Central Manchester University Hospitals NHS
NHS Foundation Trust

Peripheral Neuropathy

EPNS Neuromuscular Course

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Declarations

- PI in clinical trials for PTC Therapeutics, Summit
- Consultancy for Santhera and Biogen
- Conference fees and travel by PTC therapeutics

Topics

- Acquired neuropathy
- Genetic neuropathy
- Genetic multisystem disorders which include neuropathy

Acquired neuropathy

- Guillaine-Barre syndrome
  - AIDP
  - AMAN
  - AMSAN
- CIDP
- Drugs/toxins

GBS

Required features

- Progressive weakness >1 limb
- Areflexia, varying degree

Supportive features

- Progression stopped by 4 wks
- Relative symmetry
- Cranial N involvement
- Autonomic dysfunction
- ↑CSF protein, <10WBC
- Abnormal neurophysiology

GBS

- Pain & paraesthesiae common
- May be autonomic dysfunction, hypertension, urinary retention, cardiac dysrythmia
- 7-15% require ventilation, ↑risk rapid onset, cranial N involvement, ↑CSF protein
- Management; Supportive, IVIG, plasmapheresis

GBS Differential diagnosis

- Botulism
- Myelopathy
- Viral myositis
- Porphyria
- Tick bite paralysis
- Toxins

GBS types

- AIDP
  - Most common
  - Neurophysiology – slow NCV, dispersion, conduction block
  - 1% Miller Fisher syndrome (GQ1b ab)
- AMAN
  - C jejuni (GM1 ab)
- AMSAN

CIDP

- May be
  - Monophasic with progression over >2 months
  - Slowly progressive
  - Relapsing remitting course

CIDP diagnosis

- Neurophysiology
  - Generalised slowing NCV
  - Dispersion CMAP
  - Conduction block
- ↑CSF protein
- Exclusion of other causes
- Biopsy
  - Demyelination, inflammatory cell infiltrate

Drugs/toxins

- Heavy metals
- Organophosphates
- Drugs
  - Chemotherapy
  - Isoniazid
  - Pyridoxine
  - Itraconazole
  - Thalidomide

Chemotherapy induced peripheral neuropathy (CIPN)

- Vinca alkaloids, platinum compounds
- Vincristine
  - incidence increases with cumulative dose
  - 35% neuropathic pain
  - 78-100% neuropathy of any grade
  - neurophysiology; axonal, motor predominant
- Cis-platinin
  - incidence & characteristics less well defined
- Concomitant meds may increase risk
- Adult survivors 20% sensory, 17.5% motor impairment

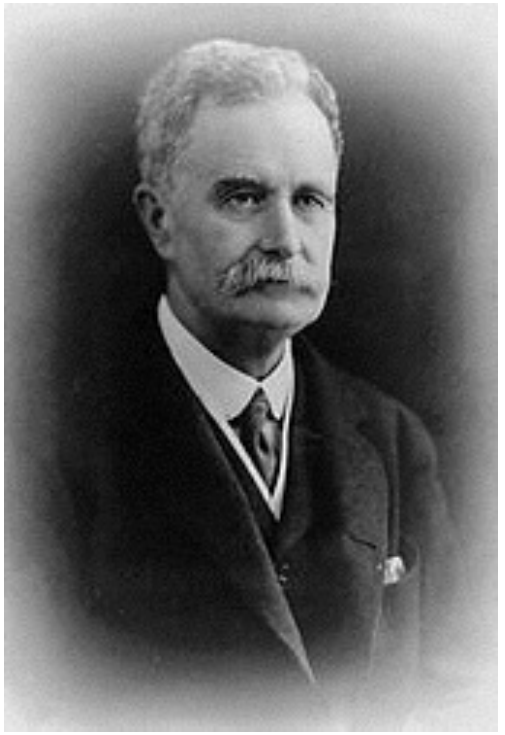
Genetic neuropathy

- Classification has been confused & confusing
- Various terms have been used; peroneal muscular atrophy, HMSN and CMT

Genetic neuropathy

- CMT motor and sensory neuropathy
- HNPP hereditary neuropathy with a liability to pressure palsies
- dHMN distal hereditary motor neuropathy
- HSAN hereditary sensory and autonomic neuropathy

