Hereditary Neuropathies

Last updated: September 5, 2017

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).

- **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.

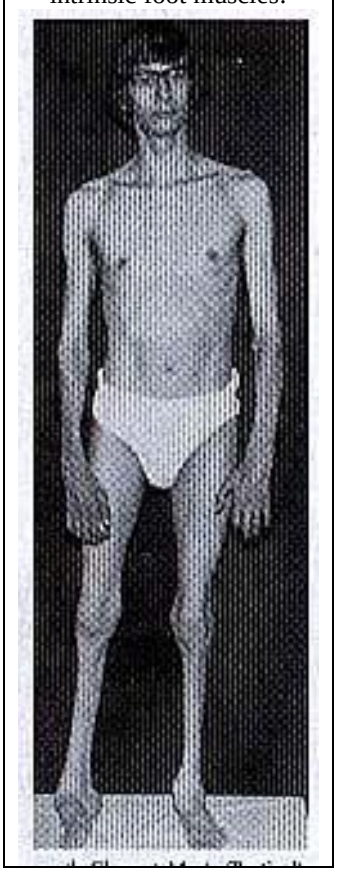
2. Careful examination reveals **sensory abnormalities** in all modalities in stocking-glove pattern (esp. elevated vibratory thresholds in toes).

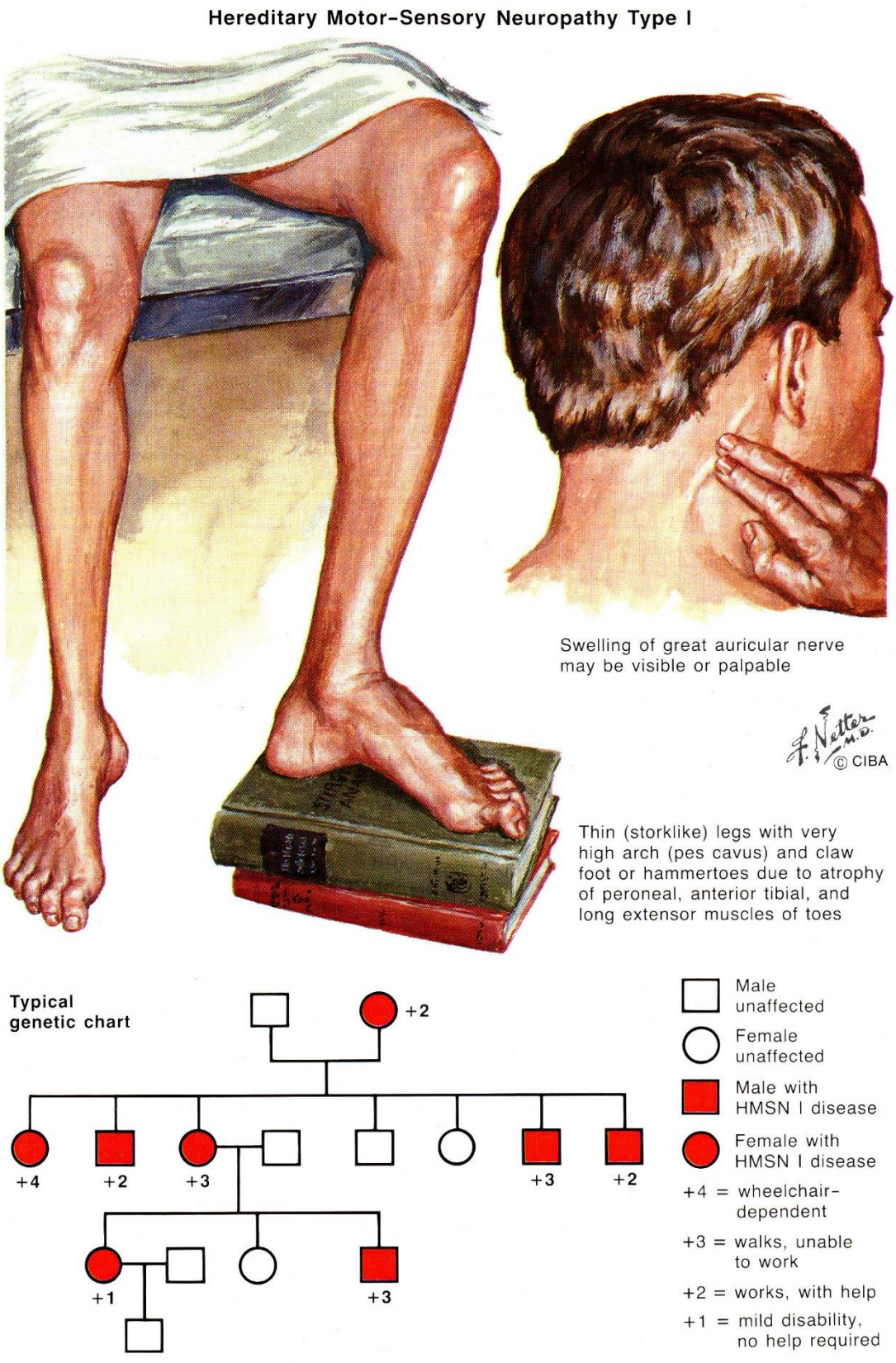
3. **Skeletal abnormalities** (≈ 60% patients) reflecting long-standing muscle imbalance - ***pes cavus***, ***hammer (claw) toes***, ***scoliosis***.
   N.B. high pedal arches or hammer toes may be only signs in less affected family members!

