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Autonomic Peripheral Neuropathy

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Most generalized peripheral polyneuropathies are accompanied by clinical or subclinical autonomic dysfunction. There is a group of peripheral neuropathies in which the small or unmyelinated fibers are selectively targeted [1]. In these neuropathies, autonomic dysfunction is the most prominent manifestation. The autonomic nervous system innervates viscera, vascular smooth muscle, endocrine and exocrine glands, the immune system, and soft tissues, and the associated signs and symptoms include impairment of cardiovascular, gastrointestinal, urogenital, thermoregulatory, pseudomotor, and pupillomotor autonomic function. A list of common peripheral neuropathies with autonomic manifestations is found in Box 1.

Diabetic autonomic neuropathy

Diabetes mellitus is the most common cause of autonomic neuropathy in the developed world [2,3]. This topic has been covered in detail in several recent reviews [4,5]. Diabetic cardiovascular autonomic neuropathy often manifests initially as an increased resting heart rate caused by a cardiac vagal neuropathy. As the autonomic neuropathy progresses, cardiac sympathetic fibers are involved and the resting tachycardia is replaced with a slowed, and ultimately fixed, heart rate [6–8]. Orthostatic hypotension occurs in diabetes as a consequence of efferent sympathetic vasomotor denervation, causing reduced vasoconstriction of the splanchnic and other peripheral vascular beds [9]. There is an increase in overall mortality and sudden death in patients with diabetic autonomic neuropathy [10–17]. In a meta-analysis of 15 studies, a significant association between cardiovascular autonomic neuropathy and subsequent mortality was observed. There was a pooled relative risk of 2.14 (95% confidence interval 1.83–2.51; $P < 0.0001$). The relative risk was stronger for studies for which two or

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Box 1. Autonomic peripheral neuropathies

Diabetes
Amyloidosis
Guillain-Barré syndrome
Acute and subacute autonomic neuropathies
Immune-mediated and paraneoplastic neuropathies
- Paraneoplastic neuropathies
- Connective tissue diseases
- Sjögren's syndrome
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Mixed connective tissue disease

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

Infectious diseases
- Chagas disease
- HIV neuropathy
- Botulism
- Leprosy
- Diphtheria

Toxic neuropathies
- Organic solvents
- Acrylamide
- Heavy metals
- Vacor
- Vincristine
- Cisplatinum
- Taxol
- Doxorubicin
- Cytosine arabinoside
- Perhexiline maleate
- Amiodarone
- Pentamidine
- Gold
- Podophyllin
- Marine toxins

more measures were used to define cardiac autonomic neuropathy. The stronger association observed in studies defining cardiac autonomic neuropathy by the presence of two or more abnormalities may be caused by more severe autonomic dysfunction in these subjects or a higher frequency of other comorbid complications that contributed to their higher mortality risk [18].

Symptoms of bladder dysfunction are observed in up to 50% of patients who have diabetes [19–21]. The earliest manifestation is impaired bladder 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, decreased peak urinary flow rate, bladder overdistension, and ultimately, urinary retention and overflow incontinence [22,23].

Erectile failure affects up to 75% of men who have diabetes and may be the earliest symptom of diabetic autonomic neuropathy [24–28]. Vascular and psychogenic causes also may contribute to this symptom. In vitro studies of isolated corpus cavernosum tissue from men who have diabetes suggest that the erectile failure is caused by impairment in autonomic and endothelial-dependent nitric oxide–mediated relaxation of corpus cavernosum smooth muscle [29]. Ejaculatory failure caused by sympathetic nervous system dysfunction may precede the appearance of erectile dysfunction, although erectile failure can occur with retained ability to ejaculate and experience orgasm. There are few studies of genital autonomic neuropathy in women who have diabetes [30]. Reduced vaginal lubrication is a commonly reported symptom [31].

Autonomic dysfunction occurs throughout the gastrointestinal tract and produces several specific clinical syndromes [32,33]. Diabetic gastroparesis—delayed gastric emptying of solids or liquids—is present in up to 50% of individuals who have diabetes [34–36]. Gastroparesis may manifest as nausea, postprandial vomiting, bloating, belching, loss of appetite, and early satiety. Many patients, however, are asymptomatic despite impaired gastric motility [33]. Gastroparesis often impairs the establishment of adequate glycemic control. Dysfunction of the vagus nerve and intrinsic enteric autonomic nerves may play a role in this disorder. Recent studies have implicated hyperglycemia as a cause of reversible impairment in gastric and small intestinal motility during fasting and after food intake [37,38].

