Brigham and Women's Hospital
Founding Member, Mass General Brigham

Autonomic Neuropathies

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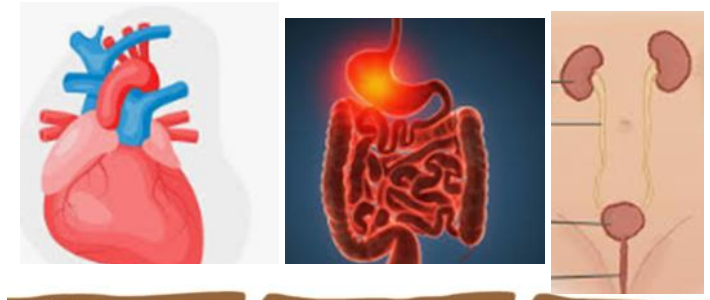
DISCLOSURES

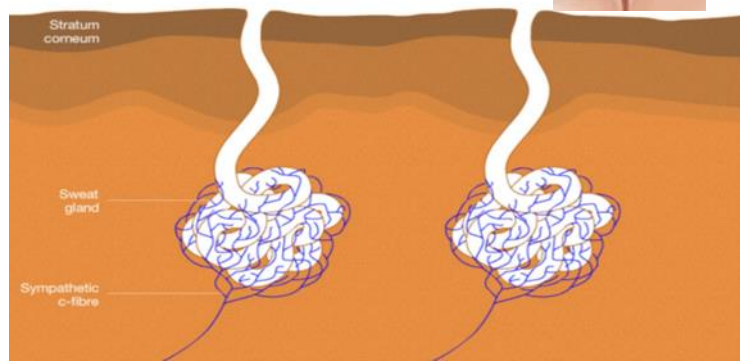
No Disclosures

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:

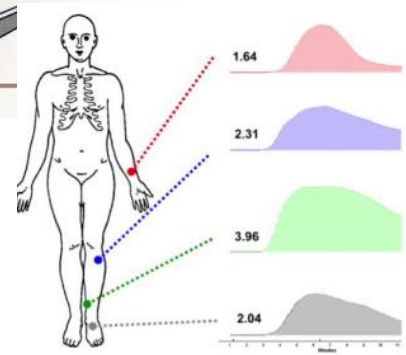
Innervate organs & structures involved in:

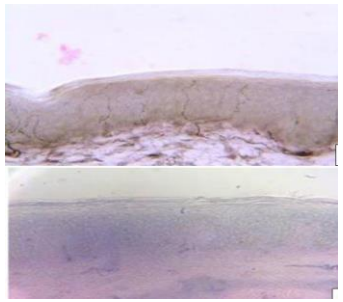
Cardiovascular
Gastrointestinal
Urogenital
Sudomotor /Thermoregulatory
Pupillary
Immune function

Image References:
Corpus ID: 38797394
https://www.ck12.org/biology/heart-1501905644.35/lesson/Heart-BIO

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, Orthostasis (Standing/Tilt)
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