CMT



Most common neuromusular condition, prevalence 40/100 000, 200 000 cases in EU

CMT Clinical features

- Foot deformity

CMT clinical features

- Clumsy gait
- Tremor
- Falls
- Pain - usually secondary to deformity
- Positive sensory symptoms uncommon
- Other features
  - Scoliosis
  - Cranial nerve palsy

CMT examination findings

- Muscle wasting
  - Peroneal muscles
  - Intrinsic hand muscles
- Muscle weakness
  - Ankle dorsiflexion, eversion
  - intrinsic hand muscles
- Absent reflexes
- Sensory loss

CMT severe forms

- Early onset
- Severe hand / foot weakness
- Proximal weakness
- May develop respiratory problems

CMT classification

- Demyelinating
  - NCV <38m/s upper limb
- Axonal
  - NCV >38m/s upper limb
- Intermediate
  - NCV 25-45m/s
  - X-linked most common GJB1

CMT classification

- CMT1 demyelinating
- CMT2 axonal
- DSN/CHN
- CMT4

HNPP

- Recurrent nerve palsy at compression sites (common peroneal, radial)
- Mildly slow NCV
- 85% deletion 17p11.2
- 15% PMP22 mutation
- can also present as mild CMT

dHMN

- Rare
- Presentation similar to CMT
- Neurophysiology motor conduction only affected
- Genes
  - HSPB1
  - HSPB8
  - GARS/BSCL2 upper limb predominance

Genetic testing

- Benefits
  - Confirms diagnosis
  - Accurate genetic advice to family
  - Non-invasive diagnostic testing
- Problems
  - Limited availability
  - Few common genes
  - Many rare genes

CMT genes

	Number of genes
CMT 1	9
Intermediate	5
CMT2	25 AD 8 AR
CMT4	13

MPZ Phenotypes

CMT1B,
Dominant intermediate type D
CMT4E
DSN
CMT2I & 2J

Genetic testing in CMT

Reilly M

CMT1 genetics

- CMT1a
  - 17p11.22 duplication 70% CMT1 Europe (10% sporadic)
  - PMP22 point mutation (also DSN/CHN)
  - CMT1b
  - 10% CMT1 MPZ mutation (also DSN/CHN & CMT2)
- Other genes rare
  - EGR2, LITAF, SIMPLE, NEFL

CHN/DSN Genetics

- PMP22 mutation
- MPZ mutation
- EGR2 mutation
- PRX mutation

CMT 2 genetics

- Mutations in 8 genes account for 25%
- Clinical phenotype important
  - "classic" CMT
    - CMT2A MFN2 (20% CMT2)
    - MPZ, NEFL, HSPB1, HSPB8
  - Prominent sensory involvement (like HSAN1)
    - CMT 2B RAB7
  - Upper limb predominance
    - GARS, BSCL2
  - CMT2C TRPV4 skeletal dysplasia, neuropathy

CMT4 genetics

- 13 genes to date
  - CMT4A GDAP1 gene, also axonal, commonest recessive, may be vocal cord/diaphragmatic involvement, rare AD mutations in CMT2
  - CMT4B1 MTNR2 vocal cord paresis, scoliosis
  - CMT4C SH3TC2, scoliosis
  - CMT4D NDRG1, Balkan gypsy population, deafness,
  - CTPD1, CCFDN congenital cataract, facial dysmorphism, neuropathy
  - LMNA, axonal, severe

- Giant axonal neuropathy, GAN
  - weakness, ataxia, frizzy hair, cognitive impairment, MRI white matter abnormality, also mild cases
- SMARD1, IGHMBP2
  - diaphragmatic weakness/eventration, distal weakness
  - sensorimotor polyneuropathy

J Inherit Metab Dis
DOI 10.1007/s10545-010-9242-z

RAPID COMMUNICATION

Brown-Vialetto-Van Laere and Fazio Londe syndrome is associated with a riboflavin transporter defect mimicking mild MADD: a new inborn error of metabolism with potential treatment