Constipation is the most frequently reported gastrointestinal autonomic symptom and is found in up to 60% of persons who have diabetes [39–41]. Diabetic diarrhea and other lower gastrointestinal tract symptoms also may occur. The diarrhea is profuse and watery and typically occurs at night. The diarrhea can last for hours or days and frequently alternates with constipation. In individuals who have type 2 diabetes, metformin therapy is a common cause of diarrhea [42]. Fecal incontinence caused by anal sphincter incompetence or reduced rectal sensation is often exacerbated by diarrhea [43,44].

Diabetic autonomic neuropathy initially results in a loss of thermoregulatory sweating in a glove and stocking distribution that can extend to the upper aspects of the limbs and anterior abdomen, conforming to the well-recognized length dependency of diabetic neuropathy [45]. Hyperhidrosis also may accompany diabetic autonomic neuropathy. Gustatory sweating, an abnormal production of sweating that appears over the face, head, neck, shoulders, and chest after eating even nonspicy foods, is observed occasionally. The pathophysiology of this phenomenon, which suggests aberrant reinnervation, is not fully elucidated [46].

Preliminary evidence indicates that impaired glucose tolerance is associated with and may be the direct cause of a peripheral neuropathy that predominantly affects small nerve fibers. The prevalence of this association is unknown. There are few community-based epidemiologic studies of this disorder, and the evidence is mainly derived from studies in tertiary care centers. Sudomotor abnormalities are a prominent manifestation of this neuropathy [47–51]. An open label diet and exercise program based on the Diabetes Prevention Program improved the metabolic parameters (including weight, lipids, and 2-hour glucose levels) and measures of small fiber structure and function. After 1 year of treatment there was a significant improvement in proximal intraepidermal nerve fiber density. The change in intraepidermal nerve fiber density correlated with pain scores. There also was a significant improvement in foot sweat volume measured by quantitative sudomotor axon reflex test (QSART) [49].

Amyloid neuropathy

Amyloidosis is caused by the deposition of insoluble fibrillar proteins in a beta-pleated sheet configuration within the extracellular space of various tissues and organs. Various amyloidogenic proteins have been associated with amyloidosis. The current classification of the systemic amyloidoses is based on the biochemistry of the precursor protein [52,53]. Although the fibril precursor proteins differ, there are strong similarities between the clinical presentations and pathology of the neuropathies associated with the different amyloidoses. Autonomic dysfunction frequently accompanies the polyneuropathy of primary ([AL] immunoglobulin light chain associated) and hereditary amyloidosis (familial amyloid polyneuropathy [FAP]) but in contrast is not common in secondary (amyloid A protein-associated) amyloidosis [52,53].

Patients who have amyloid neuropathy typically present with distal sensory symptoms, such as numbness, pain, paresthesias, and dysesthesias, although the autonomic manifestations occasionally may be the presenting feature of the neuropathy. On examination, there are signs of a sensorimotor polyneuropathy that predominantly involves the small fibers that mediate nociceptive and thermal sensation. Touch-pressure, position, and vibration perception are typically less severely impaired, particularly in patients who have FAP. Weakness is not a prominent feature and usually occurs later

in the course of the disease. Painless, trophic ulcers may occur because of sensory loss and autonomic dysfunction. Characteristic autonomic signs and symptoms include postural hypotension, early satiety, diarrhea, constipation, fecal incontinence, disturbances in bladder function, pupillary abnormalities, and erectile failure. These autonomic manifestations are similar to those described with diabetic autonomic neuropathy. Sick sinus syndrome and A-V conduction deficits also are frequently present. Tests results for assessing cardiac vagal function are often abnormal [54].

Amyloid neuropathy is characterized pathologically by the deposition of insoluble beta-fibrillar proteins in the epi-, peri-, and endoneurium, the perineuronal tissues, and the neural vasculature. Ischemic, infiltrative, inflammatory, and toxic-metabolic factors have been implicated in the pathogenesis of the peripheral neuropathy, which remains unresolved [54].

