

Hereditary Neuropathies

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1. **Hereditary sensory and motor (Charcot-Marie-Tooth) neuropathies** ≈ 90% of all hereditary neuropathies! (more common than myasthenia gravis!)
2. **Hereditary sensory and autonomic neuropathies**
3. **Neuropathy with leukodystrophy:**
 - 1) Metachromatic leukodystrophies (infantile, juvenile, adult)
 - 2) Multiple sulfatase deficiency
 - 3) Krabbe disease
 - 4) Adrenoleukodystrophy, adrenoleukoneuropathy
 - 5) Cockayne syndrome
 - 6) Pelizaeus-Merzbacher disease
4. **Friedreich ataxia**
5. **Giant axonal neuropathy**
6. **Acute intermittent porphyria**
7. **Familial amyloidotic polyneuropathy**
8. **Abetalipoproteinemia (Bassen-Kornzweig disease)**
9. **Analphalipoproteinemia (Tangier disease)**
10. **Fabry disease**
11. **Joseph disease**
12. **Lafora body disease; polyglucosan body disease**
13. **Leber hereditary optic neuropathy**
14. **Hereditary ataxias**

Onset of neuropathic *dysfunction is insidious*, and *progression is indolent*, occurring over years or decades (except porphyric neuropathies).

HEREDITARY SENSORY and MOTOR NEUROPATHIES (HSMN)

- peripheral neuropathies that affect either **autonomic, sensory, motor** fibers, or combination thereof.

EPIDEMIOLOGY

PREVALENCE 4.7-40 per 100,000.
INCIDENCE - 1 in 25,000 persons.

CLASSIFICATION

HSMN I (s. Charcot-Marie-Tooth disease 1) – hypertrophic *demyelinating* neuropathies – most common HSMN!

HNPP (hereditary neuropathy with liability to pressure palsies, s. tomaculous neuropathy) – severely hypertrophic *demyelinating* neuropathy.

HSMN II (s. Charcot-Marie-Tooth disease 2) – *axonal* neuropathies.

HSMN III (s. Dejerine-Sottas disease) – severe hypertrophic *demyelinating* neuropathies with onset in infancy.

GENETICS

Disorder	Inheritance	Gene	Product
CMT 1A	AD	Duplication (gene dosage effect) at 17p11.2-12	PMP22 (peripheral myelin protein 22)
HNPP (hereditary neuropathy with liability to pressure palsies)	AD	Deletion at 17p11.2	
Dejerine-Sottas syndrome A	AD	Point mutation at 17p11.2	
Dejerine-Sottas syndrome B	AD	Point mutation at 1q22.3	PO (myelin protein zero)
CMT 1B	AD	1q22.3	
CMT 1C	AD	?	
CMT 1 (X-linked)	X-linked	Xq13.1	Connexin 32
CMT 2A	AD	1p36-P35	?
CMT 2B	AD	3q	?
CMT 4A	AR	8q13	?
CMT 4B	AR	1q231	?
CMT 4C	AR	5q23-33	?

Peripheral myelin protein 22 (PMP22) - present in compact *myelin* of PNS.

- Schwann cells can modulate axon caliber, neurofilament density within axoplasm, etc.
- abnormal expression of PMP22 → both neuronal and Schwann cell alterations.
- PMP22 is implicated in *trembler mouse*.

Myelin protein zero (P0) - major component of PNS *myelin*.

- major role - compaction of myelin (holding opposing membranes together).
- analog in CNS is **proteolipid protein (PLP)**.

Connexin 32 - *gap junction* protein (gap junctions are at Ranvier nodes and Schmidt-Lanterman incisures - intracellular gap junctions between folds in Schwann cell cytoplasm).

DIAGNOSIS

Always search for affected family members – facilitates diagnosis!

- **genetic confirmation** (available only for CMT 1A, X-linked CMT, HNPP, Dejerine-Sottas syndrome).
- **nerve conduction studies:** Family members should be examined!
 - a) **demyelinating features** - slowed **nerve conduction velocities** (extent of velocity reduction is no longer accepted criterion for diagnosing type of CMT).
 - b) **axon-loss features** - low amplitude **evoked potentials** (normal conduction velocities!)
- sural **nerve biopsy** (important for excluding other depositions of metabolic products):

In **demyelinating** CMT forms:

 - increase in epineurium and perineurium collagen.
 - ↓number of myelinated fibers (correlates with severity of disease), segmental demyelination.
 - numerous onion bulbs*

*cause macroscopic nerve enlargement

In **axon-loss** CMT forms: wallerian degeneration.
- **EMG** and **muscle biopsy** are not usually required for diagnosis; serum CK is normal.
- **CSF** protein may be elevated, but no cells appear in CSF.

