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INVITED REVIEW

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Autonomic neuropathies

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Abstract

Autonomic neuropathies represent a complex group of disorders that preferentially target autonomic fibers and can be classified as either acute/subacute or chronic in onset. Acute-onset autonomic neuropathies manifest with such conditions as paraneoplastic syndromes, Guillain-Barre syndrome, Sjögren syndrome, infection, or toxins/chemotherapy. When the presentation is acute, immune-mediated, and without a secondary cause, autoimmune autonomic ganglionopathy is likely, and should be considered for immunotherapy. Of the chronic-onset forms, diabetes is the most widespread and disabling, with autonomic impairment portending increased mortality and cardiac wall remodeling risk. Acquired light chain (AL) and transthyretin (TTR) amyloidosis represent two other key etiologies, with TTR amyloidosis now amenable to newly-approved gene-modifying therapies. The COMPASS-31 questionnaire is a validated outcome measure that can be used to monitor autonomic severity and track treatment response. Symptomatic treatments targeting orthostatic hypotension, among other symptoms, should be individualized and complement disease-modifying therapy, when possible.

KEYWORDS

autonomic neuropathy, diagnosis, evaluation, review, treatment

1 | INTRODUCTION

The autonomic nervous system regulates a diverse group of biologic functions mediated by the parasympathetic and sympathetic systems. Disturbances that solely or predominantly affect this system are classified as autonomic disorders and can be of central or peripheral nervous system origin, or both. Autonomic disorders manifest with a myriad of symptoms, ranging from cardiovascular (hypotension, tachycardia) to gastrointestinal (bloating, early satiety, constipation) to genitourinary (neurogenic bladder, erectile dysfunction) to secretomotor (anhidrosis) to pupillomotor (blurred vision, light sensitivity), among others. In this article, we limit our review to autonomic disorders that are peripheral in origin, henceforth referred to as autonomic neuropathies. In light of improved non-invasive autonomic reflex testing, more

Abbreviations: AAG, autoimmune autonomic ganglionopathy; AL, acquired light chain (amyloidosis); CBC, complete blood count; CSF, cerebrospinal fluid; CyBorD, cyclophosphamide, bortezomib, and dexamethasone; ECG, electrocardiogram; FAP, familial amyloid polyneuropathy; FDA, United States Food and Drug Administartion; GI, gastrointestinal; gAChR, ganglionic acetylcholine receptor antibody; IVIG, intravenous immunoglobulin; LEMS, Lambert-Eaton myasthenic syndrome; QSART, quantitative sudomotor axonal reflex testing; SEID, systemic exertion intolerance disorder; TST, thermoregulatory sweat testing; IVIG, intravenous immunoglobulin; COMPASS-31, Composite Autonomic Symptom Scale-31; GBS, Guillain-Barre syndrome; AASN, acute autonomic and sensory neuropathy; AL, amyloid light chain; TTR, transthyretin; HSAN, hereditary sensory autonomic neuropathy; POTS, postural tachycardia syndrome.

The objectives of this activity are for readers to understand the diverse presentations of diabetic neuropathies, and to be able to diagnose and treat chronic and acute diabetic poly-, mono-, autonomic, and radiculoplexus neuropathies, as well as radiculopathies.

nuanced understanding of immunopathogenesis, and better classification and testing of hereditary forms of autonomic neuropathy, autonomic neuropathies now are much better understood and classified. Multiple schemata exist to classify autonomic neuropathies. For ease of classification, autonomic neuropathies can be defined temporally as pertains to disease onset (*acute/subacute* vs *chronic in onset*), etiologically (*acquired* vs *hereditary*), or spatially (*focal* vs *generalized*, *sympathetic* vs *parasympathetic predominant*), although these divisions are by no means absolute. In our current review, and in line with prior reviews, we adopt a temporal classification schema, first reviewing autonomic neuropathies with an acute/subacute onset and then those with a chronic onset,[1,2] although other approaches exist.[3] We also briefly touch on postural tachycardia syndrome (POTS). We assume that the reader is familiar with basic findings and interpretation of autonomic reflex testing, which is beyond the scope of this review, but is discussed extensively elsewhere.[4] Furthermore, we focus our review primarily on outpatient evaluation and management. In addition to providing an abbreviated review of the various disease categories, we highlight recent advances in our understanding, where appropriate. Our goal is to provide a practical reference to guide the practicing clinician to evaluate, diagnose, and manage autonomic neuropathies.

2 | AUTONOMIC NEUROPATHIES WITH AN ACUTE TO SUBACUTE ONSET

2.1 | Autoimmune autonomic ganglionopathy

AAG is an immune mediated disorder that involves the antibody-mediated targeting of autonomic nerve fibers or ganglia, and is characterized by a triad of orthostatic hypotension, anhidrosis, and severe gastrointestinal (GI) dysmotility.[5,6] 50% of patients carry a ganglionic (α-3 type) nicotinic acetylcholine receptor antibody (gAChR), with titers greater than 1.0 nmol/L deemed as quite specific for this condition.[7-9] Furthermore, although classified as acute in onset, AAG can also be subacute or chronic in presentation.[10] Patients are typically young and healthy, with a slight female preponderance (up to 65% of all cases). Patients have disproportionate GI dysfunction, reporting disabling early satiety, bloating, constipation, and/or abdominal pain often to the point of experiencing significant weight loss. Delayed transit time is often seen scintigraphically on motility studies, such as esophageal manometry, gastric emptying study, and/or small bowel transit. Males often report acute to subacute erectile dysfunction and urine retention. Autonomic reflex testing is vital to the diagnosis, and reveals marked orthostatic hypotension with impaired heart rate increment on tilt testing. Impaired late phase II and/or phase IV responses on Valsalva testing signify vascular and cardiac adrenergic impairment while reduced heart rate variation to deep breathing and Valsalva signifies cardiac vagal impairment. Secretomotor findings of global anhidrosis or hypohidrosis on quantitative sudomotor axonal reflex testing (QSART) or thermoregulatory sweat testing (TST) further raise suspicion for AAG. The physical exam finding of nonreactive or sluggish pupils, in the proper clinical context, highly suggests the condition, and can be further quantified using formal pupillometry.[11]

Anatomically, while ganglionopathies often have a widespread and length-independent distribution, the brunt of the symptoms is often due to disproportionate parasympathetic involvement. There are multiple explanations for this, but the fact that the parasympathetic ganglia are very close to end organs plays a significant role.[12] This is in contrast to length-dependent, predominantly small-fiber distal axonal neuropathies, which are often highly involved in certain autonomic neuropathies.

