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REVIEW

Autoimmune autonomic neuropathies and ganglionopathies: epidemiology, pathophysiology, and therapeutic advances

Elisabeth P. Golden[1] · **Steven Vernino**[1]

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Abstract
Autonomic disorders can be the result of autoimmunity. The classic, well-characterized example is autoimmune autonomic ganglionopathy (AAG), in which antibodies against the ganglionic nicotinic acetylcholine receptor impair autonomic transmission, causing autonomic failure, which responds to immunotherapy. However, a number of other autoimmune disorders cause autonomic failure through a variety of mechanisms. In this article, we review autoimmune disorders causing impairment of the peripheral autonomic nervous system (ganglia and nerves), including AAG, other autoimmune autonomic neuropathies, paraneoplastic autonomic neuropathies, and neuromuscular and rheumatologic diseases with autonomic symptomatology. Awareness of primary autoimmune autonomic disorders and the autonomic manifestations of other autoimmune diseases promotes timely diagnosis and appropriate management, including supportive care for unpleasant or dangerous autonomic dysfunction, a search for underlying malignancy when indicated, and the use of immunotherapy when appropriate. A better understanding of the underlying pathophysiology aids in the judicious use and selection of immunotherapy.

Keywords Autoimmune autonomic ganglionopathy · Autoimmune autonomic neuropathy · Paraneoplastic autonomic neuropathy · Immunotherapy

Introduction

The pathophysiology of autonomic failure is diverse. Mechanisms include toxic/metabolic (diabetes, amyloid), genetic defects (hereditary sensory and autonomic neuropathies), structural (baroreceptor injury), neurodegenerative (α-synucleinopathies), and autoimmune. Localization may be anywhere along the neuroaxis from central autonomic networks in the brain to peripheral small nerve fibers. In this article, we will review autoimmune disorders causing impairment of the peripheral autonomic nervous system. These include primary autonomic disorders such as autoimmune autonomic ganglionopathy, autoimmune and paraneoplastic autonomic neuropathies, and rheumatologic diseases with autonomic manifestations; see Tables 1 and 2. Checking for potential autoimmunity in autonomic disorders is important as it permits the identification of patients who might benefit from immunotherapy in addition to standard supportive care, and an awareness of autonomic manifestations in other autoimmune diseases ensures that unpleasant or dangerous autonomic symptoms are appropriately managed. The evaluation and management of these patients is often complex, given the nonspecific symptoms, difficulty establishing objective evidence of autoimmunity, and rarity of these diseases (making data regarding treatment scarce). See Fig. 1 for a summary of the general approach to a patient with a suspected autoimmune peripheral autonomic disorder.

✉ Elisabeth P. Golden
Elisabeth.golden@utsouthwestern.edu

[1] Department of Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd. MC 9368, Dallas, TX 75390, USA

Autoimmune autonomic ganglionopathy

The first case of presumed autoimmune disease restricted to the autonomic nervous system was reported by Young and colleagues in 1969 as "pure pan-dysautonomia with recovery" [1, 2]. Further description of the condition was limited to case reports until a larger series of "idiopathic autonomic neuropathy" was published in 1994 [3]. Subsequently, the entity now known as "autoimmune autonomic ganglionopathy" (AAG) was characterized clinically and pathophysiologically, with the ganglionic nicotinic acetylcholine receptor (gAChR) antibody identified as the cause in many cases.

Table 1 Autoimmune disorders of the peripheral autonomic nervous system

Autoimmune autonomic ganglionopathy (AAG)
Autonomic neuropathies
Acute autonomic and sensory neuropathy (AASN)
Idiopathic gastrointestinal dysmotility
Cholinergic neuropathy
Idiopathic anhidrosis
Paraneoplastic autonomic neuropathies
Anti-Hu (ANNA-1)
Anti-CRMP5 (CV-2)
Anti-ganglionic nicotinic acetylcholine receptor (gAChR)
Autoimmune neuromuscular conditions with prominent autonomic manifestations
Lambert–Eaton myasthenic syndrome (LEMS)
Disorders with voltage-gated potassium channel (VGKC) complex antibodies
Guillain–Barré syndrome
Rheumatologic diseases with autonomic manifestations
Sjögren syndrome
Others (systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, scleroderma)