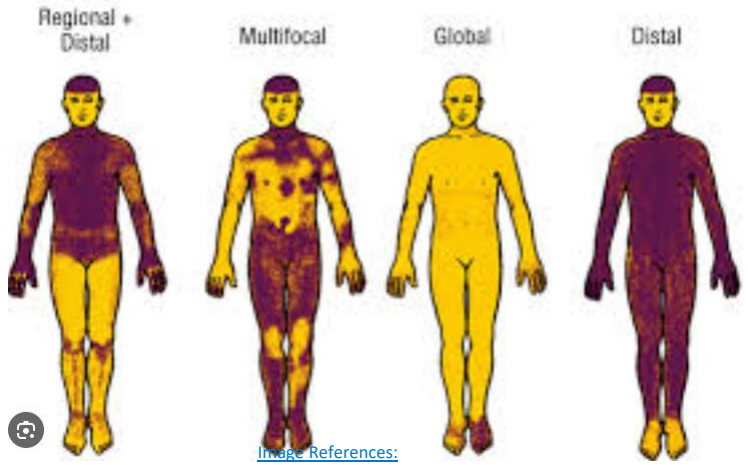
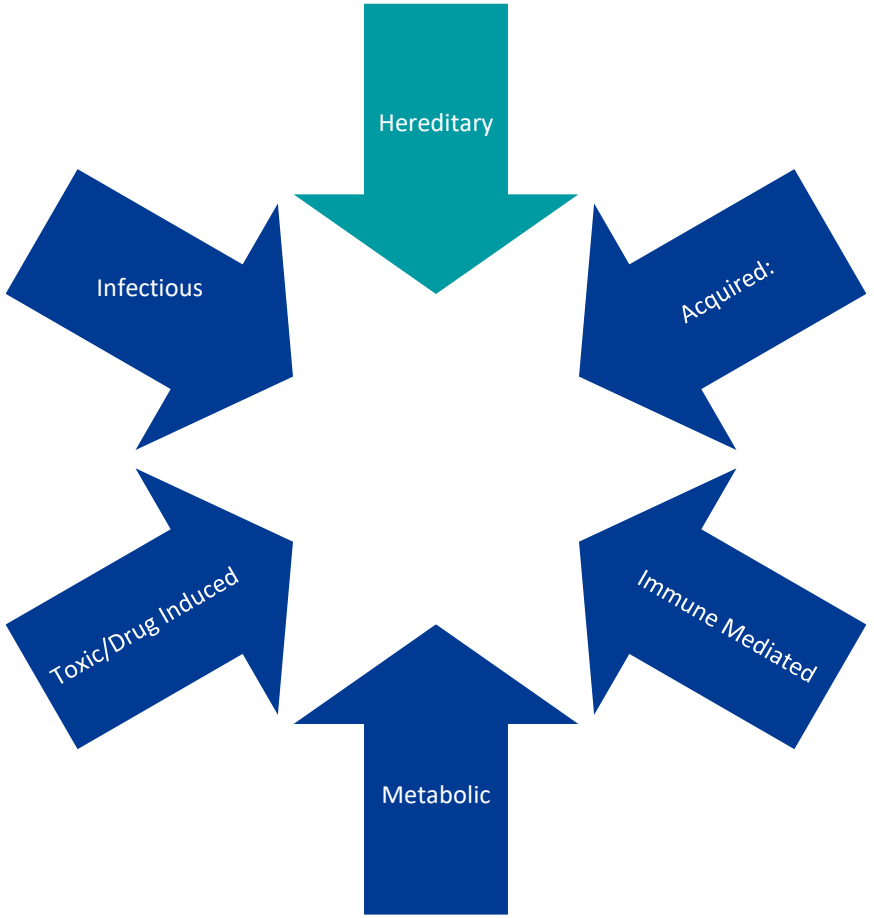


Image References:
https://www.mayoclinic.org/departments-centers/childrens-center/overview/specialty-groups/general-pediatric-adolescent-medicine/autonomic-dysfunction-clinic
PMID: 17178984.
The Dysautonomia Project

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 reflexe s, and Sensory Gait ataxia.
Baroreflex receptor dysfunction -→ 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.

