

Autonomic peripheral neuropathy

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The autonomic neuropathies are a group of disorders in which the small, lightly myelinated and unmyelinated autonomic nerve fibres are selectively targeted. Autonomic features, which involve the cardiovascular, gastrointestinal, urogenital, sudomotor, and pupillomotor systems, occur in varying combination in these disorders. Diabetes is the most common cause of autonomic neuropathy in more developed countries. Autonomic neuropathies can also occur as a result of amyloid deposition, after acute infection, as part of a paraneoplastic syndrome, and after exposure to neurotoxins including therapeutic drugs. Certain antibodies (eg, anti-Hu and those directed against neuronal nicotinic acetylcholine receptor) are associated with autonomic signs and symptoms. There are several familial autonomic neuropathies with autosomal dominant, autosomal recessive, or X-linked patterns of inheritance. Autonomic dysfunction can occur in association with specific infections. The availability of sensitive and reproducible measures of autonomic function has improved physicians' ability to diagnose these disorders.

Autonomic nerve fibres are affected in most symmetrical peripheral neuropathies. This involvement is mild or sub-clinical in many cases; however, in a group of peripheral neuropathies, the small or unmyelinated autonomic fibres are selectively or prominently targeted (table). In these neuropathies, autonomic dysfunction is a prominent manifestation. The extensive distribution of the autonomic nerves results in an array of signs and symptoms that includes impairment of cardiovascular, gastrointestinal, urogenital, thermoregulatory, sudomotor, and pupillomotor autonomic function. This Seminar covers the peripheral neuropathies in which autonomic dysfunction is a prominent and clinically important manifestation (panel 1). The diagnosis of the autonomic neuropathies has been improved by the availability of sensitive and reproducible measures of autonomic function.^{1,2} With the help of these tests and the judicious use of laboratory and electrophysiological testing, many autonomic neuropathies can be accurately diagnosed and their clinical progression monitored (panels 2 and 3).

Diabetic autonomic neuropathy

Diabetes mellitus is the most common cause of autonomic neuropathy in more developed countries.³ The autonomic neuropathy typically presents late in the course of diabetes and is generally accompanied by other features of distal sensorimotor polyneuropathy. Diabetic cardiovascular autonomic neuropathy can manifest as an increased resting heart rate when the cardiac vagus is affected. When sympathetic and parasympathetic fibres are involved, the heart rate is fixed and there is inadequate capacity to increase it in response to physiological demands.⁴ Orthostatic hypotension occurs in diabetes largely as a consequence of efferent sympathetic vasomotor denervation, causing reduced vasoconstriction of the splanchnic and other peripheral vascular beds.⁵ There is an increase in overall mortality and sudden death in patients with diabetic autonomic neuropathy. Estimates for the mortality associated with cardiovascular autonomic neuropathy range from 27% to 56% over 5–10 years.⁶ The increased mortality is probably multifactorial; patients

with severe autonomic neuropathy have concomitant cardiovascular, renal, and cerebrovascular disease. Autonomic dysfunction could cause or contribute to death by several possible mechanisms including: absent or altered perception of myocardial ischaemia;⁷ deficient haemodynamic response to cardiovascular stresses such as surgery, infection, and anaesthesia;⁸ increased predisposition to cardiac arrhythmias due to QT-interval dispersion;⁹ changes in sympathetic–parasympathetic cardiac innervation balance; and focal myocardial regions of sympathetic denervation and reinnervation.¹⁰

Symptoms of bladder dysfunction are present in up to 50% of patients with diabetes, and there is physiological evidence of bladder dysfunction in 43–87% of those with insulin-dependent diabetes.^{11,12} The earliest manifestation of autonomic dysfunction of the bladder is impaired sensation that increases the threshold for initiating the micturition reflex. A decrease in detrusor activity follows, which causes incomplete bladder emptying, an increased postvoid residual, lower peak urinary flow rate, bladder overdistension, and ultimately urinary retention and overflow incontinence.^{11,13}

Erectile failure is present in 30–75% of diabetic men¹⁴ and can be the earliest symptom of diabetic autonomic neuropathy. Vascular and psychogenic mechanisms can also contribute to this symptom. In-vitro studies of isolated corpus cavernosum tissue from diabetic men suggest that the erectile failure is due to impairment in

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Search strategy and selection criteria

I searched MEDLINE from 1990 to 2004 with the search terms "peripheral autonomic nervous system diseases", "autonomic neuropathy", and "autonomic diseases". Other search terms used included "diabetes", "amyloid", "immunology", "infectious", "inherited", "genetic", "toxic", "investigation", and "therapy". I largely selected publications from the past 10 years but did not exclude commonly referenced and highly regarded older publications. I also searched the reference lists of articles identified by this search strategy and selected those judged to be relevant. Several review articles and book chapters were included because they provide comprehensive overviews that are beyond the scope of this Seminar. The reference list was subsequently modified during the peer-review process on the basis of comments from the reviewers.

Fibre type	Function	Diameter, μm	Conduction velocity (m/s)
A	Proprioception, somatomotor	12–20	70–120
	Touch, pressure	5–12	30–70
	Motor to muscle spindle	3–6	15–30
	Pain, especially cold pain, cold, touch	2–5	12–30
B	Preganglionic autonomic	<3	3–15
C	Postganglionic autonomic	0.4–1.3	0.3–2.3
	Thermal, heat pain, mechanoreceptor	0.4–1.3	0.3–2.3

Table: Classification of nerve fibres

both autonomic and endothelium-dependent nitric-oxide-mediated relaxation of smooth muscle in the corpus cavernosum.¹⁵ Ejaculatory failure due to dysfunction of the sympathetic nervous system can precede the appearance of erectile dysfunction, although erectile failure can occur with retained ability to ejaculate and experience orgasm. Dysfunction of the sympathetic nervous system can also impair bladder-neck closure during ejaculation, which results in retrograde ejaculation. There have been few studies of genital autonomic neuropathy in female diabetic patients. Reduced vaginal lubrication is a commonly reported symptom.¹⁶