The pathogenesis of amyloid peripheral neuropathy is unresolved [54]. Proposed pathogenic processes include ischemia caused by obliteration of small arteries and arterioles of nerves by amyloid deposits [55–57], infiltration and compression of peripheral nerves, dorsal nerve root ganglia, or autonomic ganglia by amyloid [56–58], inflammation, and toxic-metabolic factors, including oxidative stress [59,60].

Amyloidosis can be diagnosed by subcutaneous fat pad aspiration, gingival biopsy, or biopsy of rectal (and other gastrointestinal tract) mucosa. Nerve biopsy may be less sensitive because of the focal distribution of the amyloid deposits [61]. Amyloid deposits have a homogeneous, eosinophilic appearance on light microscopy and reveal a characteristic yellow-green birefringence when viewed under polarized light with Congo red staining.

Primary (AL) amyloidosis is the most common form of amyloidosis in the Western world. 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 [62]. Symptoms typically appear in the sixth or seventh decade. Patients usually present with weight loss and fatigue. Peripheral neuropathy, which may be the presenting feature of the disease or an incidental finding, is present in up to 20% of patients who have AL [58]. Autonomic involvement of the cardiovascular, gastrointestinal, and urogenital systems is common [52,58,63]. 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 who have AL amyloidosis [62].

The median survival of patients who have AL amyloid neuropathy ranges from 13 to 35 months, with a 3-year survival rate of 38% to 50%. The prognosis for patients who have heart failure is considerably worse [64,65]. Treatment with melphalan and prednisone improves survival, particularly when associated with a reduction in serum or urine monoclonal protein [64,65]. Stem cell transplantation in carefully selected patients may improve survival further [66].

FAP is a manifestation of hereditary generalized amyloidosis. This disorder was first reported in Portugal in 1952 [67]. The hereditary amyloidoses are autosomal dominantly inherited diseases in which the amyloid precursor is a mutant protein. Mutant transthyretin (TTR), previously called prealbumin, 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 observed mutation is a substitution of methionine for valine at position 30 (Met-Val 30) [68,69]. This disorder, which encompasses what was previously called FAP I (Portuguese or Andrade amyloidosis) [67] and FAP II (Indiana-Swiss or Rukavina amyloidosis) [70,71], has been associated with more than 100 single or double mutations or deletions of the TTR gene [72].

TTR amyloidosis typically presents in the third to fifth decade. Characteristic features include prominent dysautonomia that accompanies a painful sensorimotor neuropathy, carpal tunnel syndrome, vitreous opacities, nephropathy, and cardiomyopathy. Sensory neuropathy and gastrointestinal symptoms are the most frequent initial symptoms. Death occurs 5 to 15 years after the appearance of symptoms [53,72]. The clinical phenotype is variable, however, and depends on the position and nature of the amino acid substitution. Variant presentations include late onset [73], isolated carpal tunnel syndrome, and a distal sensory or sensorimotor neuropathy without autonomic dysfunction [70,71]. Clusters of hereditary amyloidosis caused by mutant TTR have been found in Portugal, Japan, Sweden, United States, Spain, Finland, Ireland, France, and Germany [53,72].

A late-onset, seemingly sporadic FAP (TTR Met 30) has been documented in Portugal and Japan. Patients in the sixth decade or older typically present with lower extremity paresthesias. The autonomic features are mild and not incapacitating. This disorder has an autosomal dominant pattern of inheritance with low penetrance. There is a high male/female ratio (10.7:1) [73].

FAP is also rarely caused by mutations in other proteins besides TTR. FAP rarely may be caused by mutations in the genes encoding for apolipoprotein-A1, fibrinogen Aα, lysozyme, and gelsolin [52]. A recent report documented that almost 10% of patients with sporadic amyloidosis, presumed to be primary (AL) amyloidosis, actually had hereditary amyloidosis. In more than half of these patients, neuropathy was the dominant clinical presentation. These results suggest that hereditary amyloidosis may occur more frequently than previously suspected. Given the different prognoses and therapies for the two conditions, these findings emphasize the importance of genetic testing in patients with amyloidosis who do not have a pathologically confirmed diagnosis of AL disease. A low-grade monoclonal gammopathy was present in 24% of patients who were found later to have hereditary amyloidosis [74].

