



Brigham and Women's Hospital

Founding Member, Mass General Brigham

Autonomic Neuropathies

Aditi Varma-Doyle, MD

Instructor

Division of General Neurology, Department of Neurology

Brigham and Women's Hospital

Harvard Medical School



Aditi Varma-Doyle, MD



Neurology Residency @ Louisiana State University Health Sciences Center, New Orleans, LA

Autonomic Neurology Fellowship @Beth Israel Deaconess Medical Center, Harvard Medical School

Advanced General and Autoimmune Neurology, Massachusetts General Hospital, Harvard Medical School

Current MPH graduate student, Johns Hopkins School of Public Health, Baltimore, MD



DISCLOSURES

No Disclosures



OBJECTIVES

1. Classification and types of Autonomic Neuropathy
2. Identify clinical presentations of autonomic neuropathy
3. Management of Autonomic Neuropathies

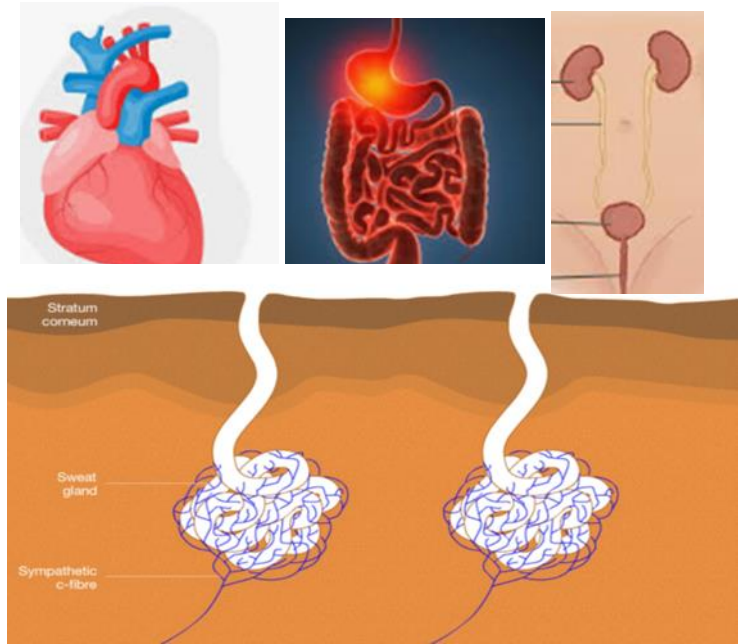


Autonomic Nerves: what and where are they?

Small, lightly myelinated or unmyelinated nerves:

Innervate organs & structures involved in:

- Cardiovascular
- Gastrointestinal
- Urogenital
- Sudomotor / Thermoregulatory
- Pupillary
- Immune function



Autonomic symptoms: nonspecific
Standard neurophysiologic studies are unable to evaluate small unmyelinated or lightly myelinated nerves

Autonomic reflex assessments:

Parasympathetic nervous system: Heart rate variability to Valsalva maneuvers, Deep Breathing

Sympathetic Adrenergic System: BP response to Valsalva, Orthostasis (Standing/Tilt), Hand Grip Test

Sympathetic Cholinergic System: Sweat Responses, QSART (Quantitative Sudomotor Axon Reflex Test), Thermoregulatory Sweat Testing

Plasma catecholamines,
Structural studies of cutaneous autonomic innervation: Skin Biopsy, Sweat Gland Density

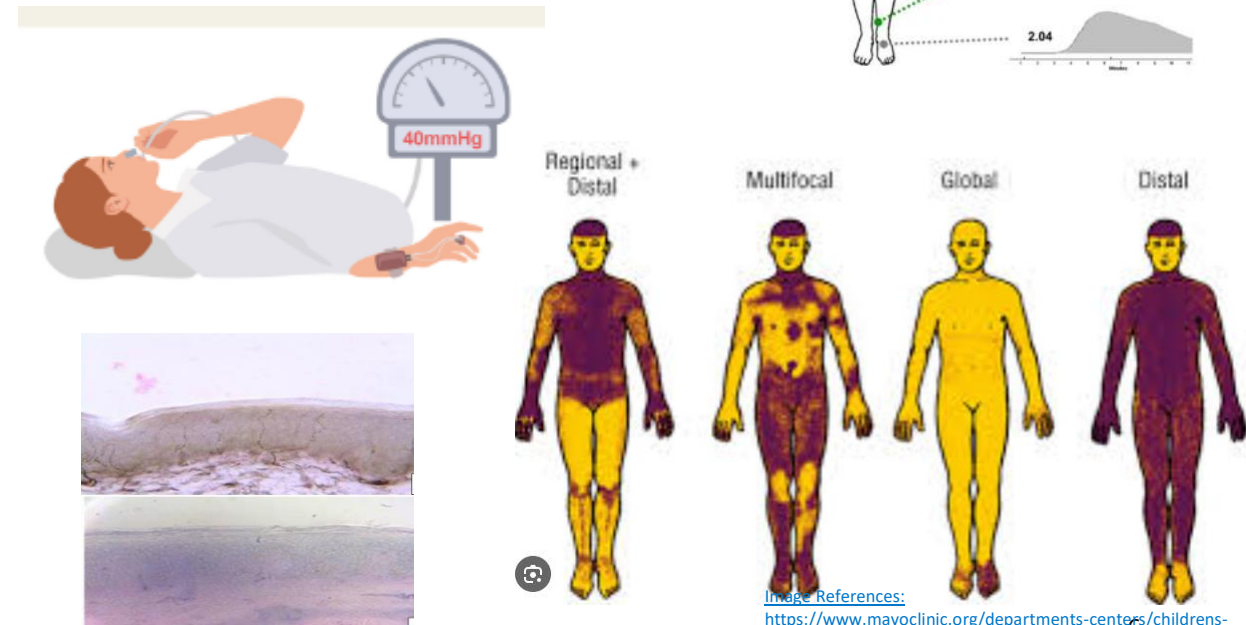
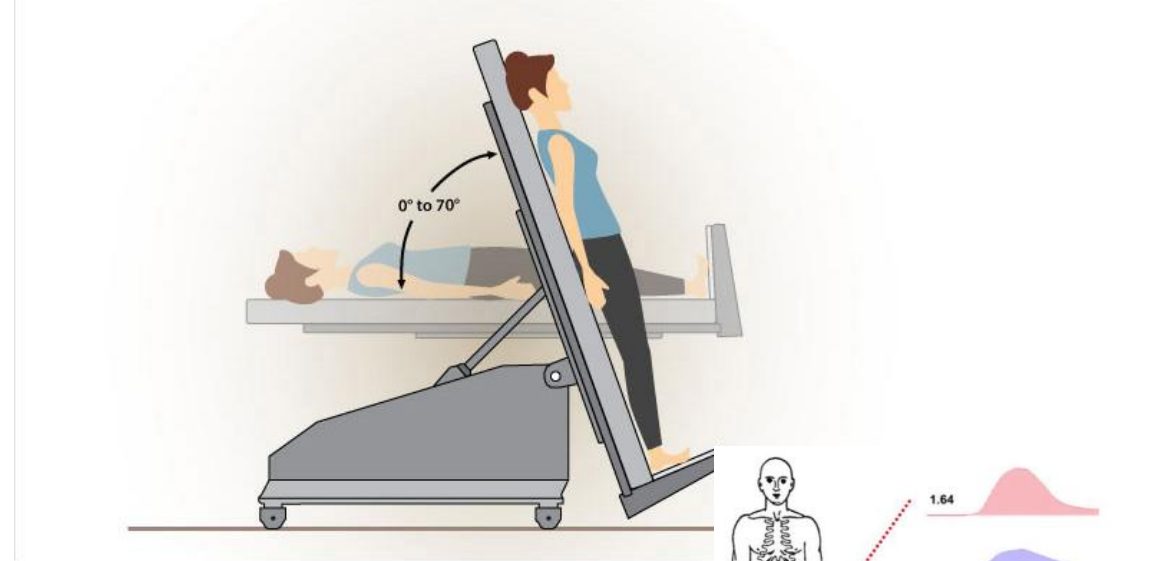
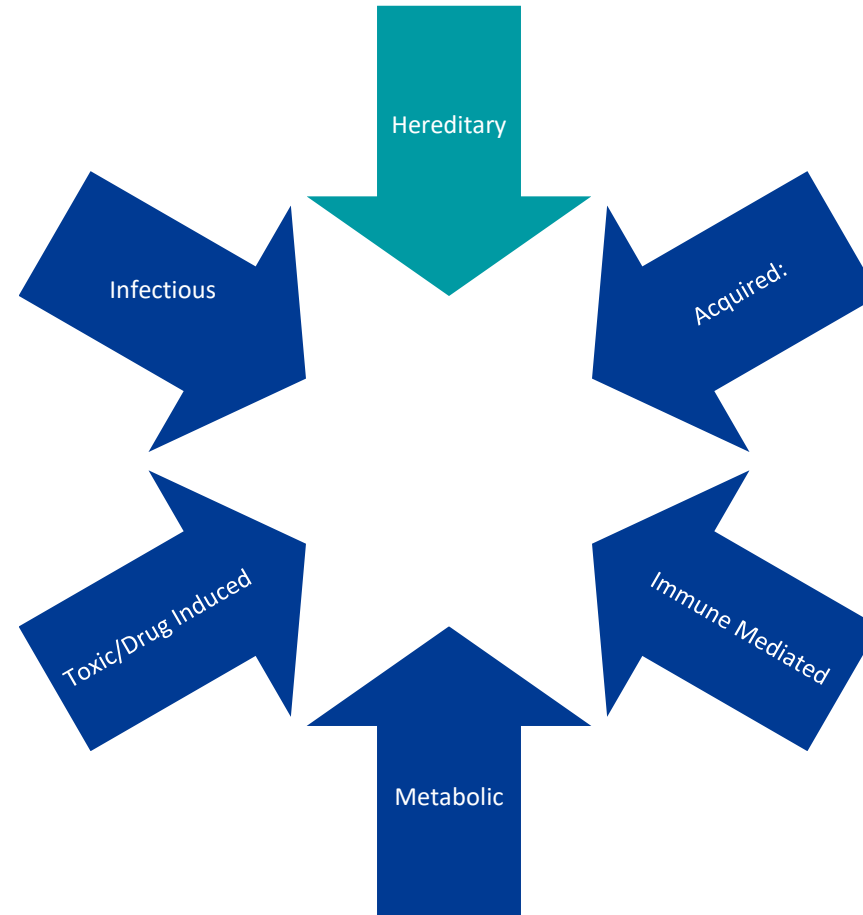


Image References:
<https://www.mayoclinic.org/departments-centers/childrens-center/overview/specialty-groups/general-pediatric-adolescent-medicine/autonomic-dysfunction-clinic>

PMID: 17178984.

