Hereditary Neuropathies

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Institute of Neurology,
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Contents of talk

1. Nomenclature of the hereditary neuropathies

2. Overview of the common subtypes

3. Illustrative clinical cases
   • Distinguishing inflammatory from genetic demyelinating neuropathies
   • Determining pathogenicity of novel variants
Clinical presentation

• Length dependent weakness or sensory loss / paraesthesia
  – Foot drop and hand weakness

• Slow progression

• Onset varies from childhood to late adulthood

• Often but not always a family history
  – De novo mutations
  – Non paternity
  – Late onset
Neurophysiology

- Is there a neuropathy
  - Sometimes only detected on EMG
- Is there involvement of motor and sensory nerve fibres
  - Hereditary motor AND sensory neuropathy (CMT) vs HMN or HSN
- Is the neuropathy demyelinating or axonal?
Diagnostic algorithm

Hereditary weakness or numbness

Neurophysiology

Demyelinating

Sensory predominant

CMT1

Axonal

Mixed motor and sensory

CMT2

Motor predominant

HSN

CMT2

HMN

Intermediate CMT (25-45 m/s) : commonest cause CMTX1 (GJB1)
CMT in most patients is due to a handful of genetic mutations.

*Mitochondrial – Mt ATPase 6
>80% autosomal dominant CMT1 is due to the 17 duplication
CMT1A = Chromosome 17p duplication
<table>
<thead>
<tr>
<th>Sensory</th>
<th>µV</th>
<th>m/s</th>
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<tbody>
<tr>
<td>Radial</td>
<td>Absent</td>
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<tr>
<td>Median</td>
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<td>Ulnar</td>
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<tr>
<td>Sural</td>
<td>Absent</td>
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<tr>
<td>Superf. Peroneal</td>
<td>Absent</td>
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<tr>
<td>Motor</td>
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<td>Median</td>
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<tr>
<td>Right</td>
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<td>Left</td>
</tr>
<tr>
<td>Common peroneal</td>
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</tr>
<tr>
<td>DML</td>
<td>7.8 ms</td>
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<tr>
<td>CV (wrist-elbow)</td>
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<td>CMAP (wrist)</td>
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<tr>
<td>DML</td>
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<tr>
<td>CV (fib neck-ankle)</td>
<td>20 m/s</td>
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<td>CMAP (ankle)</td>
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<tr>
<td>Right</td>
<td>10.8 ms</td>
<td>10.3 ms</td>
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<tr>
<td>Left</td>
<td>20 m/s</td>
<td>20 m/s</td>
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<tr>
<td>Right</td>
<td>2.1 mV</td>
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<tr>
<td>Left</td>
<td>2.6 mV</td>
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</table>
Peripheral myelin protein 22: PMP22

NORMAL

CHARCOT-MARIE-TOOTH

HNPP

1.5 Mb (CMT1A)

17q11

5 Mb (SMS)

Smith-Magenis
Hereditary Neuropathy With Liability to Pressure Palsies (HNPP)

- Autosomal dominant
- Chromosome 17p deletion (rarely PMP22 point mutations)
- Recurrent pressure palsies.
- Characteristic neurophysiology
- Care with alcohol and anaesthetics
- Avoid surgery for CTS unless refractory pain or progressive weakness

“Toilet Seat” Sciatic Neuropathy
## HNPP

<table>
<thead>
<tr>
<th>Sensory</th>
<th>µV</th>
<th>m/s</th>
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<td>51</td>
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<td>Sural</td>
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<td>43</td>
<td>CMAP (fib. Neck)</td>
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<tr>
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<td>40</td>
<td>CMAP (pop. Fossa)</td>
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<tr>
<td>Median</td>
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<tr>
<td>DML</td>
<td>5.3 ms</td>
<td>4.5 ms</td>
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<tr>
<td>CV (wrist-elbow)</td>
<td>51 m/s</td>
<td>49 m/s</td>
<td>CV (wrist-below elbow)</td>
<td>65 m/s</td>
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<td>CMAP (wrist)</td>
<td>0.7 mV</td>
<td>1.8 mV</td>
<td>CV (around elbow)</td>
<td>26 m/s</td>
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<tr>
<td>CV (around elbow)</td>
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<td>CMAP (wrist)</td>
<td>4.6 mV</td>
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</table>
1. 17p duplication
2. PMP22
3. GJB1
4. MPZ
5. MFN2 (axonal)

6. SH3TC2 (recessive demyelinating)
CMT X

Clinically similar to CMT1

No male to male transmission

Males more severe than females

Males demyelinating / females axonal

Patchy clinically (may mimic CIDP on NCS)