Because most of the mutated amyloidogenic TTR is secreted by the liver, orthotopic liver transplant is the most effective treatment for hereditary amyloidosis. Liver transplant removes the principal source of variant TTR and

reduces circulating TTR by up to 90%. In appropriately selected patients, liver transplant improves neurophysiologic measures, nerve morphology, and survival [75,76]. Although the extent of the benefits of liver transplantation on the sensorimotor peripheral neuropathy is unresolved [76,77], the features of an established autonomic neuropathy do not seem to improve significantly with this intervention [76,78,79]. Similarly, conduction system abnormalities and arrhythmias seem to progress despite liver transplantation [79]. Pharmacotherapeutic interventions that inhibit amyloidogenesis eventually may replace liver transplant [80].

Acute and subacute autonomic neuropathies

Guillain-Barré syndrome

Guillain-Barré syndrome (acute inflammatory demyelinating polyradiculoneuropathy) is a monophasic illness of immune etiology that presents as an acutely evolving sensorimotor polyneuropathy of varying severity. Autonomic manifestations such as sinus tachycardia, sinus pauses and other tachy- and bradyarrhythmias, blood pressure lability, bowel and bladder dysfunction, pupillomotor disturbances, sudomotor dysfunction, and vasomotor abnormalities frequently accompany Guillain-Barré syndrome [81,82]. Autonomic manifestations, which occasionally may be the presenting feature of Guillain-Barré syndrome [83], may be more prominent in patients with respiratory failure, severe motor deficits, and the axonal variant of Guillain-Barré syndrome [84–86]. The autonomic features can result in significant mortality and morbidity in some patients, although they are usually overshadowed by the motor features of the disorder.

Acute and subacute autonomic neuropathies

Autonomic manifestations may be the sole or predominant feature of an acute or subacute peripheral neuropathy [87]. Although acute or subacute autonomic neuropathy is usually immune-mediated or paraneoplastic, the differential diagnosis includes botulism, porphyria [88], and some toxic neuropathies (see later discussion). 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 manifestations may accompany the autonomic manifestations but are not the predominant aspect of the presentation. The autonomic features of this disorder may involve the sympathetic and parasympathetic divisions of the autonomic nervous system (pandysautonomia) [89] or the sympathetic or parasympathetic nervous system alone (also called cholinergic dysautonomia) [90]. Only 40% of cases recover fully to premorbid status. Autonomic testing in the recovery phase of illness in these

patients often shows evidence of persisting subclinical autonomic dysfunction [87].

Acute dysautonomia has been described in association with infectious mononucleosis or Epstein Barr virus [91,92], streptococcus [93], Coxsackie B virus [94], rubella [95], and herpes simplex virus [96] infections in addition to other nondiagnosed viral syndromes. Associations with malignancies [97,98] (see later discussion) and connective tissue diseases have been described in other cases [99,100]. Lending further support to the likelihood that some of these cases are immune mediated, a positive therapeutic response to intravenous immunoglobulin has been reported in uncontrolled case studies [101,102].

An acute case of subacute autonomic neuropathy may occur in association with connective tissue disease, including Sjögren's syndrome [103], rheumatoid arthritis [104], systemic lupus erythematosus [99,100], and mixed connective tissue disease. No specific autoantibodies have been associated with the dysautonomia in connective tissue diseases.

Immune-mediated and paraneoplastic autonomic neuropathies (specific autoantibody-associated autonomic neuropathies)

Autonomic dysfunction has been associated with the presence of specific autoantibodies (Box 2). The subacute appearance of autonomic symptoms, including orthostatic hypotension, pupillomotor dysfunction, sudomotor dysfunction, constipation, urinary retention, impotence, and xerophthalmia, has been associated with the presence of anti-Hu antibodies (also known as Type 1 antineuronal nuclear antibody, ANNA-1) in patients with malignancies, especially small-cell lung cancer. Other associated malignancies include non–small-cell lung cancer and malignancies of the gastrointestinal tract, prostate, breast, bladder, kidney, pancreas, testicle, and ovary [105–108]. Dysautonomia may be an isolated manifestation of a paraneoplastic disorder or part of a generalized paraneoplastic syndrome that includes a sensory neuronopathy, limbic and brainstem encephalitis, encephalomyelitis,