Autonomic dysfunction occurs throughout the gastrointestinal tract, producing several specific clinical syndromes.¹⁷ Diabetic gastroparesis, delayed gastric emptying of solids or liquids, is present in up to 50% of individuals with diabetes.¹⁸ Gastroparesis can manifest as nausea, postprandial vomiting, bloating, belching, loss of appetite, and early satiety. Many patients, however, have no symptoms despite impaired gastric motility.¹⁹ Food residue is retained in the stomach owing to impaired gastric peristalsis, which is compounded by lower-intestinal dysmotility. Gastroparesis commonly impairs the establishment of adequate control of blood glucose concentrations. Dysfunction of the vagus nerve and intrinsic enteric autonomic nerves could have a role in this disorder. Recent studies have implicated hyperglycaemia as a cause of reversible impairment in gastric and small-intestinal motility.²⁰

Constipation is the most frequently reported gastrointestinal autonomic symptom and is found in up to 60% of patients with diabetes.²¹ The pathophysiology of diabetic constipation is incompletely understood and might reflect impaired extrinsic and intrinsic autonomic innervation of the gastrointestinal tract as well as loss of

Panel 1: Autonomic peripheral neuropathies

Diabetic autonomic neuropathy
 Amyloid neuropathy
 Acute and subacute autonomic neuropathies
 Immune-mediated and paraneoplastic neuropathies
 Hereditary autonomic neuropathies
 Autonomic neuropathy due to infectious diseases
 Toxic neuropathies

the postprandial gastrocolic reflex. Diarrhoea and other lower-gastrointestinal-tract symptoms also occur. The diarrhoea is profuse and watery and typically occurs at night. It can persist for hours or days and in many cases alternates with constipation. Diabetic diarrhoea seems to be more common in type 1 than in type 2 diabetes.²² In individuals with type 2 diabetes who are being treated with oral antihypoglycaemic agents, metformin should be considered as a possible cause of diarrhoea.²² Faecal incontinence, resulting from incompetence of the anal sphincter or reduced rectal sensation, is another manifestation of diabetic autonomic neuropathy.²³ Incontinence is exacerbated by diarrhoea.

Diabetic autonomic neuropathy initially results in a loss of thermoregulatory sweating in a glove and stocking distribution that can extend to the upper parts of the limbs and the anterior abdomen, conforming to the well-recognised length dependency of diabetic neuropathy.²⁴ This process ultimately results in global anhidrosis that generally accompanies a severe autonomic neuropathy. Diabetic autonomic neuropathy can also cause hyperhidrosis. Excessive sweating could occur as a compensatory process, involving proximal regions such as the head and trunk that are spared in a dying-back neuropathy. Gustatory sweating, abnormal production of sweat that appears over the face, head, neck, shoulders, and chest after consumption of even non-spicy foods, occurs in occasional cases. The pathophysiology of this process, which suggests aberrant reinnervation, is not fully understood.²⁵

Amyloid neuropathy

Amyloidosis is due to the deposition of insoluble fibrillar proteins in a β -pleated sheet configuration within the extracellular space of tissues and organs. Various proteins have been associated with amyloidosis. The current classification of the systemic amyloidoses is based on the biochemistry of the precursor protein.^{26,27} Although the fibril precursor proteins differ, there are strong similarities among the clinical presentations and pathology of the neuropathies associated with the different amyloidoses. Autonomic dysfunction commonly accompanies the polyneuropathy of both primary (AL; associated with immunoglobulin light chains) and hereditary amyloidosis (familial amyloid polyneuropathy), but is not common in secondary (AA; associated with amyloid A protein) amyloidosis.^{26,27}

Amyloid neuropathy is characterised pathologically by the deposition of insoluble β -fibrillar proteins in the epineurium, perineurium, and endoneurium, the perineuronal tissues, and the neural vasculature. The pathogenesis of the peripheral neuropathy is not fully understood. Ischaemic, infiltrative, inflammatory, and toxic-metabolic factors have been implicated.^{28,29}

Amyloidosis can be diagnosed by aspiration of subcutaneous fat pad, gingival biopsy, or biopsy of rectal (and other gastrointestinal-tract) mucosa. Nerve biopsy is

less sensitive owing to the focal distribution of the amyloid deposits.³⁰ Amyloid deposits have a homogeneous, eosinophilic appearance on light microscopy and show characteristic yellow-green birefringence when viewed under polarised light with Congo-red staining (figure 1).

Primary (AL) amyloidosis is the most common form of amyloidosis in more developed countries. This disorder is a plasma-cell dyscrasia in which a monoclonal population of bone-marrow cells produces monoclonal immunoglobulin light chains or light-chain fragments that deposit as amyloid.²⁶ Symptoms typically appear in the sixth or seventh decade of life. Patients typically present with weight loss and fatigue. The peripheral neuropathy, which can be the presenting feature of the disease or an incidental finding, is present in up to 20% of patients with primary amyloidosis.³¹ Autonomic involvement of the cardiovascular, gastrointestinal, and urogenital systems is common.^{26,31,32} Other systemic features include hepatomegaly, macroglossia, cutaneous ecchymoses, cardiomyopathy, and nephrotic-range proteinuria. Immunofixation electrophoresis of serum or urine detects immunoglobulins or light chains in 90% of patients with primary amyloidosis.²⁶

The median survival of patients with primary amyloidosis who have amyloid neuropathy is in the range of 13–35 months, with 3-year survival of 38–50%. The prognosis for patients with heart failure is much worse.^{33,34} Treatment with melphalan and prednisone improves survival, particularly when associated with a reduction in serum or urine monoclonal protein.^{33,34} Stem-cell transplantation in carefully selected patients might improve survival further.³⁵

Familial amyloid polyneuropathy is a manifestation of hereditary general amyloidosis. These disorders have autosomal dominant inheritance, and the amyloid precursor is a mutant protein. Mutant transthyretin, a 14 kDa protein that serves as the transport protein for thyroxine and retinol-binding protein, is the most common cause of hereditary amyloidosis. It is encoded by a single gene on chromosome 18. The most commonly found mutation is a substitution of methionine for valine at position 30.³⁶ This disorder has been associated with more than 50 other aminoacid substitutions.

