Pathology of peripheral neuropathies

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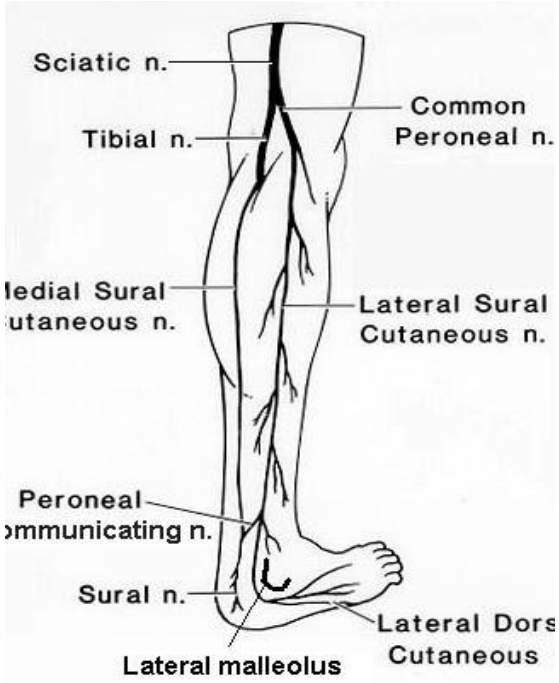
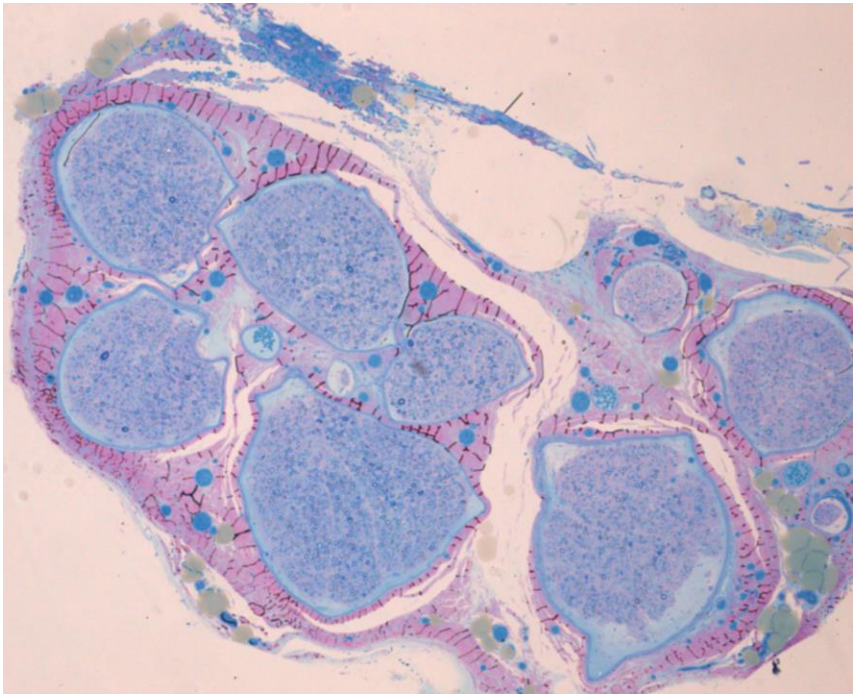
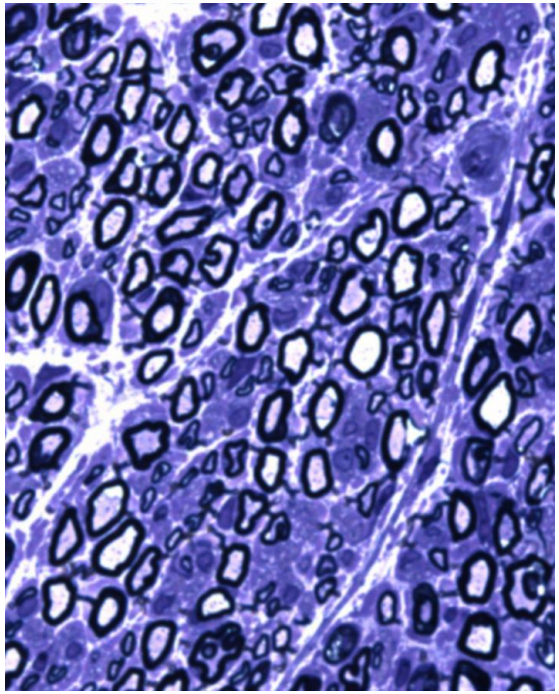
- Peripheral nerve microanatomy
- Developmental changes
- Methods of biopsy assessment
- Indications for biopsy assessment
- Major morphological disease patterns
- Illustrative examples of disease
  - ***Acquired and inherited demyelinating neuropathies***
  - ***Multisystem inherited disorders – peripheral neuropathy***
  - ***Vasculitic neuropathy***
  - ***Neurolymphomatosis***
  - ***Paraproteinaemic neuropathies***
  - ***Leprous neuropathy***