TREATMENT

No cure or effective treatment available.

- orthoses, surgical correction of joint deformities and scoliosis, physical therapy.
- **STABILIZATION OF ANKLE is primary concern:**
 - early stages - **stiff boots** that extend to midcalf
 - later stages - **lightweight plastic splints** worn inside socks.
 - complete foot drop - **external short leg braces** or **surgical fusion** of ankle.

HSMN I (s. CHARCOT-MARIE-TOOTH disease 1, PERONEAL MUSCULAR ATROPHY)

– hypertrophic* **demyelinating** neuropathies (+ sclerosis in spinal posterior column, particularly upper fasciculus gracilis).

*due to episodes of remyelination

- **CMT type 1A** – most common form (50-60% of all CMT cases).
- **CMT type 1B** – rare form (< 2% of all CMT cases).
- **X-linked CMT** (10%) – affects males (carrier females may have mild, variable clinical disease).

GENETICS

- see above >>

CLINICAL FEATURES

Wide intrafamilial variability! (affected family members may have no symptoms and minimal neurologic findings but may still show severe reduction of nerve conduction velocity)

- **clinical presentations of CMT 1A and 1B are similar**, although they are distinguishable.
- CMT 1A may have milder clinical course than 1B.
- **age of onset** ranges childhood ÷ early adulthood (2-3rd decades); may be earlier in X-linked CMT.
- progression is slow.
- cranial nerves are generally spared, intelligence is normal.

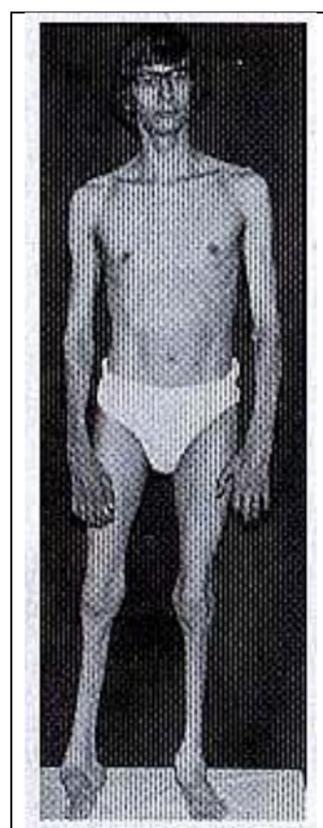
1. Symmetrical insidious **weakness & atrophy** of **intrinsic foot & peroneal muscles** (footdrop, steppage gait).

N.B. muscle atrophy is sign of axon-loss neuropathies!