Transthyretin amyloidosis typically presents in the third to fifth decade of life. Characteristic features include prominent dysautonomia that accompanies a painful sensorimotor neuropathy, carpal-tunnel syndrome, vitreous opacities, nephropathy, and cardiomyopathy. Death occurs 5–15 years after the appearance of symptoms.²⁷ The clinical phenotype is variable, however, and depends on the position and nature of the aminoacid substitution. Variant presentations include late onset,³⁷ isolated carpal-tunnel syndrome, and distal sensory or sensorimotor neuropathy without autonomic dysfunction.³⁸ Clusters of hereditary amyloidosis resulting from mutant transthyretin have been found in

Panel 2: Autonomic function testing

Both sympathetic and parasympathetic divisions of the autonomic nervous system are involved in all tests of autonomic function.

Cardiac parasympathetic-nervous-system function

Heart-rate variability with deep respiration (respiratory sinus arrhythmia); time-domain and frequency-domain assessments
Heart-rate response to Valsalva manoeuvre
Heart-rate response to standing (30 to 15 ratio)

Sympathetic adrenergic function

Blood-pressure response to upright posture (standing or tilt-table)
Blood-pressure response to Valsalva manoeuvre
Microneurography (in research studies)

Sympathetic cholinergic function

Thermoregulatory sweat testing
Quantitative sudomotor-axon-reflex test
Sweat imprint methods
Sympathetic skin response

Panel 3: Laboratory assessment of autonomic neuropathy

These tests are those most commonly used to diagnose or investigate an autonomic neuropathy. They should not be done as a set, their use should be guided by the clinical presentation.

Chemistry, haematology, and pathology

Complete blood count and differential
Fasting blood glucose or glucose tolerance test
HIV testing
Immuno-electrophoresis of blood and urine
Plasma norepinephrine (supine and standing)
Porphyrin investigations—urinary porphyrin concentration (24 h collection for aminolevulinic acid, porphobilinogen, and porphyrins); erythrocyte porphobilinogen deaminase activity (patients with type I and type III disease have about 50% enzyme activity)
Genetic testing for inherited neuropathies
Fat aspirate, rectal biopsy, or gingival biopsy for amyloid

Autoantibody assessment

Antinuclear antibody
Rheumatoid factor
Anti-Ro/SS-A
Anti-La/SS-B
Antibodies to neuronal nicotinic acetylcholine receptor
Antibodies to P/Q-type calcium channel
Antibodies to acetylcholine receptor
Paraneoplastic antibodies—anti-Hu (type 1 anti-neuronal nuclear antibody, ANNA-1); Purkinje-cell cytoplasmic antibodies type 2 (PCA-2); collapsin response-mediator protein 5 (CRMP-5)

Electrophysiological studies

Nerve conduction studies (including repetitive stimulation in suspected Lambert-Eaton syndrome or myasthenia gravis)
Quantitative sensory testing

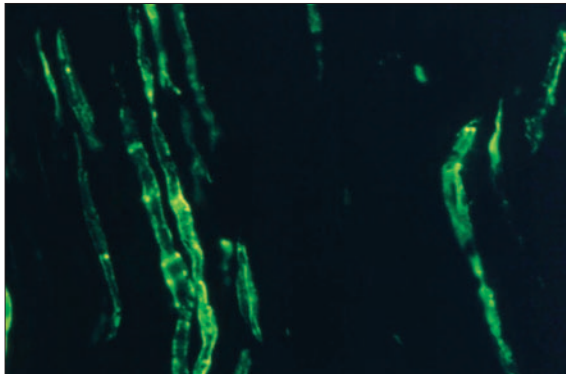


Figure 1: Longitudinal section nerve biopsy
Congo-red stain viewed under polarised light showing "apple-green" birefringence indicating amyloid deposition.

Portugal, Japan, Sweden, the USA, Spain, Finland, Ireland, France, and Germany.²⁷

Familial amyloid polyneuropathy rarely can be caused by mutations in the genes encoding apolipoprotein A1, fibrinogen A α , lysozyme, and gelsolin.²⁶ The peripheral neuropathy associated with mutated apolipoprotein A1 is phenotypically similar to the transthyretin-associated neuropathy.³⁹ Deafness and peptic-ulcer disease can also occur with this disorder.⁴⁰ Familial amyloidosis due to mutations in the gene encoding the actin-binding protein gelsolin⁴¹ presents with corneal-lattice dystrophy, dermatological manifestations, cranial neuropathies, carpal-tunnel syndrome, and peripheral neuropathy with mild dysautonomia.⁴²

Because most of the mutated amyloidogenic transthyretin is secreted by the liver, orthotopic liver transplantation is the most effective treatment for hereditary amyloidosis. This intervention substantially decreases amounts of circulating, mutated transthyretin. In appropriately selected patients, liver transplantation improves neurophysiological measures, nerve morphology, and survival.⁴³ Although the extent of the benefits of liver transplantation on the sensorimotor peripheral neuropathy is unresolved,^{43,44} the features of an established autonomic neuropathy do not appear to improve greatly with this intervention.^{43,45}

Acute and subacute autonomic neuropathies

Guillain-Barré syndrome (acute inflammatory demyelinating polyradiculoneuropathy) is a monophasic illness with an immune basis that presents as an acutely evolving sensorimotor polyneuropathy of varying severity. The syndrome is commonly accompanied by autonomic manifestations such as sinus tachycardia, sinus pauses, other tachyarrhythmias and bradyarrhythmias, blood-pressure lability, bowel and bladder dysfunction, pupillomotor disturbances, sudomotor dysfunction, and vasomotor abnormalities.⁴⁶ Autonomic manifestations, which are the presenting feature of Guillain-Barré syndrome in occasional cases,⁴⁷ are more prominent in

patients with respiratory failure, severe motor deficits, and the axonal variant of the syndrome.^{48,49} The autonomic features can result in substantial mortality and morbidity in some patients, although they are generally overshadowed by the motor features of the disorder.