The Dysautonomia Project

Peripheral Autonomic Neuropathies



HEREDITARY AUTONOMIC NEUROPATHIES

Hereditary sensory and autonomic neuropathies (HSANs): I-V: Autonomic manifestations occur to a varying degree and mode of inheritance varies

HSAN I: Autosomal dominant, hereditary sensory radiculoneuropathy, presenting in the second decade. Mutations: (SPTLC1, SPTLC2, ATL1, RAB7A, and DNMT1)

HSAN II: Autosomal Recessive/Sporadic, presenting in infancy/childhood. Is a congenital sensory neuropathy. Mutations in WNK1, RETREG1, and KIF1A

HSAN III: (also known as Riley-Day syndrome/familial dysautonomia):

Autosomal recessive; Ashkenazi Jewish descent, with prominent autonomic manifestations.

Genetic Mutations: Homozygous mutations in the ELP1 (Elongator complex protein 1) gene or I- κ -B kinase complex associated protein (IKAP)

Infancy (Hypotonic),

Sensory/Somatic Nerves are affected: Reduced pain and temperature sensation, absent deep tendon reflexes, and Sensory Gait ataxia.

Baroreflex receptor dysfunction $\rightarrow$ Orthostatic hypotension, BP lability, Abnormal cardiovascular function and ventilatory responses to hypoxia and hypercapnia.

Poor sucking and feeding, esophageal reflux with vomiting and aspiration, and swallowing dyscoordination

Defects in lacrimation, absent/hypoactive corneal reflexes, and absence of lingual fungiform papillae.

HSAN IV (Congenital Insensitivity to Pain with Anhidrosis [CIPA] or Hereditary Sensory and Autonomic Neuropathy): second most common HSAN.

Autosomal recessive,

Missense, nonsense, frameshift, and splice-site loss-of-function mutations in the NTRK1 (TRKA) gene which encodes a high-affinity tyrosine kinase receptor for nerve growth factor (NGF).

Insensitivity to pain, consequent acral ulceration, painless fractures, and other trophic injuries.

Anhidrosis, episodes of unexplained fever, Intellectual and motor developmental delay.



Fabry disease:

X-linked lysosomal storage disease

Decreased activity of alpha-galactosidase A ->lysosomal accumulations of neutral glycosphingolipids and globotriaosylceramide

Severe pain that begins in the distal extremities

Hypohidrosis: Gb3 deposition causing sweat gland dysfunction as well as damage to autonomic small fibers.

Abnormal pupillary responses to pilocarpine, reduced saliva production and tear formation

AFT: Abnormal cardiovascular responses including decreased reflex rises in plasma noradrenaline

Serology: Low alpha-Gal A activity in leukocytes or plasma

Skin biopsy usually reveals high lipid content. Lipids may also be found inside muscle fibers, endothelial cells, ganglion cells

Young adults presenting with a PROTHROMBOTIC STATE:
cerebrovascular event, (periventricular white matter, basal ganglia, supra and infratentorial, pulvinar calcifications)

+ myocardial infarction + renal dysfunction

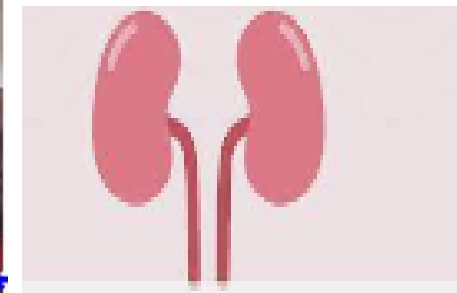
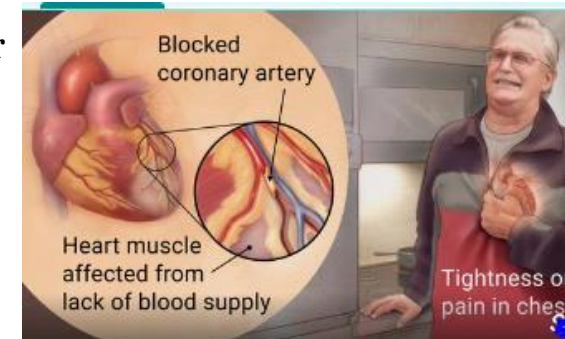
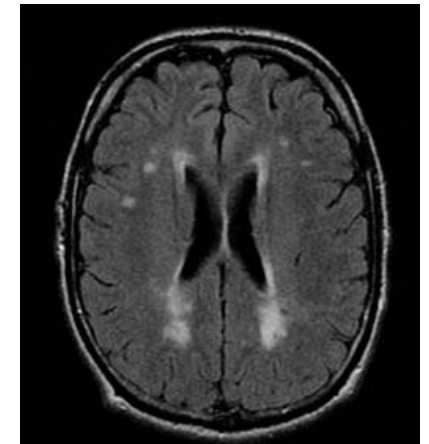
+ Skin Lesions (Skin Lesions: Angiokeratoma corporis diffusum

Treatment:

Replacement of deficient enzyme alpha-galactosidase A (alpha or beta) as soon the diagnosis is made agalsidase alfa 0.2 mg/kg every other week (EOW) (Shire) and agalsidase beta 1.0 mg/kg EOW (Fabrazyme)

Hypertension: angiotensin-converting enzyme inhibitor or angiotensin receptor blocker

Renal transplantation, continued enzyme replacement post-transplant.



Allgrove syndrome

Triple –A syndrome + autonomic =4A syndrome

Autosomal recessive. Mutations of the *AAAS* gene on chromosome 12q13-> Nuclear envelope protein known as *ALADIN* (alacrimia-achalasia-adrenal insufficiency neurologic)

ACTH resistant adrenal insufficiency(presents later), alacrimia (infancy), and achalasia (infancy/child) +progressive neurological impairment +/-mild mental retardation

Young adults: Postural dizziness, erectile dysfunction and loss of spontaneous morning erections, Diarrhea/GI/GU

AFT: abnormal reaction to intradermal histamine, abnormal sweating, orthostatic hypotension, and heart rate disturbances.

Progressive loss of cholinergic functions

Schirmer test can reveals bilateral alacrima,
Barium swallow : Achalasia cardia.

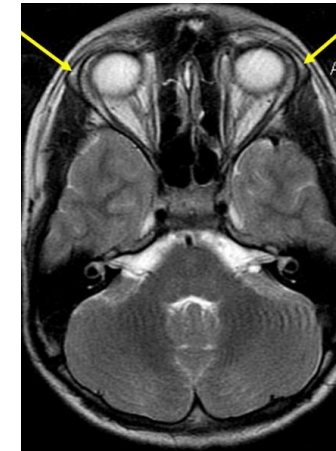
Medical Management

Glucocorticoids (hydrocortisone, prednisone, dexamethasone, and fludrocortisone)

Topical ocular lubricants

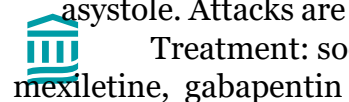
Perioperative treatment with stress doses of glucocorticoids

Pneumatic dilatation, Modified heller operation



Hereditary sodium channelopathy-related small fiber neuropathy

- Autonomic manifestations in small fiber neuropathies associated with ion channel mutations.
- **Inheritance:** Autosomal dominant
- Gene mutations (G-o-F, missense) encoding **sodium** channels NaV1.7 (SCN9A), NaV1.8 (SCN10A), and NaV1.9 (SCN11A)
- Voltage-gated sodium channel isoforms: preferentially expressed on sensory neurons, dorsal root ganglion
- Pro-excitatory changes in channel physiology -> hyperexcitability
- Neuropathic (often beginning in the distal extremities and with a burning quality) + autonomic dysfunction (e.g. orthostatic dizziness, palpitations, dry eyes and mouth)
- AFT: abnormal quantitative sensory testing
- Skin Biopsy: reduction in intraepidermal nerve fiber density.
- Large fiber functions (i.e. normal strength, tendon reflexes, and vibration sense) and nerve conduction studies are typically normal.
- PRIMARY Erythromelalgia: bilateral presentation of skin redness and burning pain distally on extremities, triggered by warmth and relieved by cooling.
- Inherited 'paroxysmal extreme pain disorder' or PEPD: aka familial rectal pain (can be seen in Infants): Paroxysms of excruciating deep burning pain often in the rectal, ocular, or jaw areas, but also diffuse..
- Autonomic manifestations predominate initially, with skin flushing in all and harlequin color change and tonic attacks (misdiagnosed as epilepsy). Dramatic syncope, with bradycardia, asystole. Attacks are triggered by factors such as defecation, cold wind, eating, and emotion.



