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REVIEW ARTICLE

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Antibody testing as a diagnostic tool in autonomic disorders

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Abstract Some forms of peripheral autonomic dysfunction (especially enteric neuropathy and subacute panautonomic failure) occur as autoimmune phenomena either in isolation or in the context of cancer. Autoimmune autonomic ganglionopathy is an example of a severe, but potentially treatable, antibody-mediated form of autonomic failure. Diagnostic evaluation of autonomic disorders can be supplemented by testing for paraneoplastic antibodies and antibodies against membrane receptors. The diagnostic antibodies most commonly associated with dysautonomia are paraneoplastic antibodies (anti-Hu and CRMP-5) and ganglionic acetylcholine receptor antibodies.

Key words paraneoplastic · autonomic ganglia

Introduction

Causes of peripheral autonomic neuropathy include genetic, toxic, metabolic, infectious and inflammatory disorders. Some peripheral neuropathies 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. Many cases of acute or subacute autonomic failure may be attributed to autoimmunity targeting the autonomic nerves and/or ganglia. When an autoimmune form of dysautonomia is suspected, the diagnostic evaluation can be supplemented with serological testing for specific neurological autoantibodies.

Antibody testing may help distinguish autoimmune disorders from degenerative forms of autonomic failure. In the setting of peripheral autonomic disorders, neurological autoantibodies fall into three general categories, (1) paraneoplastic antibodies directed against one or more intracellular onconeuronal antigens, (2) autoantibodies against membrane receptors, (3) antibodies against cell surface glycoproteins (gangliosides). The ganglioside antibodies are useful markers of immune-mediated neuropathies (for review see [37]). While some of the neuropathies associated with ganglioside antibodies have autonomic involvement (especially Guillain-Barre syndrome), none of the ganglioside antibodies are uniquely associated with dysautonomia so those antibodies are not discussed further in this review. Antibodies against ganglionic neuronal acetylcholine receptors (AChR) are of particular interest for this review since these are markers of an antibody-mediated and potentially treatable form of autonomic failure.

Paraneoplastic autoantibodies

The use and interpretation of antibody testing in suspected paraneoplastic neurological disease remains a source of confusion due to the large number of reported antibodies and the diversity of their clinical associations. There are a growing number of

Table 1 Paraneoplastic autoantibodies associated with autonomic manifestations

Antibody name[a]	Related tumor	Associated autonomic syndromes[b]
Anti-Hu/ANNA-1	SCLC	Sensory and autonomic neuropathy; Autonomic ganglionopathy; Enteric neuropathy (GI dysmotility)
CRMP-5/anti-CV2	SCLC or thymoma	Neuropathy, including autonomic neuropathy or enteric neuropathy
anti-Yo/PCA-1	Ovarian or breast cancer	Paraneoplastic cerebellar degeneration, occasionally with GI dysmotility
Anti-amphiphysin	Lung or breast cancer	Paraneoplastic neuropathies and stiff-person syndrome, occasionally with autonomic dysfunction
PCA-2	SCLC	Various syndromes including some with autonomic neuropathy
ANNA-3	SCLC	Various syndromes including some with autonomic neuropathy

[a]When alternate nomenclature exists, both are given. The neuronal and cytoplasmic antibodies are listed in approximate order of decreasing frequency
[b]Except for anti-Hu and CRMP-5 antibodies, autonomic disorders are an uncommon manifestation of paraneoplastic disease associated with these antibodies
ANNA anti-neuronal nuclear antibody, *PCA* purkinje-cell antibody, *SCLC* small-cell lung carcinoma

paraneoplastic antibodies that can be detected routinely in academic or commercial clinical laboratories as well as less common antibodies which have been reported in only a small number of cases. The majority of paraneoplastic antibodies are directed against intracellular antigens in the nucleus or cytoplasm of neurons. These antibodies recognize antigens both in neurons and in tumor cells and are important surrogate markers of a specific immune response to cancer. In these paraneoplastic disorders, the pathophysiological effect on the nervous system appears to be primarily cell-mediated damage to neurons and axons [3]. As yet, a direct pathogenic role for the antibodies appears unlikely since passive transfer of these antibodies or immunization has failed to reproduce disease in animals [27].