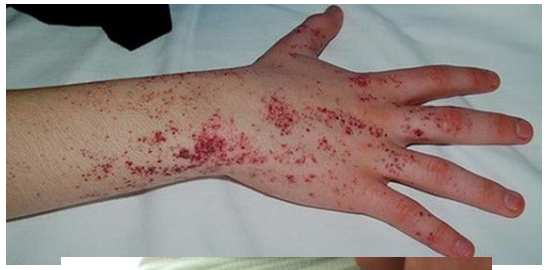
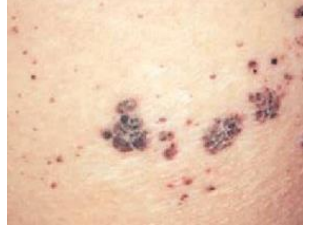
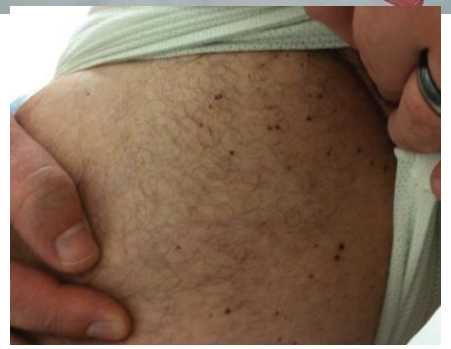
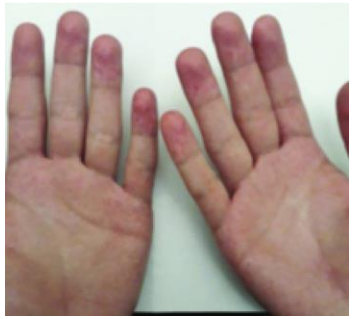
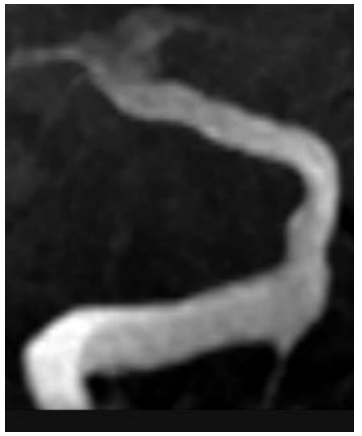
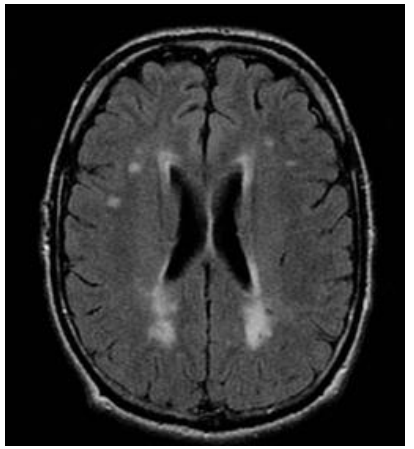
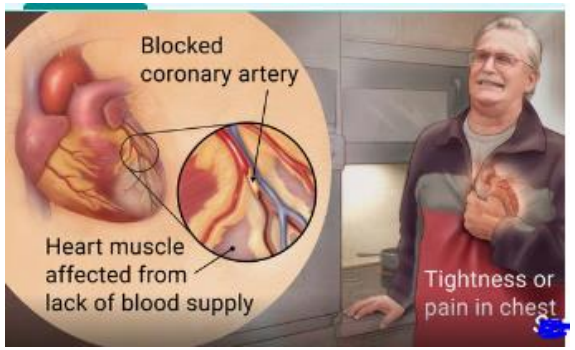
Fabry disease:
X-linked lysosomal storage disease
Decreased activity of alpha-galactosidase A ->lysosomal accumulations of neutral glycosphingolipids and globotriaosylceramide

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.

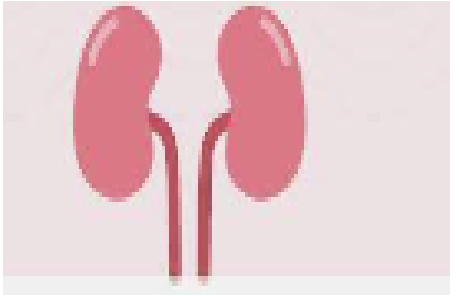


Image Reference: https://www.stroke-manual.com/fabry-disease/

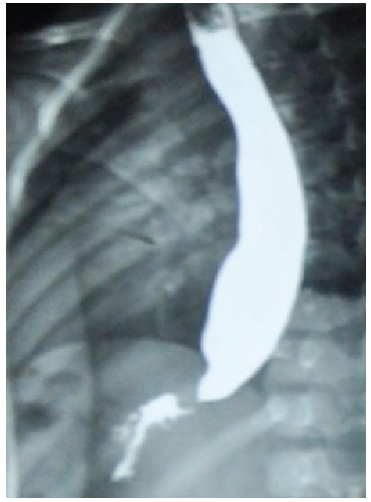
Allgrove syndrome
Triple –A syndrome + autonomic =4A syndrome