As alluded to earlier, the discovery of the α-3 type gAChR autoantibody, seen in 50% of patients, provides a clear immunologic basis for this condition, with higher titers correlating with greater disease severity.[13,9] Worth noting, however, is that the absence of antibodies does not exclude the diagnosis, and clinical suspicion, autonomic reflex testing, and GI scintigraphic findings should guide evaluation and management. Other antibodies also appear to carry some association with AAG, particularly the N-type calcium channel antibody.[14] Furthermore, although antibody testing may be negative, the presence of inflammatory serologic markers, a personal and family history of autoimmune disease and malignancy, and/or smoking history, should raise suspicion. Left untreated, one-third of patients with AAG improve spontaneously, but even then, recovery is incomplete.

Once a diagnosis of AAG has been formally made, a well-instituted and planned treatment course should be pursued. Although no standard treatment guidelines exist, existing data suggests a therapeutic role for intravenous immunoglobulin (IVIG), pulsed or daily corticosteroids, and plasma exchange.[15,16] While there is no standard dosing regimen, our centers typically use a 12-week treatment trial of either weekly 0.4 g/kg IVIG or weekly 1 g intravenous methylprednisolone.[17] Data are limited, however, in terms of optimal dosing and frequency of both therapies. We make sure to document autonomic disease severity at baseline and at completion of the 12-week treatment trial. Plasma exchange also has demonstrated benefit in small series.[18] At the completion of the 12-week treatment trial, assuming a treatment-response, long-term immunosuppressant therapy with such agents as azathioprine, mycophenolate, or rituximab can be considered, although data regarding such agents is also quite limited.

We use the Composite Autonomic Symptom Scale-31 (COMPASS-31) questionnaire, a validated, abbreviated, and internally consistent measure of autonomic symptom severity that takes 5 to 10 min to administer.[19] The COMPASS-31 questionnaire can distinguish patients with autonomic neuropathy from those without reasonably well. In diabetes, for instance, the COMPASS-31 carries a sensitivity of 75% for cardiac autonomic neuropathy.[20,21] In small fiber polyneuropathy, it is valid and reliable in distinguishing patients with small fiber polyneuropathy from those without.[22] In addition, the COMPASS-31 questionnaire was used to track autonomic symptom evolution and treatment-response in a landmark phase 3 drug study for transthyretin amyloidosis, discussed later in this review.[23]

While AAG is classically classified as a generalized autonomic neuropathy, variants and disease mimickers warrant attention. Seronegative autonomic neuropathy is of particular importance.[24] Relative to seropositive AAG, seronegative AAG is described as having more sensory symptoms, being sympathetic predominant, having less

pupillary fatigue, and showing preferential steroid-responsiveness (as opposed to IVIG or plasma exchange). In addition, enteric autoimmune neuropathy is another variant that focally and/or preferentially targets the enteric autonomic system and presents with severe gastroparesis and intestinal pseudo-obstruction.[25] Idiopathic gastroparesis is a frequent referral reason from gastrointestinal to autonomic clinics. A case series from the Mayo Clinic demonstrated an immunotherapeutic response in many patients, even those who were seronegative. The authors concluded that immunotherapeutic trials may be considered, when appropriate, as such conditions may represent enteric-restricted forms of autoimmune autonomic disease. Of note, however, some objective biomarker, such as scintigraphic evidence of GI slowing or serologic markers, should be present.[25] With regards to serology, only 10% of patients with idiopathic GI dysmotility and 50% of those with chronic intestinal pseudo-obstruction, are noted to be gAChR antibody seropositive.[26] Finally, if there are symptoms or signs of ataxia or large fiber sensory loss, nerve conduction studies and additional serologic testing can be helpful to evaluate for disease mimickers such as paraneoplastic neuronopathy, Sjögren neuronopathy, or acute autonomic and sensory neuropathy (AASN), a GBS variant,[27] all discussed later.

2.2 | Paraneoplastic autonomic neuropathy

Paraneoplastic autonomic neuropathies represent a similar, albeit distinct etiologic entity. Unlike idiopathic AAG, a truly paraneoplastic etiology occurs in the setting of malignancy, most commonly small cell carcinoma of the lung. While ANNA-1 (anti-Hu) is the most well established antibody, other antibodies should also be considered, namely PCA-2, CRMP-5, VGKC, and P/Q calcium channel antibodies.[28] Care should be taken to ensure correct antibody-phenotype correlation. In ANNA-1-associated paraneoplastic autonomic neuropathy, patients present with severe gastroparesis, and intestinal pseudo-obstruction that often precedes the diagnosis of malignancy. GI pathology reveals infiltration of the myenteric plexus with plasma cells and lymphocytes as well as neuronal and axonal degeneration. Lambert-Eaton myasthenic syndrome (LEMS) represents another paraneoplastic etiology when lung cancer is present (found in 60% of LEMS patients).[29] It is an autoimmune-mediated deficit of pre-synaptic neuromuscular transmission where antibodies target P/Q type voltage-gated calcium channels. Autonomic symptoms are present in a majority of patients, are mild, and typically manifest as acute cholinergic neuropathy, with dry eyes, pupillary fatigability, anhidrosis, and constipation. There are no definitive cures for paraneoplastic syndromes and natural history depends on the cancer itself. The appearance of peripheral nervous symptoms in a previously cancer-free patient, however, should raise concern for cancer recurrence. In terms of ancillary studies, nerve conduction studies are particularly important in the setting of antibody-confirmed paraneoplastic autonomic syndromes to assess for concomitant sensory somatic neuronopathy, which is common with anti-Hu and anti-CRMP5 syndromes. In patients with ptosis, proximal weakness, and cholinergic-predominant deficits, repetitive nerve stimulation studies (both low and high frequency) as well as pre- and post-exercise compound muscle action potential testing can be used to confirm the diagnosis of LEMS.