Autonomic manifestations can also be the sole or predominant feature of an acute or subacute peripheral neuropathy.⁵⁰ The hallmark of these autonomic neuropathies is the acute or subacute presentation, in varying combinations, of orthostatic hypotension, anhidrosis, constipation, bladder atony, impotence, secretomotor paralysis, and blurring of vision associated with tonic pupils. Mild sensorimotor features can accompany the autonomic manifestations but are not predominant. The autonomic features of this disorder can involve both the sympathetic and parasympathetic divisions of the autonomic nervous system (pandysautonomia)⁵¹ or the sympathetic or parasympathetic nervous system alone (the latter is also called cholinergic dysautonomia).⁵² Only 40% of patients recover fully to pre-morbid status. For an estimated 12%, substantial symptoms persist. Full or partial recovery, when reported, occurred over the course of months to years. Autonomic testing in the recovery phase of illness in these patients shows evidence of persisting, subclinical autonomic dysfunction in many.⁵⁰

Biopsy samples of sural nerve have shown loss of small myelinated and unmyelinated fibres in some^{53,54} but not all studies.^{51,53,55} A perivascular mononuclear infiltrate is present in some cases.⁵⁰ Other investigators have observed pathological changes in the sympathetic ganglia^{56,57} and their preganglionic and postganglionic neurons.⁵⁸

The presence of subtle sensory and motor signs and the dissociation between albumin concentrations and cell numbers in cerebrospinal fluid has prompted speculation that acute and subacute dysautonomias are variants of Guillain-Barré syndrome.⁵³ In analogy to that syndrome, infectious and parainfectious immune-mediated mechanisms could be involved in the pathogenesis of these autonomic neuropathies. Acute dysautonomia has been described in association with infectious mononucleosis (or Epstein-Barr virus)⁵⁹ and infections with streptococcus,⁶⁰ coxsackie B virus,⁶¹ rubella virus,⁶² and herpes simplex virus,⁶³ in addition to other non-diagnosed viral syndromes. Associations with malignant^{64,65} and connective-tissue disorders have been described in other cases.⁶⁶⁻⁶⁸ Further evidence that some of these cases are immune mediated comes from the positive therapeutic response to intravenous immunoglobulin reported in uncontrolled case studies.^{69,70}

Immune-mediated and paraneoplastic autonomic neuropathies

Autonomic peripheral neuropathies have been associated with the presence of specific autoantibodies (panel 3). These neuropathies present subacutely in most cases, although acute and chronic presentations have been

reported. Paraneoplastic autonomic neuropathy occurs frequently in association with anti-Hu antibodies. These antibodies are commonly found in patients with small-cell lung cancer, but they can also occur in non-small-cell lung cancer and malignant disorders of the gastrointestinal tract, prostate, breast, bladder, kidney, pancreas, testicle, and ovary.^{71–74} Peripheral neuropathy develops in 60–95% of patients with malignant disease and anti-Hu antibodies.⁷³ Subacute sensory neuronopathy, caused by injury to the bodies of the sensory nerve cells in the dorsal nerve root ganglia, is the most common neuropathy associated with anti-Hu.

Paraneoplastic autonomic neuropathy is characterised by the subacute onset of symptoms including bowel hypomotility, intestinal obstruction, bladder dysfunction, orthostatic hypotension, blood-pressure instability, pupillomotor and sudomotor dysfunction, impotence, and xerophthalmia. Autonomic neuropathy can be the sole manifestation of an anti-Hu-related paraneoplastic disorder or part of a general paraneoplastic syndrome that variably includes sensory neuronopathy, limbic and brainstem encephalitis, encephalomyelitis, cerebellar degeneration, and sensorimotor peripheral neuropathy. In recent series of patients with anti-Hu antibodies, dysautonomia was present in 10%⁷⁵ to 30%^{73,74} of patients and was the predominant symptom at presentation in 4%⁷⁵ to 9%.⁷³

Paraneoplastic autonomic neuropathy has been associated with other antibodies in addition to anti-Hu, including Purkinje-cell cytoplasmic antibodies type 2⁷⁶ and antibodies to collapsin response-mediator protein 5, which occurs in neuronal cytoplasm.⁷⁷

High concentrations of blocking and binding auto-antibodies specific for neuronal nicotinic acetylcholine receptors in the autonomic ganglia also have been found in patients with idiopathic and paraneoplastic autonomic neuropathy. Malignant disorders associated with these antibodies include small-cell lung carcinoma, thymoma, bladder carcinoma, and rectal carcinoma. Characteristic features of this disorder are a subacute onset of symptoms that include gastrointestinal dysmotility, dry eyes and mouth, and abnormal pupillary responses to light and accommodation. There is a positive correlation between high titres of ganglionic-receptor antibodies and the severity of autonomic dysfunction, which suggests that the antibodies have a pathogenetic role.⁷⁸ These antibodies can be present in patients with the clinical phenotype of pure autonomic failure.⁷⁹ When cholinergic features are prominent, the diagnosis of an immune-mediated autonomic neuropathy should be considered.⁸⁰

Acute, subacute, and chronic autonomic dysfunction can occur in the setting of connective-tissue diseases including systemic lupus erythematosus, mixed connective-tissue disease, scleroderma,⁸¹ and Sjögren's syndrome.^{66–68,82–84} Symptoms of autonomic dysfunction and abnormalities of the sympathetic and parasympathetic nervous systems can be a prominent

feature of Sjögren's syndrome and the sicca syndrome. The characteristic serological abnormalities associated with Sjögren's syndrome, SS-A and SS-B antibodies, are not present in many patients, and tissue might be needed for diagnosis.^{68,82–84}