Box 2. Specific antibodies associated with autonomic neuropathies

Anti-Hu antibodies (Type 1 anti-neuronal nuclear antibody, ANNA-1)
Purkinje cell antibodies Type 2 (PCA-2)
Collapsing response mediator protein-5 (CRMP-5)
Neuronal nicotinic acetylcholine receptor antibodies
P/Q-type Ca2 + channel antibodies
Acetylcholine receptor antibodies

cerebellar degeneration, and a sensorimotor peripheral neuropathy. Other autoantibodies that are associated with a paraneoplastic autonomic neuropathy include Purkinje cell cytoplasmic antibodies Type 2 (PCA-2) [109] and antibodies to the neuron cytoplasmic protein, collapsin response-mediator protein-5 (CRMP-5) [110].

Patients who have autoantibodies to ganglionic acetylcholine receptors typically present with a subacute autonomic neuropathy with progression to panautonomic failure [111]. Based on studies in animals, these antibodies impair ganglionic synaptic transmission by depleting acetylcholine receptors on the ganglionic neuron [112]. The typical clinical findings in autoimmune autonomic neuropathy include dry eyes and mouth, fixed heart rate, impaired pupillary response to light and accommodation, gastrointestinal dysmotility, and urinary retention [111,113,114]. Orthostatic hypotension can be the most incapacitating feature, with frequent syncopal episodes and restrictions on activities of daily living. Laboratory studies reveal substantially reduced levels of plasma catecholamines [112]. Some [115], but not all [116], patients respond to plasmapheresis and immune modulation. Malignancies associated with these antibodies include small-cell lung carcinoma, thymoma, bladder carcinoma, and rectal carcinoma. These antibodies may be present in patients with the clinical phenotype of pure autonomic failure [117]. When cholinergic features are prominent, the diagnosis of an immune-mediated autonomic neuropathy should be entertained [113].

Celiac disease (gluten-sensitive enteropathy) is the most common manifestation of gluten sensitivity; however, diverse manifestations may accompany the disorder [118,119]. Several recent reports have drawn attention to the association between gluten sensitivity with elevated antigliadin antibodies and neurologic disorders [118,119], although given the high percentage of antigliadin antibodies in the general population (6%–12%), the etiologic significance of this association is uncertain in most patients [120,121]. We have documented that 2.4% of patients referred for autonomic testing had biopsy-proven celiac disease and dysautonomia [122], a frequency of celiac disease similar to that reported in idiopathic peripheral neuropathy [119]. In these patients, nausea, which was postural in nature, was the primary symptom for referral. Other reported autonomic symptoms included lightheadedness, palpitations, fatigue, presyncope, and syncope. Autonomic test results revealed abnormalities in sympathetic and parasympathetic nervous system function [122]. Esophageal dysmotility and subclinical abnormalities of cardiovascular reflexes, which were present in 19% of patients, also have been reported in patients who have celiac disease [123].

Hereditary autonomic neuropathies

The hereditary autonomic neuropathies are a heterogeneous group of disorders, some of which have significant involvement of autonomic fibers (see Box 1) [124–127]. Autonomic features are most prominent in the hereditary

sensory and autonomic neuropathies (HSAN) and Fabry's disease [124–127]. Other hereditary autonomic neuropathies include Allgrove syndrome [128], Tangier disease [129–131], a sensory and autonomic neuropathy with arthropathy that is present in Navajo children [132,133], and multiple endocrine neoplasia, type 2b [134]. HSANs are characterized by prominent sensory loss without motor involvement and by often striking dysautonomia. The axon reflex-mediated vasomotor response (the flare) after intradermal histamine is absent in all HSAN.

Hereditary sensory and autonomic neuropathy type I

HSAN type I is an autosomal dominant, hereditary sensory radiculoneuropathy that presents in the second decade. Patients who have this disorder present with distal pain that is associated with sensory loss that predominantly involves nociceptive and thermal perception while relatively sparing touch-pressure sensation and proprioception. The sensory loss progresses gradually and is accompanied by anhidrosis, trophic ulcers, acral injuries, stress fractures, and osteomyelitis [125,126]. HSAN type I has been associated with a mutation in the SPTLC1 gene on chromosome 9q22.1-q22.3 that encodes for subunit 1 of serine palmitoyltransferase—the rate limiting enzyme for the synthesis of the sphingolipids, ceramide, and sphingomyelin [135,136]. A variant of this disorder, associated with chronic cough and gastroesophageal reflux, has been mapped to a locus on chromosome 3p22-p24 [137].