2.3 | Sjögren syndrome

Sjögren syndrome is an autoimmune disorder with a lymphocytic inflammatory predilection for exocrine glands and ducts, thus explaining its classic sicca (dry eyes and dry mouth) complex. The autonomic system is frequently perturbed in Sjögren, and in the proper clinical context, Sjögren should be part of the differential.[30,31] Sjögren involves both the sympathetic and parasympathetic divisions, and often presents with fixed tachycardia and orthostatic hypotension, but can also overlap with postural tachycardia syndrome. Suggestive clues on history include the presence of sicca as well as dry cough, dry nasal passages, acid reflux, and abdominal pain, particularly after fatty meals. The diagnosis is established via serologic testing for anti-Ro (SSA) and anti-La (SSB) antibodies, although minor lip salivary gland biopsy should be pursued if suspected, as antibodies can be falsely negative in many cases.[32] In terms of its natural history, autonomic and somatic sensory deficits not uncommonly precede sicca symptoms in Sjögren neuropathy patients. The presence of ataxia on exam or sensory neuronopathy on nerve conduction testing should further raise suspicion. Conversely, whenever nerve conduction studies show a length-independent preferential or selective loss of sensory nerve action potentials, Sjögren should remain at the top of the differential diagnosis unless proven otherwise, even if anti-Ro and anti-La serology is negative, as it is insensitive. A retrospective review conducted at the Mayo Clinic identified various phenotypes associated with Sjögren, and identified its potential treatment-responsiveness, particularly to IVIG, although no definitive therapies exist.[33]

2.4 | Guillain-Barre syndrome

Guillain-Barre syndrome (GBS) is an autoimmune-mediated length independent radiculoneuropathy that predominantly targets the somatic system, but also autonomic fibers. Autonomic disturbances predominantly affect the cardiovascular and gastrointestinal systems and are present in two-thirds of patients.[34,35] Cardiac disturbances manifest in the form of over-reactive or blunted cardiac vagal and cardiac adrenergic responses, with patients often exhibiting sinus tachycardia, dysrhythmias (sometimes potentially fatal arrhythmias), systemic hypertension, bradycardia, and/or blood pressure fluctuation. GI dysmotility and urine retention can occur as well. Demyelination of autonomic fibers in the vagal, glossopharyngeal, and preganglionic sympathetic efferents is thought to underlie GBS-induced autonomic injury, with lymphocytic infiltration, neurotoxic cytokine production, and autoantibody targeting thought to impede norepinephrine synthesis and transmission. The diagnosis of GBS is often suggested by the presence of dysautonomia, but other clinical features should alert the clinician and distinguish it from other inflammatory or immune neuropathies, namely chronology of symptoms,

respiratory involvement, craniobulbar symptoms, and often an antecedent infection. Whenever autonomic symptoms present rapidly, especially in the setting of associated somatic motor and/or sensory deficits, GBS should always be considered.

As discussed earlier, the GBS variant AASN, which is quite prevalent among Asians, should be considered.[27] AASN patients have severe orthostatic hypotension, atonic bladder, gastroparesis, and low plasma norepinephrine levels. Affected patients typically have somatic large and small fiber involvement, with minimal motor impairment. In addition to nerve conduction testing and cerebrospinal fluid (CSF) evaluation, antibody testing (GD1a) can be helpful in diagnosing axonal forms of GBS.[36] Autonomic dysfunction and, in particular, cardiac vagal impairment, portend worse disease severity and increased mortality in GBS. Dysrhythmias, including potentially fatal arrhythmias, carry the greatest cardiovascular risk of morbidity and mortality. Thus, all GBS patients with autonomic involvement should be monitored with cardiac telemetry while inpatient. In terms of short term prognosis, dysautonomia, along with other clinical factors, such as rapidity of disease progression, bulbar dysfunction, and bilateral facial weakness factors predict a greater likelihood of progression to mechanical ventilation.[37] In terms of outcome, GBS patients with dysautonomia have a 6% mortality as compared to 2% for those without.[38]

3 | AUTONOMIC NEUROPATHIES WITH A CHRONIC ONSET

3.1 | Diabetic autonomic neuropathy

Diabetic autonomic neuropathy is underappreciated in diabetics, as symptoms tend to be superseded by more commonly reported complaints from painful somatic neuropathy. Cardiac vagal function is often affected early and symptoms should be screened for as patients may not report them. The exact prevalence of diabetic autonomic neuropathy varies and depends upon diagnostic criteria, patient cohort, and testing modality,[39,40] with estimates ranging from as low as 7% to as high as 90%. A community-based study in Oxford, England revealed a 17% prevalence based on heart rate variability.[41] A separate community-based study showed parasympathetic dysfunction in 65% of patients at 10-y follow-up, with sympathetic dysfunction manifesting in only 24%.[42] The overall prevalence of autonomic impairment varies by the type of diabetes, with type 1 having a prevalence of 54% and type 2 a prevalence of 73%. Prevalence is impacted by disease duration, age, glycemic control, and metabolic syndrome features, particularly in type 2 diabetes.[43] Clinically, diabetic autonomic neuropathy presents with a myriad of symptoms and affects all major autonomic fibers, although distal small fiber neuropathy, which involves sympathetic sudomotor post-ganglionic secretomotor function, is quite common. In addition, diabetic patients with autonomic deficits may benefit from nerve conduction testing to evaluate for large fiber neuropathy, especially when sensory symptoms are present. On exam, skin changes often occur due to denervation of sweat glands, which results in trophic skin changes and hair loss.