Lambert-Eaton myasthenic syndrome is a subacute autoimmune disorder of neuromuscular transmission. This disorder is characterised by the production of antibodies directed against presynaptic, voltage-gated calcium channels; the action of the antibodies impairs acetylcholine release and leads to weakness, hyporeflexia, and autonomic dysfunction.^{85,86} Many cases are paraneoplastic. Dysautonomia is a common manifestation of the Lambert-Eaton syndrome in patients with and without malignant disease.⁸⁵ Symptoms suggesting cholinergic dysfunction, such as dry mouth, erectile failure, constipation, blurred vision, and impaired sweating, occur most frequently. Autonomic tests showing unresponsive pupils that constrict to dilute pilocarpine, reduced sweating, and salivary and lacrimal secretomotor failure, suggest that the abnormality is predominantly restricted to the parasympathetic nervous system, although adrenergic abnormalities are seen also.⁸⁶ Treatment is directed at any underlying tumour, with immunosuppression used for idiopathic and refractory cases. Motor and autonomic symptoms improve in some patients with the use of 3,4-diaminopyridine, which increases acetylcholine release.⁸⁷

Myasthenia gravis is an autoimmune disorder characterised by antibodies directed at the postsynaptic acetylcholine receptor. These antibodies disrupt neuromuscular transmission, leading to fluctuating weakness, with a predilection for ocular and bulbar muscles. An autonomic neuropathy accompanies myasthenia gravis in rare cases. Investigators have documented autonomic dysfunction with features of both sympathetic and parasympathetic nervous systems.⁸⁸ Antibodies against muscle acetylcholine receptor were present in all patients and against neuronal ganglionic acetylcholine receptors in 42% of patients. Gastrointestinal dysmotility, which is a prominent manifestation, can improve after the administration of an acetylcholinesterase inhibitor.⁸⁸

Hereditary autonomic neuropathies

The hereditary autonomic neuropathies are listed in panel 4. Autonomic features are most prominent in the

Panel 4: Hereditary neuropathies with autonomic involvement

Hereditary sensory and autonomic neuropathies
Fabry's disease
Triple A (Allgrove's) syndrome
Navajo Indian neuropathy
Tangier disease
Multiple endocrine neoplasia, type 2b

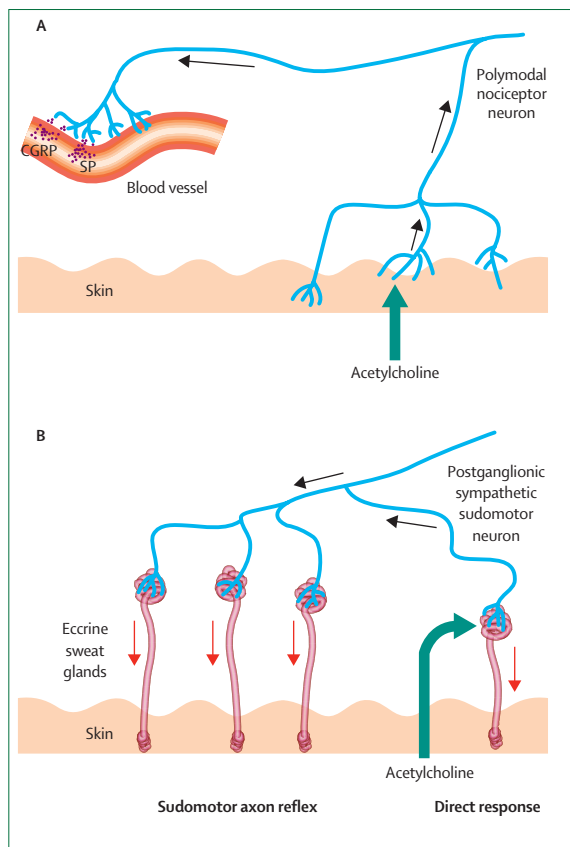


Figure 2: Axon-reflex-mediated neurogenic flare response and direct and axon-reflex-mediated sudomotor response

A: The axon-reflex neurogenic flare is evoked by the activation of cutaneous polymodal nociceptor C-fibres. The impulses generated in these afferent fibres travel orthodromically to a branch point and then antidromically, leading to the release of vasodilating neuropeptides from the terminals of the small nerve fibres. The reflex can be evoked by chemical stimuli, such as acetylcholine and histamine, and physical stimuli. Black arrows indicate direction of nerve impulses; green arrow indicates iontophoresis of acetylcholine. SP=substance P; CGRP=calcitonin-gene-related peptide.

B: the sudomotor axon reflex is provoked by cholinergic agonists that bind to nicotinic receptors on sudomotor nerve terminals. The evoked impulses travel antidromically to a branch point and then orthodromically to stimulate a neighbouring population of eccrine sweat glands. The direct response is evoked by direct stimulation of the muscarinic receptors on sweat glands. The direct and axon-reflex-mediated responses are evoked by cholinergic agonists such as acetylcholine and methacholine. Black arrows indicate direction of nerve impulses; green arrow indicates iontophoresis of acetylcholine; red arrows indicate sweat production.

hereditary sensory and autonomic neuropathies and Fabry's disease.⁸⁹ Other hereditary autonomic neuropathies include the triple A (Allgrove's) syndrome,⁹⁰ Tangier disease,⁹¹ multiple endocrine neoplasia type 2b,⁹² and a sensory and autonomic neuropathy with arthropathy that is present in Navajo children.^{93,94}

Hereditary sensory and autonomic neuropathies

These neuropathies are characterised by prominent sensory loss without motor involvement and by striking dysautonomia. The axon-reflex-mediated, vasomotor

response (the flare) after intradermal histamine is absent in all hereditary sensory and autonomic neuropathies (figure 2).