Immune Mediated Autonomic Neuropathies:

Autonomic Disorders With Definite Autoimmune Etiology

- ◆ **Autoimmune autonomic ganglionopathy**
- ◆ **Paraneoplastic autonomic/enteric neuropathy**

Unclear Autoimmune Etiology

Immune-mediated sensory and autonomic neuropathies

Postural tachycardia syndrome

Autoimmune Disorders With Prominent Autonomic Features

Lambert-Eaton myasthenic syndrome

Guillain-Barré syndrome

N-methyl-D-aspartate (NMDA) receptor encephalitis

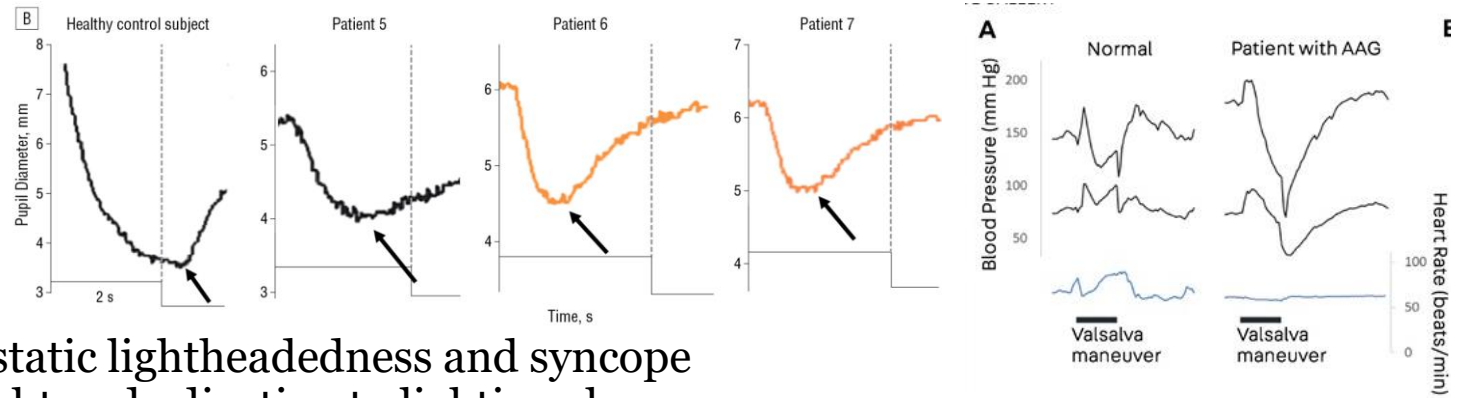
Leucine-rich glioma inactivated protein 1 (LGI1) and contactin-associated proteinlike 2 (CASPR2) antibody disorders (including Morvan syndrome)

Dipeptidyl-peptidase–like protein 6 (DPPX)–associated encephalitis

Sjögren syndrome, SLE, RA, Ankylosing Spondylitis, Sarcoid



Case 1



A 50-year-old woman presented with orthostatic lightheadedness and syncope
Dry mouth, dry eyes, difficulty driving at night and adjusting to lighting changes
Severe constipation

Urinary retention with overflow incontinence, chronic intermittent urinary catheterization was required.

On autonomic testing:

Heart rate variability to deep breathing and Valsalva: reduced

Adrenergic blood pressure response to Valsalva impaired with delayed pressure recovery time phase IV

Tilt-table testing, her supine blood pressure was 172/79 mm Hg with a heart rate of 68 beats/min. After 5 minutes of head-up tilt, her blood pressure fell to 90/59 mm Hg with a heart rate of 65 beats/min.

QSART: Reduced at all sites

Quantitative pupillometry reveals premature pupillary re-dilation to prolonged light stimulus (pupillary fatigue)

Diagram, Muppidi S et al. 2012

Composite Autonomic Severity Score (CASS) indicating moderate to severe impairment

Question: What antibody should be checked for in serum?

Serum ganglionic nicotinic acetylcholine (ACh) receptor antibodies



Autoimmune Autonomic Ganglionopathy

Autoantibodies specific for the ganglionic nicotinic ACh receptor the $\alpha 3$ subunit

Diffuse failure of sympathetic, parasympathetic, and enteric systems

Usually 5th-7th decade but can be seen in younger patients.

2:1 female: male Also, transient neonatal autoimmune autonomic ganglionopathy due to placental transfer of maternal antibodies can occur.

Occasionally, sensory, neuropsychiatric symptoms

EMG/NCS are typically normal. CSF analysis may reveal mildly elevated protein without pleocytosis. Sural nerve biopsy: nonspecific, +/- decreased numbers of small fibers

Antibody levels **greater than 1.0 nmol/L** are fairly specific for autoimmune autonomic ganglionopathy, correlates with severity of disease

< 0.2 nmol/L: non specific

0.2 nmol/L-1.0 nmol/L: Chronic slowly progressive AAG, isolated gastrointestinal dysmotility (10%), chronic intestinal pseudoobstruction (50%), PAF

Low levels of gAChR antibodies: autoimmune neurologic and rheumatologic diseases and malignancies, postural orthostatic tachycardia syndrome

Treatment:

IV immunoglobulin (IVIg) and plasma exchange
combination therapies with oral immunosuppressants

Rituximab, Mycophenolate mofetil



Isolated cholinergic neuropathy

+/-gAChR antibodies (low levels)

Idiopathic anhidrosis: Heat intolerance due to inadequate sweating, skin flushing, lightheadedness

Rash (cholinergic urticaria),

Compensatory hyperhidrosis of other areas (face, axillae, palms, and soles).

Treatment:

Steroids, particularly if administered early in the course.



Seronegative autonomic ganglionopathy and neuropathy

50% of idiopathic subacute autonomic failure

Response to immunotherapy has been reported in seronegative cases.

Guillain–Barré syndrome

Molecular mimicry between epitopes on the infectious agent (eg *Campylobacter jejuni*) and neuronal gangliosides

Autonomic dysfunction : 2/3 of cases, even with mild motor symptoms.

More common in acute inflammatory demyelinating polyradiculoneuropathy (AIDP) than in the motor axonal (AMAN) or Miller Fisher variants

Cardiovascular manifestations: sinus tachycardia, and also hypertension (posterior reversible encephalopathy syndrome), bradyarrhythmias, which can be life-threatening

Gastrointestinal dysfunction: paralytic ileus, diarrhea, urinary retention

Abnormal sweat responses, Horner syndrome

Treatment: Immunotherapy (either PE: caution in patients with cardiovascular instability, or IVIG)

Careful monitoring and meticulous supportive care for respiratory and autonomic deterioration (HR, BP).

Intensive care is indicated for those with hemodynamic instability and severely debilitated patients.

Immune Mediated Autonomic and Sensory Neuropathy

Acute onset, often with an antecedent upper respiratory infection.

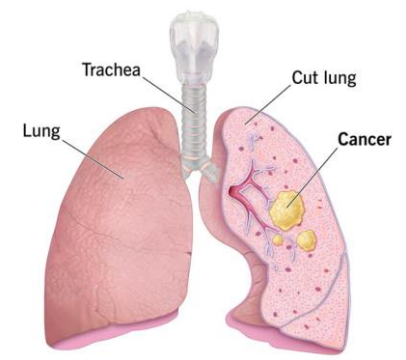
Sensory symptoms, including neuropathic pain, sensory ataxia

Objective evidence of small or large fiber sensory involvement.

Treatment: High-dose IV steroids, even when antibody-targeted therapies (IVIg, plasma exchange, rituximab) were ineffective.



PARANEOPLASTIC AUTONOMIC OR ENTERIC NEUROPATHY



In context of systemic malignancy

Onset of paraneoplastic neurologic syndromes usually precedes the diagnosis of malignancies, or early stage

Limbic encephalitis, cerebral ataxia, or sensory neuronopathy

The most common antibodies associated with paraneoplastic autonomic neuropathy are.

Anti-Hu : small cell lung carcinoma (SCLC)

Anti-CRMP5 : SCLC or thymoma.

gAChR: Paraneoplastic disease due to gAChR antibodies (lung cancer, thymoma) is clinically indistinguishable

Anti-Hu and anti-CRMP5 are both directed against intracellular antigens Neuronal injury: cell-mediated ; irreversible.

Eradicate the malignancy, + agents that target cellular autoimmunity.



Lambert–Eaton myasthenic syndrome

Motor symptoms (proximal **leg weakness**, areflexia, mild oculobulbar weakness)

Cholinergic autonomic impairment (Dry mouth, erectile dysfunction, and constipation.)

Pathophysiology of LEMS: **decreased presynaptic acetylcholine release due to antibodies against the P/Q voltage-gated calcium channel**

The diagnosis of LEMS : search for underlying SCLC or other malignancy.

Responds well both to treatment of the underlying cancer and to immunotherapy (IVIG, PE, oral immunosuppression, or rituximab)



Autonomic neuropathic dysfunction associated with central neurological disorders

Autonomic manifestations seen with antibodies to the **voltage-gated potassium channel complex: contactin-associated proteinlike 2 (CASPR2) and leucine-rich glioma inactivated protein 1 (LGI1)**. Morvan syndrome, autonomic manifestations + neuromyotonia and neuropsychiatric features.