In terms of autonomic symptoms, erectile dysfunction is the most common symptom in males. Cardiovascular, gastrointestinal, and genitourinary symptoms are the most disabling sequelae of diabetic autonomic neuropathy, and are reviewed system-by-system below. Our current understanding of diabetic end-organ damage has shown that the mechanism of nerve injury is unique and separate from retinal or renal injury. In addition, extensive literature now shows that type 1 and type 2 diabetes are largely different disease processes, with type 1 responding favorably to glycemic control, while type 2 responds to treatments aimed at metabolic syndrome, such as lifestyle modification and exercise.[44-46]

The prevalence of cardiac autonomic neuropathy varies from 1% to 90% for type 1 and 20% to 73% for type 2 diabetics.[47] It is the most life-threatening form of diabetic autonomic neuropathy, and independently portends a poor prognosis, with patients having a 27% to 56% mortality rate at 5- to 10-y follow-up and an increased risk of sudden cardiac death.[48] A separate study evaluating type 1 diabetic patients with nephropathy found that the presence of abnormal heart rate variation, a marker of cardiac autonomic neuropathy, was associated with an increased risk of fatal and nonfatal cardiovascular disease.[49] A meta-analysis found a strong association between cardiovascular autonomic instability (orthostatic hypotension, resting tachycardia, exercise intolerance and silent myocardial ischemia) and mortality in diabetic patients. All physiologic cardiac functions, such as chronotropy and dronotropy, are impacted. Vagus nerve denervation leads to unopposed sympathetic drive, manifesting as reduced heart rate variability on deep breathing and Valsalva. This then evolves into resting tachycardia and orthostatic hypotension.

With continued disease progression, sympathetic cardiac denervation leads to orthostatic hypotension and bradycardia. In light of such findings, silent myocardial infarction (also called cardiac denervation syndrome) in diabetics warrants special mention.[50] A National Registry of Myocardial infarction survey showed that 32% of diabetic patients with myocardial infarction did not present with any chest pain.[51] Orthostatic hypotension is typically a late manifestation of cardiovascular autonomic neuropathy, present in 6% to 30% of diabetics (even if asymptomatic), and attributable to impaired sympathetic vasoconstriction of the splanchnic mesenteric and peripheral vascular beds. A prospective Mayo Clinic study found that the most common symptoms on 5 min standing were lightheadedness, weakness, cognitive impairment, and blurred vision.[52] As with all forms of orthostatic hypotension, patients should be asked about exacerbating factors, such as time of day (worse in morning), meals, and hot showers. Orthostatic hypotension is formally defined as a greater than 20 mmHg systolic and/or 10 mmHg diastolic drop in pressure within 2 min of standing, although this carries lower specificity than the more stringent cutoff of 30 mmHg systolic/15 mmHg diastolic drop, which has been studied in some populations, such as Parkinson patients[53].

Gastrointestinal autonomic neuropathy manifests with dysmotility at nearly any level in the alimentary tract from the esophagus through the rectum, and presents with such symptoms as dysphagia, early satiety, bloating, abdominal pain, constipation, and diarrhea, of which constipation is most common.[54] Beginning in the stomach, gastroparesis is

defined as delayed emptying of gastric contents without any evidence of mechanical obstruction, and should be confirmed on gastric emptying studies. It manifests with nausea, vomiting, bloating, and also impaired glycemic control, due to poor food absorption and resultant difficulty in matching insulin requirement. Intestinal neuropathy manifests as diabetic diarrhea, which typically appears as slowed transit time on small bowel studies. Diabetic diarrhea is sudden, explosive, episodic, and disabling, and may also occur with sphincter dysfunction, which furthers fecal incontinence. Constipation results from denervation of the colon and the gastrocolic reflex, and occurs in two-thirds of diabetics. Gastric dysrhythmia refers to a combined picture of constipation, due to bradygastria or slowing of peristaltic movements, and diarrhea, due to tachygastria or enhanced peristaltic movements.

Genitourinary autonomic neuropathy in diabetics presents with such symptoms as neurogenic bladder and erectile dysfunction. Neurogenic bladder, a major problem particularly in type 1 diabetics, manifests with increased post-void residual, overflow incontinence, weak flow, reduced micturition reflex, and atonic bladder. In men, erectile dysfunction occurs in anywhere from one-third to three-fourths of patients with established autonomic neuropathy and may be the first symptom.[55] In erectile dysfunction, parasympathetic fiber denervation leads to impaired smooth muscle relaxation in the corpus callosum. Of note, patients with erectile dysfunction warrant evaluation for cardiovascular disease, as it can be the first sign of cardiovascular injury. In patients with sympathetic injury, retrograde ejaculation may also occur.

3.2 | Treatment-induced neuropathy of diabetes

Treatment-induced diabetic neuropathy is an iatrogenic neuropathy that preferentially targets small and autonomic fibers within weeks of glycemic overcorrection. Although it presents acutely, we include it in this section as a distinct disease category to consider within the broader context of diabetic autonomic neuropathy. It can be precipitated by insulin, hypoglycemic medication, or diet-induced glycemic control, and is generally suspected whenever there is a drop in hemoglobin A1c of at least two points over a 3-month period.[56] Although most patient and provider focus is typically directed towards painful small fiber symptoms, autonomic symptoms are quite common. Patients report orthostatic intolerance, bloating, sweat changes, and sexual dysfunction.[57] Autonomic symptom severity correlates with degree of hemoglobin A1c decline,[58] and a strong correlation exists between the degree of parasympathetic and sympathetic adrenergic impairment and the magnitude of drop of hemoglobin A1c.[56] Natural history is altered by glycemic control, as autonomic findings on formal testing show improvement in patients with stable glycemic control, with sympathetic adrenergic and parasympathetic impairment normalizing after 8-y follow-up in one study.[58] In patients with unstable glycemic control, autonomic testing shows continued worsening. A 2010 study shed some additional light on differences between type 1 and type 2 diabetics. Type 1 diabetics reported more frequent and severe autonomic symptoms as compared to type 2 patients, typically with respect to orthostatic intolerance and GI dysfunction.[59] In addition, natural history varies by type. On 18-month follow-up, type 1 patients reported improvement in autonomic symptoms, while type 2 patients did not.

3.3 | Amyloidosis

Amyloidosis involves the excessive generation and deposition of insoluble fibrillary proteins in β-pleated sheets in various organ systems, and has acquired and hereditary forms. While autonomic symptoms overlap and will be discussed together, we discuss each condition's pathophysiology and treatment separately in this section.

