Inherited Neuropathies

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Hereditary Neuropathies

- Charcot-Marie-Tooth/HSAN/Others
  - Common
    - Genetic neuropathies constitute up to ½ previously undiagnosed PN
    - 3/10,000 CMT alone
  - CMT largest group and consists of a number of different genetic entities

Symptoms

- Frequent tripping, falling
- Recurrent ankle injuries
- Slow running; difficulty with jumping
- Difficulty finding shoes that fit
- Gait disturbance (“walk like a duck”)
- “FLF” (funny-looking feet)
- As a child, leg cramps (especially nocturnal)
- Accelerated fatigue with walking even short distances
- “Athletic divergence”
- High (pes cavus) or flat (pes planus) arches
- Hammertoes
- Champagne bottle legs
- Asymmetry
- Peroneal muscle atrophy

- Distal predominant
- Sensory loss without pain as prominent feature
- Distal weakness; if severe, steppage gait or drop foot
- Foot deformities

- Feet may be flat
- Decreased EDB bulk
- Thin ankles
- Ankle ± or hypo-reflexia; sometimes hyporeflexia more proximally

- Enlarged, palpable nerves in demyelinating forms
- Variable degree of interosseous wasting
- Increased angle of distal leg to dorsal foot
- Varus deformity

- Is it hereditary?
- Never know until you have a positive genetic test, or...
- Family history!
  - AD: ~1/2, both ♀ and ♂
  - AR: in sibs but not parents
  - XL: no ♂ to ♀ transmission
  - Beware of variable expression/age-dependent penetrance
Sporadic, recessive, insufficient family history?

- Other clues to genetic etiology
  - Evidence of chronicity
    - Childhood clumsiness, longstanding difficulty with specific physical activities,
  - Signs > symptoms
    - No pain or non-neuropathic pain
    - Motor predominant signs and symptoms
  - NCS abnormalities > clinical signs
- Foot and ankle deformities

Suspect hereditary; now what?

- Mode of inheritance
  - AD (CMT1, 2, DI)
  - AR (CMT4)
  - X (CMTX)

- Electrophysiology
  - Axonal: Median MNCV > 32 m/s
  - Demyelinating: Median MNCV < 32 m/s
  - Dominant intermediate: 25-30 m/s
  - CMTX: 22-25 m/s

- Genetic subtyping
  - Letter designations correspond to genes, or chromosomal loci, or distinctive phenotype.

Inheritance patterns

- Autosomal dominant
  - Each child will have ½ chance of being affected
  - CMT1 or CMT2

- Autosomal recessive
  - Each child will have ¼ chance of being affected
  - CMT4

- X-linked
  - Each boy will have a ½ chance of being affected
  - Each girl will have a ½ chance of being a carrier
  - Fathers cannot pass it along to sons
  - CMTX

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**Median nerve conduction study in CMT1A**

- Uniform NCS slowing
- Median nerve conduction study in normal nerve

**Pathology and Electrophysiology**

- Normal nerve NCV normal
- Demyelinating CMT1 NCV slow
- Axonal CMT2 NCV near normal

**Suspect hereditary; now what?**

- Mode of inheritance
  - AD (CMT1, 2, DI)
  - AR (CMT4)
  - X (CMTX)
- Electrophysiology
  - Axonal: Median MNCV >32 m/s
  - Demyelinating: Median MNCV <32 m/s
  - Dominant intermediate: 25-50 m/s
  - CMTX: 25-40 m/s
- Genetic subtyping
  - Letter designations correspond to genes, OR chromosomal loci, OR distinctive phenotype

**Genetic Heterogeneity**

- CMT1:CMT2 = 2:1
- CSF protein may be elevated
- Foot deformities tend to be more classic
- NCS should not show significant progression with time
### CMT1A

- PMP22 = peripheral myelin protein
- 14% PMP22 deletions
- 40% CMT1 patients have duplication of PMP22
- Some CMT1A patients have hypermyelination