- Anatomical compartments – epineurium, perineurium
- and endoneurium
- Vasculature – epineurial and endoneurial
- Myelinated and unmyelinated fibres – size and distribution
- Normal cellular constituents
- Endoneurial matrix







Key developmental changes – human peripheral nerve

- Myelination commences at around 18 weeks gestation
- Maximum density of axons at birth
- Gradual maturation through childhood; increase in size and separation of fibres
- Higher G-ratio (axon diameter/full myelinated axon diameter) at birth 0.7-0.8 indicating relative hypomyelination – adult values (0.5-0.7) reached by 5 years
- Fibre diameter frequency unimodal at birth – transition to bimodal distribution at 1 year
- Internodal length 200-300 microns at birth increases to 200-1800 microns by adulthood

Ageing – human peripheral nerve

- Increased endoneurial area and collagen
- Decrease in myelinated fibre frequencies throughout adult life
- Increased frequency of axonal degeneration and regeneration throughout adult life
- Increased frequency of segmental de- and remyelination – increased scatter of G ratio
- Hyalinisation and thickening of endothelial capillary and perineurial cell basement membranes

Methods of biopsy assessment

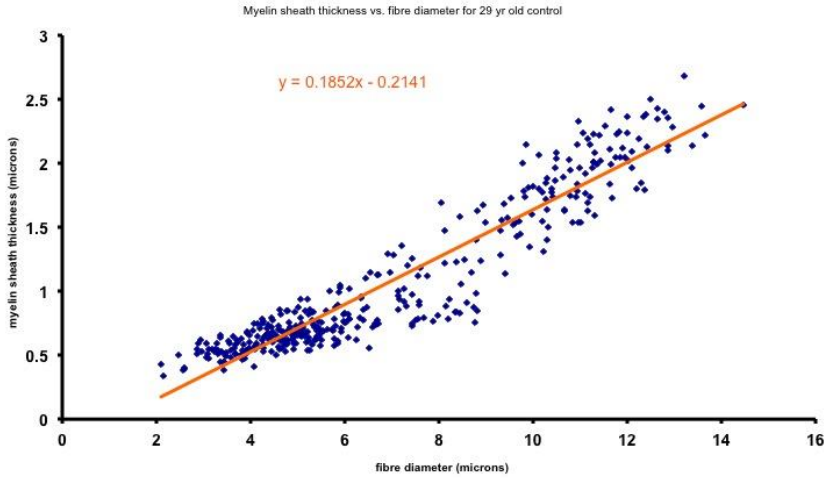
- Light microscopy – histology
- and immunohistochemistry
- Standard panel of stains – HE, EVG