Anti-NMDA receptor encephalitis: autonomic instability in 69% of patients
Cardiac dysrhythmia, temperature, blood pressure fluctuations, hyperhidrosis, and sialorrhea
Sympathetic dysfunction, patients with impaired cardiac autonomic function may have poorer outcomes

Dipeptidyl peptidase-like protein-6 (DPPX) abs: syndrome of encephalopathy, central hyperexcitability, and autonomic manifestations involving GI(diarrhea and weight loss).
Serum from an anti-DPPX patient was shown to cause hyperexcitability of enteric neurons.

IgLON5 antibodies : sleep disorders, bulbar symptoms, gait problems, movement disorders, dysautonomia

Cardiac autonomic dysfunction and autonomic symptoms have also been reported in patients with neuromyelitis optica spectrum disorders (NMOSD), MS.



NEUROPATHIC SUB-TYPE POSTURAL TACHYCARDIA SYNDROME POTS

>30 bpm in heart rate on standing associated with symptoms of lightheadedness.

The clinical syndrome of POTS is likely heterogeneous.: Brain fog, sensory symptoms, GI symptoms
Parasympathetic dysfunction and sudomotor function, symptoms that suggest GI/GU dysfunction
?autoimmunity or chronic inflammation may contribute to the pathophysiology

young women : demographic seen in many systemic autoimmune diseases.

Personal or family history of autoimmunity +/-

Subset of patients with POTS: Chronic inflammatory, autoimmune conditions = persistent activation of the sympathetic nervous system; small fiber neuropathy

+A variety of autoantibodies have been reported in association with POTS (antinuclear, antiphospholipid, and Sjögren antibodies).

Autoantibodies against autonomic nervous system : α -adrenergic and β -adrenergic receptors, angiotensin II type 1 receptors, (in low titers) ganglionic nicotinic ACh receptors

Acute or subacute onset after an immunologic stimulus (infection or physical stressor)

 Immunomodulatory therapy is not indicated for POTS at this time.

Sjögren syndrome and other rheumatologic diseases

Sicca symptoms, lymphocytic infiltration of exocrine glands.

Peripheral nervous system involvement : sensory ganglionopathy and small-fiber neuropathy
50%autonomic dysfunction: decreased cardiovagal function, impaired sympathetic vasomotor activity, and tachycardic response to head-up tilt.

Autonomic features may precede the diagnosis of SS.

The pathophysiology of autonomic dysfunction in SS: immune-mediated small fiber neuropathy affecting autonomic nerves.

Systemic lupus erythematosus: parasympathetic dysfunction

Rheumatoid arthritis: increased sympathetic nerve activity, reduced cardiac baroreflex sensitivity

Improvement in markers of autonomic function after the initiation of synthetic or biologic disease-modifying antirheumatic drugs.

Sarcoid, Scleroderma and psoriatic arthritis, AS



CHRONIC: DIABETIC AUTONOMIC NEUROPATHY

Most common cause of somatic and autonomic neuropathy
The pathogenesis is complex, multifactorial

- generalized diabetic autonomic neuropathy:
- autonomic neuropathy associated with the prediabetic state
- treatment-induced neuropathy
- hypoglycemia-associated autonomic failure

Generalized Diabetic Autonomic Neuropathy

GRADUALLY PROGRESSIVE

Cardiovascular, gastrointestinal, urogenital, sudomotor, and pupillomotor function

Diabetic cardiovascular autonomic neuropathy : associated morbidity and mortality of diabetes mellitus.

Parasympathetic HRV abnormalities:

Increase in the patient's resting heart rate due to loss of vagal innervation

loss of heart rate modulation, resulting in a fixed heart rate

Arrhythmias due to sympathovagal imbalance, prolonged QT, and silent myocardial infarction.

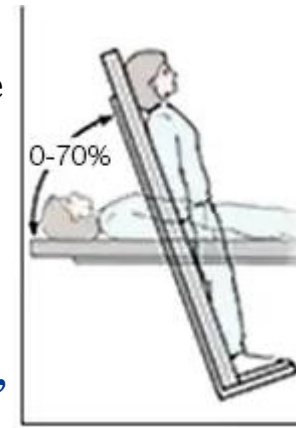
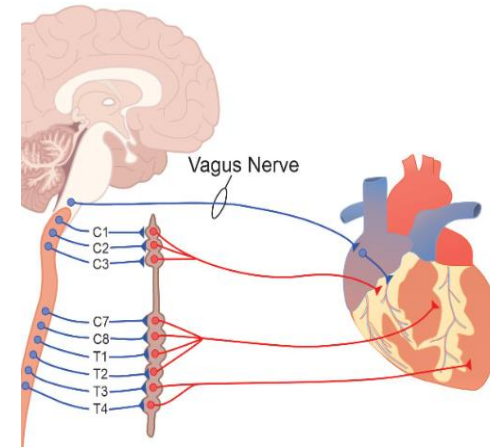
NEUROGENIC ORTHOSTATIC HYPOTENSION

Impaired vasoconstriction in dependent areas in response to orthostasis/postural change: due to

sympathetic vasomotor denervation resulting in blood pooling in the splanchnic and peripheral vascular beds

loss of heart rate modulation.

Proportional to **disease duration, patient age, poor glycemic control, presence of microvascular complications, metabolic syndrome components: hyperlipidemia, and hypertension**



	BP	HR
Supine	165/79 mm Hg	65 bpm
Tilt	90/60 mm Hg	63 bpm

Image References:

PMID: 33776789

<https://endocrinology.medicinetoday.com.au/et/2016/february/regular-series/diabetic-autonomic-neuropathy-of-neglected-entity>

<https://www.mayoclinic.org/departments-centers/childrens-center/overview/specialty-groups/general-pediatric-adolescent-medicine/autonomic-dysfunction-clinic>



GI dysfunction: extrinsic innervation and the intrinsic enteric nervous system

Altered sensory perception: Increase in blood glucose concentration->may slow gastric emptying

Esophageal symptoms: Reflux, regurgitation, and dysphagia; Incidence of Barrett esophagus in DM

Diabetic gastroparesis: 50%, Food may remain in the stomach for many hours or even days.

Impaired gastric accommodation, visceral hypersensitivity, and gastric dysrhythmia

Implications for glycemic control : challenging to match insulin requirements with the slow, unpredictable food absorption.

Aggravates OH: blood pooling in the splanchnic and mesenteric bed

Constipation: Worsened by gastroparesis with loss of gastrocolic reflex.

Diarrhea, Fecal incontinence due to anal sphincter incompetence or reduced rectal sensation,

Small intestinal bacterial overgrowth, a consequence of slow intestinal transit

GU: Neurogenic bladder: Reduced sensation-> increased volume and pressure required to trigger the micturition reflex, → Reduced detrusor activity → weak flow, incomplete emptying, atonic bladder with overdistention/overflow incontinence.

Voiding dysfunction: frequency, nocturia, urinary retention, and incontinence.

Afferent and efferent autonomic nerve dysfunction, bladder smooth muscle urothelial dysfunction

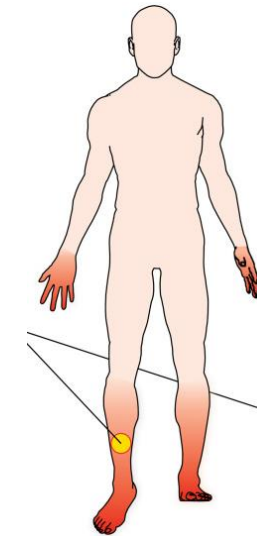
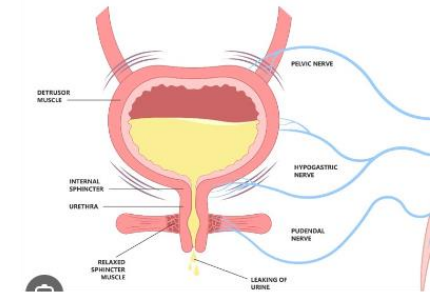
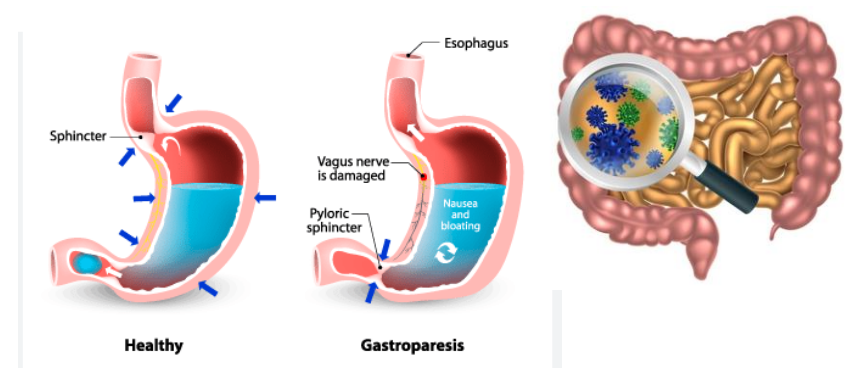
Erectile failure: retrograde ejaculation due to impaired bladder neck closure during ejaculation.

Autonomic neuropathy, vascular insufficiency with reduced nitric oxide production from the endothelium

Women: impaired lubrication

Sudomotor dysfunction: impaired sweating in a stocking-glove distribution, Sudomotor function is progressively lost: Compensatory hyperhidrosis in cranial and truncal regions.