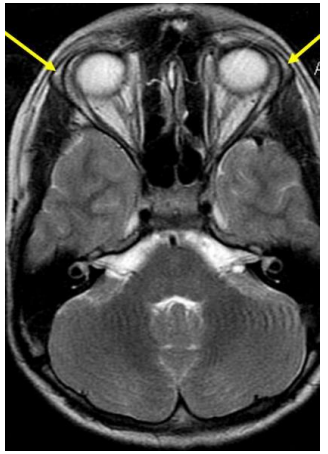
Autosomal recessive. Mutations of the *AAAS* gene on chromosome 12q13-> Nuclear envelope protein known as *ALADIN* (alacrimia-achalasia-adrenal insufficiency neurologic)
ACTH resistant adrenal insufficiency(presents later), alacrimia (infancy), and achalasia (infancy/child) +progressive neurological 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





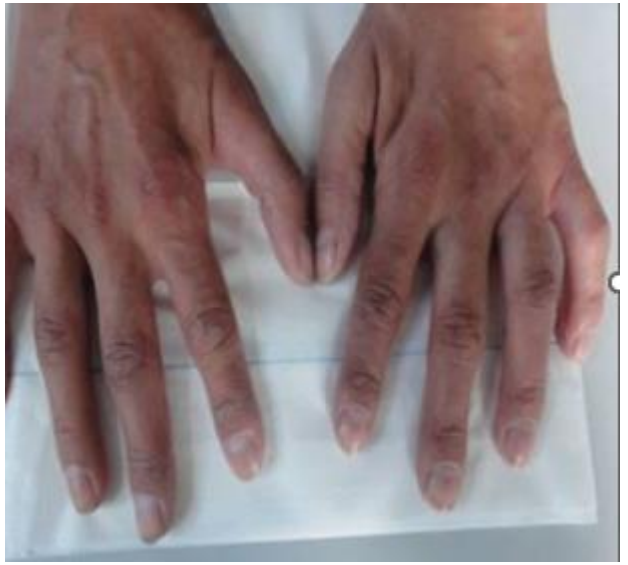


Image References
PMID: 15217518
PMID: 34992981
PMID: 27671188

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 extermities 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.

Treatment: sodium channel blocking agents, such as carbamazepine and lidocaine, mexiletine, gabapentin