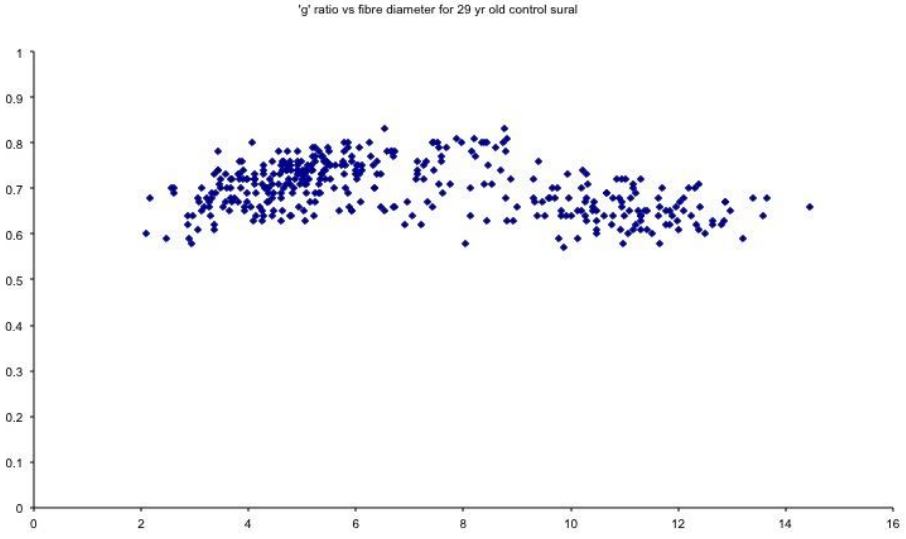
Congo Red, PAS, myelin (SMI94R), axons (neurofilaments), inflammatory markers (CD45, CD3, CD8, CD20, CD79a, CD138 CD68)

- Resin semi-thin sections
- Morphometry

Quantitative analysis of axon number, diameter, myelin sheath thickness (G ratio)