Hereditary sensory and autonomic neuropathy type II

HSAN type II (congenital sensory neuropathy or Morvan's disease) is an autosomal recessive or sporadic disorder that presents in infancy or early childhood. This disorder is associated with profound sensory loss that involves large and small fiber modalities (pain and temperature perception and proprioception). Marked hypotonia and decreased deep tendon reflexes are common [127]. Trophic changes are present in the upper and lower extremities. Painless fractures may occur. Autonomic features include episodic hyperhidrosis, tonic pupils, constipation, and apneic episodes [125,126]. Tearing may be delayed but is eventually normal. Sural nerve biopsy reveals depletion of large and small myelinated fibers but only slightly decreased number of unmyelinated fibers. This disorder has been associated with a mutation on a gene, HSN2, with a locus that maps to chromosome 12p13.33 [138].

Hereditary sensory and autonomic neuropathy type III

Autonomic manifestations are prominent in HSAN type III (Riley-Day syndrome or familial dysautonomia). This autosomal recessive disorder is

seen primarily in Ashkenazi Jewish children. The incidence of familial dysautonomia is 1 in 3700 live births among Ashkenazi Jews, and the carrier frequency is 1 in 32 individuals [139,140]. The defective gene that causes familial dysautonomia has been mapped to the long arm of chromosome 9 (9q31) [141]. Most (99.5%) patients who have familial dysautonomia have a single, splicing mutation in the I-kappa B kinase associated protein (*IKBKAP*) gene that results in tissue-specific expression of a truncated IKAP protein [142].

HSAN III presents in infancy. The clinical features of this disease include insensitivity to pain and temperature stimuli but sparing visceral pain, absence of tears (alacrima), hypoactive corneal and tendon reflexes, and absence of lingual fungiform papillae. Poor suck and feeding, esophageal reflux with vomiting and aspiration, and swallowing dyscoordination may be the first clinical manifestations [140,143]. Autonomic disturbances may 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.

Hereditary sensory and autonomic neuropathy type IV

HSAN type IV (congenital insensitivity to pain with anhidrosis, anhidrotic sensory neuropathy), the second most common HSAN, 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 [127]. The skin appears thick, hyperkeratotic, and callused because of the anhidrosis. Virtual absence of unmyelinated fibers has been noted in peripheral nerves [144,145]. Skin biopsy morphology of patients who have HSAN IV reveals deficient C and A delta fibers in the epidermis and absent or hypoplastic dermal sweat glands without innervation [146,147]. Intradermal injection or iontophoresis of cholinergic agonists, such as acetylcholine or methacholine, does not produce direct sweat gland–stimulated or axon reflex–mediated sweating [148]. Frame-shift, splice, and missense mutations have been documented in the NTRK1 (TRKA) gene located on chromosome 1 (1q21-q22). This gene encodes for neurotrophic tyrosine kinase receptor type I, which is autophosphorylated in response to nerve growth factor [149].

Hereditary sensory and autonomic neuropathy type V

This rare disorder presents in infancy with loss of pain perception that leads to acral ulcers, painless fractures, and other trophic injuries. Sudomotor abnormalities are present [150]. A mutation in the NTRK1 gene also may be responsible for this neuropathy [151].

Fabry's disease

Fabry's disease, or angiokeratoma corporis diffusum, is an X-linked, recessively inherited disorder that is associated with deficiency of the enzyme alpha-galactosidase A (ceramide trihexosidase). The enzyme deficiency results in the 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 [152]. The neurologic manifestations of this disorder are caused by the deposition of glycolipids in autonomic and dorsal root ganglia, perineurial cells, and unmyelinated and myelinated axons [153–155].