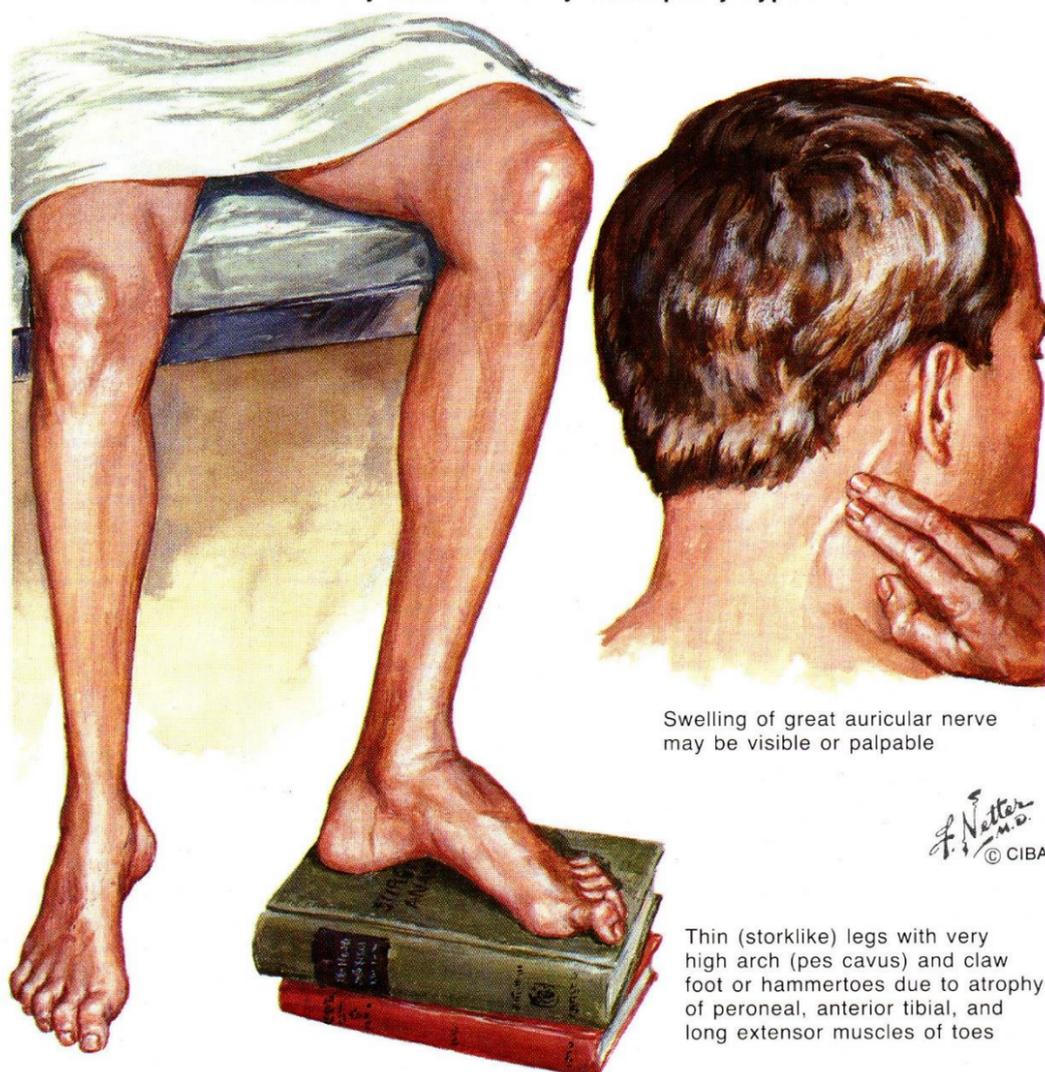
 - patients report frequent ankle sprains.
 - later may be involved - **calf** ("champagne-bottle" legs; "stork" legs), **thigh, intrinsic hand** muscles.
 - **cramps & fasciculations** after exercise.
 - **reflexes disappear:** ankle → patellar → arm.
2. Careful examination reveals **sensory abnormalities** in all modalities in stocking-glove pattern (esp. elevated vibratory thresholds in toes).

marked wasting of calf and intrinsic foot muscles:

3. **Skeletal abnormalities** ($\approx 60\%$ patients) reflecting long-standing muscle imbalance - *pes cavus*, *hammer (claw) toes*, *scoliosis*.
N.B. high pedal arches or hammer toes may be only signs in less affected family members!
4. **Cool anhidrotic skin** over distal leg.
5. **Enlargement & hardening of nerves** ($\approx 25\%$ patients); especially:
 - 1) *ulnar nerve* at elbow;
 - 2) *greater auricular nerve* running from posterior margin of sternocleidomastoid muscle to base of ear.



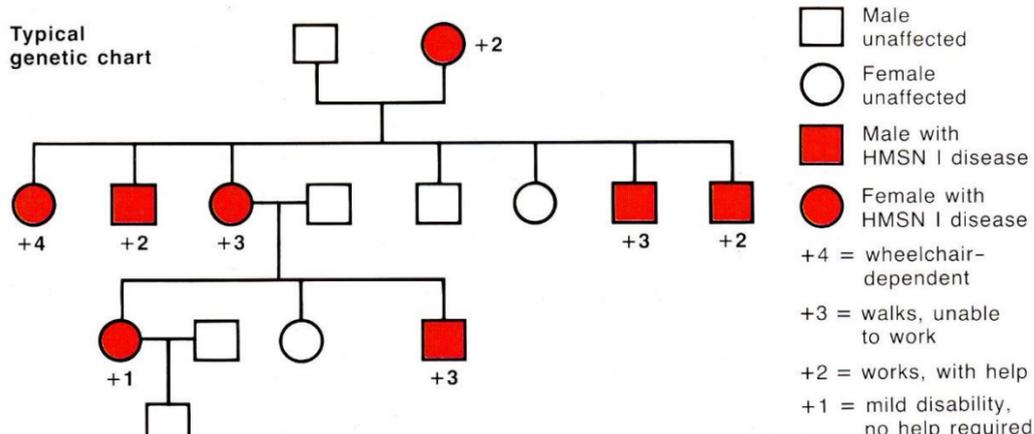
Hereditary Motor-Sensory Neuropathy Type I



