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!

1. **demyelinating features** - slowed ***nerve conduction velocities*** (extent of velocity reduction is no longer accepted criterion for diagnosing type of CMT).
2. **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

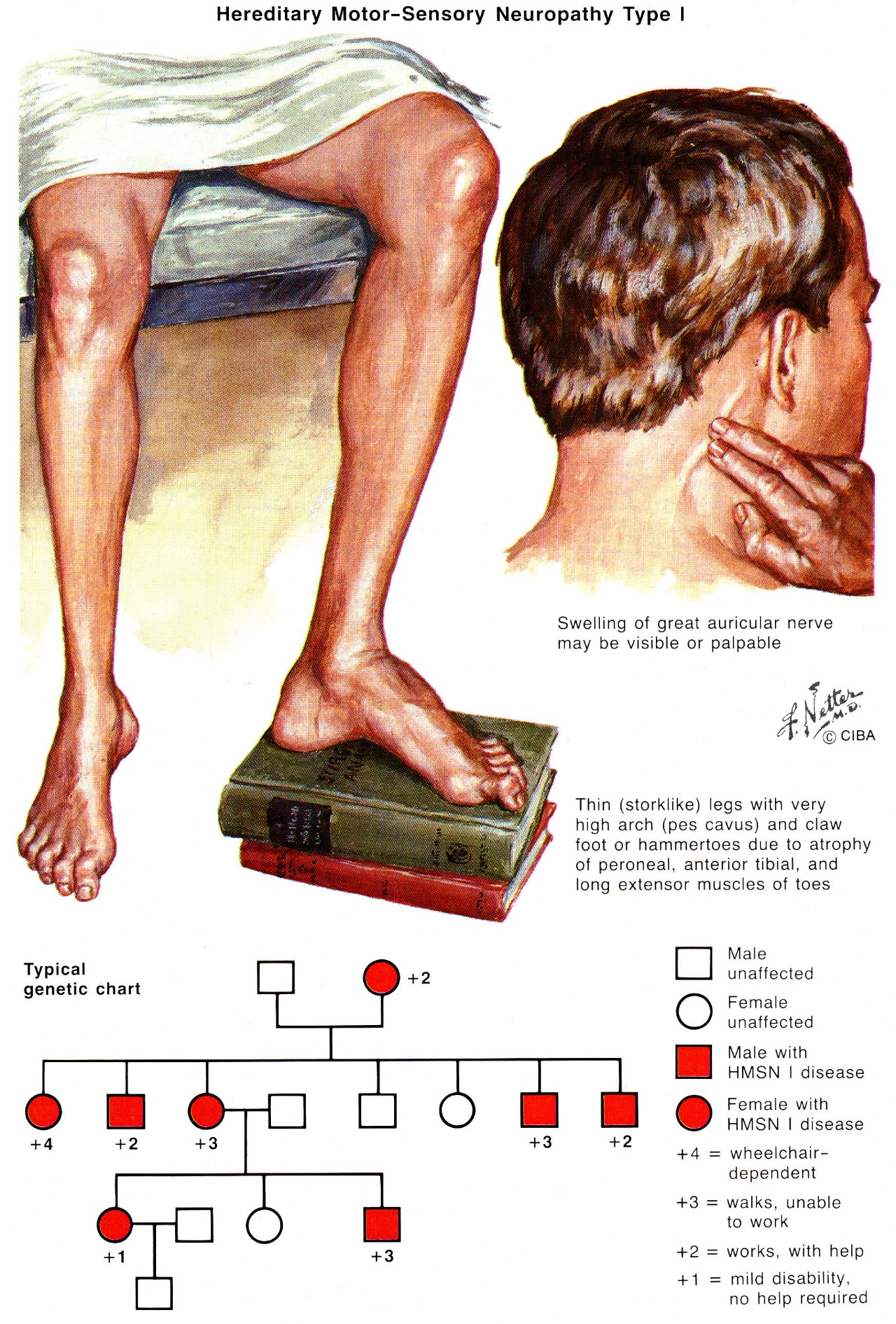
- [see above >>](#Genetics)

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.   1. Careful examination reveals **sensory abnormalities** in all modalities in stocking-glove pattern (esp. elevated vibratory thresholds in toes).   2. **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!   * 1. **Cool anhidrotic skin** over distal leg.   2. **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:  D:\Viktoro\Neuroscience\PN. Peripheral Neuropathies\00. Pictures\CMT.jpg |



Diagnosis

- [see above >>](#Diagnosis)

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 >>](#Genetics)

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 >>](#Genetics)

* **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 >>](#Genetics)

Clinical Features

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

Diagnosis

- [see above >>](#Diagnosis)

Prognosis

≈ CMT 1.

HSMN III (s. Dejerine-Sottas disease)

– severe hypertrophic ***demyelinating*** neuropathies.

Genetics

- [see above >>](#Genetics)

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 >>](#Diagnosis)

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:

1. fail to develop
2. 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.
  1. insensitivity to pain in feet → plantar ulcers, recurring paronychia, stress foot fractures, recurrent cellulitis, resorption of foot bones → **pedal deformity & mutilations**.
  2. **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:  D:\Viktoro\Neuroscience\PN. Peripheral Neuropathies\00. Pictures\HSAN2.jpg |

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):
  + - 1. ***no nervous system lesions*** at all
      2. ***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) >>](http://www.neurosurgeryresident.net/USMLE%202\Hematology%20(1501-1649)\1589%20(7).%20Amyloidosis.pdf)
* in *amyloid neuropathy*, extracellular amyloid deposition in **peripheral nerves** predominates.

Amyloid neuropathy:

**acquired** - **Ig-derived** amyloid (AL). [see p. 1589 (1-6) >>](http://www.neurosurgeryresident.net/USMLE%202\Hematology%20(1501-1649)\1589%20(7).%20Amyloidosis.pdf)

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

1. **transthyretin (TTR)** – produced in liver, involved in transport of thyroid hormones and vitamin A (gene maps to 18q11.2-q12.1).
2. **apolipoprotein A1**
3. **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!):
  1. in **connective tissue** of peripheral nerves (→ compressive damage).
  2. in **endoneurial tissue** (→ nerve ischemia).
  3. 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 >>](http://www.neurosurgeryresident.net/PN.%20Peripheral%20Neuropathies\PN.%20Bibliography.pdf)

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