.

Patients who have SS predominantly are female. Diagnosis consists of symptoms and objective evidence of dry mouth and dry eyes along with confirmatory salivary gland biopsy showing inflammation or presence of antibodies. The antibodies that are associated most closely with SS are anti-Ro/SS-A and anti-La/SS-B. These antibodies are found in approximately 60% of patients who have SS. Other serologic findings include ANA and RF antibodies.

Celiac neuropathy

Celiac disease is a T-cell–mediated autoimmune disorder associated with sensitivity to ingested gluten protein in people who are genetically

predisposed. Patients develop antibodies against tissue transglutaminase (TTG) and other intestinal antigens and pathologically show injury to small bowel mucosa. Typical symptoms are diarrhea, weight loss, and dermatitis herpetiformis [68]. Various studies suggest that axonal distal sensory PN is common in patients who have celiac disease [9]. It is unclear if the neuropathy results from an associated autoimmune attack against nerve or relates to nutritional deficiency resulting from impaired intestinal function. Neuropathy and other neurologic symptoms (ie, ataxia) can occur even in the absence of gastrointestinal symptoms. The neuropathy usually is a mild sensory PN. Various studies show an incidence of celiac disease that is higher than expected (2.5% or higher) in patients who have idiopathic sensory neuropathy [9]. The significance of the association between celiac disease and neuropathy, therefore still remains somewhat controversial.

For diagnostic purposes, antibody tests are useful as screening tools, but definitive diagnosis of celiac disease requires endoscopic biopsy of small bowel mucosa. The most readily available antibody tests are for antigliadin antibodies. Serum antigliadin IgA is more specific for celiac disease because gliadin IgG antibodies can be found in normal healthy controls [69]. IgA antiendomysial antibodies and TTG antibodies are more specific than gliadin antibodies. These antibodies associate with the presence of intestinal disease, however, and are less common in patients who have neurologic disease without bowel involvement. Thus, the usefulness of serologic testing for celiac disease in the evaluation of PN remains unclear. These antibody tests can be used as screening tools in patients who have idiopathic sensory or sensorimotor neuropathy (especially in patients who have gastrointestinal symptoms or the suggestive dermatitis herpetiformis rash). Positive results should prompt further evaluation with gastrointestinal endoscopic studies. Recent studies have described the frequent presence of IgG ganglioside antibodies (including anti-GM1 and anti-GD1b) in 20% to 60% of celiac patients who have neurologic symptoms [9,70,71]. The significance remains unclear because many celiac patients who do not have neurologic symptoms also may harbor ganglioside antibodies.

The current treatment for celiac disease is maintenance of a restricted gluten-free diet. Dietary modification is effective for treating the bowel manifestations, but there is no conclusive evidence that the associated PN improves.

Clinical guidelines for autoantibody testing

The initial evaluation of PN should include a thorough evaluation to define the neuropathy on clinical grounds (symmetric versus asymmetic, sensory versus motor, and so forth) and to determine (1) whether the process primarily is axonal or demyelinating and (2) whether conduction block is present. If a cause of the PN is not apparent, SPEP with IFE is important to detect the presence of a monoclonal protein. Additional specific antibody tests are warranted depending on the presenting features.

Sensorimotor or sensory polyneuropathy

In the setting of an idiopathic sensorimotor PN, autoantibody testing can be considered in certain circumstances. If there is evidence of demyelination on NCS (in particular prolonged distal latencies) anti-MAG testing may help clarify the diagnosis and help distinguish this neuropathy from CIDP. Also, because many patients who have anti-MAG antibodies have an IgM monoclonal protein, anti-MAG antibodies can be sought for any patients who have PN with IgM monoclonal proteins. Routine testing for antiganglioside or antisulfatide autoantibodies in the setting of axonal neuropathies is not established.

Testing for serologic markers of celiac disease (gliadin, endomysial, and transglutaminase antibodies) can be considered in cases of idiopathic progressive neuropathy. At present, the nature and treatment of celiac neuropathy remains unclear, so antibody testing is not a routine part of a PN evaluation. These tests might be considered when there are suggestive gastrointestinal symptoms. Further, these tests are not specific for celiac disease, so additional evaluations always are necessary to establish a diagnosis of gluten sensitivity.

In patients presenting with sensory neuronopathy (asymmetric and proximal sensory deficits), paraneoplastic antibody testing is indicated, particularly because a positive antibody result allows early diagnosis and treatment of an underlying malignancy. The role of paraneoplastic antibody testing in symmetric, slowly progressive neuropathies of unknown cause remains controversial. A rational approach is to test patients who have neuropathy and who have a significant smoking history, constitutional symptoms suggestive of cancer (such as unexplained weight loss), or additional neurologic impairment, such as cerebellar ataxia, limbic encephalitis, or gastrointestinal dysmotility. Serologic testing for SS (ANA, SS-A, and SS-B) also is appropriate in the setting of sensory predominant neuropathy, particularly if there are complaints of dry eyes and dry mouth or other rheumatologic symptoms. Sulfatide antibodies probably are not useful in routine evaluation of neuropathy, but in cases where gait ataxia is a prominent feature, testing for sulfatide and GALOP antibodies can be considered.

Painful asymmetric involvement of individual nerves (mononeuritis multiplex) is suggestive of vasculitis of nerve. In addition to nerve biopsy, antibody tests can be useful. Tests for ANCA, RF, and ANA may provide some evidence of systemic autoimmune disease.

Motor neuropathy

When evaluating a predominantly motor neuropathy, autoantibody testing can help in certain scenarios. Anti-GM1 antibodies should be considered in patients who have acquired, chronic, distal lower motor neuron syndromes whether or not there is evidence of conduction block on nerve conduction studies. When definitive upper motor neuron signs are present, anti-GM1 antibodies are not useful, because results cannot distinguish

between MMN and motor neuron disease (MND). Anti-GM1 testing also can be considered in cases of GBS when electrophysiologic studies suggest significant axonal loss. Rationale for this testing mainly is to inform on prognosis because several studies demonstrate that anti-GM1 antibodies tend to predict a more severe GBS picture with worse recovery [4,5]. Anti-GM1 antibodies should not be used routinely as a diagnostic test for GBS. Anti-GD1a testing should be approached in a similar manner.

Anti-GQ1b antibodies can be used in patients who have suspected MFS or related syndromes characterized by acute ophthalmoplegia or cerebellar ataxia to distinguish these presumed immune-mediated neuropathies from other conditions, such as posterior fossa strokes and botulism. The presence of IgG anti-GQ1b antibodies suggests that treatment with plasmapheresis or intravenous gammaglobulin may be beneficial.

Autonomic neuropathy

When evaluating a predominantly autonomic neuropathy, antibody testing may help distinguish autoimmune causes from degenerative forms of autonomic failure. In recent onset autonomic failure (especially when gastrointestinal symptoms are prominent), paraneoplastic antibody testing helps identify patients who have an occult malignancy. Approximately 50% of patients who have autoimmune autonomic neuropathy have antibodies against ganglionic AChRs. Seropositivity can identify patients who may respond to plasma exchange or intravenous immunoglobulin [72].

Summary

There is a definite role for autoantibody testing in the evaluation of PN. The use and interpretation of antibody results always should depend on the clinical and electrophysiologic presentation of a patient. The presence of autoantibodies provides evidence of autoimmunity that may contribute to the pathophysiology of neuropathy. Some antibodies have clear significance in terms of guiding diagnosis (eg, paraneoplastic antibodies) or prognosis and treatment (eg, GM1 antibodies). Most of the autoantibodies, however, do not define a specific clinical syndrome and do not have a proved direct pathogenic role.

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