Type I is an autosomal dominant, hereditary sensory radiculoneuropathy that presents in the second decade of life. Patients with this disorder present with distal pain associated with sensory loss that predominantly involves nociceptive and thermal perception while sparing touch-pressure sensation and proprioception. The sensory loss progresses gradually and is accompanied by anhidrosis, trophic ulcers, acral injuries, stress fractures, and osteomyelitis. These features, which are most prominent in the legs and feet, are due to loss of the unmyelinated and small myelinated fibres. Type I hereditary sensory and autonomic neuropathy has been associated with a mutation in the *SPTLC1* (serine palmitoyltransferase, long-chain base subunit 1) gene, which maps to chromosome 9q22.1–q22.3. This gene encodes serine palmitoyltransferase, the rate-limiting enzyme for the synthesis of the sphingolipids ceramide and sphingomyelin.⁹⁵

Type II (congenital sensory neuropathy or Morvan's disease) is an autosomal recessive or sporadic sensory and autonomic neuropathy that presents in infancy or early childhood. This disorder is associated with profound sensory loss that involves modalities of both large and small fibres (pain and temperature perception and proprioception). Striking hypotonia and decreased deep tendon reflexes are common.⁸⁹ Trophic changes are present in the arms and legs. Autonomic features include episodic hyperhidrosis, tonic pupils, constipation, and apnoeic episodes. Biopsy samples of sural nerve show depletion of large and small myelinated fibres but only slightly decreased numbers of unmyelinated fibres. This disorder has been associated with a mutation on the gene *HSN2*, with a locus that maps to chromosome 12p13.33.⁹⁶

Autonomic manifestations are prominent in type III hereditary sensory and autonomic neuropathy (Riley-Day syndrome or familial dysautonomia). This autosomal recessive disorder is seen primarily in Ashkenazi Jewish children. It occurs in 1 in 3700 livebirths among Ashkenazi Jews, and the carrier frequency is 1 in 32 individuals.⁹⁷ The defective gene causing familial dysautonomia has been mapped to the long arm of chromosome 9 (9q31). Most (more than 99%) of patients with familial dysautonomia have a single, splicing mutation in the gene encoding I- κ B-kinase-associated protein (*IKBKAP*), which results in tissue-specific expression of a truncated protein.⁹⁸ The disorder presents in infancy. The clinical features include insensitivity to pain and temperature stimuli but sparing visceral pain, absence of tears, hypoactive corneal and tendon reflexes, and absence of lingual fungiform papillae. Poor sucking and feeding, oesophageal reflux with vomiting, aspiration, and swallowing dyscoordination can be the first clinical manifestations. Hypotonia and delayed acquisition of developmental milestones are common. Later in the

course of the illness, vibratory sensory loss and impaired limb coordination appear.⁹⁷ Autonomic disturbances can be prominent at any point in the disease. Autonomic manifestations include episodic hyperhidrosis, vasomotor instability with defective temperature homeostasis, breath-holding episodes, protracted episodes of vomiting, postural hypotension, hypertensive crises, and supersensitivity to cholinergic and adrenergic agents.

Type IV hereditary sensory and autonomic neuropathy (congenital insensitivity to pain with anhidrosis or anhidrotic sensory neuropathy), the second most common of these neuropathies, is an autosomal recessive disorder that manifests in the first months of life with insensitivity to pain, anhidrosis, episodes of unexplained fever, and mental and motor developmental retardation. The sensory impairment involves modalities of both large and small nerve fibres. The profound sensory loss results in self-mutilation, unrecognised fractures, autoamputation, Charcot joints, osteomyelitis, and corneal scarring despite normal tear flow.⁸⁹ The skin appears thick, hyperkeratotic, and callused owing to the anhidrosis. Unmyelinated fibres are virtually absent from peripheral nerves.⁹⁹ Skin biopsy samples from patients with type IV hereditary sensory and autonomic neuropathy have deficiency of C and A δ fibres in the epidermis and absent or hypoplastic dermal sweat glands without innervation.¹⁰⁰ Intradermal injection or iontophoresis of cholinergic agonists such as acetylcholine or methacholine does not produce direct sweat-gland-stimulated or axon-reflex-mediated sweating (figure 2).¹⁰¹ Frame-shift, splice, and missense mutations have been documented in the *NTRK1* (*TRKA*) gene located on chromosome 1 (1q21–q22). This gene encodes neurotrophic tyrosine kinase receptor type 1, which is autophosphorylated in response to nerve growth factor.¹⁰² This neurotrophin induces neurite outgrowth and promotes growth and survival of the small sensory and sympathetic neurons.

The rare type V hereditary sensory and autonomic neuropathy presents in infancy with absence of pain perception that leads to acral ulcers, painless fractures, and other trophic injuries. Sudomotor abnormalities are present.¹⁰³ A mutation in *NTRK1* could also be the cause of this neuropathy.¹⁰⁴

Fabry's disease

Fabry's disease or angiokeratoma corporis diffusum is an X-linked, recessively inherited disorder that is associated with deficiency of α -galactosidase A (ceramide trihexosidase). The enzyme deficiency results in accumulation of ceramide trihexoside and other neutral glycosphingolipids in homozygotes. There is extensive lipid deposition in various tissues, including the skin, nervous system, vascular endothelium, kidney, cardiovascular system, and eye.¹⁰⁵

The neurological manifestations of this disorder are due to the deposition of glycolipids in autonomic and dorsal root ganglia, in perineurial cells, and in unmyelinated and

myelinated axons.¹⁰⁶ Young male patients with this disorder typically present with severe, paroxysmal pains and tenderness in the hands and feet, a truncal reddish-purple maculopapular rash, and angiectases of the skin, conjunctiva, nail bed, and oral mucosa. The corpora angiokeratoma that result from deposition of the glycolipid in skin, together with the painful distal peripheral neuropathy, progressive renal disease, corneal opacities, and cerebrovascular accidents in adult life are the typical clinical manifestations of this disorder.

The autonomic manifestations include hypohidrosis or anhidrosis, reduced saliva and tear formation, impaired cutaneous flare response to scratch and histamine, and disordered intestinal motility. Gastrointestinal symptoms can be as severe as the sensory complaints. Pupillary constriction to dilute pilocarpine has been documented, suggesting denervation supersensitivity, although cardiovascular autonomic reflexes in one series were normal.¹⁰⁷ The general anhidrosis suggests that sweat-gland dysfunction, perhaps due to intracytoplasmic inclusions in the eccrine glands, has a role in the anhidrosis.¹⁰⁸ Enzyme replacement therapy might improve the natural course of this disorder.