Sometimes, upper limb predominant

Central nervous system
<table>
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<tr>
<th>Sensory</th>
<th>µV</th>
<th>m/s</th>
<th>Motor</th>
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<td>Radial</td>
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<td>Common peroneal</td>
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<tr>
<td>Median</td>
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<td>DML (EDB)</td>
<td>5.9 ms</td>
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<td>Ulnar</td>
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<td>CMAP (ankle)</td>
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<td>Sural</td>
<td>Absent</td>
<td></td>
<td>CMAP (pop. Fossa)</td>
<td>0.1 mV</td>
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<tr>
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<td></td>
<td>Ulnar</td>
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<tr>
<td>DML</td>
<td>6.8 ms</td>
<td>6.4 ms</td>
<td>DML</td>
<td>5.3 ms</td>
<td>5.4 ms</td>
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<tr>
<td>CV (wrist-elbow)</td>
<td>24 m/s</td>
<td>-</td>
<td>CV (wrist-below elbow)</td>
<td>30 m/s</td>
<td>32 m/s</td>
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<tr>
<td>CMAP (wrist)</td>
<td>0.6 mV</td>
<td>0.1 mV</td>
<td>CV (around elbow)</td>
<td>31 m/s</td>
<td>35 m/s</td>
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<tr>
<td>CMAP (elbow)</td>
<td>0.3 mV</td>
<td>No response</td>
<td>CMAP (wrist)</td>
<td>6.3 mV</td>
<td>2.2 mV</td>
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Split hand in CMTX1

Weakness and wasting of APB > ADM or FDIO
Non-coding mutations in GJB1 account for 10% of cases of CMTX

Promoter region not covered in older panels or GJB1 sequencing (2012)
For CMT2, HSN and HMN, most genes are unknown.
CMT2A (MFN2)

- Mutations in MFN2 are the commonest cause of axonal CMT (10-20%)
- Majority autosomal dominant
  - Can be recessive
  - Associated with optic atrophy in a minority
- Traditionally severe
  - Young onset
  - Wheelchair by 20
RESEARCH REPORT

MFN2 deletion of exons 7 and 8: founder mutation in the UK population

MLPA

Copy number variations (deletions / duplications) will not be detected on most ‘hereditary neuropathy’ panels

Deletion of MFN2 exons 7 and 8
Hereditary motor neuropathies

- 5q Spinal Muscular Atrophy (SMA)
  - Most common form
  - Due to autosomal recessive mutations in SMN1

- Non 5q SMA (rarer)
  - SMALED (DYNC1H1 and BICD2)

Proximal > distal weakness
(Non length dependent)

Distal > proximal weakness
(Length dependent)

- Distal HMN (also called distal SMA)
  - Lower limbs (HSPB1 and BSCL2)
  - Upper Limbs (GARS and BSCL2)
Non-5q SMA
Spinal Muscular Atrophy Lower Extremity Dominant (SMALED)

p.R399G in DYN1C1H1

p.R501P BICD2
Distal hereditary motor neuropathy

- No agreed classification
- Dominant, recessive or X-linked
- Originally referred to as distal spinal muscular atrophy
  - Selective motor nerve involvement thought to localise pathology to the motor neuron cell bodies in the spinal cord
  - Now thought to be a ‘dying back’ axonopathy
Phenotypic clues in dHNM

- Lower limb onset dHMN (dHMN II or HMN II)
  - Dominant mutations in the small heat shock protein (*HSPB1*)
    - Molecular chaperone that prevents protein misfolding
  - Predominant calf wasting
  - Dominant mutations in *BSCL2*
    - Spasticity

- Upper limb onset dHMN (dHMN V or HMN 5)
  - Dominant mutations in *GARS* and *BSCL2*
Hereditary sensory neuropathy

- Commonly due to dominant mutations in serine palmitoyl transferase 1 (SPTLC1)
- Early pain and temperature loss
- NO autonomic involvement
- Motor involvement
- Motor conduction velocity slowing in males
Sphingolipids are a class of lipids important in signal transmission and cell recognition.

Mutations in the SPTLC1 subunit of SPT (Serine palmitoyltransferase) promote the substitution of serine by alanine or glycine and the production of toxic sphingolipids.
A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DELAYED-START TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF L-SERINE IN SUBJECTS WITH HEREDITARY SENSORY AND AUTONOMIC NEUROPATHY TYPE 1 (HSAN1) (S45.001)

Eighteen HSAN1 patients were equally randomized to L-serine or placebo for 1 year.
Participants randomized to L-serine experienced a significant decline in the CMTNS over 1 year relative to placebo (−1.8 units, 95% CI −3.3 to −0.3, p = 0.02)
1-deoxySL levels declined significantly among subjects on L-serine vs. those on placebo
Illustrative clinical cases
Case 1.

• 52-year old right handed lady.

• Normal birth, walked at 10 months, able runner in the first decade.

• Aged 12 started to trip and was noted to be flat footed.

• Early 20s: Bilateral ankle osteotomies

• Late 20’s: Developed a waddling gait, prescribed ankle/foot orthoses.

• No family history
Neurophysiology aged 14

Referred by: DR. MACKENZIE. OP.

Right sural nerve:
S.A.P. amplitude (antidromic)  : 4 uV
" latency to onset (10.5 cm)  : 3.0 msec (CV_max 35 m/sec)
" latency to -ve peak        : 4.3 msec
" form                       : dispersed

Left sural nerve:
S.A.P.                        : absent.