AAG is a rare disease. Patients are typically middle-aged (mean ages 45–61), with a 2:1 female predominance [3, 4]. The classic presentation is acute to subacute, often with an antecedent event. However, the identification of the causative antibody also allowed for identification of a chronic phenotype (clinically similar to pure autonomic failure), which accounts for about half of seropositive patients [4]. Patients typically manifest diffuse failure of sympathetic, parasympathetic, and enteric systems. The most common symptom is orthostatic hypotension (OH), and cholinergic failure is prominent, including sicca syndrome (dry mouth and dry eyes), poorly reactive pupils, anhidrosis, upper and lower gastrointestinal dysfunction, and neurogenic bladder. Symptoms can be severe, with a significant impact on quality of life. Spontaneous recovery (typically incomplete) is seen in about one-third of patients [3, 4]; improvement is also seen with immunomodulatory therapy, as described below.

About a quarter [3, 5] to half [6] of patients report subjective paresthesias, but pain is not a feature of this disease, and objective evidence of somatic nerve dysfunction is not seen. Cognitive impairment is occasionally reported [6–9] and may be independent of OH [10]. Several additional features have been reported in Japanese cohorts, including psychiatric symptoms, coughing episodes, and endocrine dysfunction [5, 6, 11].

Laboratory autonomic testing reveals diffuse autonomic failure, with the Composite Autonomic Severity Score (CASS) [12] indicating moderate to severe impairment [3, 4]. Both ganglionic and post-ganglionic sudomotor deficits may be seen [13]. Quantitative pupillometry reveals premature pupillary redilation to prolonged light stimulus ("pupillary fatigue"); see Fig. 2. This is a unique feature of AAG and is hypothesized to represent impairment of ganglionic synaptic transmission similar to the muscular fatigue of myasthenia gravis [14]. Nerve conduction studies and electromyography are typically normal. CSF analysis may reveal mildly elevated protein without pleocytosis [3]. Sural nerve biopsy may show decreased numbers of small fibers and other nonspecific abnormalities [3, 15–18].

About half of patients with AAG are found to have antibodies against the ganglionic nicotinic acetylcholine receptor (gAChR) [5, 19], which mediates fast synaptic transmission at all autonomic ganglia. The gAChR comprises two α3 subunits and three other subunits (usually β4). The antibodies in AAG bind specifically to the α3 subunit [20]. As this subunit is specific to the ganglionic receptor, there is minimal cross-reactivity between antibodies against gAChR and antibodies against the muscle AChR (which cause myasthenia gravis) [21, 22].

Several lines of evidence have established the pathogenicity of α3 gAChR antibodies in AAG. In vitro, the application of IgG from AAG patients decreases gAChR current in cultured neuroblastoma cells [23]. Mice with genetically engineered null mutations in the α3 subunit show decreased autonomic ganglionic transmission, with a clinical phenotype of urinary retention, dilated and nonreactive pupils, and increased mortality [24]. Active immunization of rabbits against the α3 subunit produces an experimental model (EAAG) characterized by gastrointestinal hypomotility, urinary retention, and impaired pupillary light reflex, with a reduction in gACh receptors on postsynaptic ganglionic neurons and impaired synaptic transmission [25, 26]. EAAG rabbits also demonstrate the premature pupillary redilation seen in AAG patients [27]. Passive antibody transfer also causes disease: mice treated with IgG from affected rabbits or humans develop self-limited autonomic failure [28].