### CMT1B

Position of MPZ mutations determines electrophysiologic characteristics

- Hattori and colleagues demonstrated a bimodal distribution of median MCVs; >38 m/s or <38 m/s
- Siblings within a family showed good concordance of NCVs
- Therefore, demyelinating and axonal phenotypes are closely related to the position and nature of MPZ mutation (Hattori et al. '03; Bird et al. '97; Shy et al. '94)

### HNPP: Hereditary Neuropathy with Liability to Pressure Palsies

- Onset, young adults
- Classic history is of episodic nerve paresis with minor trauma/compression (40%), exercise, stretching, on awakening, etc.
- Associated with a mild axonal PN
- Differential includes
  - Recurrent neuralgic amyotrophy
  - Multiple lesions at common entrapment sites
  - Pachyaxonal neuropathy
  - PMP-22 point mutation
- Pathologic hallmark: tomacula

### CMT2

<table>
<thead>
<tr>
<th>Gene</th>
<th>Autosomal Dominant</th>
<th>Autosomal Recessive</th>
<th>X-linked</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPZ</td>
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<tr>
<td>PMP22</td>
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<tr>
<td>MTM2</td>
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<td></td>
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<tr>
<td>MFN2</td>
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<td></td>
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<td>GARS</td>
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<td>HSPB1</td>
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<tr>
<td>GDAP1</td>
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<tr>
<td>NDRG1 (LOM)</td>
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<td>SH3TC2</td>
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<tr>
<td>NEFL</td>
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</tbody>
</table>

Medications:
- Mitotane
- Prednisone
- Steroids

Electrophysiologic characteristics:
- Median MNCV ± 5 mm/s
- PALS (proximal) = weakness
- PALS (distal) = atrophy
- Sensory symptoms
  - Paresthesias
  - Hypalgesia

Onset, young adults

### CMT3

- Median MNCV >33 m/s
- SH3TC2 axonal/demyelinating/DI
- Therefore, demyelinating and axonal phenotypes are closely related to the position and nature of MPZ mutation (Hattori et al. '03; Bird et al. '97; Shy et al. '94)
The fog is only slowly lifting

Demyelinating Axonal AD AR CMTX DICMT dHMN HSMN HSN RAB7 GARS HSPB8 HSPB1 MFN2 GDAP1 LMNA MFN2 HSPB8 HSPB1 GARS GJB1 YARS DNM1 MPZ GDAP1 SH3TC2 PRX MTMR2 SBF2 NDRG1 PMP22 LITAF EGR2 MPZ NEFL

**General Rules: Buyer Beware!**

- Hard to ever exclude MPZ!
- Demyelinating + family history: PMP22, MPZ
- Demyelinating + little family history: CMT4, CMTX (GJB1)
- Mixed NCS: CMT4, CMTX (GJB1), YARS, DNM2, MPZ
- Axonal + family history: MFN2, MPZ (NEFL)
- Axonal + sensory predominant: RAB7, GARS (HSPB8)
- Axonal + hoarseness: 2C, GDAP1
- Axonal + motor predominant: GARS, HSPB1,8
- Axonal + optic atrophy: MFN2
- Axonal + spasticity: GDAP1

**Hereditary Sensory Autonomic Neuropathies**

- Sensory/autonomic disturbance out of proportion to motor
- Includes congenital insensitivity to pain
- Acral mutilations, foot ulcers, lost digits
- Autonomic features:
  - Impaired or labile sweating (FUO or episodic fever)
  - Labile BP, temperature, OH
  - Impotence