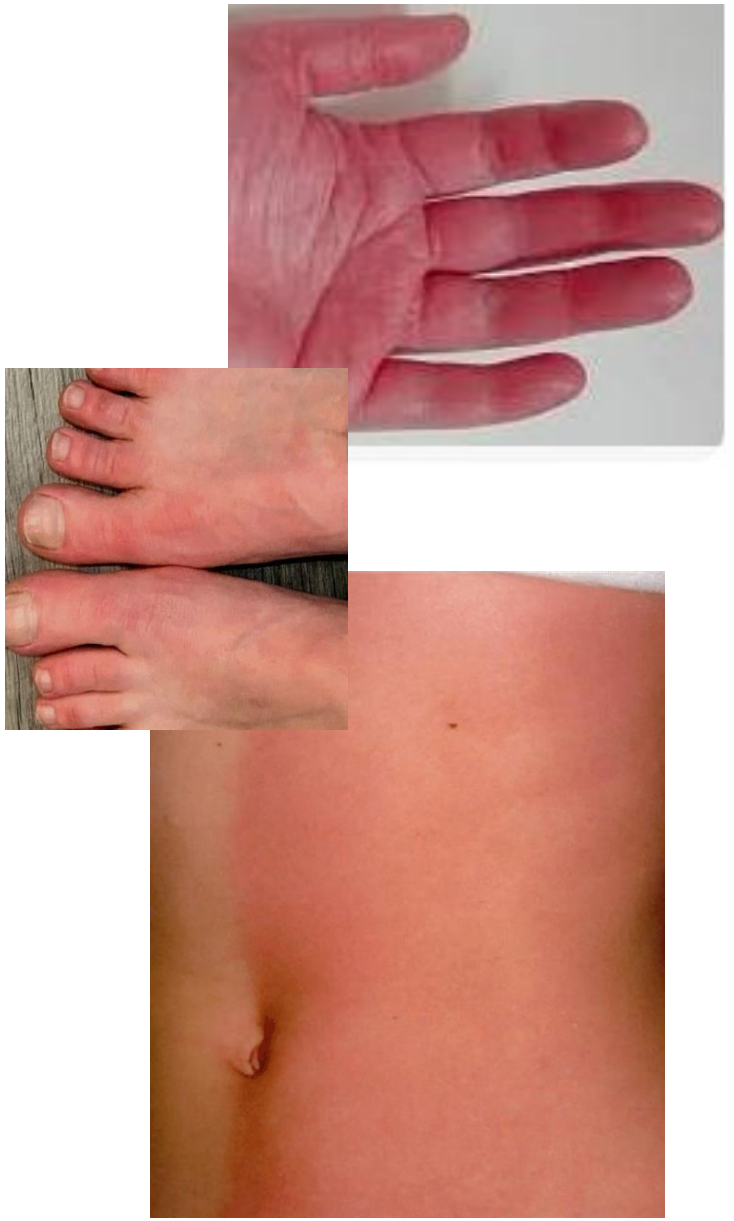


Image References:
https://www.healthline.com/health/erythromelalgia
PMID: 32404070

Immune Mediated Autonomic Neuropathies:

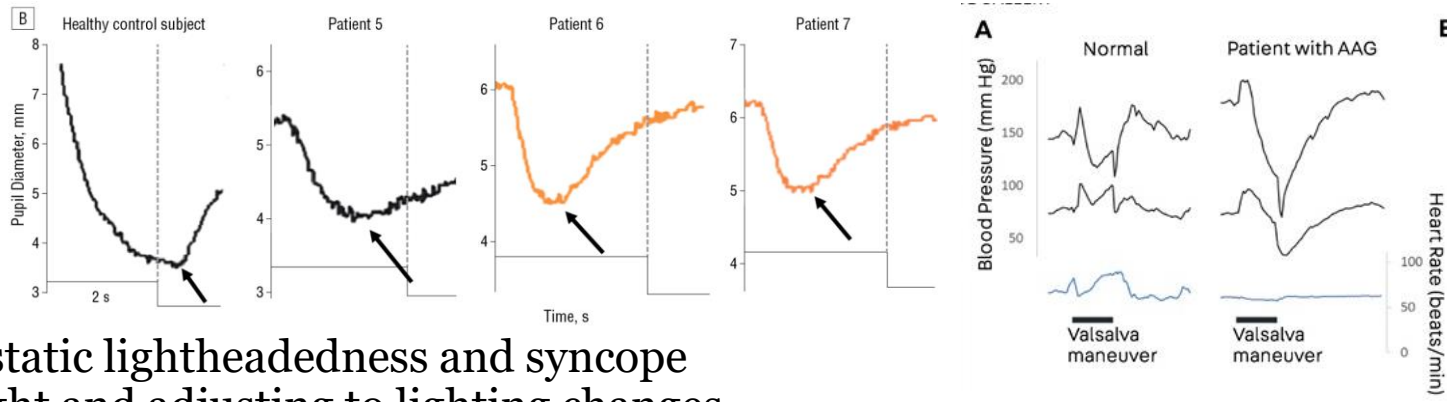
Autonomic Disorders With Definite Autoimmune Etiology
- **Autoimmune autonomic ganglionopathy**
- **Paraneoplastic autonomic/enteric neuropathy**