Sural-nerve biopsy studies have shown degeneration and loss of unmyelinated fibres.¹⁰⁶ Skin biopsy samples show decreased numbers of intraepidermal small nerve fibres.¹⁰⁹ Fabry's disease can be diagnosed by assay of α -galactosidase A in leucocytes or skin fibroblasts.¹⁰⁷

Autonomic neuropathy due to infectious diseases Botulism

Binding of a neurotoxin from the anaerobic bacterium *Clostridium botulinum* to the presynaptic nerve terminal prevents release of synaptic vesicles containing acetylcholine and leads to this acute neuromuscular disorder (panel 5). The illness begins with gastrointestinal manifestations, followed by autonomic symptoms and a descending paralysis that spreads from the extraocular and bulbar muscles to the limbs.¹¹⁰ Autonomic symptoms result from cholinergic dysfunction; they include constipation, blurred vision, urinary hesitancy and retention, and dry mouth and eyes. Dilated pupils, with poor response to light and accommodation, are characteristic autonomic signs. Orthostatic hypotension is also present in some cases. Autonomic symptoms can occur in botulism, even in the absence of the characteristic abnormalities of motor and cranial nerves.^{110,111}

Panel 5: Infectious diseases with autonomic involvement

- Chagas' disease
- HIV neuropathy
- Botulism
- Leprosy
- Diphtheria

Autonomic symptoms can persist after resolution of the infection in many cases. Botulism can manifest as a subacute cholinergic disturbance without associated clinical or electromyographic evidence of motor-endplate disorder.¹¹² Treatment involves provision of supportive measures and elimination of sources of toxin. Intravenous trivalent equine antitoxin can prevent progression and lower the mortality rate, which remains at around 5–15%.

HIV infection

Autonomic dysfunction can occur in patients with HIV infection. Although it seems to be more frequent and more severe in patients with AIDS, several reports have suggested that HIV-seropositive patients and those in the early stages of infection also show evidence of dysautonomia. The severity of autonomic dysfunction seems to show a continuum from the early to later stages of HIV infection.^{113,114} In addition to direct viral effects and interactions between virus and host, toxins, drugs, vitamin deficiency, and malnutrition could have roles in the manifestations of this syndrome in the later stages of illness. The symptoms of dysautonomia have included orthostatic hypotension, syncope, presyncope, sweating disturbances, bladder and bowel dysfunction, and impotence.¹¹³ Autonomic testing shows abnormalities of sympathetic and parasympathetic nervous systems.¹¹³

Chagas' disease

This disorder, which results from a parasitic infection by the protozoan *Trypanosoma cruzi*, is found predominantly in Latin America. Owing to immigration patterns, the incidence of the disease in the USA is increasing, and its autonomic manifestations should be considered in the differential diagnosis of dysautonomia in non-endemic areas. Vectorial transmission is the most common mode of infection in Latin America, whereas in non-endemic areas transmission by blood transfusions is more common.¹¹⁵

Clinical manifestations occur in two stages, the acute and chronic phases, separated by an indeterminate phase. Autonomic abnormalities occur in the chronic phase of the disease and are characterised by severe gastrointestinal and cardiovascular dysfunction. Gastrointestinal complaints include dysphagia, sialorrhoea, and constipation; reduced bowel motility, megaesophagus, and megacolon are the most frequent gastrointestinal findings. These abnormalities are due to denervation of the intrinsic enteric neurons of the submucosal (Meissner) and myenteric (Auerbach) plexuses.¹¹⁶

Cardiovascular manifestations include impaired blood-pressure response to standing, resting bradycardia, conduction-system abnormalities, arrhythmias, cardiomegaly, and cardiac failure.^{117,118} Cardiac vagal and sympathetic dysfunction is present¹¹⁹ even in patients without symptoms.¹²⁰ The autonomic abnormalities can precede the appearance of left-ventricular systolic dysfunction.¹¹⁸ The pathogenesis of the autonomic dysfunction is unresolved; it could be direct neural injury

during the acute illness, an immune-mediated response, or both.

Leprosy

Autonomic dysfunction is observed in patients with leprosy neuropathy due to infection by the bacillus *Mycobacterium leprae*. Focal anhidrosis, which is the best-documented autonomic abnormality, occurs in association with impaired pain and temperature perception in the cooler parts of the body. These symptoms are the earliest neurological manifestations of leprosy and are associated with the loss of cutaneous innervation.¹²¹ More general autonomic symptoms such as syncope, gustatory sweating, and erectile dysfunction also occur.¹²² Autonomic testing shows impaired axon-reflex-mediated and direct sweat-gland-stimulated sudomotor function induced by cholinergic agonists. The impaired sweating is related to both loss of small nerve fibres and sweat-gland injury.¹²¹ Other abnormalities shown by autonomic tests include impaired axon-reflex-mediated vasomotor flare response induced by histamine or capsaicin, impaired cutaneous and muscle vasomotor reflexes, and abnormalities of sympathetic and parasympathetic cardiac autonomic function.^{121,123} Cutaneous autonomic abnormalities and small-nerve-fibre sensory dysfunction are present in patients with lepromatous, tuberculoid, and borderline leprosy and are not restricted to one particular immunopathological diagnosis.¹²¹

Diphtheria

A toxin-mediated sensorimotor neuropathy occurs some weeks after pharyngeal or cutaneous diphtheria.¹²⁴ Cranial mononeuropathies, symmetrical limb weakness, sensory ataxia (diphtheric pseudotabes), and decreased or absent deep tendon reflexes are hallmarks of diphtheric neuropathy. Accommodation paralysis, with preserved light responses, is an early manifestation in 10–50% of cases. The sparing of the light reflex is a clinical feature that distinguishes diphtheria-related from botulism-related pupillary changes. Bladder and bowel control can be impaired. Cardiac vagal abnormalities (resting tachycardia, possibly related to myocarditis) occur.^{124,125}