Abnormal sweating (such as gustatory sweating) due to Receptor supersensitivity, aberrant regenerating nerve fibers



Case

A 32-year-old woman with type 1 diabetes mellitus presents with a 2-week history of orthostatic lightheadedness, diarrhea, and severe distal pain in her arms and legs.

On examination, she had a resting tachycardia with orthostatic hypotension and postural tachycardia. Sensory examination revealed impaired pain and temperature sensation to her knees with hyperalgesia and allodynia.

Her hemoglobin A1c was 6.5%. Ten weeks previously, her hemoglobin A1c was 17%.
What is the likely diagnosis?

Subacute onset of a painful sensory and autonomic neuropathy in association with a rapid decrease in hemoglobin A1c causes treatment-induced neuropathy of diabetes mellitus.



AMYLOID NEUROPATHY

Insoluble, low-molecular-weight fibrillar proteins in a beta-pleated sheet configuration
Amyloid fibrils are rigid, linear, and nonbranching, measuring ~ 7.5 nm to 10 nm in width.

The structure of the beta-pleated sheet permits Congo red stain binding-> apple-green birefringence.

- 1) Primary immunoglobulin light chain (AL) amyloidosis
- 2) Hereditary transthyretin amyloidosis with neuropathy (also known as familial amyloid polyneuropathy)

Primary (AL) Amyloidosis:

Pathogenesis: monoclonal population of bone marrow plasma cells produce kappa or lambda type immunoglobulin light chains or light chain fragments

AL amyloidosis may be preceded by an increase in serum levels of free light chains.

May start as Weight loss and fatigue, -> hepatomegaly, cutaneous ecchymoses, nonischemic cardiomyopathy with hypertrophy, nephrotic-range proteinuria

Autonomic involvement of the cardiovascular, gastrointestinal, and urogenital systems Autonomic dysfunction + pain and a length-dependent generalized polyneuropathy.

Serological diagnosis: **immunofixation electrophoresis of serum and urine and serum free light chain assay.**

If normal, AL amyloidosis is unlikely.

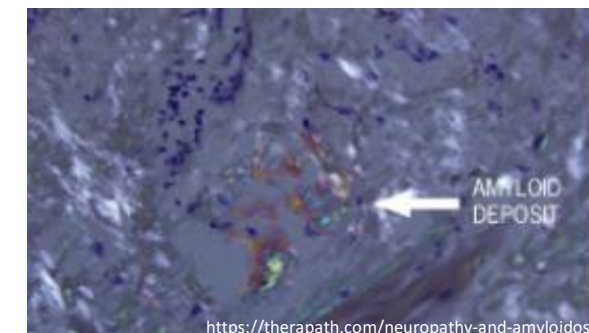
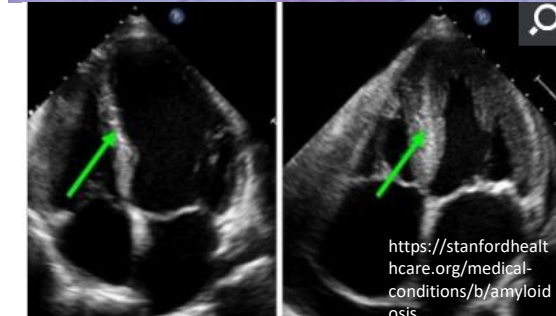
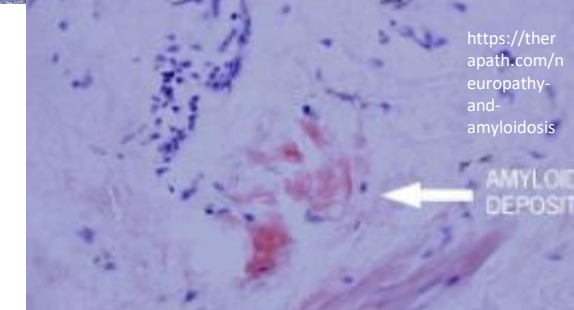
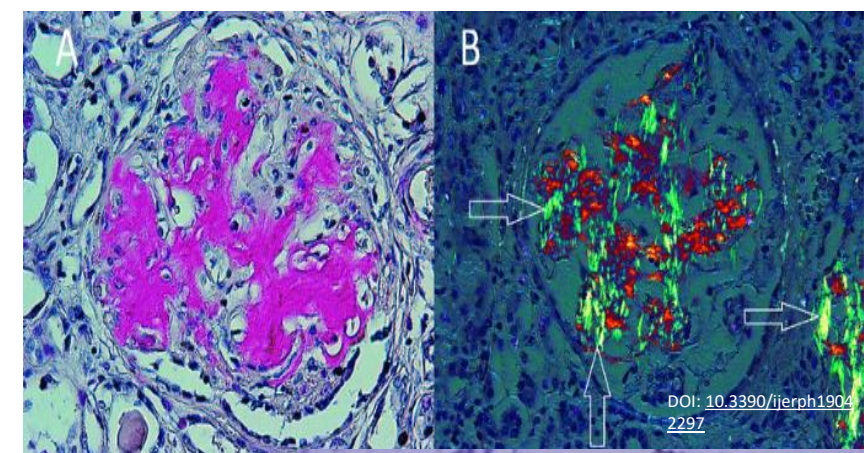
If positive, the diagnosis should **be confirmed pathologically by bone marrow, fat aspirate, or lip biopsy.**

Treatment: melphalan and corticosteroids (dexamethasone or prednisolone).

This treatment improves survival, particularly reduction in serum or urine monoclonal protein.

Stem cell transplantation (not suitable for all patients)

Immunomodulating drugs: thalidomide, and lenalidomide; the proteasome inhibitor bortezomib + alkylating agents such as melphalan and cyclophosphamide



Hereditary Transthyretin Amyloidosis

Progressive, debilitating, multisystem, life-threatening disease, 3rd-5th decade
Deposition of misfolded transthyretin in tissues

Autosomal dominant inherited disease
amyloid precursor is a mutant protein. >120 mutations of the TTR gene

Mutant transthyretin is a 14-kDa 127 amino acid : transport protein for thyroxine and retinol-binding protein
Most commonly observed mutation is a substitution of methionine for valine at position 30 (Val30Met).
Less frequent mutations in the genes encoding for apolipoprotein A-I, fibrinogen A α , lysozyme, and gelsolin

Portugal, Brazil, and Sweden.

Other TTR variants are seen in Japan, Europe, and the Americas

Phenotypic differences exist, even among individuals carrying the same mutation. These differences depend in part on geographic location

Autonomic manifestations are prominent and may be the presenting feature

Orthostatic intolerance; GI/GU

Sensory symptoms such as numbness, pain, paresthesia, dysesthesia

Diagnosis of pathogenic mutation : **TTR gene sequencing.**

Pathologic confirmation requires histologic confirmation of amyloid deposition (eg: skin biopsy amyloid deposition)

Mass spectrometry–based proteomics: Diagnosis and typing of AL and hereditary amyloidosis (high specificity but limited sensitivity)

Magnetic resonance neurography and diffusion tensor imaging: non-invasively identify early subclinical microstructural changes in pre-symptomatic carrier

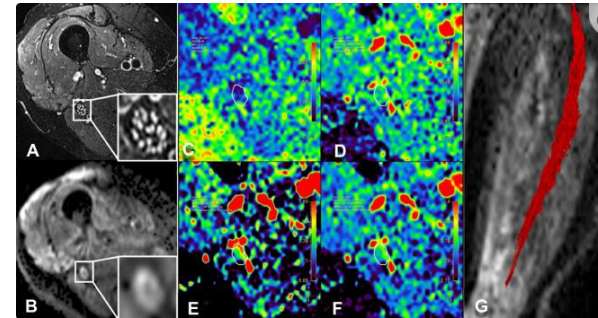
TREATMENT: Liver transplant: removes principal source of variant transthyretin and reduces circulating transthyretin by up to 90%,

Pharmacotherapeutic interventions that inhibit amyloidogenesis:

FDA – approved: Patisiran, a small interfering RNA delivered as an IV infusion every 3 weeks

FDA –approved: Inotersen, an antisense oligonucleotide administered subcutaneously 3 times a week on alternate days in the first week and then once weekly for 64 weeks

Other pharmacologic interventions include the mutant transthyretin stabilizers tafamidis, diflunisal



Colombat M, et al. PMID: 35924579



TOXIC AUTONOMIC NEUROPATHIES

CHRONIC

ALCOHOL INDUCED AUTONOMIC NEUROPATHY

Axonal sensorimotor neuropathy + sudomotor dysfunction
Cardiovascular autonomic dysfunction, Visceral autonomic neuropathy: a/w higher TLDE (Total Daily Alcohol Consumption x 365 x no. of years)

Malnutrition is not required for the presence of autonomic dysfunction (autonomic dysfunction can occur in absence of B₁₂ deficiency)

Abstinence:, positive impact, though the evidence base is weak.

Effect of abstinence on respiratory sinus arrhythmia (12 weeks follow-up), HRV as early as 1-6 weeks → 6-24 months, sweating after 12 months

CYTOTOXIC AGENTS/CHEMOTHERAPY:

vincristine, which can induce vagal neuropathy (resulting in significant gastrointestinal dysmotility), bladder dysfunction, and orthostatic hypotension.

vinca alkaloids; platinum derivatives; taxanes; proteasome inhibitors such as bortezomib;

immunomodulatory agents such as thalidomide,

lenalidomide, and pomalidomide; the epothilones;

doxorubicin; and cytosine arabinoside

ACUTE/SUBACUTE

ENVIRONMENTAL TOXINS, INDUSTRIAL TOXINS:

Marine toxins: affect ion transport (sodium and calcium)

Ciguatoxins are potent sodium channel-activating toxins; paresthesia, dysesthesia, and pain + Autonomic features include hypersalivation, bradycardia, hypotension, and mydriasis. IV mannitol may reverse the acute manifestations.