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

Image References:
PMID: 22232207
PMID: 31996621

Autoimmune Autonomic Ganglionopathy

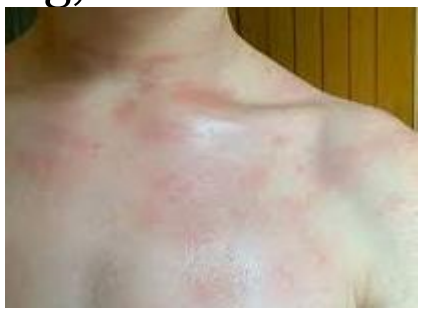
Autoantibodies specific for the ganglionic nicotinic ACh receptor the α3 subunit
Diffuse failure of sympathetic, parasympathetic, and enteric systems
Usually 5^{th}-7^{th} decade but can be seen in younger patients.
2:1 female: male Also, transient neonatal autoimmune autonomic ganglionopathy due to 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

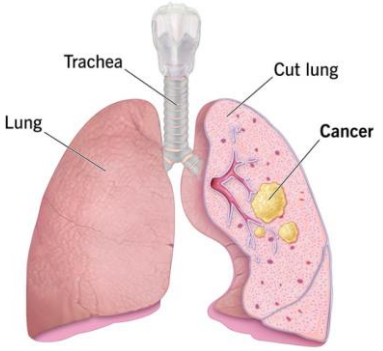
Acute onset, often with an antecedent upper respiratory infection.

Sensory symptoms, including neuropathic pain, sensory ataxia

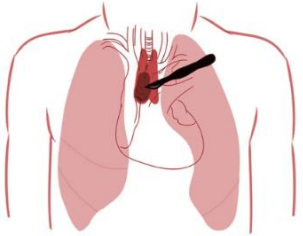
Objective evidence of small or large fiber sensory involvement.

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 indistinguish
Anti-Hu and anti-CRMP5 are both directed against intracellular antigens Neuronal injury: cell-mediated a
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

Image References:
https://my.clevelandclinic.org/health/diseases/6202-small-cell-lung-cancer
https://drarvindkumar.com/treatment-options-for-thymoma.

Autonomic neuropathic dysfunction associated with central neurological disorders

Autonomic manifestions 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

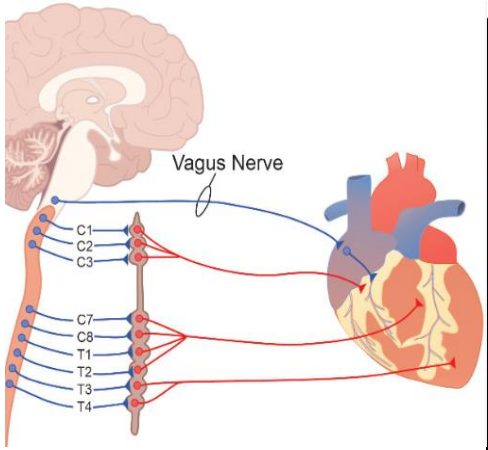
CHRONIC: DIABETIC AUTONOMIC NEUROPATHY

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

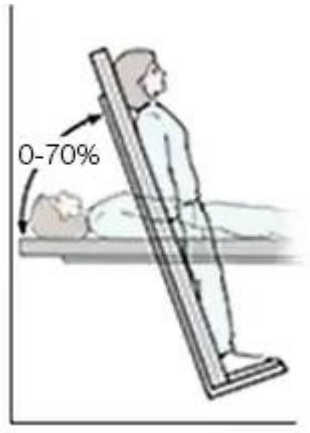
-generalized diabetic autonomic neuropathy:
-autonomic neuropathy associated with the prediabetic state
-treatment-induced neuropathy
- hypoglycemia-associated autonomic failure

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.