Swelling of great auricular nerve may be visible or palpable

F. Netter M.D.
© CIBA

Thin (storklike) legs with very high arch (pes cavus) and claw foot or hammertoes due to atrophy of peroneal, anterior tibial, and long extensor muscles of toes



DIAGNOSIS

- see above >>

PROGNOSIS

- life expectancy is not reduced and patients remain ambulatory throughout their lives.

ROUSSY-LEVY disease

- combination of **HMSN I** and **Friedreich ataxia**; autosomal dominant inheritance, gene locus has not been identified.

HEREDITARY NEUROPATHY with liability to PRESSURE PALSIES (s. HNPP, TOMACULOUS neuropathy)

- *demylinating* neuropathy.

GENETICS

- see above >>

CLINICAL FEATURES

- age of onset - 2-3rd decades.
- **recurring** sensory and motor nerve **palsies brought on by mild pressure or trauma** to nerve (insult from which normal person would quickly recover results in residual nerve damage that may take days ÷ months to resolve).
- most commonly affected - **ulnar, median, peroneal nerves, brachial plexus**.

DIAGNOSIS

- see above >>

- **nerve conduction velocities** are slow even between attacks!; conduction block is possible (vs. HSMN I).
- myelin on **nerve biopsy** (teased nerve fibers and electron microscopy) has **sausage-like appearance** (Lat. TOMACULA - sausage);
it is normal in nerves with increasing age, so evaluation may require quantitative study (morphometry).

HSMN II (s. CHARCOT-MARIE-TOOTH disease 2)

- **axonal** neuropathies:
 - 1) no histologic evidence of demyelination
 - 2) normal conduction velocities!
 - 3) no hypertrophic nerves!

GENETICS

- see above >>

CLINICAL FEATURES

- onset – 3-5th decades of life (later than CMT 1).
- ≈ CMT 1.

DIAGNOSIS

- see above >>

PROGNOSIS

≈ CMT 1.

HSMN III (s. DEJERINE-SOTTAS disease)

– severe hypertrophic **demyelinating** neuropathies.

GENETICS

- see above >>

CLINICAL FEATURES

- more malignant than HSMN I & II:
 - onset in infancy (1st decade).
 - **progressive generalized** (trunk and limb!!!) muscle weakness (children may never walk!)
 - severe sensory loss, limb ataxia.
 - marked hypertrophy of peripheral nerves (palpably enlarged at early age).
 - may be mentally retarded.

DIAGNOSIS

- see above >>

Marked onion bulbs with hypomyelination!

CMT 4

CMT 4A – **demyelinating** neuropathy with onset in 1st decade.

HEREDITARY SENSORY and AUTONOMIC NEUROPATHIES (HSAN)

- primary **sensory & autonomic** neurons:
 - a) fail to develop
 - b) undergo system atrophy and degeneration.

Two large divisions:

HSAN I - *progressive* disorder with onset in **≥ 2nd decade** with primarily **lower extremities** affected.

HSAN II-V - *static congenital* disorders that are **generalized**.

Prominent **sensory loss** and **dysautonomia**

Common feature among all types is **INSENSITIVITY TO PAIN!**

- **dysautonomia** is mild in **HSAN I-II** but prominent in **HSAN III**.
- **sensory loss** may be profound → **mutilating deformities** of hands and feet (*sensory neurogenic arthropathy, mutilating acropathy*).
- there may be weakness, skeletal changes similar to HSMN.