Autonomic neuropathy symptoms in amyloid are widespread.[60] Symptoms tend to be more severe and rapidly progressive than in other chronic conditions, but not typically as abrupt as AAG, for example. Patients can describe widespread anhidrosis with compensatory hyperhidrosis, significant GI dysmotility (confirmed on scintigraphy), orthostatic intolerance (manifest on autonomic testing), as well as erectile dysfunction in males. Orthostatic hypotension from vascular and cardiac adrenergic impairment often leads to syncope or near syncope. As with AAG, amyloid can produce pan-dysautonomia on autonomic reflex testing, with marked and, oftentimes global, reduction in sudomotor sweat output and significantly blunted cardiac vagal, as well as cardiac and vascular adrenergic function. In addition to autonomic symptoms, other clinical and electrodiagnostic clues are often present. The presence of cardiomyopathy, nephrotic syndrome, axonal peripheral neuropathy, weight loss, macroglossia, hepatomegaly, and/or significant GI dysmotility should raise concern for amyloidosis. Scalloping of the pupillary margin is sometimes noted on exam. Nerve conduction testing typically reveals a length dependent sensorimotor axonal peripheral neuropathy, often with superimposed carpal tunnel syndrome. Additional diagnostic tests include fat pad aspiration, rectal or gingival mucosal biopsy, or nerve biopsy evaluation with Congo red staining. Nerve histopathology reveals deposition of amyloid protein as seen on Congo red staining, predominantly involving small myelinated or unmyelinated fibers and the autonomic ganglia. When the hereditary form is suspected, genetic testing should be pursued prior to any biopsy evaluation.

3.3.1 | Amyloidosis: amyloid light chain subtype

Amyloid light chain (AL) amyloidosis is the most common form of amyloid in the United States, and generally affects patients ages 50 to 80, with a 2:1 male to female predilection. It involves the mis-folding of the light chain antibody, either lambda or kappa, and its deposition in tissue. Bone marrow or tissue biopsy is usually required to positively secure the diagnosis, although other tests can be highly suggestive, including immunofixation electrophoresis, free light chains, 24 h urine immunofixation, alkaline phosphatase, troponin, and N-terminal brain natriuretic peptide (NT-proBNP). In addition, echocardiographic findings can include ventricular wall thickening, significant diastolic impairment, and a restrictive filling pattern. MR imaging can reveal diffuse and irregular hyperenhancement of myocardium that is usually circumferential and subendocardial. The peripheral neuropathy tends to

progress with or without treatment, although mortality is typically due to other medical complications.[61] For AL amyloid, first-line therapy consists of cyclophosphamide, bortezomib, and dexamethasone (CyBorD therapy).[62] Emerging therapies also show promise, including the newly FDA approved daratumumab, a CD-38 directed monoclonal antibody.[63] In selected patients, stem cell transplant can also prolong survival.[64-66]

3.3.2 | Amyloidosis: transthyretin familial amyloid polyneuropathy subtype

Within the broad family of familial amyloid polyneuropathy (FAP), which refers to all hereditary forms of amyloidosis, we focus our discussion on TTR-associated FAP patients. 75% of TTR-FAP patients have autonomic neuropathy.[67] In TTR amyloidosis, the liver produces mutated TTR protein that causes unstable tetramers, which subsequently dissociate into monomers, and which then form oligomers and fibrils. The fibrils subsequently deposit in multiple end organs, including autonomic and somatic sensory nerves as well as heart, kidney, gastrointestinal tract, vitreous fluid, spinal canal, and carpal tunnel. A family history of unexplained peripheral neuropathy or recurrent carpal tunnel syndrome should raise concern for TTR amyloidosis. TTR amyloidosis itself is associated with numerous variants, the most common of which is the Val30Met mutation, prevalent in Portugal, Brazil, Sweden, and Japan.[68] Amongst African Americans, the Val122Ile mutations is the most common.[69] TTR is further subdivided into early onset (<50 y) and late onset (>50 y), with early onset having a significant degree of autonomic impairment, in contradistinction to late onset. In addition to tissue biopsy and other serum and urine based tests discussed previously, genetic testing for TTR is now commercially available. Technetium-99 pyrophosphate cardiac imaging is a useful confirmatory test in cases of suspected TTR cardiomyopathy, often precluding the need for endomyocardial tissue biopsy.[70] Autonomic symptoms can be associated with high morbidity, with arrhythmias contributing to sudden death in some. The severity of cardiac autonomic impairment, however, does not always correlate with the severity of somatic neuropathy in TTR amyloid, and both fiber types (somatic and autonomic) should be given full independent consideration in any patient.[71]

For TTR amyloidosis, the emergence of two new FDA-approved therapies holds great promise. Patisiran, an RNA interference therapy, is administered intravenously once every 3 weeks, and has been shown to halt and even reverse neuropathy.[72] It also lessens autonomic impairment in TTR amyloid patients as compared to untreated patients. Inotersen, an antisense oligonucleotide administered intravenously once weekly, is another recently FDA-approved therapy that inhibits hepatic production of transthyretin by binding to TTR mRNA and targeting it for degradation via RNAase. It improves neurologic disability scores as well as quality of life. Both drugs work by targeting the 3′ untranslated region of transthyretin mRNA. Other therapies available include tafamidis[73] as well as diflunisal. Finally, liver transplant remains a consideration for TTR, particularly those with the Val30Met mutation (74% post-transplant survival).[74]

3.4 | Hereditary sensory autonomic neuropathies

Hereditary sensory autonomic neuropathies (HSANs) are a heterogeneous group of familial disorders that preferentially target autonomic

TABLE 1 The most common hereditary sensory autonomic neuropathies: clinical features and inheritance