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

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

Image References:
PMID: 33776789
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

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

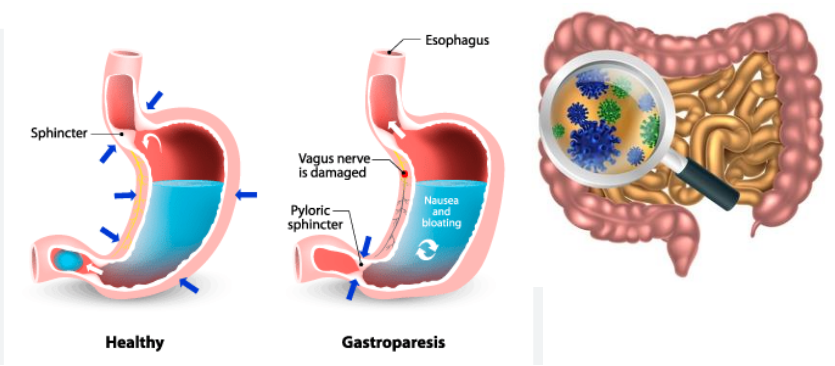
Implications for glycemic control : challenging to match insulin requirements with the slow, unpredictable food absorption.
Aggravates OH: blood pooling in the splanchnic and mesenteric bed

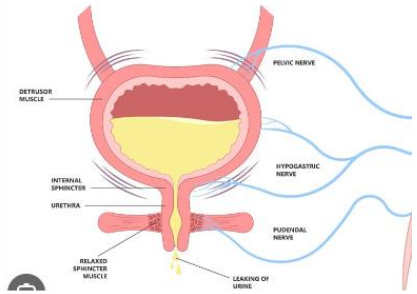
Constipation: Worsened by gastroparesis with loss of gastrocolic reflex.
Diarrhea, Fecal incontinence due to anal sphincter incompetence or reduced rectal sensation,
Small intestinal bacterial overgrowth, a consequence of slow intestinal transit

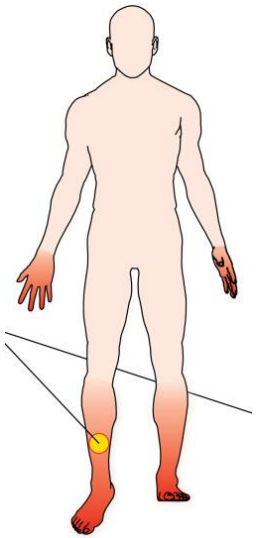
GU: Neurogenic bladder: Reduced sensation-> increased volume and pressure required to trigger the micturition reflex, → Reduced detrusor activity → weak flow, incomplete emptying, atonic bladder with overdistention/overflow incontinence.
Voiding dysfunction: frequency, nocturia, urinary retention, and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







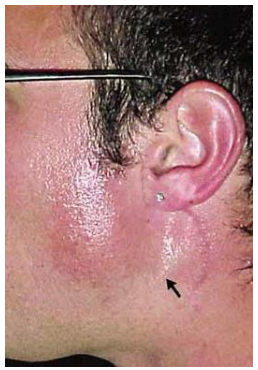


Image References:
https://badgut.org/information-centre/a-z-digestive-topics/gastroparesis/
https://www.cmuh.cmu.edu.tw/HealthEdus/Detail_EN,
PMID: 29029847.
https://exodontia.info/freys-syndrome-gustatory-sweating/

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)

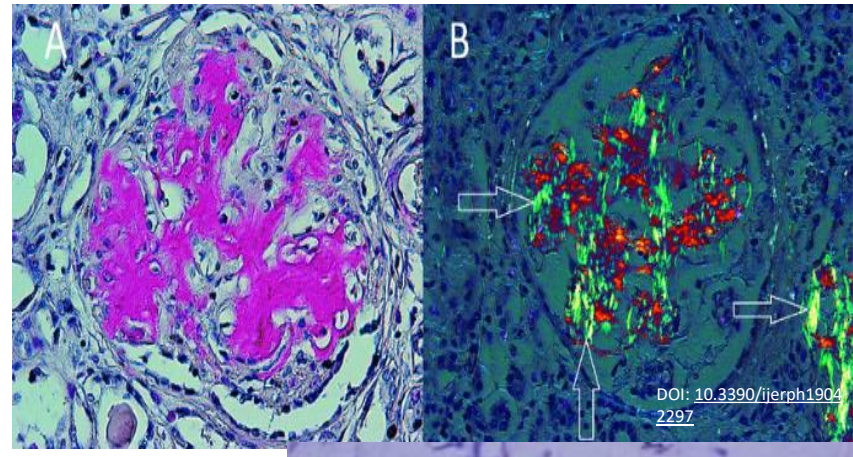
Primary (AL) Amyloidosis:
Pathogenesis: monoclonal population of bone marrow plasma cells produce kappa or lambda type immunoglobulin light chains or light chain fragments
AL amyloidosis may be preceded by an increase in serum levels of free light chains.