Table 2 Clinical features of peripheral autoimmune autonomic disorders

Disorder	Autonomic features	Other neurological features	Pathophysiology	Use of immunotherapy	Additional considerations
Autoimmune autonomic ganglionopathy	Diffuse autonomic failure with OH, upper GI, and bladder impairment. Prominent cholinergic symptoms with higher antibody levels. Premature pupillary redilation in seropositive patients	Paresthesias, but no objective sensorimotor deficits. Cognitive impairment reported, as well as psychiatric symptoms, coughing spells, and endocrine dysfunction in Japanese cohorts	50% are positive for gAChR antibodies, which are pathogenic	Antibody-directed therapy. IVIG and PE are first-line, also reports of benefit with rituximab. Seronegative cases also respond to immunotherapy	May present subacutely or chronically. Chronic cases may be clinically indistinguishable from pure autonomic failure
Acute autonomic and sensory neuropathy	Initial presentation often GI dysmotility, progressing to diffuse autonomic failure	Small-fiber sensory deficits with neuropathic pain, progressing to large-fiber deficits and sensory ataxia in more than half of patients. Also psychiatric symptoms, cough, sleep apnea	Unknown, but seems to localize to sensory and autonomic ganglia	Variable response to immunotherapy	Most patients improve over time, the autonomic more so than sensory symptoms
Limited autonomic neuropathy	Isolated GI dysmotility, cholinergic neuropathy, or anhidrosis	None	GI dysmotility and cholinergic neuropathy may be associated with low levels of gAChR antibody	May use IVIG or PE for autoimmune GI dysmotility. Idiopathic anhidrosis may respond to corticosteroids	
Paraneoplastic autonomic neuropathy	Diffuse autonomic failure or limited enteric neuropathy	Sensory ganglionopathy, sensorimotor neuropathy, cerebellar ataxia, limbic encephalitis, dementia, chorea, and others	Anti-Hu, anti-CRMP5 (markers of cancer autoimmunity; pathology is cell-mediated), less often gAChR antibodies. Commonly associated with SCLC or thymoma	Treat underlying malignancy, may add immunotherapy for cellular autoimmunity (or IVIG/PE for gAChR antibody)	Autonomic neuropathy often precedes cancer diagnosis. Aggressive and continued search for underlying malignancy may be necessary in anti-Hu and anti-CRMP5
Lambert–Eaton myasthenic syndrome	Cholinergic impairment (dry mouth, erectile dysfunction, constipation)	Proximal leg weakness with areflexia, mild oculobulbar weakness	Decreased pre-synaptic acetylcholine release due to antibodies against P/Q voltage-gated calcium channel. Often associated with SCLC	Treat underlying malignancy if applicable, also responds well to IVIG, PE, oral immunosuppression, or rituximab	Thorough search for underlying malignancy is indicated. 3,4-Diaminopyridine can be used for symptomatic improvement in motor and autonomic symptoms
Voltage-gated potassium channel complex antibody disorders	Hyperhidrosis, tachycardia, blood pressure abnormalities, urinary symptoms	Peripheral nerve hyperexcitability (cramps, fasciculations, neuromyotonia, myokymia), encephalopathy	LGI1 and CASPR2 antibodies, may have underlying malignancy (most often thymoma)	Treat underlying malignancy if applicable, also may consider IVIG, PE, corticosteroids	Peripheral nerve hyperexcitability may respond to carbamazepine
Guillain–Barré syndrome	Sinus tachycardia, hypertension, episodic hypotension, bradyarrhythmias, GI dysmotility, urinary retention	Subacute ascending weakness (often requiring ventilatory support at the nadir), demyelinating polyradiculoneuropathy	Molecular mimicry between epitopes on an immunogenic agent (especially *Campylobacter jejuni*) and neuronal gangliosides	IVIG or PE (with caution in hemodynamically unstable patients), most effective when started < 2 weeks from onset	Autonomic dysfunction associated with difficult ventilator weaning. If treatment of hemodynamic instability is necessary, use low doses of short-acting agents. Meticulous supportive care to reduce hospital complications, early involvement of rehab

Table 2 (continued)

Disorder	Autonomic features	Other neurological features	Pathophysiology	Use of immunotherapy	Additional considerations
Sjögren syndrome	Secretory dysfunction, impaired cardiovagal function, impaired sympathetic vasomotor function, tachycardic response to head-up tilt	Sensory ganglionopathy, small-fiber neuropathy	Unclear	May respond to IVIG	

OH orthostatic hypotension, *GI* gastrointestinal, *gAChR* ganglionic nicotinic acetylcholine receptor, *IVIG* intravenous immunoglobulin, *PE* plasma exchange, *SCLC* small cell lung carcinoma

Transient neonatal AAG from maternal antibodies has also been reported [29].

Antibody levels are clinically meaningful, based on a characterization of seropositive AAG patients. Levels above 0.20 nmol/L are fairly specific for AAG [30]. High levels correlate with overall disease severity, prominent cholinergic symptoms [4, 31], and orthostatic hypotension, which becomes clinically significant and increasingly severe with antibody levels > 1 nmol/L [31]. Antibody levels are not, however, associated with the acuity of the clinical course (subacute vs. chronic presentations) [4, 31]. Antibody levels fall with spontaneous recovery [19] and track with the clinical course after plasmapheresis [32, 33].