**Hereditary Sensory & Autonomic Neuropathy Syndromes**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene</th>
<th>Chromosome</th>
<th>Inheritance</th>
<th>Onset</th>
<th>Age</th>
<th>Clinical Features</th>
<th>Axon Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSAN1</td>
<td>SPTLC1</td>
<td>9q22</td>
<td>Dominant</td>
<td>&gt; 20 years</td>
<td>Pan-sensory loss</td>
<td>Acromutilation</td>
<td>Small &gt; Large</td>
</tr>
<tr>
<td>HSAN2</td>
<td>WNK1/HSN2</td>
<td>12p13</td>
<td>Recessive</td>
<td>Congenital, or Early childhood</td>
<td>Sensory loss</td>
<td>Acromutilation</td>
<td>Large &amp; Small</td>
</tr>
<tr>
<td>HSAN3</td>
<td>IKBKAP</td>
<td>9q31</td>
<td>Recessive</td>
<td>Congenital, or Early childhood</td>
<td>Sensory neuropathy</td>
<td>Impaired or labile sweating (FUO or episodic fever)</td>
<td>Large &amp; Small</td>
</tr>
<tr>
<td>HSAN4</td>
<td>TRKA/NGF receptor</td>
<td>1q21</td>
<td>Recessive</td>
<td>Congenital, or Early childhood</td>
<td>Sensory neuropathy</td>
<td>Anhidrosis</td>
<td>C-axon loss</td>
</tr>
<tr>
<td>HSAN5</td>
<td>NGF-β</td>
<td>1p13</td>
<td>Recessive</td>
<td>Early childhood to Adult</td>
<td>Absence of pain</td>
<td>No anhidrosis</td>
<td>Aδ &amp; C-axon loss</td>
</tr>
<tr>
<td>HSAN6</td>
<td>SCN9A</td>
<td>2q24</td>
<td>Recessive</td>
<td>Congenital</td>
<td>Absence of pain</td>
<td>No anhidrosis</td>
<td>None</td>
</tr>
<tr>
<td>HSAN7</td>
<td>SCN9A</td>
<td>2q24</td>
<td>Dominant</td>
<td>Childhood</td>
<td>Pain, distal</td>
<td>Episodic</td>
<td>None</td>
</tr>
<tr>
<td>Biemond ataxia</td>
<td>19q13</td>
<td>19 to 30 years</td>
<td>Dominant</td>
<td>Sensory loss</td>
<td>Ataxia</td>
<td>Large axons</td>
<td></td>
</tr>
<tr>
<td>Spastic paraparesis</td>
<td>5p15</td>
<td>1 to 5 years</td>
<td>Dominant</td>
<td>Sensory loss</td>
<td>Ataxia</td>
<td>Large axons</td>
<td></td>
</tr>
<tr>
<td>Ulceration</td>
<td>5p15</td>
<td>5 to 30 years</td>
<td>Dominant</td>
<td>Acromutilation</td>
<td>Large &amp; Small</td>
<td>Spastic paraparesis</td>
<td></td>
</tr>
</tbody>
</table>

- HSAN1 most common; only dominant form
- Normal or mildly abnormal NCS in 1, 5 (NGF-associated)
- Most result in insensitivity to pain, while HSAN5 patients are indifferent to pain
- Despite this, lancinating pains are prominent feature
- HSAN5 has normal NCS, QST, SSR
Other Hereditary Neuropathies

- Lysosomal storage disorders
  - Accumulation of lysosomal products (sphingolipids, mucolipids, etc) in neurons
  - CNS>CNS
  - Metachromatic Leukodystrophy, Krabbe Disease, Fabry Disease

- Peroxisomal disorders
  - Peroxisomes have enzymes involved in FA oxidation, bile/cholesterol synthesis, aa metabolism
  - ALD/AMN, RD (HMSN IV), Tangiers, CTX

- Hereditary ataxias
  - FA, vitamin E deficiency, abetalipoproteinemia
  - Defective DNA repair
  - Ataxia-telangiectasia, Cockayne syndrome