Hereditary sensory autonomic neuropathy (HSAN)	Onset	Inheritance	Sensory	Motor	Autonomic	Allied features
HSAN I	Juvenile to adult	AD	Marked	Minimal	Minimal	Foot ulcers or amputations; bone deformities and osteomyelitis; hearing loss occurs occasionally
HSAN II	Childhood	AR	Marked	Minimal	Absent or minimal	Some patients develop ulcers, atrophy, and hyporeflexia
HSAN III/ Familial dysautonomia	Congenital	AR	Modest Decreased sensitivity to pain and temperature	Absent	Marked Autonomic crises	Recurrent pneumonias; absence of tears
HSAN IV	Congenital/ childhood	AR	Modest Congenital sensory loss affecting perception of pain and temperature	Absent	Modest Anhidrosis	Oral self-mutilation; fingertip biting; repeated bone fractures and joint trauma
HSAN V	Early childhood to adult	AR	Modest Congenital reduced pain and anhidrosis	Absent	Minimal Sweating normal or reduced	Charcot joints and fracture

Note: HSAN, hereditary sensory autonomic neuropathy; AD, autosomal dominant; AR, autosomal recessive.
Source: From Iodice and Sandroni (2014).[1] Reproduced in its original format by written permission from Wolters Kluwer Health.

and small fibers, traditionally divided into five subtypes, with nuanced phenotype-genotype correlations (Table 1).[75] In this section, only HSAN-I is discussed in detail as it is the only subtype that presents in adulthood. In general, any unexplained dysregulation of sweating, lacrimation, breathing pattern, pain sensitivity, or temperature control, especially in children, should prompt consideration for genetic testing for any HSAN subtype. HSAN I is autosomal dominant and associated with a pathogenic mutation in the *SPTLC1* gene on chromosome 9q22.1 to q22.3. Clinically, patients develop pain and temperature loss early, often in the second decade of life, and may develop position and vibration sensory loss later in disease course.[76] Sweating disturbances are the most commonly observed autonomic impairment.[77] Nerve conduction testing typically shows a sensory axonal peripheral neuropathy, with sural nerve biopsies showing concordant axonal loss. Management of HSAN I, as well as most other HSAN subtypes, follows similar guidelines as for diabetic foot care, including proper ulcer care to prevent infection as well as counseling to avoid ulcer development.[77]

3.5 | Postural orthostatic tachycardia syndrome

Postural tachycardia syndrome (POTS) is a disorder that is not classically considered an autonomic neuropathy, but warrants attention in this context. It is defined by a sustained heart rate increase from baseline of 30 beats/min or more in the absence of orthostatic hypotension on tilt table testing.[78] Clinically, it is characterized by suggestive patient profile, clinical complaints, and the absence of more widespread autonomic neuropathy. It is most commonly seen in the 15- to 50-y age range and has a 4:1 female to male preponderance. Symptoms are widespread, but tend to revolve around fatigue, palpitations, cognitive slowing, orthostatic intolerance, exercise intolerance, diffuse body pain, GI complaints, among a host of other symptoms. Associations exist with preceding trauma, viral illness, or pregnancy, as well as the presence of such concomitant conditions as anxiety, Chiari malformation, mitral valve prolapse, mast cell activation syndrome, and Ehlers Danlos syndrome. The prognosis is generally favorable for most POTS patients, especially with treatment, although a subset of patients, especially those with a systemic exertion intolerance disorder (SEID) phenotype, may not respond or continue to decline.

Other acute and chronic causes of autonomic neuropathy are summarized in Table 2.

4 | A PROPOSED APPROACH TO THE EVALUATION AND TREATMENT OF AUTONOMIC NEUROPATHIES

4.1 | Evaluation

The proper evaluation of autonomic neuropathy rests upon a complete history and examination, followed by formal autonomic reflex screening and appropriate ancillary testing to corroborate such findings (Figure 1). A thorough autonomic review of systems should be conducted, screening for such symptoms as dry eyes, dry mouth, orthostatic intolerance or lightheadedness, exertional intolerance, dyspnea, chest pressure, fatigue, abdominal pressure, bloating, constipation, diarrhea, early satiety, urinary urgency, urinary frequency, erectile dysfunction, decreased libido, anhidrosis, heat or cold intolerance, as well as acral redness or swelling or numbness, to name some of the more common symptoms. Personal or family history of autoimmune disease (particularly connective tissue disease), cancer, or genetic disorder should be queried. Chemotherapy or other toxic drug exposure, travel history, and alcohol consumption should also be screened for. Medications and supplements that could contribute to autonomic symptoms should be reviewed. Disease mimickers should also be excluded, such as pheochromocytoma, adrenal insufficiency, thyroid disorders, anemia, or structural cardiac disease. Depending on symptomatic presentation, testing should include serum and urine catecholamines, serum cortisol, CBC, ECG, echocardiogram, and Holter monitor evaluation.

In patients with autonomic neuropathy, the examination should note the presence of pupillary non-responsiveness, acral sensory pinprick and vibratory loss, proprioceptive or ataxic proprioceptive sensory loss, and areflexia. One should evaluate for skin discoloration, change in skin temperature, acral swelling, trophic changes, and joint hypermobility.

Temporal disease onset is also particularly useful in the evaluation of etiology. Acute or subacute autonomic symptom onset should prompt consideration for AAG, paraneoplastic peripheral autonomic neuropathy, GBS, botulism, toxins, or infections. The presence of tonic or sluggishly reactive pupils raises concern for AAG, and formal pupillometer testing can be very helpful. In the setting of severe GI dysmotility, urine retention, anhidrosis, and/or erectile dysfunction, AAG should be further entertained, even in the absence of gAChR antibody. GI scintigraphic studies should be pursued if AAG is suspected. TST is also helpful in AAG both in its diagnosis and in monitoring its treatment response. Sicca symptoms should prompt consideration of Sjögren, which should be screened for with anti-Ro and anti-La antibodies, and minor lip salivary gland biopsy if suspicion is high.