Each of the paraneoplastic neuronal nuclear and cytoplasmic antibodies can be associated with a number of different neurological syndromes but are typically highly specific for the presence of cancer and predictive of the cancer type (Table 1). Different paraneoplastic antibodies frequently co-exist in a single patient [24, 46]. Anti-Hu (ANNA-1) and CRMP-5 (anti-CV2) antibodies deserve special attention because of their frequent association with peripheral sensorimotor or autonomic neuropathy. However, no individual neuronal paraneoplastic antibody is a very sensitive diagnostic tool. Even when the most complete battery of paraneoplastic antibodies is obtained, many patients with a subacute neurological syndrome and proven cancer have no paraneoplastic antibody detected [1, 15]. Thus, negative antibody tests cannot exclude a paraneoplastic cause of neuropathy.

The titer of a serum paraneoplastic antibody does not correlate with the severity of the neurological syndrome or with the type of symptoms. Thus, it is not practical to use antibody titer to monitor response to treatment. In general, antibody titers decrease slowly after successful treatment of the underlying malignancy, so an increase in titer suggests persistence or recurrence of tumor.

Anti-Hu (ANNA-1) antibodies

Anti-Hu antibodies (also known as anti-neuronal nuclear antibody—type 1, ANNA-1) bind to a family of 35–40 kDa proteins expressed in the nuclei of neurons of the central nervous system, dorsal root ganglia, autonomic ganglia, and myenteric plexus. These antigens are also expressed in certain tumor cells, most notably small cell lung carcinoma. Elevated antibody titers are associated with a wide variety of neurologic syndromes ranging from limbic encephalitis to neuropathy. Peripheral neuropathy is the most common initial manifestation, occurring in 70–80% of patients with anti-Hu antibody [20]. Half of these paraneoplastic neuropathies are sensory. About 25% of patients with anti-Hu have some features of dysautonomia, the most common manifestation is gastrointestinal dysmotility (paraneoplastic enteric neuropathy) [19, 20].

Upon detection of a positive serology for anti-Hu, patients should be aggressively screened for underlying malignancy, beginning with chest CT since chest radiographs are less sensitive to mediastinal lymphadenopathy. More than 80% of adult patients with anti-Hu antibodies will have cancer, usually small-cell lung carcinoma [24]. Bronchoscopy, mediastinoscopy, or metabolic imaging with positron emission tomography may identify occult tumors when initial radiologic studies are indeterminate [20, 43]. If a chest malignancy is not found, the search should be widened to include other tumors, including neuroblastoma or small-cell carcinomas arising in other organs. Periodic follow-up imaging every few months is recommended if initial screening is unremarkable.

CRMP-5 (anti-CV2) antibodies

Collapsing-response mediator proteins (CRMP) are a family of neuronal cytoplasmic proteins present in adult central and peripheral neurons, and in small-cell lung carcinomas. Antibodies against CRMP-5 are

associated with a wide variety of paraneoplastic syndromes [46]. Although the reported specificity of CRMP-5 antibody differs slightly from an earlier description of an antibody named anti-CV2 [9], these two paraneoplastic antibodies appear to have the same implications and are usually considered together. CRMP-5 antibodies are proving to be one of the most common markers of paraneoplastic neurological disorders.

The neurological syndromes associated with CRMP-5 antibodies are very diverse (much like those associated with anti-Hu antibodies) and include peripheral neuropathy, limbic encephalitis, ataxia, as well as paraneoplastic chorea or optic neuritis. Peripheral neuropathy, usually axonal sensorimotor type, is present in about one-half of patients [46]. Autonomic neuropathy occurs in about one-third. Lung carcinoma (small-cell type) is eventually found in nearly 80% of seropositive patients. CRMP-5 antibodies can also be found in patients with thymoma, with or without neurological symptoms [33, 46].

Paraneoplastic autonomic neuropathy

Paraneoplastic autonomic neuropathy typically presents as a subacute panautonomic neuropathy (indistinguishable from non-paraneoplastic autoimmune autonomic neuropathy, discussed below). Standard autonomic testing demonstrates the autonomic deficits but does not differentiate paraneoplastic autonomic neuropathy from other causes of severe peripheral autonomic failure. Limited presentations may also 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 only locally metastatic (regional lymph nodes). Hence, since the patient has no symptoms directly referable to metastatic cancer, the autonomic symptoms cannot be attributed to direct effects of the tumor, non-specific consequences of chronic illness or to chemotherapy-induced neuropathy.