- Other
  - GAN, Infantile Neuroaxonal Dystrophy, Porphyria, Erythromelalgia

Summary of important features

<table>
<thead>
<tr>
<th>Inheritance</th>
<th>Onset</th>
<th>NCS</th>
<th>Gene</th>
<th>Lab</th>
<th>Associated features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lysosomal storage</td>
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<tr>
<td>Metachromatic LD</td>
<td>AR</td>
<td>i. late infantile</td>
<td>Arylsulfatase A</td>
<td>↓ arylsulfatase A activity (urine)</td>
<td>Dementia</td>
</tr>
<tr>
<td>ii. juvenile</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>iii. adult</td>
<td></td>
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</tr>
<tr>
<td>Krabbe Disease</td>
<td>AR</td>
<td>i. late infantile</td>
<td>β-galactosidase</td>
<td>↓ β-galactosidase activity (blood)</td>
<td>Dementia</td>
</tr>
<tr>
<td>ii. adult</td>
<td></td>
<td></td>
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<tr>
<td>Fabry Disease</td>
<td>XL</td>
<td>i. childhood</td>
<td>α-galactosidase</td>
<td>↓ β-galactosidase activity (blood)</td>
<td>Skin angiokeratomas, early CVAs</td>
</tr>
<tr>
<td>ii. early adult</td>
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<tr>
<td>Peroxisomal disorders</td>
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<tr>
<td>ALD/AMN</td>
<td>XL</td>
<td>early adult</td>
<td>Peroxisomal transmembrane adenosine triphosphate-binding cassette transporter gene (ABC transporter gene)</td>
<td>↑ VLCFA (urine), + adrenal insufficiency</td>
<td>Dementia; may look like MS</td>
</tr>
<tr>
<td>Tangier Disease</td>
<td>AR</td>
<td>late infantile</td>
<td>Phytanoyl-CoA α-hydroxylase (PAHX)</td>
<td>↑ Phytanic acids (serum)</td>
<td>Ichthyosis, anosmia</td>
</tr>
<tr>
<td>ii. adult</td>
<td></td>
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</tr>
<tr>
<td>Cerbrotendinous Xanthomatosis</td>
<td>AR</td>
<td>early adult</td>
<td>Sterol 27 hydroxylase</td>
<td>↑ cholestanol</td>
<td>Tendon xanthomas</td>
</tr>
<tr>
<td>Cerebrotendinous Xanthomatosis</td>
<td>AR</td>
<td>early adult</td>
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<tr>
<td>Hereditary ataxias</td>
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<tr>
<td>Friedreich ataxia</td>
<td>AR</td>
<td>childhood</td>
<td>Frataxin (trinuc repeat)</td>
<td>Gait ataxia; dysarthria</td>
<td></td>
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<tr>
<td>Vitamin E deficiency</td>
<td>AR</td>
<td>childhood</td>
<td>αtocopherol transfer protein gene</td>
<td>↓ vit E ataxia</td>
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<tr>
<td>Abetalipoproteinemia</td>
<td>AR</td>
<td>childhood</td>
<td></td>
<td>↓ abetaliprotein levels; acanthocytosis</td>
<td>Ataxia, RP, steatorrhea, distal extremity sensory loss</td>
</tr>
<tr>
<td>Disorders DNA repair</td>
<td></td>
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<tr>
<td>Ataxia-telangiectasia</td>
<td>AR</td>
<td>childhood</td>
<td>ATM gene (phosphatidyl inositol 3)</td>
<td>↑αFetoprotein</td>
<td>oculocutaneous telangiectasias; frequent sinopulmonary infections</td>
</tr>
<tr>
<td>Cockayne syndrome</td>
<td>AR</td>
<td>childhood</td>
<td>RNA polymerase II transcription factors</td>
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<tr>
<td>Progeria</td>
<td></td>
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<tr>
<td>Erythromelalgia</td>
<td>AD</td>
<td>any age</td>
<td>Nav1.7 gene</td>
<td>intense burning/warmth</td>
<td></td>
</tr>
</tbody>
</table>

More general clues

- PN + Dementia: MLD, KD, ALD/AMN (GAN)
- PN + ataxia: FA, vitamin E, abetalipoproteinemia, GAN
- PN + angio keratomas: Fabry
- PN + orange tonsils: Tangier
- PN + tendon xanthomas: CTX
- PN + ichthyosis: Refsum

Questions?