Toxic neuropathies

Several industrial toxins, environmental toxins, marine toxins, and therapeutic drugs can cause autonomic dysfunction (panel 6). Autonomic-test abnormalities have been reported in individuals exposed to organic solvents,¹²⁶ industrial-use acrylamide,¹²⁷ arsenic,¹²⁸ thallium,¹²⁹ and other heavy metals.¹³⁰ Clinically important autonomic abnormalities are rarely observed with exposure to these toxins. Distal hyperhidrosis and hypohidrosis are the most common autonomic abnormalities.^{127,128} Ingestion of the rat poison Vacor (N-3-pyridylmethyl-N'-para-nitrophenyl urea) causes severe autonomic dysfunction. Full recovery is unusual.¹³¹ Marine toxins can also cause autonomic

symptoms. The most common of these disorders, caused by ingestion of ciguatoxic fish, results in orthostatic hypotension, bradycardia, pupillary changes, and hypersalivation. These abnormalities are reversible in most cases but may become chronic in some.¹³²

Autonomic neuropathy can follow treatment with cytotoxic agents used in cancer chemotherapy. Clinically evident dysautonomia occurs most consistently with vincristine and includes bowel hypomotility, bladder atony, and orthostatic hypotension. The abnormalities generally reverse several months after treatment is stopped.¹³³ Autonomic abnormalities are also observed in patients treated with cisplatin¹³⁴ and paclitaxel.¹³⁵ Improvement occurs gradually but some abnormalities can persist. Other drugs that can cause autonomic dysfunction include amiodarone,¹³⁶ perhexiline,¹³⁷ and pentamidine.¹³⁸

Treatment of autonomic neuropathy

Although many of the autonomic neuropathies are not reversible, the symptoms of autonomic dysfunction respond to several specific interventions. This topic has been covered in detail in several recent reviews.^{139,140}

Orthostatic hypotension

Education of the patient and action to address reversible causes of orthostatic hypotension are the cornerstones of its treatment. Nevertheless, many patients need pharmacological intervention. The first step is volume repletion with fluid (up to 10 L daily) and salt (up to 10 g daily) supplemented by the mineralocorticoid 9- α -fluorohydrocortisone (0.1–0.3 mg daily). A sympathomimetic agent can be added should symptoms persist. Midodrine, a direct, peripherally acting α -1-adrenoceptor agonist, is the most widely used of these pressors. The dose should be titrated from 2.5 mg to 10.0 mg three times a day to limit the risk of an exaggerated pressor response due to denervation supersensitivity.

Gastrointestinal autonomic dysfunction

Initial treatment of gastroparesis in patients with diabetic autonomic neuropathy should include rigorous control of blood glucose concentrations, which improves gastric motility. Patients should be advised to eat many small meals and to lower the fat content of their diet. Prokinetic agents used to treat gastroparesis include metoclopramide (10 mg orally 30 min before meals), domperidone (10–20 mg four times a day), and erythromycin (250 mg three times a day). Most patients can be treated with these medical interventions, and placement of a jejunostomy tube is rarely necessary.

Bowel hypomotility in autonomic neuropathy can be substantially improved by a regimen that includes increased fibre with a concomitant increase in fluid, stool softeners, and an osmotic laxative. Contact cathartics should be used infrequently. Bowel hypomotility is accompanied by intermittent bowel hypermotility in some patients. Trials of a gluten-free diet and restriction of

Panel 6: Toxic autonomic neuropathies

- Organic solvents
- Marine toxins
- Acrylamide
- Heavy metals
- Vacor
- Vincristine
- Cisplatin
- Paclitaxel
- Perhexiline maleate
- Amiodarone
- Pentamidine

lactose should be attempted. Cholestyramine, clonidine, somatostatin analogues, pancreatic enzyme supplements, and antibiotics such as metronidazole benefit some patients.

Genital autonomic neuropathy

Oral medications are the primary therapy for neuropathic erectile failure. They should be used in conjunction with counselling and a medical history that excludes other causes of sexual dysfunction, particularly concomitant medications. Medical treatment should be initiated with an inhibitor of phosphodiesterase type 5 which, by inhibiting the breakdown of cyclic GMP, increases smooth-muscle relaxation and increases blood flow in the corpus cavernosum. Sildenafil (50 mg) is the most widely used of these agents, although tadalafil (20 mg) and vardenafil (20 mg) have also been used in patients with autonomic neuropathy. These agents should not be used by individuals with unstable ischaemic heart disease, with clinically significant hypotension or orthostatic hypotension, or those using glyceryl trinitrate or other nitrate-based medications. Other therapies include intracorporeal injection of vasoactive substances such as papaverine, phentolamine, and prostaglandin E₁, transurethral delivery of vasoactive agents, and the use of mechanical devices such as the vacuum erection device or constricting rings. Penile prosthetic implants can be used if these therapies fail or are not tolerated by the patient. Vaginal lubricants and oestrogen creams help restore vaginal lubrication in women with autonomic dysfunction.

Autonomic dysfunction of the urinary tract

The initial therapeutic approach should emphasise timed voiding schedules with bladder contractions increased by a Valsalva or Credé (suprapubic pressure) manoeuvre. Clean intermittent self-catheterisation, however, is the primary therapy for impaired or absent detrusor muscle activity due to an autonomic neuropathy. The interval between catheterisations should be designed to maintain a residual volume of less than 100 mL and avoid incontinence. Pharmacotherapy with cholinergic agonists

such as bethanechol (10–30 mg three times a day) has a limited role in the treatment of detrusor areflexia. Stimulation of muscarinic, postganglionic receptors results in greater bladder contractility.

Hyperhidrosis

Distal hyperhidrosis can occur early in the course of autonomic peripheral neuropathy, whereas hyperhidrosis with a proximal distribution commonly occurs later in the course. Gustatory hyperhidrosis, a common accompaniment to diabetic neuropathy, is an example of this process. Hyperhidrosis can be attenuated by anticholinergic agents such as trihexyphenidyl and propantheline. High doses of these agents are generally needed, and therapy is limited by other anticholinergic side-effects, such as dry mouth, urinary retention, and constipation. Glycopyrrolate, which does not cross the blood–brain barrier, might have a better side-effect profile. Intracutaneous injection of botulinum toxin type A is beneficial in many cases. Sympathectomy is rarely required. There is no effective treatment for hypohidrosis.

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