Paraneoplastic disorders often present as multifocal neurological disorders. When subacute autonomic failure develops in combination with another peripheral or central neurological syndrome, paraneoplastic disease should be strongly considered. Common examples are paraneoplastic gastroparesis in combination with limbic encephalitis or subacute autonomic neuropathy in combination with sensory ganglionopathy (paraneoplastic sensory and autonomic ganglionopathy). Paraneoplastic dysautonomia also commonly occurs in the setting of paraneoplastic ataxia or brainstem encephalitis, Lambert-Eaton syndrome and Morvan syndrome (discussed later). The autoantibody most commonly associated with paraneoplastic autonomic neuropathy and small cell lung cancer is anti-Hu (ANNA-1). Patients without anti-Hu antibodies may have antibodies against ganglionic AChR.

Autonomic symptoms are not typically seen with myasthenia gravis (MG). This may reflect the fact that antibodies against muscle-type AChR in patients with MG rarely recognize neuronal nicotinic AChR [35]. However, rare cases of subacute autonomic neuropathy have been reported in association with thymoma or with MG [25]. In these cases, gastrointestinal symptoms (such as intestinal pseudoobstruction) have been prominent. Some patients with thymoma have both ganglionic and muscle AChR antibodies [33].

Paraneoplastic enteric neuropathy

Gastrointestinal hypomotility is a common and disabling feature of paraneoplastic autonomic neuropathy. Quite often, the paraneoplastic syndrome can be limited to the gut and is better classified as a paraneoplastic enteric neuropathy. This syndrome can occur in patients with known malignancy but more typically precedes the diagnosis of cancer [2, 20]. Features vary from severe gastroparesis, intestinal pseudoobstruction, severe constipation, or a combination of these. Esophageal dysmotility (including achalasia) has also been reported [18, 20, 33]. Patients present with nausea, early satiety, bloating, abdominal pain, constipation and resultant weight loss. Patients may regurgitate undigested food many hours after eating. In severe cases, even fluid intake may be compromised leading to dehydration. Imaging studies show dilated loops of bowel, and motility studies reveal delayed gastric emptying, diffuse intestinal hypomotility, and absent or incoordinated motor complexes. Such patients are often presumed to have bowel obstruction, but endoscopy and exploratory laparotomy fail to identify an obstruction.

Pathologically, paraneoplastic enteric neuropathy has been associated with inflammatory destructive process affecting myenteric ganglia of the gut. In postmortem or surgical samples of the gut, the enteric plexus shows reduction in neurons and axons, and lymphocytic infiltration [2, 11].

Among patients with ANNA-1 (anti-Hu) antibodies, more than 10% had a paraneoplastic syndrome limited to gastrointestinal dysmotility [20]. At least one case of thymoma-associated gastric pseudo-

Table 2 Membrane receptor antibodies associated with dysautonomia

Antibody name	Related tumor	Associated autonomic syndromes
P/Q-type VGCC	SCLC (~50%)	Lambert-Eaton syndrome (LES)
N-type VGCC	SCLC or breast	Various, including LES or sensorimotor and autonomic neuropathy
Ganglionic (α3) AChR	SCLC (<10%)	Autoimmune Autonomic Ganglionopathy, Postural tachycardia, GI dysmotility
VGKC	Thymoma (<20%) or SCLC(<5%)	Neuromyotonia, limbic encephalitis with autonomic hyperactivity, or Gastrointestinal dysmotility
Muscarinic (M3) AChR		Sjögren syndrome

VGCC voltage-gated calcium channel, *AChR* acetylcholine receptor, *VGKC* voltage-gated potassium channel, *SCLC* small-cell lung carcinoma

obstruction was associated with antibodies to voltage-gated potassium channels (and associated neuromyotonia) [38].

Membrane receptor antibodies

A distinct category of antibodies that can be found in patients with both paraneoplastic and non-paraneoplastic disorders are those that bind to surface membrane receptors (Table 2). The antigens include voltage-gated calcium channels, voltage-gated potassium channels, and nicotinic and muscarinic AChR. Unlike the paraneoplastic antibodies discussed above, membrane receptor antibodies each associate closely with a particular neurological disorder but do not predict the presence of cancer. The best characterized of this category of antibodies is the muscle AChR antibody associated with myasthenia gravis. Antibodies associated with autonomic disorders include neuronal ganglionic AChR, voltage-gated calcium and potassium channel and muscarinic AChR antibodies.