4. **Cool anhidrotic skin** over distal leg.

5. **Enlargement & hardening of nerves** (≈ 25% patients); especially:
   1) ***ulnar nerve*** at elbow;
   2) ***greater auricular nerve*** running from posterior margin of sternocleidomastoid muscle to base of ear.

marked wasting of calf and intrinsic foot muscles:





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)

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

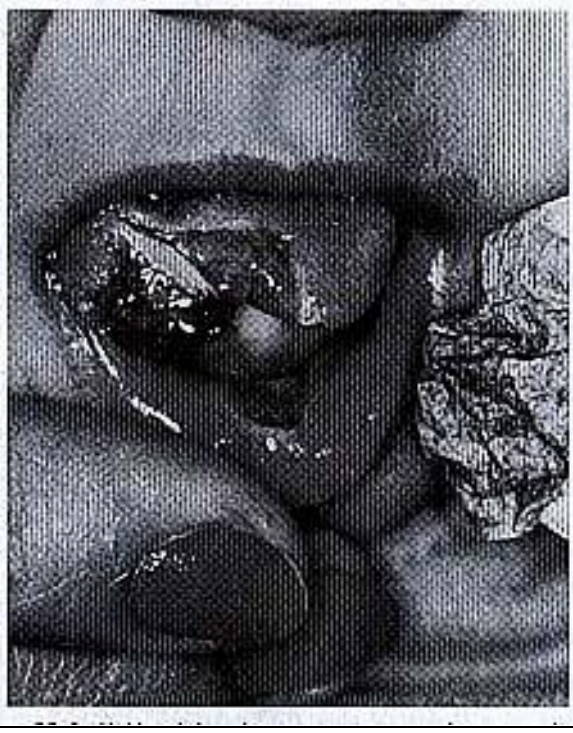
Proper foot care!!! - regular inspections, soaked daily + petrolatum lotion (to seal in moisture), proper shoes, aggressive treatment of ulcers, etc.

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 (↓↓↓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 (→ 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 (→ corneal abrasions), cold hands & feet, erythematous skin blotching, difficulty in swallowing* with regurgitation + hypersalivation → aspirations → 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** (→ 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 → 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 → 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** ↓.
- *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 anhydrosis, congenital insensitivity to pain)

- selective loss of small myelinated axons with almost complete absence of unmyelinated fibers.
- similar to HSAN II, with addition of **anhydrosis** (***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 l:

- 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 >>