Type	Inheritance
HSAN I	Primarily AD, gene at 9q22.1-q22.3 (AR and X-linked pedigrees have been identified)
HSAN II	AR
HSAN III	AR, almost exclusively Ashkenazi Jews (gene on D9S58, 9q31-33 - unknown gene product)
HSAN IV	AR, rare
HSAN V	< 10 cases reported

HSAN I (hereditary sensory radicular neuropathy)

- slowly *progressive* disorder with onset in **≥ 2nd decade** with primarily **lower extremities** affected.
- predominantly sensory neuropathy (dysautonomia very mild – loss of sweating in legs).
- chronic **axonal** degeneration (mostly myelinated fibers) with myelin remodeling.
- does not seem to decrease lifespan.

A) insensitivity to pain in feet → plantar ulcers, recurring paronychia, stress foot fractures, recurrent cellulitis, resorption of foot bones → **pedal deformity & mutilations**.

B) **spontaneous foot pain** (burning or aching), worsened with weight bearing, decreased at night; or disabling lancinating pain in deep tissues of feet, legs, or shoulder.

Proper foot care!!! - regular inspections, soaked daily + petrolatum lotion (to seal in moisture), proper shoes, aggressive treatment of ulcers, etc.

HSAN II (congenital sensory neuropathy)

- **generalized** predominantly sensory (in all modalities) neuropathy, presenting in *infancy*.

- **axonal** degeneration (profound loss of myelinated fibers in cutaneous nerves, esp. sural); degenerative process begins in utero or in infancy.
- mutilations are more severe than in HSAN I:
 - 1) begin *earlier* when patients cannot understand problem and cooperate.
 - 2) **hands** are also seriously affected.
- loss of sweating over acral parts (but no postural hypotension).
- no prominent muscle weakness.
- **nerve conduction studies** - no sensory nerve action potentials elicitable in ulnar, median, sural nerves.
 - N.B. conduction velocities of motor fibers of same nerves are normal!
- provide *adequate educational opportunities* to develop intellectual potential in spite of severe physical handicaps.

destruction of tongue tissue due to insensitivity to pain:



HSAN III (familial dysautonomia, RILEY-DAY syndrome)

- almost exclusively *Ashkenazi Jews* (carrier state is estimated to be 1%).

PATHOLOGY, PATHOPHYSIOLOGY

- pathophysiologic findings:
 - 1) decreased levels of **dopamine- β -hydroxylase** (decreased synthesis of noradrenaline from dopamine)
 - 2) increased levels of **β unit of nerve growth factor (NGF)**.
 - postmortem studies (vary widely):
 - a) **no nervous system lesions** at all
 - b) **extensive damage:**
 - **CNS** (esp. cortex, brain stem reticular formation, long tracts of cord);
 - **peripheral nerves** - **axonal degeneration** mostly in *unmyelinated* fibers ($\downarrow\downarrow$ number* of unmyelinated fibers of cutaneous nerves), **loss of ganglion cells** (sensory and autonomic).
- *nerve conduction velocities are within normal range

CLINICAL FEATURES

LACK OF FUNGIFORM PAPILLAE on tongue (\rightarrow hypogeusia) - highly distinctive feature!!!

Prominent dysautonomia!!!

- presents at birth* (frequently low birth weight and breech presentation): muscle hypotonia, absent tendon reflexes, absent corneal reflexes, poor Moro response, poor cry, inability to suck.
 - *vs. Shy-Drager syndrome
- progresses: failure to thrive, unexplained fevers (40% with seizures), lack of tearing (\rightarrow corneal abrasions), cold hands & feet, erythematous skin blotching, difficulty in swallowing* with regurgitation + hypersalivation \rightarrow aspirations \rightarrow pneumonia.
 - *some infants require tube-feeding
- **breath-holding spells** followed by syncope are common in first 5 yr.
- 40% patients experience **seizures** (during hyperpyrexia, breath-holding spells).
- after age 3 yrs DYSAUTONOMIC CRISES begin - cyclic **vomiting**, diaphoresis, hypertension, tachycardia, thermal instability irritability, self-mutilation, negativistic behavior.
 - markedly elevated serum NOREPINEPHRINE (causes hypertension) and DOPAMINE (causes vomiting) levels.
 - prominent **gastric distention** may occur, **hematemesis** may complicate pernicious vomiting.
- **decreased pain sensation** (\rightarrow Charcot's joints; newly erupting teeth cause tongue ulcerations).
- ataxia (proprioceptive), intolerance for general anesthetics.
- possible **GI abnormalities:** megaesophagus, pylorospasm, gastric ulcer, jejunal distention, megacolon.
- 50% patients develop **kyphosis, scoliosis**.
- in adolescence: vomiting and dysautonomic crises tend to decrease; delayed puberty; complaints center on decreased exercise tolerance, poor general coordination, emotional difficulties, and postural hypotension.
- IQ is frequently ≥ 20 points below unaffected siblings.
- **abnormal responses to altered atmospheric air** (hypercapnia and hypoxia do not produce expected increases in ventilatory effort): drowning has occurred, because air hunger did not develop under water; coma has occurred in high altitudes.
- 20% adult patients have ischemic-type glomerulosclerosis.
- **most patients do not survive to adulthood** (oldest surviving patient in one series was 38 years old).