Because these antibodies can reach their targets on intact neurons, they have a greater potential to directly affect neuronal function. For some disorders, there is convincing evidence of an antibody-mediated pathophysiology. Patients may improve clinically after plasma exchange or other immunotherapies, and the conditions can be transferred to experimental animals by injection of patients' IgG [14, 31, 39]. Also, the level of the antibody often correlates with the severity of disease; improvement in symptoms may be associated with a decrease in antibody level.

Autoimmune autonomic ganglionopathy

Acute pure dysautonomia was first described as a discrete clinical entity by Young et al. [44, 45] in 1969. This disorder is characterized by subacute onset and monophasic course with partial recovery. There is sympathetic, parasympathetic and enteric failure with no significant evidence of somatic peripheral neuropathy [8, 28]. Specific antibodies directed against the neuronal ganglionic AChR in autonomic ganglia have been found in about 50% of patients with this disorder [36]. This receptor is a pentameric transmembrane complex consisting of two AChR α3 subunits in combination with AChR β subunits. The α3-type ganglionic AChR mediates fast synaptic transmission in all peripheral autonomic ganglia and is homologous but immunologically distinct from the AChR at the neuromuscular junction. These antibodies can inhibit the function of ganglionic AChR in cultured cells and impair synaptic transmission in isolated autonomic ganglia [42]. Based on these findings, the term autoimmune autonomic ganglionopathy (AAG) is used to highlight the nature of the disorder.

The clinical features of AAG are essentially indistinguishable from paraneoplastic autonomic neuropathy. The distinction may not be possible until cancer is diagnosed or another neurological syndrome becomes evident. As with the paraneoplastic form, the symptoms of AAG reflect involvement of parasympathetic, sympathetic and enteric nervous systems. Less common patterns are those of selective cholinergic failure, selective adrenergic neuropathy, or isolated gastrointestinal dysmotility. The characteristic presentation is severe pandysautonomia evolving over a few weeks in a previously healthy individual [12, 28]. Common presenting symptoms are orthostatic hypotension and gastrointestinal dysfunction; each of these symptoms occurring in more than 70% of patients. Parasympathetic failure is also prominent with dry eyes, dry mouth, impaired pupillary light reflex, and disturbances of bladder and bowel function. A presumed antecedent viral infection may be reported in about 60% of cases [28]. The spinal fluid protein is often elevated [8, 28].

Although the finding of high levels of ganglionic AChR antibody is specific for the diagnosis of AAG, a negative antibody test does not rule out the diagnosis. Ganglionic AChR antibodies are not found in normal control subjects but can occasionally be found in patients with lung cancer- and thymoma-related

Table 3 Clinical disorders associated with ganglionic AChR antibodies

Clinical disorder	Ab frequency	Antibody level
Subacute monophasic AAG	~50%	High (>1.0 nmol/L)
Paraneoplastic AAG (thymoma or SCLC)	~20%	High (>0.5)
Chronic AAG	Unknown	Moderate (0.2–1.0)
Restricted AAG (e.g. pure cholinergic failure)	Unknown	Moderate (0.1–0.5)
Postural tachycardia	7–15%	Low (<0.5)
Isolated gastrointestinal dysmotility	~10%	Low (<0.5)
Other autoimmune disorders (e.g. MG, LES, neuromyotonia)	<10%	Low (<0.2)

Estimates of antibody level and frequency are based on the author's experience and references [29, 30, 32, 35, 36]
AAG autoimmune autonomic ganglionopathy, *LES* Lambert-Eaton syndrome, *MG* myasthenia gravis

paraneoplastic disorders [33, 36]. Recognition of ganglionic AChR antibodies has allowed for the serological classification of autoimmune autonomic disorders and led to a better appreciation of the spectrum of autoimmune dysautonomia, including the recognition that some AAG cases have insidious onset, initially indistinguishable from degenerative forms of autonomic failure [5, 12]. Patients with autoimmune dysautonomia can be broadly divided into several groups based on the clinical presentation and the ganglionic AChR antibody level (Table 3). Patients with the classic presentation of subacute panautonomic failure (including prominent pupil and gastrointestinal involvement) have highest antibody levels. Moderate ganglionic AChR antibody levels are found in patients with chronic progressive AAG and in some patients with restricted forms of autonomic failure (such as idiopathic anhidrosis or pure cholinergic failure). Low levels of antibody may be found in a minority of patients with postural tachycardia syndrome (up to 15%) or isolated gastrointestinal dysmotility (5–10%).