Should the autonomic neuropathy be chronic in onset, diabetic autonomic neuropathy must always be evaluated for using fasting and 2 h glucose tolerance testing, although TIND presents acutely. In addition, immunofixation electrophoresis should be pursued to evaluate for AL amyloid. Free light chain, urine 24 h protein, TTR genetic testing, tissue biopsy, and/or PYP cardiac scintigraphic scanning can be added as needed. If suspected, celiac disease testing can be pursued through IgA or IgG gliadin and tissue transglutaminase testing, and if need be, endoscopic small intestinal biopsy. Genetic testing for HSAN can be considered, especially in the setting of a suggestive history and/or pes cavus. For all such chronic autonomic neuropathies, intraepidermal nerve fiber density evaluation through skin biopsies (not part of the autonomic reflex screen) are very helpful. POTS should also be considered in the evaluation of autonomic neuropathies. Acral redness and blanching erythema, especially upon standing, should raise concern for vascular insufficiency or venous pooling, especially

TABLE 2 Other causes of autonomic neuropathy

Etiology	Onset	Sensory	Motor	Autonomic	Associated findings	Interventions
Toxic						
Chronic alcohol[80]	Chronic	Most common	Can present, dependent on total lifetime dose	Reduced HR variability, reduced expiratory/inspiratory ratio	Parasympathetic impairment correlates with total lifetime dose	Drug discontinuation
Vincristine[81]	Acute	Painful paresthesias	Can develop wrist extensor and toe extensor weakness	Orthostatic hypotension, urine retention, constipation (but not common)	Neurotoxicity develops at cumulative dose of 5-15 mg/m^2	Drug withdrawal
Cisplatin[82,83]	Acute	Can be moderate to severe – sometimes a sensory ganglionopathy	Minimal	Orthostatic hypotension, ileus. One series showed no autonomic involvement[83]	Neurotoxicity develops at cumulative dose 200-400 mg/m^2. Coasting phenomenon. Painful	Drug withdrawal
Amiodarone[84]	Acute	Moderate to severe	Moderate to severe	Orthostatic hypotension	Sural nerve biopsy shows lamellated inclusion bodies	Drug withdrawal
Infectious						
Botulism[85]	Acute	Minimal	Ptosis, dysphagia, extraocular weakness.	Cholinergic failure – dry eye, dry mouth, mydriasis, urine retention	Low CMAPs on NCS. High frequency RNS shows increment	Supportive, antitoxin
Leprosy[86]	Acute/ Subacute	Length-independent sensory loss pattern	Minimal	Focal anhidrosis, loss of skin temperature regulation, vasomotor dysfunction, erectile dysfunction, cardiac autonomic neuropathy	Cutaneous, temperature-dependent damage can damage face, iris, and scalp. Can have nerve enlargement. Most cases in India.	For Paucibacillary – dapsone + rifampin For Multibacillary – dapsone, rifampin, and clofazimine
Chagas disease[87]	Acute/ subacute	Mild	Minimal	Palpitations, syncope, orthostatic hypotension; GI dysmotility varies from mild to severe megacolon and megaesophagus	GI pathology – submucosal and mesenteric plexus denervation. Benznidazole itself can cause peripheral neuropathy. Predominantly in South America.	Anti-parasitic therapy - benznidazole and nifurtimox
Hepatitis C virus[88,89]	Chronic	Can occur, axonal	Can occur, axonal	Baroreflex sensitivity and cardiac vagal impairment present	-	Antiviral therapy
Autoimmune						
Celiac[90]	Chronic	Small fiber predominant	Minimal	Syncope, palpitations, nausea. Cardiac vagal and sympathetic impairment	Cerebellar ataxia	Gluten-free diet
Small fiber neuropathy						
Small fiber neuropathy – anhidrosis and ulcers[91,92]	Chronic	Temperature loss, pain insensitivity	Absent	QSART abnormalities in up to 75%, cardiac vagal in up to 63%, and orthostatic hypotension in up to 42%		Reversal of cause

Abbreviations: CMAP, compound muscle action potential; HR, heart rate; NCS, nerve conduction studies; RNS, repetitive nerve stimulation.