- Ultrastructure

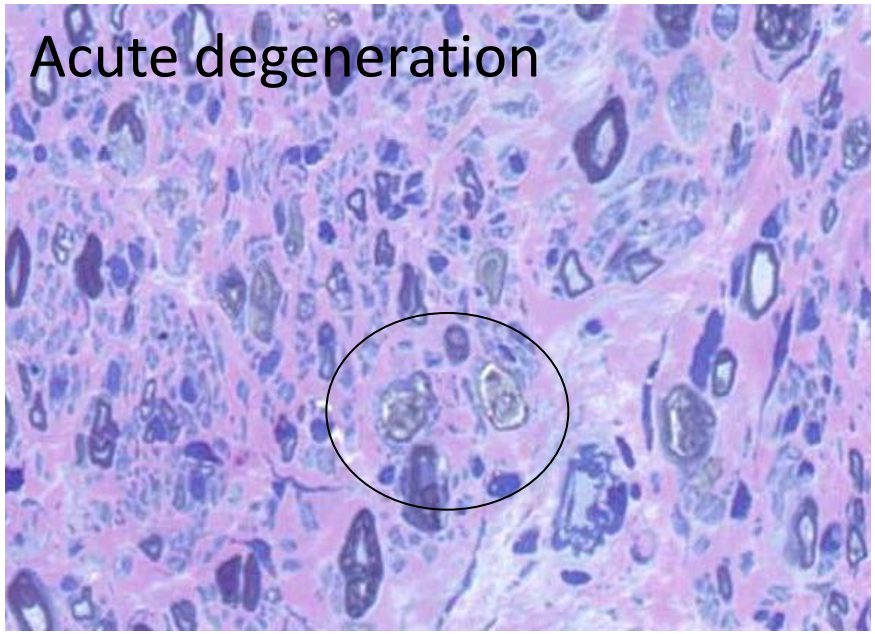


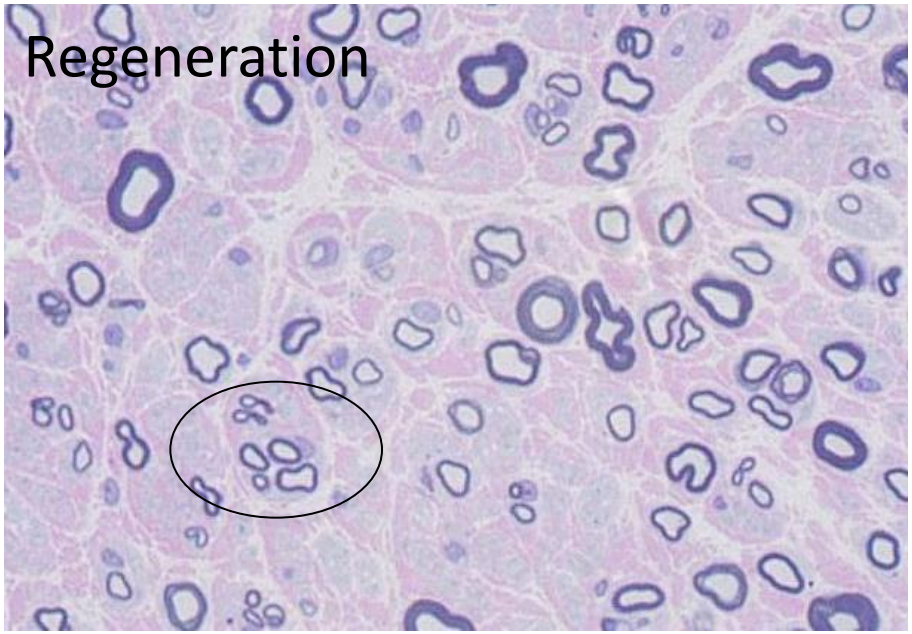


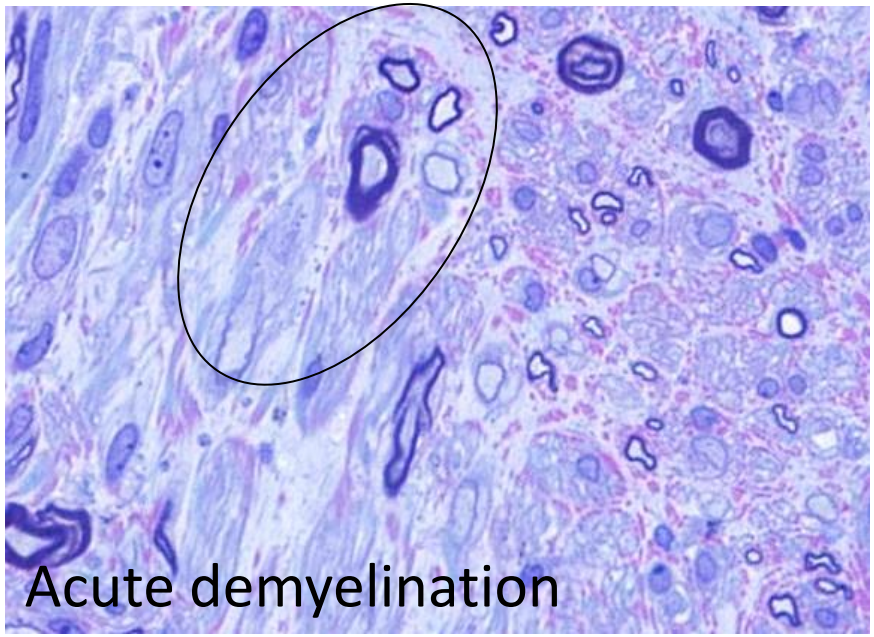
When to biopsy?