Lambert-Eaton myasthenic syndrome

LES is an acquired, antibody-mediated disorder of neuromuscular junction transmission. Antibodies against P/Q-type voltage-gated calcium channels cause impairment in presynaptic calcium influx and a reduction in the release of acetylcholine [14, 40]. Calcium channel antibodies are found in nearly 100% of patients with LEMS, but these antibodies can also be associated with other autoimmune neurological disorders (notably paraneoplastic cerebellar ataxia) [6, 41]. Many adult LEMS patients (50–60%) have a malignancy, most commonly small-cell lung carcinoma.

Weakness and fatigability are the usual presenting complaints, but autonomic symptoms are present in about three-quarters of patients. Often the autonomic symptoms are mild, and patients do not volunteer them unless specifically asked. Dry mouth and impotence (in men) are extremely common. Other cholinergic autonomic symptoms may be present, including dry eyes, reduced sweating, abnormal pupillary function, and constipation [23]. Symptoms of sympathetic failure (postural hypotension) may occur but are less common. While autonomic complaints are relatively few, autonomic tests may show widespread autonomic abnormalities.

Neuromyotonia and Morvan's syndrome

Several other autoimmune neuromuscular disorders are associated with autonomic dysfunction. Acquired neuromyotonia is an autoimmune disorder characterized by peripheral nerve hyperexcitability. Electromyography shows spontaneous firing of motor units in multiplet discharges at irregular intervals with a high intraburst frequency. These discharges are often characterized as myokymia or neuromyotonia. Clinical features include muscle stiffness, cramps, myokymia, hyperhidrosis and hypersalivation [7, 22]. Serum from about 40% of patients contains antibodies (IgG) that precipitate ^{125}I-dendrotoxin-voltage-gated potassium channels (VGKC) of the Kv1.1, 1.2 and 1.6 subtypes [26, 34].

Excessive autonomic activity is suggested by new onset hypertension, piloerection, vasomotor instability in the hands and feet, tachycardia, extrasystoles and increased urinary or serum catecholamines [10, 16, 17]. Paroxysms of sweating, piloerection, lacrimation and salivation can occur. In addition to autonomic hyperactivity, patients with autoimmune neuromyotonia may also experience autonomic failure including constipation, intestinal pseudoobstruction [38], orthostatic hypotension and cardiovagal failure [10]. This disorder can be associated with thymoma and, less commonly, SCLC. It appears that the incidence of VGKC antibodies is higher in those cases with a tumor [7]. VGKC antibodies can also be associated with gastric motility defects in non-tumor cases [13].

Neuropathy with Sjögren and sicca syndrome

The exact frequency of neuropathy associated with primary Sjögren syndrome (SS) is unknown but estimated to be about 10% [4]. A variety of neuropathies can be encountered, and neuropathy may be the initial presentation of the autoimmune disease.

Patients with SS are predominantly female. Diagnosis consists of symptoms and objective evidence of dry mouth and dry eyes along with presence of anti-Ro/SS-A and anti-La/SS-B antibodies. These antibodies are found in about 60% of patients with SS. Other serological findings include ANA and RF antibodies.

Autonomic features are often present, characterized by sweating abnormalities and constipation. In a minority of cases, tonic unresponsive pupils can occur. Several studies have suggested that antibodies against muscarinic (M3-type) AChR are associated with the autonomic neuropathy of SS [21]. Testing for these antibodies is not yet widely available but may eventually prove to be a useful tool for evaluating patients with primarily secretomotor autonomic deficits.

Summary

Clinicians should be aware that some forms of peripheral autonomic dysfunction (especially enteric neuropathy and subacute panautonomic failure) occur as autoimmune phenomena either in isolation or in the context of cancer. Autoimmune autonomic ganglionopathy is an example of a severe, but potentially treatable, antibody-mediated form of autonomic failure. Diagnostic evaluation of autonomic disorders can be supplemented by testing for paraneoplastic antibodies and antibodies against membrane receptors.

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