DIAGNOSIS

- (1) absence of **fungiform papillae** on tongue
- (2) absent **deep tendon reflexes**
- (3) intradermal injection of **HISTAMINE** \rightarrow no pain, no normal flare.
- (4) absence of overflow tearing with crying (normal until 2-3 mo of age!)
- (5) conjunctival instillation to one eye of 2.5% **METHACHOLINE** or 0.0625% **PILOCARPINE** \rightarrow miosis, restored tearing.

N.B. pupillary responses to light and accommodation appear normal!

Supersensitivity to **cholinergic** and **adrenergic** agents

- exaggerated pressor response to IV **NOREPINEPHRINE**.
- urinary ratio **vanillylmandelic acid / homovanillic acid** \downarrow .
- **prenatal diagnosis** is possible.

TREATMENT

1. Ranitidine
2. Diazepam, chlorpromazine (for crises)
3. Methylcellulose eye drops
4. Gastrostomy, fundoplication

HSAN IV (familial sensory neuropathy with anhidrosis, congenital insensitivity to pain)

- selective loss of small myelinated axons with almost complete absence of unmyelinated fibers.

- similar to HSAN II, with addition of **anhidrosis** (*episodes of fever* related to environment rather than infection).
- mild mental retardation.

HSAN V (congenital sensory neuropathy with selective loss of small myelinated fibers)

- congenital insensitivity to pain.
- normal strength and tendon reflexes in extremities.

HEREDITARY SENSORY NEUROPATHIES (HSN)

- age at onset – 1-3rd decades.
- selective involvement of **dorsal root ganglia neurons** (neuronopathy).
- frequent **distal mutilations** (hands and feet).

HSN-I

- **autosomal dominant** inheritance (gene unknown); some families have sensorineural deafness.

HSN-II

- **autosomal recessive** inheritance (gene unknown); may be less severe than HSN-I.

OTHER HEREDITARY NEUROPATHIES

GIANT AXONAL NEUROPATHY

- disorder of **neurofilament synthesis or organization**.

- **autosomal recessive** inheritance, but high proportion of spontaneous cases.
- pathology – intermediate (10 nm) filament masses in variety of cell types.
- onset in early childhood (1st decade):
 - 1) characteristically abnormal **TIGHT CURLY BLACK-REDDISH HAIR**.
 - 2) slowly progressive **motor & sensory neuropathy**.
 - 3) slowly progressive **encephalopathy with Rosenthal fibers** - intellectual impairment, optic atrophy, cerebellar ataxia and nystagmus, corticospinal disturbance.
- **death** usually in adolescence.
- diagnosis:
 - 1) mildly reduced conduction velocities and action potentials.
 - 2) **nerve biopsy** - **axonal** loss with massive focal axonal enlargements (neurofilament accumulations); myelin sheath intact.
- management - supportive.

FAMILIAL AMYLOID POLYNEUROPATHY (FAP)

- AMYLOID (glycoprotein with **fibrillar β sheet** structure) may be derived from variety of precursor proteins.
- in **amyloidosis**, extracellular amyloid deposition occurs in **variety of organs**. see p. 1589 (1-6) >>
- in **amyloid neuropathy**, extracellular amyloid deposition in **peripheral nerves** predominates.

Amyloid neuropathy:

ACQUIRED - Ig-derived amyloid (AL). see p. 1589 (1-6) >>

HEREDITARY (familial amyloid polyneuropathy) – amyloid (AF) derived from serum proteins:

- a) **transthyretin (TTR)** – produced in liver, involved in transport of thyroid hormones and vitamin A (gene maps to 18q11.2-q12.1).
- b) **apolipoprotein A1**
- c) **gelsolin**.