Treatment of AAG is directed at the antibody-mediated pathology. Due to the rarity of the disease, evidence is limited to case reports and series; see Table 3. Antibody depletion via plasma exchange (PE) or modulation with intravenous immunoglobulin (IVIG) appears to be beneficial and is considered first-line therapy [34–37]. Combination therapy with immunosuppressant medications may yield an additional benefit [32, 35, 36]. In particular, rituximab, a B cell depleting agent which would decrease antibody production, has shown promise [38–43]. Supportive symptomatic treatment should also be offered as indicated, including nonpharmacologic and pharmacologic management of orthostatic hypotension, cholinergic agents and artificial tears and saliva for sicca symptoms, bowel regimen for constipation, and urologic management of neurogenic bladder.

Seronegative autonomic ganglionopathy and neuropathy

About half of cases of idiopathic subacute autonomic failure are seronegative for gAChR antibodies [19]. Seropositive cases are more likely to have prominent cholinergic failure and pupillary abnormalities [44]. Response to immunotherapy has been reported in seronegative cases [35, 45].

A recent case series of six patients [46] described a distinct subset of seronegative autoimmune autonomic failure. These patients presented with acute to subacute onset of orthostatic hypotension and gastrointestinal symptoms; three had prominent sensory deficits and severe neuropathic pain. The pattern of autonomic failure was different than seropositive AAG, with predominant sympathetic deficits. There was poor response to standard AAG immunotherapy, and remarkable response to high-dose steroids in three of the patients. Length-dependent sensory symptoms and QSART deficits suggested localization of the pathology to the nerve (particularly small fibers) rather than the autonomic ganglia, and the response to steroids rather than antibody-targeted therapies (IVIG, PE, rituximab) suggested a cell-mediated or inflammatory mechanism rather than an antibody-mediated process. Whether