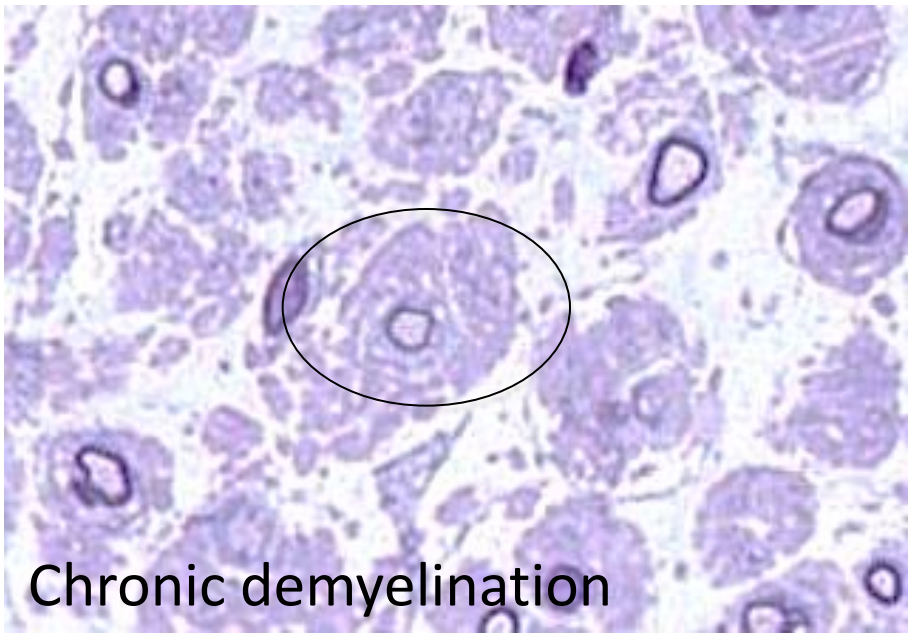
- Investigation of a suspected inflammatory neuropathy that is potentially treatable
- Suspected vasculitis is a major indication (particularly non-systemic vasculitic neuropathy)
- Other inflammatory/dysimmune neuropathies such as CIDP, sarcoid
- Paraproteinaemic neuropathies (may have associated inflammatory component)
- Amyloid neuropathy (potentially treatable)
- Infections (HIV, leprosy)
- Toxic neuropathies
- Selected inherited neuropathies with negative genetic testing and in the paediatric setting (genetic vs acquired demyelination)

Patterns of axonal and Schwann cell response









GBS

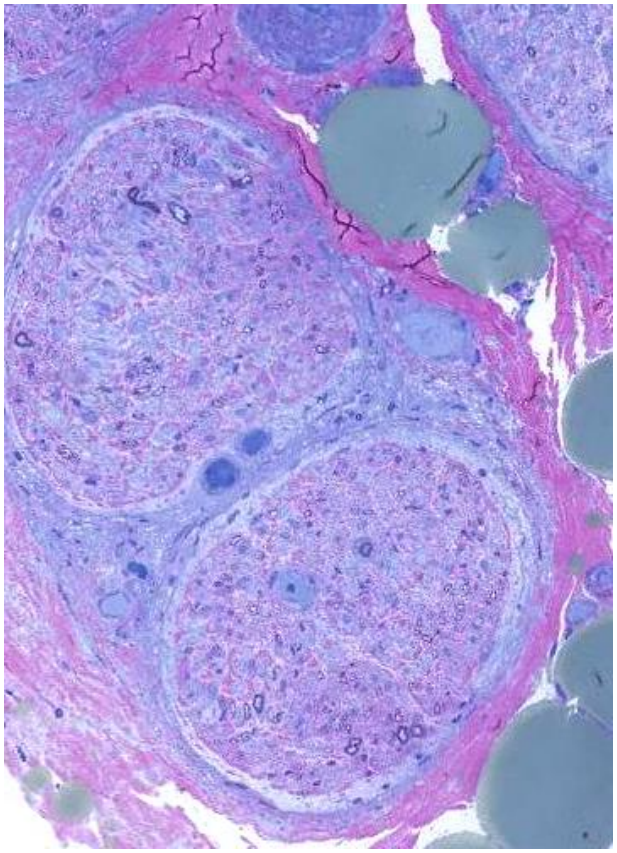
18 F; rapid onset radicular leg pain, ascending sensory disturbance and motor weakness