FAP type		Clinical Phenotype	Amyloid Precursor	Common Mutation
FAP 1	(Portuguese)	Lower limb neuropathy	Transthyretin	Met 30 (plus others)
	(Irish/Appalachian)			Ala 60
FAP 2 (Indiana)		Upper limb neuropathy	Transthyretin	Ser 84, His 58 plus others
FAP 3 (Iowa)		Lower limb neuropathy Nephropathy Gastric ulcers	Apolipoprotein A1	Arg 26
FAP 4 (Finnish)		Cranial neuropathy Corneal dystrophy	Gelsolin	Asp 187, Tyr 187

- all are AUTOSOMAL DOMINANT conditions with reduced penetrance.

PATHOGENESIS

FAP 1 - **axonal** loss (**unmyelinated** and **small myelinated** fibers → **large** fibers).

- segmental **demyelination** is also evident (due to compressive effect of amyloid deposits).
- hypothesis - neuropathy results from generalized metabolic disorder (amyloid deposition is only secondary event).
- amyloid may have *diffuse* or *patchy* distribution.
- amyloid deposition may be present only in *proximal* nerves and absent in *distal* nerves.
- patterns of amyloid deposition (CNS is spared!):
 - a) in **connective tissue** of peripheral nerves (→ compressive damage).
 - b) in **endoneurial tissue** (→ nerve ischemia).
 - c) in **vasa nervorum** (may alter vascular permeability → endoneurial edema → compressive damage).

EPIDEMIOLOGY

FAP 1 (Portuguese) - *most common FAP* - 500 Portuguese families.

FAP 4 - 200 Finnish families.

Other FAP - single families.

CLINICAL FEATURES

FAP 1

- age of onset varies with ethnic origin:

FAP 1 (Portuguese) - twenties ÷ late fifties;

FAP 1 (Irish-Appalachian) - sixth and seventh decades.

- onset: *painful dysesthesia* with attacks of stabbing pain in **lower limbs** + *autonomic dysfunction* + *loss of pain and temperature sensation* → foot ulcers, Charcot joints, etc.
- slowly progresses - eventually involves all nerve fiber types and all sensory modalities + motor & autonomic fibers.
- later may become involved - upper limbs (carpel tunnel syndrome may occur), heart, kidneys.
- death from sepsis and systemic disease occurs **7-15 years** from onset.

FAP 2

- onset - middle life: **upper limbs** (e.g. bilateral carpal tunnel syndrome – due to amyloid deposition) and *vitreous opacities*.
- may spread to lower limbs; autonomic neuropathy can occur.
- individuals may survive as long as **35 years** with some disability.

FAP 3

≈ FAP 1:

- **upper** and **lower** extremities are affected (no associated carpal tunnel syndrome).
- peripheral neuropathy can be severe.
- *peptic ulceration*.
- renal, liver, adrenal glands, testes involvement also occurs.
- peripheral neuropathy becomes disabling over 10 years; death (renal failure) - over 20-year period.

FAP 4

- 1) asymptomatic *corneal lattice dystrophy* begins in thirties.
- 2) progressive **cranial neuropathy** (principally CN7, although CN5, CN12, and CN8 may also be involved).
- 3) mild generalized *sensory & autonomic neuropathy*.
- 4) facial skin: thickened → atrophic.

DIAGNOSIS

Search for **monoclonal antibodies** (urine and serum) - to exclude acquired amyloidosis.

Electrophysiology - *axonal* neuropathy (in early stages when only small-diameter fibers are involved, sensory nerve action potentials may be preserved!).

- sensory and motor conduction velocities are usually normal.

Biopsy - amyloid deposition (staining with Congo red, and characteristic green birefringence with polarizing filters).

Immunohistochemistry - to characterize amyloid nature (e.g. TTR antibody immunohistochemistry).

DNA analysis - for common TTR mutations (sequencing of entire TTR gene may be justified in absence of one of common mutations).

TREATMENT

- supportive.

- **plasma exchange** - in hope of removing circulating amyloid protein (usually not successful).
- **liver transplantation** (> 90% TTR is synthesized in liver).

BIBLIOGRAPHY for ch. "Peripheral Neuropathies" → follow this [LINK](#) >>