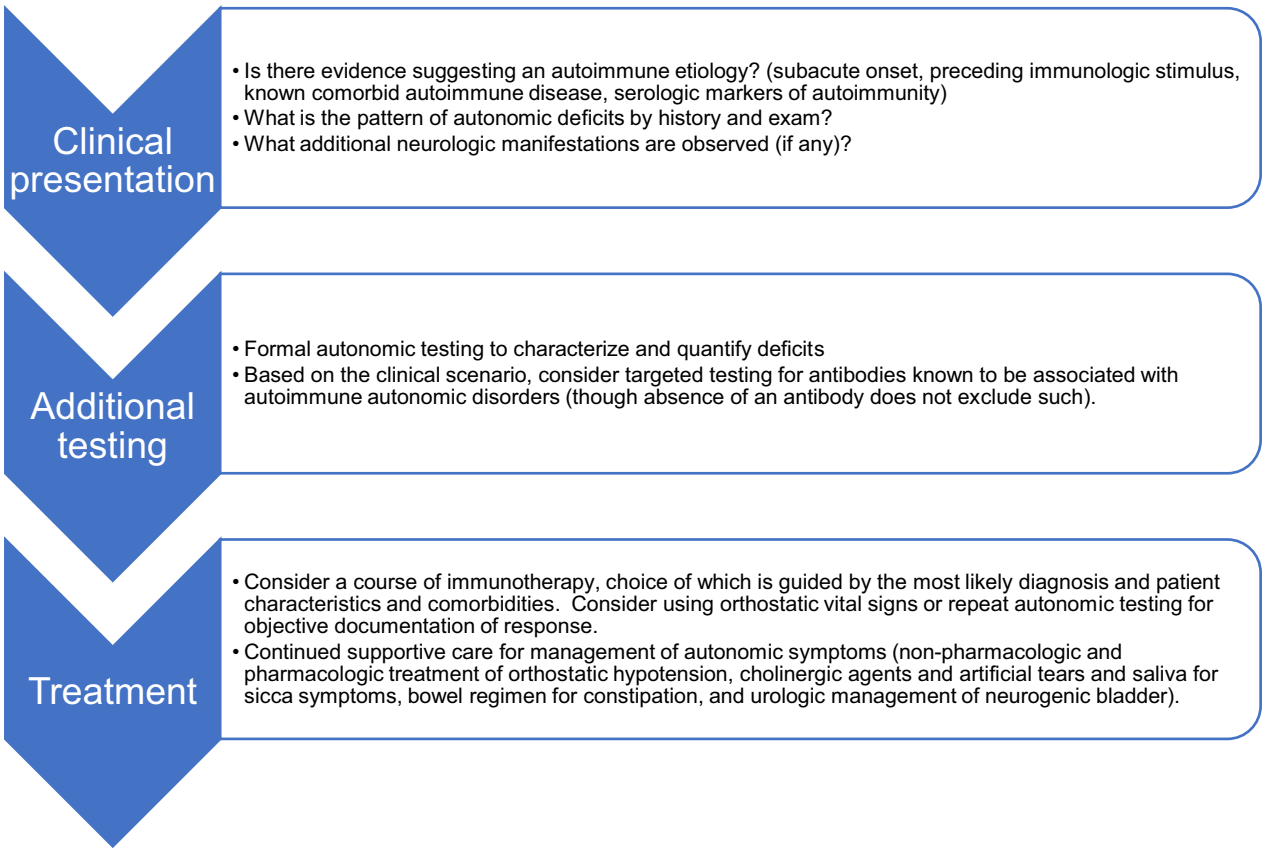

Fig. 1 Approach to a patient with a suspected peripheral autoimmune autonomic disorder

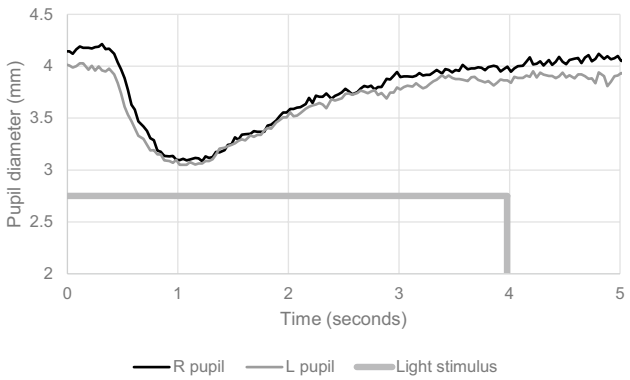

Fig. 2 Pupil reaction to prolonged (4 s) light stimulus in an autoimmune autonomic ganglionopathy patient. Note that the pupil redilates and returns to baseline despite continued light stimulus

these patients represent a distinct nosological entity or are more similar to acute autonomic and sensory neuropathy (discussed below) will require further study [47].

Limited autonomic neuropathy

Limited presentations of autonomic failure have been associated with gAChR antibodies, generally at levels ranging from 0.05 to 0.20 nmol/L [48]. Antibody positivity has been documented in 10% of patients with idiopathic gastrointestinal dysmotility [19], and as many as 50% of patients with chronic intestinal pseudo-obstruction [49]. Patients with chronic orthostatic hypotension, clinically similar to pure autonomic failure, may have positive antibodies and respond to immunotherapy [33]. Low levels of gAChR antibodies have been reported in a wide variety of autoimmune neurologic and rheumatologic diseases [30], malignancies [7, 19, 30], and postural orthostatic tachycardia syndrome [19, 50–54]. The clinical significance of these results is unclear, and in most cases the antibody is likely a nonspecific reflection of underlying systemic autoimmunity.

Other limited forms of presumed autoimmune autonomic failure have also been described. Isolated cholinergic neuropathy without evidence of sympathetic vasomotor dysfunction has been reported [55]. These patients are sometimes positive for gAChR antibodies at low levels [48]. Idiopathic anhidrosis presents with heat intolerance due to inadequate sweating, with symptoms including skin

Table 3 Immunotherapy for autoimmune autonomic ganglionopathy

Treatment	Discussion	Selected references
Intravenous immunoglobulin	Generally regarded as first-line therapy. Multiple case reports with benefit, though not all patients respond	Iodice [35], Iodice [37]
Plasma exchange	Generally regarded as first-line therapy. Clinical status may correlate with antibody levels before and after exchanges	Schroeder [33], Imrich [39], Gibbons [32]
Corticosteroids	Not often used as monotherapy. May provide benefit as part of combination immunotherapy	Iodice [36]
Rituximab	Multiple case reports of benefit	Bouxin [42], Gupta [38], Hollenbeck [40], Benizri [41], Dumitrascu [43]
Mycophenolate mofetil	Reports of benefit in several patients, both as monotherapy after first-line therapy failed and as part of combination therapy	Iodice [35], Gibbons [32]
Azathioprine	Occasional reports of benefit as part of combination therapy	Iodice [35], Schroeder [33]
Combination therapy	Addition of immunosuppressive therapy may provide additional benefit when first-line therapies alone fail	Gibbons [32], Iodice [36]

flushing, lightheadedness, rash (cholinergic urticaria), and hyperhidrosis of areas with preserved sweat function (face, axillae, palms, and soles). The condition may respond to steroids, particularly if administered early in the course [56].