The autonomic manifestations include hypo- or anhidrosis, reduced saliva and tear formation, impaired cutaneous flare response to scratch and histamine, and disordered intestinal motility. Gastrointestinal symptoms may be as severe as their sensory complaints. The generalized presentation of the anhidrosis has suggested that sweat gland dysfunction, perhaps caused by intracytoplasmic inclusions in the eccrine glands, may play a role in the anhidrosis [156]. Sural nerve biopsies studies have demonstrated degeneration and loss of unmyelinated fibers [153–155]. Skin biopsies show decreased intraepidermal small nerve fibers [157]. Fabry's disease can be diagnosed by assaying the enzyme alpha-galactosidase A in leukocytes or skin fibroblasts [158].

Enzyme replacement therapy leads to a modest improvement in the clinical manifestations of the small-fiber neuropathy associated with this disorder. QSART testing may even normalize in some patients; however, no evidence indicates that these functional changes are associated with improvement in intraepidermal innervation [159,160].

Allgrove's syndrome

Allgrove's syndrome is an autosomal recessive disorder characterized by achalasia, alacrima, autonomic impairment, and adrenocorticotropin hormone (ACTH) insensitivity and progressive neurologic dysfunction. Affected individuals have between two and four of these relatively common symptoms occurring in varying combinations. Because these are relatively common clinical conditions, individuals with this syndrome may be undiagnosed [128]. The pattern of inheritance is autosomal recessive. Most cases of Allgrove's syndrome have no family history. A locus on chromosome 12q13 has been identified using genetic linkage analysis in a small number of families [128]. The disorder rarely may be unrecognized until adulthood [161].

Other hereditary autonomic neuropathies

Autonomic neuropathies are associated with several other hereditary disorders, including Tangier disease [129–131], a sensory and autonomic

neuropathy with arthropathy that is present in Navajo children [132,133], and multiple endocrine neoplasia, type 2b [134].

Autonomic neuropathy caused by infectious diseases

The peripheral neuropathies associated with several infectious diseases have prominent accompanying autonomic manifestations.

Botulism

Botulism is an acute neuromuscular disorder caused by the binding of a neurotoxin from the anaerobic bacterium, *Clostridium botulinum*, to the presynaptic nerve terminal, preventing acetylcholine release [162]. 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 [163–166]. Autonomic symptoms result from cholinergic dysfunction and 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 also may be present. Autonomic symptoms may occur in botulism, even in the absence of the characteristic motor and cranial nerve abnormalities [163–165]. Among toxigenic strains of *C botulinum*, types A, B, and E account for most human cases [162].

Bowel and bladder symptoms often persist after resolution of the infection. Diagnosis is based on the clinical and electrophysiologic findings and is verified by demonstrating neurotoxin in the serum, stool, or contaminated food or by culturing *C botulinum* from the stool. Botulism may manifest as a subacute cholinergic disturbance without associated clinical or electromyographic evidence of motor-endplate pathology [167,168]. Treatment involves eliminating sources of toxin. Intravenous trivalent equine antitoxin can prevent progression and reduce mortality, which remains at approximately 5% to 15%. Case studies of patients with the subacute onset of cholinergic disturbance without associated clinical or electromyographic evidence of motor-endplate pathology [167] underscore that dysautonomia may occur in botulism without the typical motor abnormalities [168].

HIV infection

Autonomic dysfunction may occur in patients with HIV infection. Although autonomic dysfunction seems to occur more frequently and with greater severity in patients who have AIDS, several reports suggest that seropositive patients and patients in the early stages of infection exhibit evidence of dysautonomia. The severity of autonomic dysfunction seems to constitute a continuum from the early to later stages of HIV infection [169–172]. In addition to direct virus effects and virus host interactions, toxins, medications, vitamin deficiency, and malnutrition may play a role

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 [169]. Autonomic testing reveals sympathetic and parasympathetic nervous system abnormalities [169,173].

Chagas' disease

Chagas' disease, which is caused by a parasitic infection by the protozoan *Trypanosoma cruzi*, is found predominantly in Latin America. Because of immigration patterns, there is an increasing incidence of Chagas' disease in the United States, and the autonomic manifestations of this disease should be considered in the differential diagnosis of dysautonomia in nonendemic areas. Vectorial transmission is the most common mode of infection in Latin America, whereas in nonendemic areas, transmission via blood transfusions is more common [174].