Jellyfish -> massive catecholamine release -> Irukandji syndrome (Headache, muscle pain, tachycardia, hypertension, N/V, Diaphoresis abdominal pain, pulmonary edema)

Box jellyfish venom: vasospasm, arrhythmias, and parasympathetic failure. Treatment with verapamil can be lifesaving.

Organic solvents, arsenic, mercury, thallium, and other heavy metals, acrylamide, rat poison



INFECTIOUS AUTONOMIC NEUROPATHIES

RETROVIRAL INFECTIONS:

Human immunodeficiency virus (HIV) (Heart rate variability is reduced even in early stages of infection)

Human T-lymphotropic virus (Orthostatic hypotension, urinary dysfunction and hypohidrosis)

Herpes viruses, flavivirus, enterovirus and lyssavirus infections.

Varicella zoster reactivation from autonomic ganglia: visceral disease and chronic intestinal pseudo-obstruction.

Tick-borne encephalitis virus infections (Urinary retention and intestinal pseudo-obstruction)

Rabies: Hydrophobia, hypersalivation, dyspnea, photophobia, and piloerection:

Chagas Disease: Autonomic dysfunction from vagal denervation (parasympathetic), neuronal depopulation in chagasic heart disease and myenteric plexus, megacolon, megaesophagus and cardiomyopathy.

Leprosy: Subclinical autonomic neuropathy (anhidrosis, impaired sweating function, localised alopecia ,and reduced HRV)

Diphtheritic polyneuropathy, tetanus and botulism: Toxins affect the autonomic nervous system.



General Treatment of Autonomic Manifestations:

Orthostatic hypotension

Non Pharmacological Interventions: Fluids, Salt/electrolytes, Compression Stockings, Abdominal Binders

Pharmacological Interventions: Mineralocorticoid (fludrocortisone), midodrine, α -1-adrenoreceptor agonist

Orthostatic intolerance with postural tachycardia

Propranolol, ivabradine

Pyridostigmine

Gastrointestinal autonomic dysfunction

control of blood glucose concentrations: improves gastric motility.

Small portions, frequent meals, protein better

Gastroparesis: metoclopramide, domperidone, erythromycin

Constipation: fiber, fluids, stool softeners, osmotic laxative.

Genital autonomic neuropathy:

Bladder diary, voiding schedules

Self-Catheterisation

Cholinergic agents: bethanechol

ED: Phosphodiesterase type 5 inhibitors: inhibit breakdown of cyclic GMP, increases smooth-muscle relaxation and blood flow; eg:

Sildenafil, tadalafil. Intracorporeal injection of vasoactive substances, devices, implants.

Vaginal lubricants for women

Sweating abnormalities:

Hyperhidrosis:

Anticholinergic agents such as trihexyphenidyl, glycopyrrolate

Intracutaneous injection of botulinum toxin type A, Sympathectomy



Hypohidrosis:

Cooling agents, avoidance of heat

Summary/Key Take-Away Points

Among the Hereditary Sensory Autonomic Neuropathies:

Riley Day syndrome/familial dysautonomia is with prominent autonomic manifestations

Fabry's disease must be considered in young adults presenting with sensory and autonomic neuropathy + cerebrovascular + myocardial manifestations+ renal dysfunction + skin findings. Enzyme Replacement is key

Sodium channelopathies are associated with small fiber neuropathy, extreme pain and erythromelalgia, and respond to sodium channel blocking agents

Among the immune mediated autonomic neuropathies:

Autoimmune autonomic ganglionopathy presents as a subacute/acute pandysautonomia and have antibodies against ganglionic nicotinic ACh receptor ($\alpha 3$ subunit) typically greater than 1.0 nmol/L and respond to immunomodulatory/immunosuppressant therapy

Paraneoplastic autonomic neuropathies typically seen with anti-Hu, anti-CRMP5 antibodies

Systemic autoimmune disorders namely Sjogrens, SLE, RA and others are associated with autonomic (small fiber neuropathy)

Among the chronic autonomic neuropathies:

Diabetic autonomic neuropathy can be general, a/w prediabetic, and treatment-induced DAN. Cardiac autonomic neuropathy is frequent cause of morbidity/mortality in DAN

Amyloid neuropathies can be primary or hereditary, with multisystem manifestations. In primary amyloid neuropathy, screening includes SPEP with IF; In hereditary amyloid neuropathy : genetic testing, followed by pathological confirmation in both

Toxic autonomic neuropathies can be caused from alcohol, chemotherapeutic agents and environmental and marine toxins.

Remember glycemic control, control of metabolic syndrome risk factors and alcohol abstinence play a significant role in autonomic neuropathy (halting progression and /or improvement)

Infectious autonomic neuropathies can be seen in a variety of retroviral diseases, lyme disease, Chagas disease, and others



REFERENCES

Vernino S. Autoimmune Autonomic Disorders. *Continuum* (Minneap Minn). 2020 Feb;26(1):44-57.

Freeman R. Autonomic Peripheral Neuropathy. *Continuum* (Minneap Minn). 2020 Feb;26(1):58-71.

•Young RR, Asbury AK, Corbett JL, Adams RD. Pure pan-dysautonomia with recovery. *Brain* 1975;98(4):613–636.

•Suarez GA, Fealey RD, Camilleri M, Low PA. Idiopathic autonomic neuropathy: clinical, neurophysiologic, and follow-up studies on 27 patients. *Neurology* 1994;44(9):1675–1682.

• Vernino S, Low PA, Fealey RD, et al. Autoantibodies to ganglionic acetylcholine receptors in autoimmune autonomic neuropathies. *N Engl J Med* 2000;343(12):847–855

Baker SK, Chow BM, Vernino SA. Transient neonatal autoimmune autonomic ganglionopathy. *Neural Neuroimmunol Neuroinflamm* 2014;1(3):e35.

•Klein CM, Vernino S, Lennon VA, et al. The spectrum of autoimmune autonomic neuropathies. *Ann Neurol* 2003;53(6):752–758. Gibbons CH, Freeman R. Antibody titers predict clinical features of autoimmune autonomic ganglionopathy. *Auton Neurosci* 2009;146(1–2):8–12

•Cutsforth-Gregory JK, McKeon A, Coon EA, et al. Ganglionic antibody level as a predictor of severity of autonomic failure. *Mayo Clin Proc* 2018;93(10):1440–1447.

•McKeon A, Lennon VA, Lachance DH, et al. Ganglionic acetylcholine receptor autoantibody: oncological, neurological, and serological accompaniments. *Arch Neurol* 2009;66(6):735–741.

•Li Y, Jammoul A, Mente K, et al. Clinical experience of seropositive ganglionic acetylcholine receptor antibody in a tertiary neurology referral center. *Muscle Nerve* 2015;52(3):386–391

•Kimpinski K, Iodice V, Sandroni P, et al. Sudomotor dysfunction in autoimmune autonomic ganglionopathy. *Neurology* 2009;73(18):1501–1506.

•Schroeder C, Vernino S, Birkenfeld AL, et al. Plasma exchange for primary autoimmune autonomic failure. *N Engl J Med* 2005;353(15):1585–1590.

•Muppidi S, Scribner M, Gibbons CH, et al. A unique manifestation of pupillary fatigue in autoimmune autonomic ganglionopathy. *Arch Neurol* 2012;69(5):644–648.

Iodice V, Kimpinski K, Vernino S, et al. Efficacy of immunotherapy in seropositive and seronegative putative autoimmune autonomic ganglionopathy. *Neurology* 2009;72(23):2002–2008

Imrich R, Vernino S, Eldadah BA, et al. Autoimmune autonomic ganglionopathy: treatment by plasma exchanges and rituximab. *Clin Auton Res* 2009;19(4):259–262.

•Koike H, Watanabe H, Sobue G. The spectrum of immune-mediated autonomic neuropathies: insights from the clinicopathological features. *J Neurol Neurosurg Psychiatry* 2013;84(1):98–106. Golden EP, Bryarly MA, Vernino S. Seronegative autoimmune autonomic neuropathy: a distinct clinical entity. *Clin Auton Res* 2018;28:115–123.

•Colan RV, Snead OC 3rd, Oh SJ, Kashlan MB. Acute autonomic and sensory neuropathy. *Ann Neurol* 1980;8(4):441–444

•Koike H, Atsuta N, Adachi H, et al. Clinicopathological features of acute autonomic and sensory neuropathy. *Brain* 2010;133(10):2881–2896.

•Lucchinetti CF, Camilleri M, Lennon VA. Gastrointestinal dysmotility spectrum in patients seropositive for paraneoplastic type 1 anti-neuronal nuclear autoantibodies. *Clin Auton Res* 1994;4:206.

•Rauer S, Andreou I. Tumor progression and serum anti-HuD antibody concentration in patients with paraneoplastic neurological syndromes. *Eur Neurol* 2002;47(4):189–195.

•Wirtz PW, Lang B, Graus F, et al. P/Q-type calcium channel antibodies, Lambert-Eaton myasthenic syndrome and survival in small cell lung cancer. *J Neuroimmunol* 2005;164(1–2):161–165.