Acute autonomic and sensory neuropathy

Acute autonomic and sensory neuropathy (AASN) was first reported by Colan in 1980 [57]. Most of the literature consists of sporadic case reports, but a larger case series of 21 patients in Japan summarized the key features of the disease [58]. Presentation was acute, with an antecedent event (mostly upper respiratory tract infections) occurring in two-thirds of patients. Initial symptoms were sensory (numbness or pain) or autonomic (often gastrointestinal). These progressed to severe and diffuse autonomic failure (sympathetic, parasympathetic, and enteric), segmental small-fiber sensory deficits with prominent neuropathic pain, and sensory ataxia in more than half the patients. Autoimmune etiology was presumed based on acute onset with antecedent immunologic stimulus, and localization appeared to be at the level of the sensory and autonomic ganglia based on diffuse autonomic deficits, the segmental pattern of sensory involvement, and, in some patients, spinal cord imaging showing T2 hyperintensities in the dorsal columns. Response to immunotherapy was variable. Most patients showed improvement over time, albeit more so in cases with autonomic symptoms than in those with sensory symptoms. There are also reports in the literature of acute autonomic sensory and motor neuropathy (AASMN), but given the similarity to Guillain–Barré syndrome (a primary motor and sensory disease often with prominent autonomic manifestations), the existence of a distinct nosological entity is uncertain [55].

Paraneoplastic autonomic neuropathy

Autonomic neuropathy or ganglionopathy can be the result of a paraneoplastic process; see Table 4. Patients may present with subacute diffuse autonomic failure, clinically indistinguishable from AAG; the coexistence of additional features such as sensory ganglionopathy, limbic encephalitis, myasthenic syndrome, or cerebellar ataxia should heighten suspicion for a paraneoplastic process [59]. Patients may also present with a limited enteric neuropathy, with symptoms including dysphagia, nausea, and vomiting, bloating, early satiety, weight loss, and constipation. Motility abnormalities in these patients are varied, including achalasia, gastroparesis, chronic intestinal pseudo-obstruction, chronic constipation, and megacolon [60, 61]. Lambert–Eaton myasthenic syndrome and Morvan syndrome may also occur as paraneoplastic phenomena and are discussed further below. The paraneoplastic syndrome often precedes the diagnosis of cancer, which may be at an early and limited stage at presentation.

The most common antibodies associated with paraneoplastic autonomic neuropathy are anti-Hu (ANNA-1), anti-CRMP5 (anti-CV2), and gAChR antibodies. Anti-Hu is highly associated with underlying malignancy (88%), particularly small cell lung carcinoma (SCLC), whose diagnosis may be elusive [62]. 18% of patients with anti-Hu have features of autonomic neuropathy, and 12% may present initially solely with enteric neuropathy. Additional syndromes may include sensory or sensorimotor neuropathy, cerebellar ataxia, limbic encephalitis, and others [62]. Anti-CRMP5 is similarly highly associated with cancer (91%), most commonly SCLC or thymoma. In addition to autonomic or enteric neuropathy, patients may exhibit somatic neuropathy, cerebellar ataxia, dementia, chorea, and cranial neuropathy [63]. Paraneoplastic disease due to gAChR antibodies is clinically indistinguishable from AAG. These antibodies

Table 4 Paraneoplastic antibodies associated with peripheral autonomic failure

Antibody	Autonomic manifestations	Other manifestations	Cancer frequency (%)	Cancer type	Antigen location
Anti-Hu (ANNA-1)	Diffuse autonomic failure, enteric neuropathy	Sensory ganglionopathy, sensorimotor neuropathy, cerebellar ataxia, limbic encephalitis	88	SCLC	Intracellular
Anti-CRMP5 (CV-2)	Diffuse autonomic failure, enteric neuropathy	Somatic neuropathy, cerebellar ataxia, dementia, chorea, cranial neuropathy	91	SCLC, thymoma	Intracellular
Anti-gAChR	Diffuse autonomic failure, enteric neuropathy	None	15	SCLC, thymoma, adenocarcinomas	Cell surface
Anti-P/Q VGCC	Cholinergic impairment (dry mouth, constipation, erectile dysfunction)	Proximal leg weakness with areflexia, mild oculobulbar weakness	60	SCLC	Cell surface
Anti-VGKC complex	Hyperhidrosis, tachycardia, urinary symptoms, blood pressure abnormalities, postganglionic sudomotor deficits	Peripheral nerve hyperexcitability, encephalopathy, limbic encephalitis	13–44	Thymoma, SCLC, other	Cell surface

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

are associated with underlying malignancy in a minority of cases (15%) [30]. The classic association is with SCLC or thymoma [19], although a variety of other cancers have been identified with these antibodies, including lymphoma and adenocarcinomas [7].