Clinical manifestations occur in two stages, the acute and chronic phases of the disease, which are separated by an indeterminate phase. Acute infection is characterized by fevers, myalgias, and sweating. Congestive heart failure may be present. Autonomic abnormalities occur in the chronic phase of the disease and are characterized by severe gastrointestinal and cardiovascular dysfunction. Gastrointestinal complaints include dysphagia, sialorrhea and constipation; reduced bowel motility, megaesophagus, and megacolon are the most frequent gastrointestinal findings. These abnormalities are caused by denervation of the intrinsic enteric neurons of the submucosal (Meissner) and myenteric (Auerbach) plexuses [175–177]. Cardiovascular manifestations include impaired blood pressure response to standing, resting bradycardia, conduction system abnormalities, arrhythmias, cardiomegaly, and cardiac failure [178–183]. The pathogenesis of the autonomic dysfunction is unresolved and may be caused by direct neural injury during the acute illness, an immune-mediated response, or both.

Leprosy

Autonomic dysfunction is observed in patients with leprous neuropathy caused by infection by the acid-fast bacillus *Mycobacterium leprae*. Focal anhidrosis, which is the best documented autonomic abnormality, occurs in association with impaired pain and temperature perception in the cooler regions of the body. These are the earliest neurologic manifestations of leprosy and correlate with the loss of cutaneous innervation [184]. More generalized autonomic symptoms, such as syncope, gustatory sweating, and erectile dysfunction, also may occur [185].

Diphtheria

A toxin-mediated sensorimotor neuropathy occurs some weeks after pharyngeal or cutaneous diphtheria. Early palatal paralysis in the disease is

probably a direct effect of diphtheria toxin but can occur at any time between the first and seventh weeks after infection [186,187]. Accommodation paralysis, with preserved light responses, is an early manifestation in 10% to 50% of cases [186]. The sparing of the light reflex is a clinical feature that distinguishes diphtheritic from botulism-related pupillary changes. Temporary loss of bladder or bowel control has been reported. Resting tachycardia and an often serious myocarditis are other features. Abnormalities on tests of cardiac vagal function have been documented [187,188].

Toxic neuropathies

Several industrial and environmental toxins and medications can cause autonomic neuropathy (see Box 1). Autonomic neuropathy has been reported in individuals exposed to organic solvents [189,190], arsenic [191], mercury [192], other heavy metals [193], industrial-use acrylamide [194], thallium [192,195], and the rat poison, Vacor (N-3-pyridylmethyl-N'-para-nitrophenyl urea) [196].

Autonomic neuropathy also may follow treatment with cytotoxic agents used in cancer chemotherapy. Clinically evident dysautonomia occurs most consistently with the vinca-alkaloid, vincristine [197,198]. Autonomic abnormalities are also observed in patients treated with cisplatin [199–202] and paclitaxel [203–206]. There are interindividual differences in susceptibility to chemotherapy-induced peripheral neuropathies; however, patients with pre-existing peripheral nerve injury caused by diabetes mellitus, ethanol, and inherited and other peripheral neuropathies may show a greater predisposition to the development of chemotherapy-induced neurotoxicity. Other medications that may cause autonomic dysfunction include the anti-arrhythmic agent, amiodarone [207], the coronary vasodilator, perhexiline [208], and pentamidine [209].

Marine toxins may affect ion transport, induce channels or pores in neural and muscular cellular membranes, alter intracellular membranes of organelles, and release mediators of inflammation. The box jellyfish, particularly *Chironex fleckeri*, which is in the Indo-Pacific region, is the world's most venomous marine animal and causes severe sympathetic and parasympathetic nervous system dysfunction in exposed patients [210]. Ciguatera poisoning is the most prevalent marine toxic exposure. Ciguatoxins are potent heat stable, non-protein, lipophilic sodium channel activator toxins that bind to the voltage sensitive sodium channel. The toxin is stored in the viscera of fish that have eaten the photosynthetic dinoflagellate and is progressively concentrated upwards along the food chain. The initial manifestations are characteristically sensory and include paresthesias, dysesthesias, and pain. Autonomic features may be prominent, including hypersalivation, bradycardia, hypotension, mydriasis, and meiosis [210–212]. Intravenous mannitol may reverse the acute sensory and autonomic features of ciguatera toxicity [212].

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