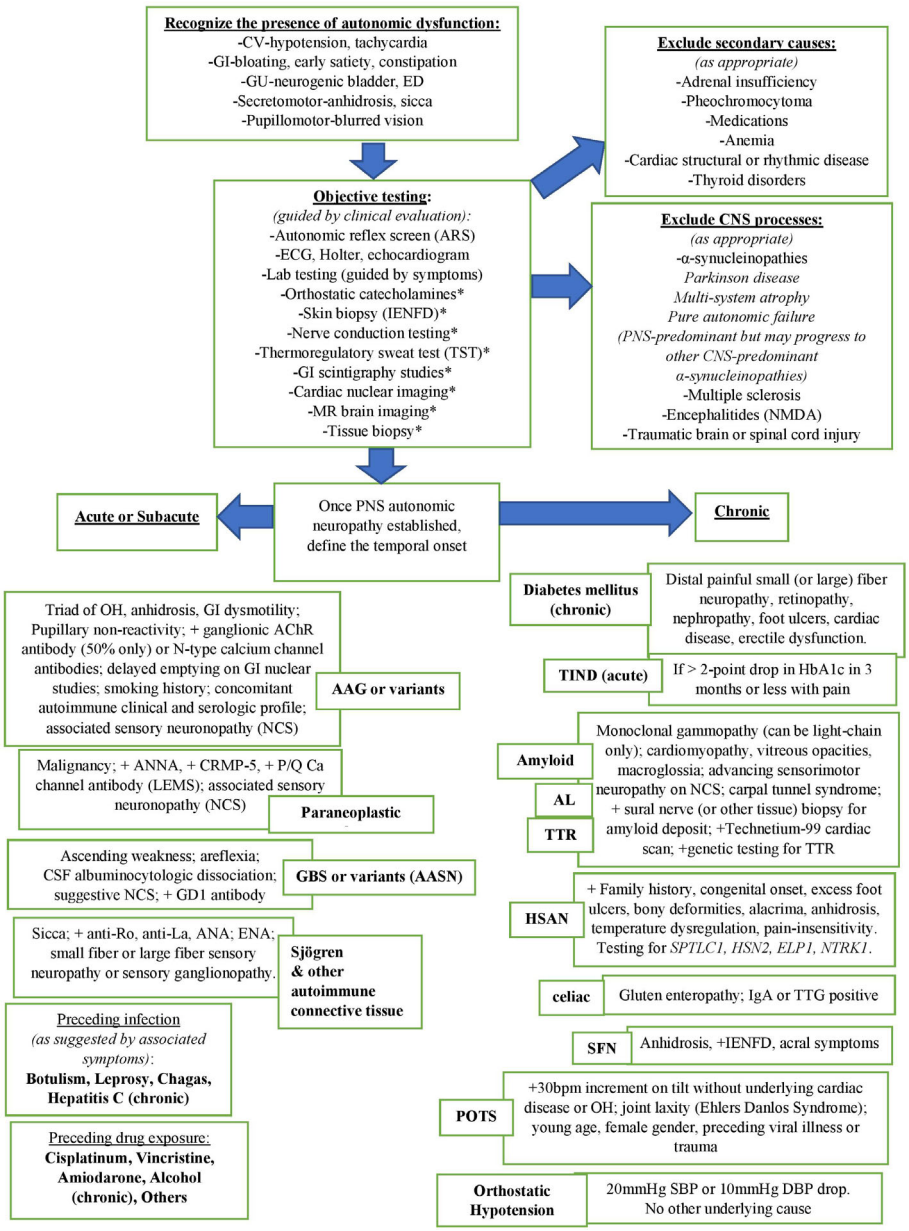

FIGURE 1 Diagnostic approach to autonomic neuropathies. CV, cardiovascular; GI, gastrointestinal; GU, genitourinary; ED, erectile dysfunction; ARS, autonomic reflex screen; ECG, electrocardiogram; TST, thermoregulatory sweat test; MR, magnetic resonance; PNS, peripheral nervous system; CNS, central nervous system; NMDA, anti-N-methyl D-aspartate (NMDA) encephalitis; OH, orthostatic hypotension; NCS, nerve conduction studies; AAG, autoimmune autonomic ganglionopathy; LEMS, Lambert Eaton Myasthenic syndrome; ANNA-1, anti-neuronal nuclear antibody type 1; CRMP-5, Collapsin response mediator protein 5; ANA, antinuclear antigen; ENA, extractable nuclear antigen; GBS, Guillain-Barre syndrome; AASN, acute autonomic and sensory neuropathy; TIND, treatment-induced neuropathy of diabetes; AL, acquired light chain; TTR, transthyretin; HSAN, Hereditary sensory autonomic neuropathy; TTG, tissue transglutaminase; IENFD, intraepidermal nerve fiber density; POTS, postural tachycardia syndrome; OH, orthostatic hypotension; SBP, systolic blood pressure; DBP, diastolic blood pressure

in the presence of associated joint hypermobility. Supine and standing catecholamines can be helpful to evaluate for hyperadrenergic POTS.

4.2 | Symptomatic treatment

Disease-modifying therapies are discussed in their respective sections. In this section, we discuss the general therapeutic approach to autonomic neuropathies, including symptomatic therapies. Treatment for autonomic neuropathies rests on three pillars, namely (1) disease modifying therapy, when possible; (2) dietary/behavioral based therapy; and (3) symptomatic pharmacologic therapy. Aggravating factors should be addressed, including the avoidance of certain medications (beta-blockers, phosphodiesterase-5 inhibitors, alpha-blockers, diuretics, calcium channel blockers, and tricyclic antidepressants) as well as the treatment of anemia, thyroid disorders, or adrenal insufficiency, as seen appropriate. With regard to disease modifying therapy for such conditions as AAG, AL amyloid, and TTR amyloid, it is important to assess baseline and post-treatment disease activity using such validated outcome measures as the COMPASS-31. Autonomic reflex testing can also be performed at baseline and post-treatment for objective surveillance.

For dietary/behavioral and symptomatic pharmacologic therapy, these are individualized per autonomic system involved, but largely center on the gastrointestinal, genitourinary, and cardiovascular systems. For treatment of orthostatic hypotension, for example, various non-pharmacologic and pharmacologic therapies exist. Non-pharmacologic treatment includes volume expansion via increased salt intake, increased fluid intake, compression of legs (thigh high, 20-30 mmHg) and abdomen, raising the head of the bed 4 to 6″, and graded exercise tolerance training. Multiple medications exist and medication choice should be guided by adverse effect profile.

Droxidopa is a recently FDA-approved therapy for the treatment of orthostatic hypotension. It seems to have the greatest impact on patients with supine norepinephrine <200 pg/mL. Concomitant use with norepinephrine reuptake inhibitors or adrenergic agonists should be done cautiously. Fludrocortisone is an excellent once-daily choice for orthostatic hypotension, but can worsen supine hypertension. One should monitor blood pressure, especially in those with essential or supine hypertension, in addition to serum potassium and renal function. Midodrine is also a reasonable alternative and is dosed thrice daily. Choice of treatment is guided by disease state, medication adverse event profile, and cost. POTS alone has an evolving spectrum of medicinal interventions that are now routinely prescribed.

For symptomatic treatment of GI dysmotility, bladder dysfunction, sicca, and heat intolerance, treatments are to be guided by complaints, adverse event profile, and patient preference.[1] For constipation, for example, increased dietary fiber, pelvic floor training, stool softeners, laxatives, and pro-motility agents are helpful, while for bowel incontinence, pelvic floor training, sanitary devices, and regular bowel habits are helpful. For bladder retention, self-catheterization and neural stimulation may be indicated, while for overflow incontinence, pelvic floor strengthening and antimuscarinic and/or beta-3-receptor agonists may be considered. For patients with significant dryness of eyes, pilocarpine drops, artificial tears, and lubricating ointments are helpful, while for dryness of mouth, numerous sialogogues exist. Offending drugs should be eliminated. For heat intolerance and anhidrosis or hypohidrosis, offending agents should be eliminated prior to initiation of potential drug therapy.

5 | CONCLUSION

Autonomic neuropathies are complex and debilitating disorders that warrant a nuanced and systematic approach in their evaluation and treatment, not unlike that employed in the evaluation of somatic neuropathies. After classifying disease by temporal onset and clinical presentation, autonomic reflex testing should be performed expeditiously to permit prompt and appropriate treatment, and should complement a careful history, exam, serologic testing, electrodiagnostic testing, scintigraphic testing, imaging and tissue biopsy, where appropriate. The emergence of disease modifying therapies makes this even more urgent, as the timely application of such therapies can potentially improve patient function and quality of life.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DISCLOSURES

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