Anti-Hu and anti-CRMP5 are both directed against intracellular antigens and serve as markers of underlying cancer autoimmunity rather than as pathogenic antibodies. Paraneoplastic neuronal injury in these conditions is cell-mediated and often irreversible [64]. Treatment of paraneoplastic neuropathies is first directed at identifying and eradicating the underlying malignancy. Additional immunotherapy can be offered with agents that target cellular autoimmunity.

Lambert–Eaton myasthenic syndrome

Autonomic symptoms are a common component of Lambert–Eaton myasthenic syndrome (LEMS). In addition to the motor symptoms (proximal leg weakness with areflexia, mild oculobulbar weakness), the vast majority of patients exhibit some degree of cholinergic autonomic impairment. The most common symptoms are dry mouth, erectile dysfunction, and constipation [65, 66]. The pathophysiology of LEMS is related to decreased presynaptic acetylcholine release due to antibodies against the P/Q voltage-gated calcium channel [67]. About 60% of cases are paraneoplastic, most commonly associated with SCLC, and there is a male predominance and older age of onset compared to non-paraneoplastic cases [66]. The diagnosis of LEMS should prompt a thorough and persistent search for underlying SCLC or other malignancy. The syndrome responds well both to treatment of the underlying cancer and to immunotherapy (IVIG, PE, oral immunosuppression, or rituximab), and 3,4-diaminopyridine can be used for symptomatic improvement in motor and autonomic symptoms [68].

Disorders with VGKC-complex antibodies

Autonomic manifestations are often seen in disorders with antibodies against components of the voltage-gated potassium channel (VGKC) complex, including leucine-rich glioma inactivated protein 1 (LGI1) and contactin-associated protein-like 2 (CASPR2). These antibodies are clinically associated with Isaacs syndrome (peripheral nerve hyperexcitability), Morvan syndrome (peripheral nerve hyperexcitability, dysautonomia, and encephalopathy), and limbic encephalitis [69]. Autonomic impairment as well as hyperactivity can be seen in these patients. Hyperhidrosis is the most common autonomic symptom; those with Morvan syndrome may also have tachycardia, blood pressure abnormalities, and urinary symptoms [70]. Formal autonomic testing may reveal orthostatic hypotension and postganglionic sudomotor deficits [71, 72]. LGI1 and CASPR2 antibodies may be associated with thymoma (found in one-third of patients with Morvan syndrome [70]), SCLC [69], or other assorted malignancies (cancer detection 13% in LGI1, 20% in CASPR2, and 44% in double-positive patients [71]). Management of disorders associated with VGKC-complex antibodies may include immunotherapy and an appropriate search for an underlying malignancy.

Guillain–Barré syndrome

Autonomic dysfunction is common in Guillain–Barré syndrome (GBS), occurring in about two-thirds of cases. Manifestations of autonomic dysfunction are varied and may indicate hyper- or hypofunctioning of the sympathetic and/or parasympathetic nervous systems. Cardiovascular manifestations include most commonly sinus tachycardia, and also hypertension (which can be severe enough to cause posterior reversible encephalopathy syndrome), postural hypotension, reversible cardiomyopathy, episodic hypotension, and bradyarrhythmias, which can be life-threatening and may require pacemaker placement. Autonomic dysfunction is common amongst severely debilitated patients and can be associated with sudden death and difficulty with ventilator weaning; however, even patients with milder weakness can exhibit autonomic dysfunction [73, 74]. Other autonomic manifestations include gastrointestinal dysfunction such as paralytic ileus and diarrhea, urinary retention, increased or decreased sweat responses, and Horner syndrome [74, 75].

GBS is classically a post-infectious illness, in many cases reflecting molecular mimicry between epitopes on the infectious agent (especially *Campylobacter jejuni*) and neuronal gangliosides [76]. Several subtypes differ in their clinical and immunologic characteristics. Symptomatic autonomic dysfunction is more common in acute inflammatory demyelinating polyradiculoneuropathy (AIDP) than in the motor axonal (AMAN) or Miller Fisher variants [74]. The pathophysiology of autonomic dysfunction in GBS is not well understood [76].