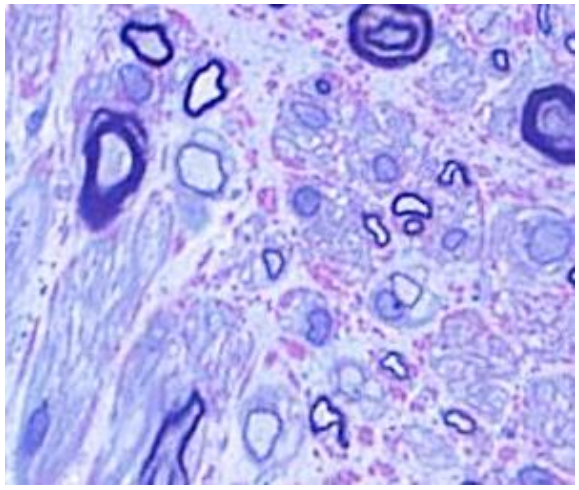
NCS – severe demyelinating sensorimotor neuropathy with secondary axonal loss and active denervation

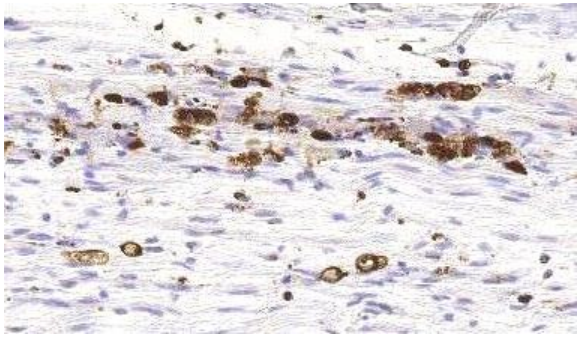
Progressed despite IvIg; developed LMN facial weakness

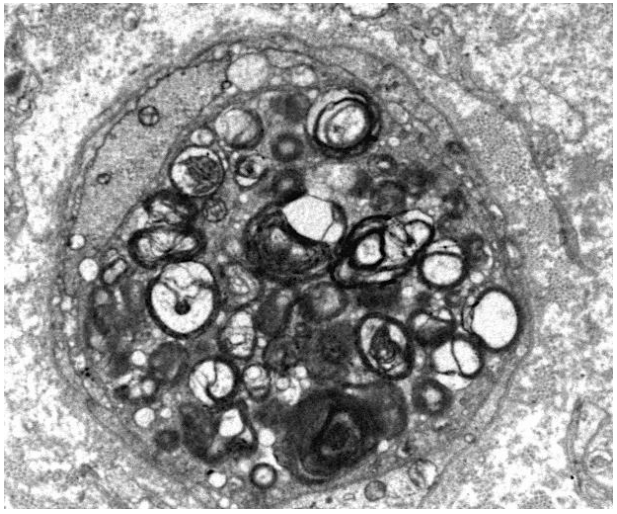
? atypical GBS/vasculitis

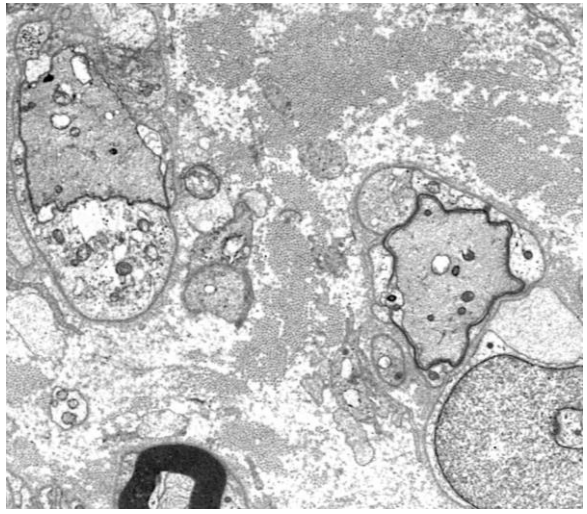
Left sural nerve – acute macrophage mediated demyelination; macrophage predominant inflammation