Right median nerve:
S.A.P. amplitude (F11)       : 12 uV Ts 3 mA
" latency to onset (11.5 cm) : 2.4 msec (CV_max 48 m/sec)
" latency to -ve peak        : 3.2 msec
" form                       : broad

Distal motor latency to thenar:
M.C.V. elbow - wrist (22 cm) : 4.7 msec

Thenar M.A.P. amplitude ( -ve phase )
stim. wrist                   : 3.0 mV  dispersed
" elbow                      : 2.5 mV  more dispersed
" wrist                      : 35 msec

'F' wave latency

Left medial popliteal nerve:
Distal motor latency to Abd.hallucis : 9.3 msec
M.C.V. (pOp.fossa - ankle (37 cm)   : 21 m/sec
Case 1

- Early 30s: Started using a wheelchair.
  - Unilateral vocal cord palsy

- Early 40s: No longer able to weight bear
  - Re-investigated in the form of repeat neurophysiology, lumbar puncture (protein 0.7g) and a nerve biopsy.
    - **Neurophysiology:**
      - Median SAP of 5.9, radial SAP of 7.1
      - Temporal dispersion of the right median and ulnar nerves
    
    - **Sural nerve biopsy:** “Severe axonal loss with some onion bulb formation. The onion bulb formation is irregular contrary to the usual appearances in CMT1...... and favours an acquired neuropathy.”

- Treated with steroids for one year with no improvement.
- Aged 45: Developed left sided trigeminal neuralgia
  - Commenced on non invasive ventilation
Case 1

• Aged 49:
  – Stridor, but all other cranial nerves normal
  – Proximal upper limb weakness (shoulder abduction grade 4). No movement of the intrinsic hand muscles.
  – Grade 1 power at the hip and knee and grade 0 of ankle dorsi and plantar flexion.
  – Areflexia

• Genetics:
  – 17p duplication, PMP22, MPZ, GJB1, LITAF, SH3TC2 all negative
CMT1D due to mutation in EGR2

- c.1141C>T p.(Arg381Cys) heterozygous pathogenic mutation detected in EGR2
- Autosomal dominant and recessive mutations described
- May present as a severe early onset demyelinating neuropathy in the 1st/2nd decade
- Ophthalmoplegia, scoliosis, vocal cord palsy and deafness described.
Case 2

• 26-year old male
• Rapid development of a wasted left arm over a period of 2 years
• Previous diagnosis of a congenital hypomyelinating neuropathy (CMT1)
  – walked late at 26 months of age
  – wheelchair at 13 years of age
  – Mild symmetric weakness and preserved function in both hands two years prior to presentation
• Healthy unrelated parents
Case 2

- No improvement in left arm function following a 5-day course of 500 mg methylprednisolone
- Nerve conduction studies performed at the age of 13 years, 19 years and at 26 years
  - demyelinating neuropathy with dispersed proximal responses
  - A fall in the conduction velocity in the right median nerve from 16 m/s to 4 m/s over 6 years
  - Conduction block in the right median nerve.
- EMG: Fibrillations and PSW in left hand
- Frequent large thinly myelinated nerve fibres surrounded by concentric Schwann cell profiles (onion bulbs)
- No inflammatory cell infiltrate
• **Compound heterozygous mutations in FIG4**
  - I41T point mutation in exon 2
  - 8-bp deletion in exon 8 (p.K278YfsX5)
Case 3

- 20 year old male
- Presented with delayed walking and poor balance in the first decade of life.
- Slowly progressive course
- Distal amyotrophy predominantly involving the upper limbs and lower limb spasticity (Silver syndrome).
- His past medical history is notable for congenital cataracts, mild learning difficulties and left ventricular impairment
Case 3

• Neurophysiology
  – Normal sensory action potentials
  – Small compound muscle action potentials of distal muscles and neurogenic changes on EMG

  – Consanguineous parents
  – Affected sibling
Whole exome sequencing

- Filtering revealed 43 homozygous variants present at a frequency of <1%
- Filtering of known CMT, dHMN, SMA, ALS, HSP genes revealed 2 variants
  - IKBKAP: MAF 0.5%, phenotype ≠ Riley-Day syndrome (familial dysautonomia)
  - RTN2, R191*: Novel, nonsense mutation in exon 4
  - Heterozygous nonsense/missense mutations in RTN2 previously reported as a cause of HSP
Mutations in the ER-shaping protein reticulon 2 cause the axon-degenerative disorder hereditary spastic paraplegia type 12

HSP type 12 postulated to be due to RTN2 halpo-insufficiency
Case 3

• However....
  – Both parents heterozygous for RTN2, R191* loss of function allele and normal
  – What is the risk of the proband’s offspring developing HSP/dHMN?
Case 3

- 43 loss of function alleles out of 250,000 control alleles in GNOMAD (healthy control database)
- RTN2 deletion in original paper only reported in a sporadic case
- Therefore, haplo-insufficiency unlikely to be pathogenic
  - Low risk for future generations
Mary Reilly
Julian Blake
James Polke
Matilde Laura
Sebastian Brandner
Gita Ramdharry
Zane Jaunmuktane

QUESTIONS?