O’Suilleabhain P, Low PA, Lennon VA. Autonomic dysfunction in the Lambert–Eaton myasthenic syndrome: serologic and clinical correlates. *Neurology* 1998;50(1):88–93.

Zaeem Z, Siddiqi ZA, Zochodne DW. Autonomic involvement in Guillain–Barré syndrome: an update. *Clin Auton Res* 2018.

•Josephs KA, Silber MH, Fealey RD, et al. Neurophysiologic studies in Morvan syndrome. *J Clin Neurophysiol* 2004;21(6):440–445.

•Salehi N, Yuan AK, Stevens G, et al. A case of severe anti-N-methyl D-aspartate (anti-NMDA) receptor encephalitis with refractory autonomic instability and elevated intracranial pressure. *Am J Case Rep* 2018;19:1216–1221

• Boronat A, Gelfand JM, Gresó-Arribas N, et al. Encephalitis and antibodies to dipetidyl-peptidase-like protein-6, a subunit of Kv4.2 potassium channels. *Ann Neurol* 2013;73(1):120–128.

•Goodman BP, Crepeau A, Dhawan PS, et al. Spectrum of autonomic nervous system impairment in Sjögren syndrome. *Neurologist* 2017;22(4):127–130

•Goodman BP. Immunoresponsive autonomic neuropathy in Sjögren syndrome—case series and literature review. *Am J Ther* 2019;26:e66–e71.

• Matusik PS, Matusik PT, Stein PK. Heart rate variability in patients with systemic lupus erythematosus: a systematic review and methodological considerations. *Lupus* 2018;27(8):1225–1239.

•Adlan AM, Paton JF, Lip GY, et al. Increased sympathetic nerve activity and reduced cardiac baroreflex sensitivity in rheumatoid arthritis. *J Physiol* 2017;595(3):967–981.

•Adlan AM, Lip GY, Paton JF, et al. Autonomic function and rheumatoid arthritis: a systematic review. *Semin Arthritis Rheum* 2014;44(3):283–304.

•Amaral TN, Peres FA, Lapa AT, et al. Neurologic involvement in scleroderma: a systematic review. *Semin Arthritis Rheum* 2013;43(3):335–347.

•Synge A, Verma I, Garg N, Krishan P. Autonomic dysfunction in psoriatic arthritis. *Clin Rheumatol* 2013;32(7):1059–1064

•Vernino S, Stiles LE. Autoimmunity in postural orthostatic tachycardia syndrome: Current understanding. *Auton Neurosci* 2018;215:78–82. Thieben MJ, Sandroni P, Sletten DM, et al. Postural orthostatic tachycardia syndrome: the Mayo clinic experience. *Mayo Clin Proc* 2007;82(3):308–313

• Shaw BH, Stiles LE, Bourne K, et al. The face of postural tachycardia syndrome: a cross-sectional community-based survey. *Heart Rhythm* 2016;13:S32867.

•Blitshteyn S. Autoimmune markers and autoimmune disorders in patients with postural tachycardia syndrome (POTS). *Lupus* 2015;24(13):1364–1369.

•Freeman R, Chapleau MW. Testing the autonomic nervous system. *Handb Clin Neurol* 2013;115:115–136

Cheshire WP Jr. Autonomic history, examination, and laboratory evaluation. *Continuum* (Minneap Minn) 2020;26(1, Autonomic Disorders):25–43.

•Neil HA, Thompson AV, John S, et al. Diabetic autonomic neuropathy: the prevalence of impaired heart rate variability in a geographically defined population. *Diabet Med* 1989;6(1):20–24.

• Töyrä JP, Niskanen LK, Mäntyselkä MJ, et al. Occurrence, predictors, and clinical significance of autonomic neuropathy in NIDDM. Ten-year follow-up from the diagnosis. *Diabetes* 1996;45(3):308–315.

• Zoppini G, Cacciatori V, Raimondo D, et al. Prevalence of cardiovascular autonomic neuropathy in a cohort of patients with newly diagnosed type 2 diabetes: the Verona newly diagnosed type 2 diabetes study (VNDS). *Diabetes Care* 2015;38(8):1487–1493.

•Smith AG. Impaired glucose tolerance and metabolic syndrome in idiopathic neuropathy. *J Peripher Nerv Syst* 2012;17(Suppl 2):15–21.

•Gibbons CH, Freeman R. Treatment-induced neuropathy of diabetes: an acute, iatrogenic complication of diabetes. *Brain* 2015;138(1):43–52.

•Rao AD, Bonyhay I, Dankwa J, et al. Baroreflex sensitivity impairment during hypoglycemia: implications for cardiovascular control. *Diabetes* 2016;65(1):209–215.

•Adler GK, Bandyopadhyay I, Failing H, et al. Antecedent hyperglycemia impairs autonomic cardiovascular function: implications for rigorous glycemic control. *Diabetes* 2009;58(2):360–366.

•Brooks RP, et al. Triple-A syndrome with prominent ophthalmic features and a novel mutation in the AAAS gene: a case report. *BMC Ophthalmol*. 2004 Jun 24;4:7.

•Mathis S, Magy L, Dialla L, et al. Amyloid neuropathy mimicking multifocal demyelinating polyneuropathy. *Muscle Nerve* 2012;45(1):26–31.

•Planté-Bordeneuve V, Ferreira A, Lulu T, et al. Diagnostic pitfalls in sporadic transthyretin familial amyloid polyneuropathy (TTR-FAP). *Neurology* 2007;69(7):693–698.

•Conceição I, Gonzalez-Duarte A, Obici L, et al. “Red-flag” symptom clusters in transthyretin familial amyloid polyneuropathy. *J Peripher Nerv Syst* 2016;21(1):5–9.

•Gertz MA. Immunoglobulin light chain amyloidosis: 2018 update on diagnosis, prognosis, and treatment. *Am J Hematol* 2018;93(9):1169–1180.

•Falk RH, Skinner M. The systemic amyloidoses: an overview. *Adv Intern Med* 2000;45:107–137

• Cohen AD, Comenzo RL. Systemic light-chain amyloidosis: advances in diagnosis, prognosis, and therapy. *Hematology Am Soc Hematol Educ Program* 2010;2010:287–294.

•Wang AK, Fealey RD, Gehring TJ, Low PA. Patterns of neuropathy and autonomic failure in patients with amyloidosis. *Mayo Clin Proc* 2008;83(11):1226–1230.

•Kumar SK, Gertz MA, Lacy MQ, et al. Recent improvements in survival in primary systemic amyloidosis and the importance of an early mortality risk score. *Mayo Clin Proc* 2011;86(1):12–18.

•Mittlerung NC, Boogerd W. Chemotherapy-induced neuropathy: a comprehensive survey. *Cancer Treat Rev* 2014;40(7):872–882

• Ando Y, Nakamura M, Araki S. Transthyretin-related familial amyloidotic polyneuropathy. *Arch Neurol* 2005;62(7):1057–1062.

•Benson MD, Kincaid JC. The molecular biology and clinical features of amyloid neuropathy. *Muscle Nerve* 2007;36(4):411–423.

•Saraiva MJM, Costa PP, Goodman DS. Biochemical marker in familial amyloidotic polyneuropathy, Portuguese type. Family studies of transthyretin (prealbumin)-methionine-30 variant. *J Clin Invest* 1985;76(6):2171–2177.

1. Hund E, Linke RP, Willig F, Grau A. Transthyretin-associated neuropathic amyloidosis. Pathogenesis and treatment. *Neurology* 2001;56(4):431–435.

•Planté-Bordeneuve V, Said G. Familial amyloid polyneuropathy. *Lancet Neurol* 2011;10(12):1086–1097.

• Koike H, Tanaka F, Hashimoto R, et al. Natural history of transthyretin Val30Met familial amyloid polyneuropathy: analysis of late-onset cases from non-endemic areas. *J Neurol Neurosurg Psychiatry* 2012;83(2):152–158.

•Mitsu K, Hattori N, Nagamatsu M, et al. Late-onset familial amyloid polyneuropathy type I (transthyretin Met30-associated familial amyloid polyneuropathy) unrelated to endemic focus in Japan. *Clinicopathological and genetic features*. *Brain* 1999;122(pt 10):1951–1962.

•Ebenzer GJ, Liu Y, Judge DP, et al. Cutaneous nerve biomarkers in transthyretin familial amyloid polyneuropathy. *Ann Neurol* 2017;82(1):44–56.

•Vrana JA, This JD, Dasari S, et al. Clinical diagnosis and typing of systemic amyloidosis in subcutaneous fat aspirates by mass spectrometry-based proteomics. *Haematologica* 2014;99(7):1239–1247.

•Kollmer J, Hund E, Homung B, et al. In vivo detection of nerve injury in familial amyloid polyneuropathy by magnetic resonance neurography. *Brain* 2015;138(pt 3):549–562.

•Yamamoto S, Wilczek HE, Nowak G, et al. Liver transplantation for familial amyloidotic polyneuropathy (FAP): a single-center experience over 16 years. *Am J Trans* 2007;7(11):2597–2604

• Adams D, Gonzalez-Duarte A, Cruz HD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med* 2018;379:11–21

• Benson MD, Waddington-O’Riordan M, Berk JL, et al. Intersens treatment for patients with hereditary transthyretin amyloidosis. *N Engl J Med* 2018;379:22–31.

•Coelho F, Moia LF, Martins da Silva A, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. *Neurology* 2012;79(8):785–792.

•Berk JL, Suhr OB, Obici L, et al. Repurposing diflunisal for familial amyloid polyneuropathy: a randomized clinical trial. *JAMA* 2013;310(24):2658–2667.