Annet M. Bosch · Nico G. G. M. Abeling · Lodewijk IJlst · Hennie Knoester · W. Ludo van der Pol · Alida E. M. Stroomer · Ronald J. Wanders · Gepke Visser · Frits A. Wijburg · Marinus Duran · Hans R. Waterham

BVVL
Cranial neuropathies, deafness
Diaphragmatic weakness
Sensorimotor polyneuropathy
SLC52A1, SLC52A2, SLC52A3

CMTX

- Consider when no male to male transmission
- GJB1 (connexin)
  - Occassionally white matter abnormality on MRI, may be transient severe CNS involvement (ADEM like)

CMT with pyramidal signs

- Overlap with HSP with distal amyotrophy

CMT Management

- Prevention/limitation of deformity
  - Splinting
  - stretching
  - casting
- Surgery
- Supportive for severe

HSAN clinicial features

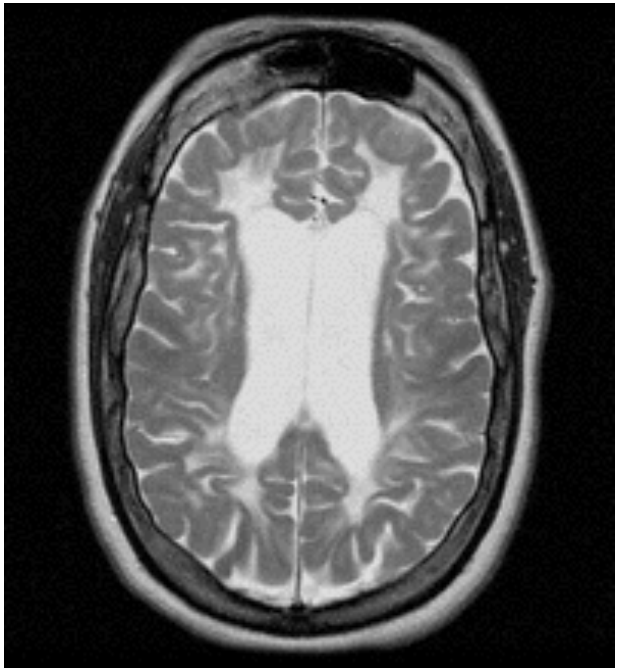
- Injuries
  - Trauma, burns
  - Self inflicted injury
  - Infections
  - Charcot joints
- Anhidrosis
  - Recurrent pyrexia
- May be associated LD

HSAN

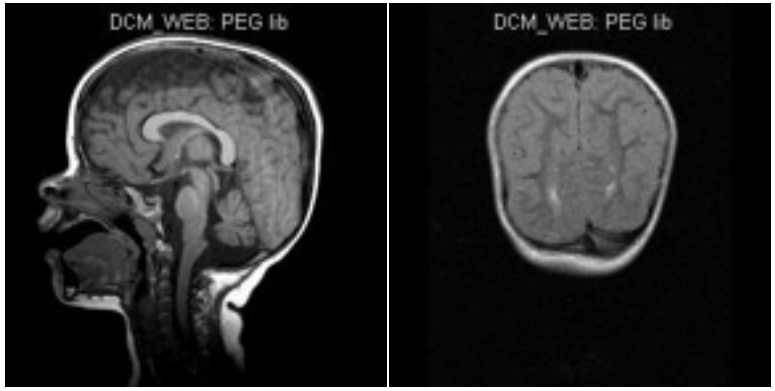
- HSAN1
  - AD onset 2nd decade, SPTLC1/SPTLC2
- HSAN2
  - AR HSN2, severe, mild anhydrosis
- HSAN3 Riley-Day syndrome
- HSAN4
  - AR NTRK1 mutations, severe, anhydrosis, LD
- HSAN5

Neuropathy in multisystem disorders

- Leucodystrophies
  - Rarely may be presenting feature



INAD PLA2G6



Neuropathy in multisystem disorders

- Mitochondrial disorders
  - often unrecognisable due to prominent central features, may assist with syndrome classification
- Peroxisomal disorders
- CDG
- Refsum disease
- Fabry

Summary

- Neuropathy is relatively common
- May be acquired
- May be genetic
- May occur as part of a multisystem disorder in which it may be presenting feature or an essential clue