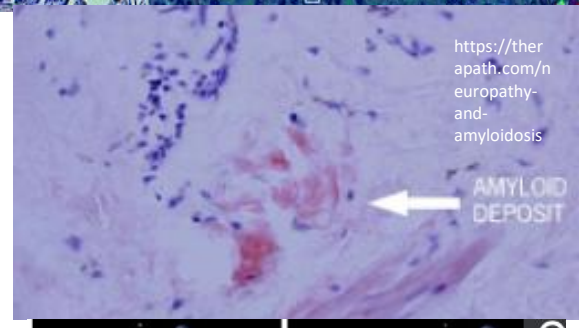
May start as Weight loss and fatigue, -> hepatomegaly, cutaneous ecchymoses, nonischemic cardiomyopathy with hypertrophy, nephrotic-range proteinuria

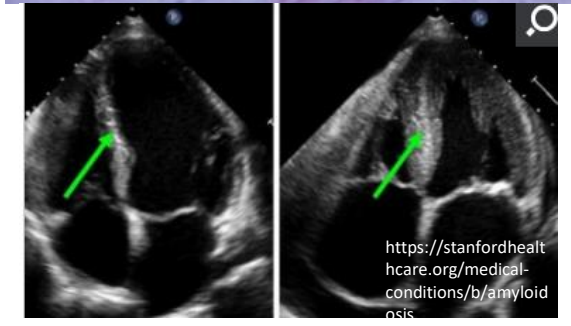
Autonomic involvement of the cardiovascular, gastrointestinal, and urogenital systems Autonomic dysfunction + pain and a length-dependent generalized polyneuropathy.

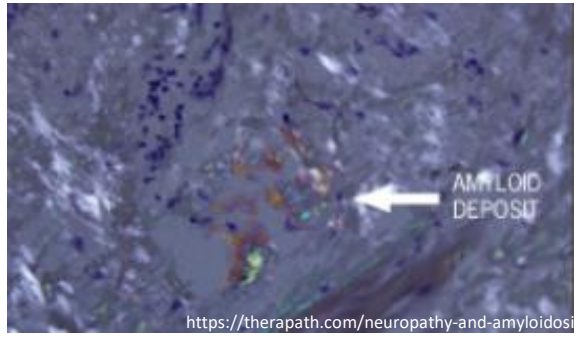
Serological diagnosis**: immunofixation electrophoresis of serum and urine and serum free light chain assay.**
If normal, AL amyloidosis is unlikely.
If positive, the diagnosis should **be confirmed pathologically by bone marrow, fat aspirate, or lip biopsy.**

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

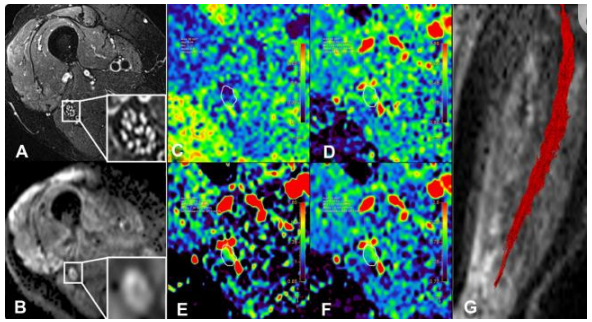
Mutant transthyretin is a 14-kDa 127 amino acid : transport protein for thyroxine and retinol-binding protein
Most commonly observed mutation is a substitution of methionine for valine at position 30 (Val30Met).
Less frequent mutations in the genes encoding for apolipoprotein A-I, fibrinogen Aα, lysozyme, 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 B_{12} 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 (fluorocortisone), 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 (α3 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

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