Treatment of GBS consists of immunotherapy (either PE, which must be used with caution in patients with cardiovascular instability, or IVIG), careful monitoring for respiratory and autonomic deterioration in the acute phase, meticulous supportive care to avoid complications of hospitalization and immobility, and comprehensive rehabilitation [76]. Careful monitoring of blood pressure and heart rhythm should be undertaken in the acute phase, and transfer to intensive care is indicated for those exhibiting hemodynamic instability. GBS patients are often quite sensitive to the effects of vasoactive medications, so these should have a short half-life and be used sparingly [74, 77]. Similar to the somatic manifestations of GBS, clinical autonomic dysfunction typically resolves over time, although formal testing may reveal persistent subclinical deficits [74].

Central autoimmune autonomic disorders

A number of central autoimmune disorders also have autonomic manifestations. A study of 58 epilepsy patients with peri-ictal autonomic findings found a high prevalence (29%) of neuronal autoantibodies [78]. In addition to the peripheral syndromes discussed above, VGKC-complex antibodies can cause limbic encephalitis with autonomic manifestations [71]. Anti-NMDA receptor encephalitis causes autonomic instability in 69% of patients, with manifestations including cardiac dysrhythmia, temperature and blood pressure fluctuations, hyperhidrosis, and sialorrhea [79]. Heart rate variability analysis suggests sympathetic dysfunction, and patients with impaired cardiac autonomic function may have poorer outcomes [80]. Antibodies against dipeptidyl peptidase-like protein-6 (DPPX) cause a syndrome of encephalopathy, central hyperexcitability, and autonomic manifestations primarily involving the gastrointestinal tract (diarrhea and weight loss) [81]. Serum from an anti-DPPX patient was shown to cause hyperexcitability of enteric neurons [82]. A substantial proportion of patients with multiple sclerosis have autonomic dysfunction, including impaired cardiovascular autonomic function as well as bowel, bladder, and sexual dysfunction. This is hypothesized to reflect not only demyelinating lesions in relevant parts of the brain and spinal cord, but also pathologic interactions between the dysregulated immune system and adrenergic receptors on lymphocytes [83]. Cardiac autonomic dysfunction and autonomic symptoms have also been reported in patients with neuromyelitis optica spectrum disorders (NMOSD) [84].

Sjögren syndrome and other rheumatologic diseases

Primary Sjögren syndrome (SS) is a rheumatologic disease characterized by sicca symptoms and lymphocytic infiltration of exocrine glands. Peripheral nervous system involvement may occur, particularly sensory ganglionopathy and small-fiber neuropathy [85]. More than half of SS patients report symptoms of autonomic dysfunction [86]. Objective characterization of autonomic manifestations has yielded varying results, including secretory dysfunction out of proportion to histological changes in the salivary gland [87], decreased cardiovagal function [87–89], impaired sympathetic vasomotor activity [90], and tachycardic response to head-up tilt [91]. Autonomic features may precede the diagnosis of SS [91]. The pathophysiology of autonomic dysfunction in SS is not well understood, although some patients may respond to immunotherapy [91].

Autonomic function has been studied in other rheumatologic diseases as well, although conclusions regarding the extent and prevalence of autonomic dysfunction are limited by widely varying methodologies and patient populations. Patients with systemic lupus erythematosus tend to have decreased heart rate variability and abnormalities on various components of the Ewing battery; these abnormalities do not tend to correlate well with disease activity [92, 93]. Studies in rheumatoid arthritis have shown increased sympathetic nerve activity, reduced cardiac baroreflex sensitivity [94], and a variety of other markers of autonomic dysfunction

[95]; these are also independently associated with pain [94] and less consistently with markers of inflammation [95]. Interestingly, a pilot study of rheumatoid arthritis and ankylosing spondylitis patients [96] demonstrated improvement in several markers of autonomic function after the initiation of synthetic or biologic disease-modifying antirheumatic drugs. Parasympathetic and sympathetic dysfunction has also been described in scleroderma [97] and psoriatic arthritis [98].

Conclusion

Autoimmunity may underly primary peripheral autonomic disorders, and autoimmune neurological and rheumatological diseases may have prominent autonomic symptoms. An understanding of the underlying pathophysiology aids in the appropriate use of immunotherapy as well as the appropriate management of autonomic symptoms.

Compliance with ethical standards

Conflict of interest Dr. Golden has no conflict of interest to report. Dr. Vernino has received research support from Grifols, Genentech, Dysautonomia International, and Theravance.

Ethical statement The manuscript does not contain clinical studies or patient data.

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