•Faber CG, Hoeijmakers JG, AHN HS, et al. Gain of function Nav1.7 mutations in idiopathic small fiber neuropathy. *Ann Neurol* 2012;71(1):26–39

• Han C, Hoeijmakers JG, Liu S, et al. Functional profiles of SCN9A variants in dorsal root ganglion neurons and superior cervical ganglion neurons correlate with autonomic symptoms in small fiber neuropathy. *Brain* 2012;135(pt 9):2613–2628. Han C, Hoeijmakers JG, AHN HS, et al. Nav1.7-related small fiber neuropathy: impaired slow-inactivation and DRG neuron hyperexcitability. *Neurology* 2012;78(21):1635–1643.

•Huang J, Yang Y, Zhao P, et al. Small-fiber neuropathy Nav1.8 mutation shifts activation to hyperpolarized potentials and increases excitability of dorsal root ganglion neurons. *J Neurosci* 2013;33(35):14087–14097.

•Faber CG, Lauria G, Merkies IS, et al. Gain-of-function Nav1.8 mutations in painful neuropathy. *Proc Natl Acad Sci U S A* 2012;109(47):19444–19449

•Huang J, Han C, Estacion M, et al. Gain-of-function mutations in sodium channel Nav1.9 in painful neuropathy. *Brain* 2014;137(pt 6):1627–1642.

•Klein CJ, Lennon VA, Aston PA, et al. Chronic pain as a manifestation of potassium channel-complex autoimmunity. *Neurology* 2012;79(11):1136–1144.

•Ivan SR, Pettigill P, Kleopa KA, et al. Morvan syndrome: clinical and serological observations in 29 cases. *Ann Neurol* 2012;72(2):241–255

• Godtho A, Pittcock SJ, Dubey D, et al. Expanded phenotypes and outcomes among 256 LGI1/CASPR2-IgG-positive patients. *Ann Neurol* 2017;82(1):79–92.

•Rothier A, Baets J, Timmerman V, Janssens G. Mechanisms of disease in hereditary sensory and autonomic neuropathies. *Not Rev Neurol* 2012;8(2):73–85.

•Norcliffe-Kaufmann L, Slougenhaupt SA, Kaufmann H. Familial dysautonomia: History, genotype, phenotype and translational research. *Prog Neurobiol* 2017;152:131–148.

• Slougenhaupt SA, Blumenfeld A, Gill SP, et al. Tissue-specific expression of a splicing mutation in the IKBKAP gene causes familial dysautonomia. *Am J Hum Genet* 2001;68(3):598–605

•Naeije-Vig VG, Norcliffe-Kaufmann L, Gutierrez J, et al. Can loss of muscle spindle afferents explain the ataxic gait in Riley-Day syndrome? *Brain* 2011;134(pt 11):3198–3208.

•Norcliffe-Kaufmann L, Axelrod F, Kaufmann H. Afferent baroreflex failure in familial dysautonomia. *Neurology* 2010;75(21):1904–1911.

•Vindo Y. Nerve growth factor and the physiology of pain: lessons from congenital insensitivity to pain with anhidrosis. *Clin Genet* 2012;82(4):341–350.

•Rothier A, Baets J, Vriendt ED, et al. Genes for hereditary sensory and autonomic neuropathies: a genotype-phenotype correlation. *Brain* 2009;132(pt 10):2699–2711.

• Begstroten M, van Schaik IN, Wieling W, et al. Autonomic neuropathy in Fabry disease: a prospective study using the Autonomic Symptom Profile and cardiovascular autonomic function tests. *BMC Neurol* 2010;10:38

•Kimber J, McLean BN, Prevett M, Hammons SR. Allgrove or 4 “A” syndrome: an autosomal recessive syndrome causing multisystem neurological disease. *J Neurol Neurosurg Psychiatry* 2003;74(5):654–657. 95. Grisold A, Grisold W, Weinbank AJ, Staff NP. Chemotherapy-induced peripheral neuropathy: a current review. *Ann Neurol* 2017;81(6):772–781.

•Freeman R. Autonomic peripheral neuropathy. *Lancet* 2005;365(9466):1259–1270. Burnett JW, Weinrich D, Williamson JA, et al. Autonomic neurotoxicity of jellyfish and marine animal venoms. *Clin Auton Res* 1998;8(2):125–130.

•Corad-Artal FJ. Infectious diseases causing autonomic dysfunction. *Clin Auton Res*. 2018 Feb;28(1):67–81.

•Freeman R. Diabetic autonomic neuropathy. *Handb Clin Neurol* 2014;126:63–79

•Du YT, Royner CK, Jones KL, et al. Gastrointestinal symptoms in diabetes: prevalence, assessment, pathogenesis, and management. *Diabetes Care* 2018;41(3):627–637.

•Schwarz E, Palmer M, Aman J, et al. Physiological hyperglycemia slows gastric emptying in normal subjects and patients with insulin-dependent diabetes mellitus. *Gastroenterology* 1997;113(1):60–66.

•Thazhath SS, Jones KL, Horowitz M, Royner CK. Diabetic gastroparesis: recent insights into pathophysiology and implications for management. *Expert Rev Gastroenterol Hepatol* 2013;7(2):127–139.

•Maleki D, Locke GR 3rd, Camilleri M, et al. Gastrointestinal tract symptoms among persons with diabetes mellitus in the community. *Arch Intern Med* 2000;160(18):2808–2816.

•Kempster P, Amareno G, Freeman R, et al. Management strategies for gastrointestinal, erectile, bladder, and sudomotor dysfunction in patients with diabetes. *Diabetes Metab Res Rev* 2011;27(7):665–677.

•Frimodt-Moller C, Mortensen S. Treatment of diabetic cystopathy. *Ann Intern Med* 1980;92(2 pt 2):327–328.

•Yuan Z, Tang Z, He C, Tang W. Diabetic cystopathy: a review. *J Diabetes* 2015;7(4):442–447.

• Golbidi S, Lahder L. Bladder dysfunction in diabetes mellitus. *Front Pharmacol* 2010;1:136.

•Abojo AB, Hall SA, Ganz P, et al. Does erectile dysfunction contribute to cardiovascular disease risk prediction beyond the Framingham risk score? *J Am Coll Cardiol* 2010;55(4):350–356

• Enzlin P, Mathieu C, Van den Briel A, et al. Sexual dysfunction in women with type 1 diabetes: a controlled study. *Diabetes Care* 2002;25(4):672–677. |

•Fealey RD, Low PA, Thomas JE. Thermoregulatory sweating abnormalities in diabetes mellitus. *Mayo Clin Proc* 1989;64(6):617–628.

Blair DJ, Sogel J, Taylor I. Diabetic gustatory sweating. *South Med J* 2002;95(3):360–362.

Golebowski T, et al. Multisystem Amyloidosis in a Coal Miner with Silicosis: Is Exposure to Silica Dust a Cause of Amyloid Deposition? *Int J Environ Res Public Health*. 2022 Feb 17;19(4):2297. doi: 10.3390/ijerph19042297. PMID: 35206498; PMCID: PMC8871531.

Colombat M, et al. Mass spectrometry-based proteomics in clinical practice amyloid typing: state-of-the-art from a French nationwide cohort. *Haematologica*. 2022 Dec 1;107(12):2983-2987. doi: 10.3324/haematol.2022.281431. PMID: 35924579; PMCID: PMC9713554.

<https://therapath.com/neuropathy-and-amyloidosis>

<https://badgut.org/information-centre/a-z-digestive-topics/gastroparesis/>

https://www.cmuh.cmu.edu.tw/HealthEdu/Detail_EN

Terkelsen AJ, et al. The diagnostic challenge of small fibre neuropathy: clinical presentations, evaluations, and causes. *Lancet Neurol*. 2017 Nov;16(11):934-944.

<https://exodntia.info/freys-syndrom-gustatory-sweating/>

• Espinoza L, Fedorchak S, Boychuk CR. Interplay between Systemic Metabolic Cues and Autonomic Output: Connecting Cardiometabolic Function and Parasympathetic Circuits. *Front Physiol*. 2021 Mar 12;624595.

•Marathe C, Horowitz M. Diabetic autonomic neuropathy: an oft neglected entity. <https://endocrinology.medicinetoday.com.au/et/2016/february/regular-series/diabetic-autonomic-neuropathy-oft-neglected-entity>

<https://www.mayoclinic.org/departments-centers/childrens-center/overview/specialty-groups/general-pediatric-adolescent-medicine/autonomic-dysfunction-clinic>

•Stepien A, et al. Paroxysmal extreme pain disorder in family with c.3892G > T (p.Val1298Phe) in the SCN9A gene mutation - case report. *BMC Neurol*. 2020 May 13;20(1):182

•Kronenberg Get al. The Classic Triad of Triple A (Allgrove) Syndrome. *Neural Clin Pract*. 2021 Dec;11(6):e916-e917.

•Afif S, et al. Allgrove Syndrome: Adrenal Insufficiency with Hypertensive Encephalopathy. *J Coll Physicians Surg Pak*. 2016 Sep;26(9):790-2.

•Davis MD, Genebrère J, Sandroni P, Fealey RD. Thermoregulatory sweat testing in patients with erythromelalgia. *Arch Dermatol*. 2006 Dec;142(12):1583-8.

Nevolet ML. Sudomotor Function Testing: The Science, Clinical Applications, and Prospects for Preventive, Diagnostic, and Clinical Care. Medicine 2012