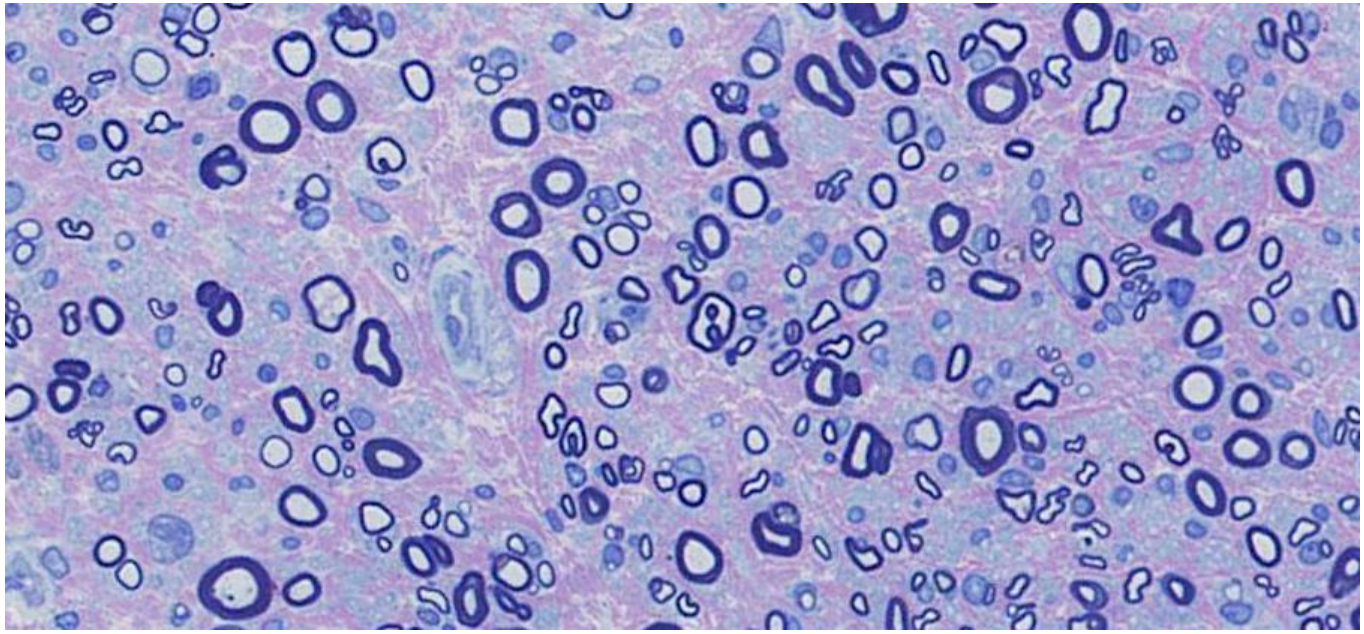
CIDP

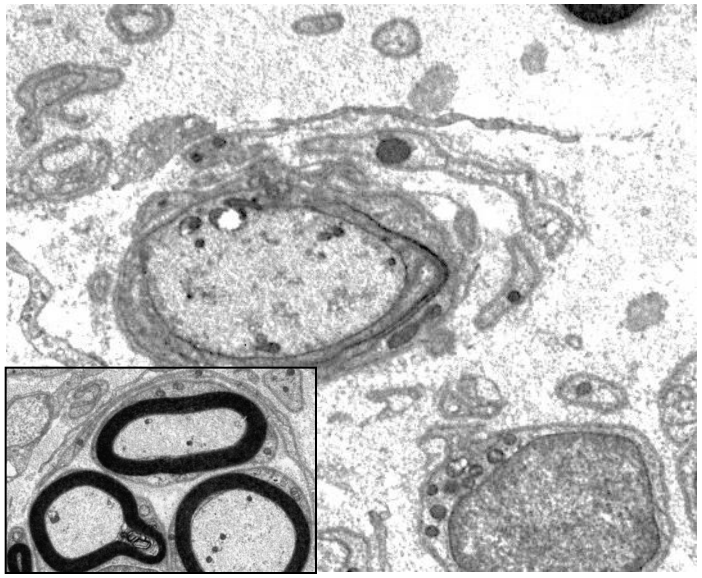
36 F

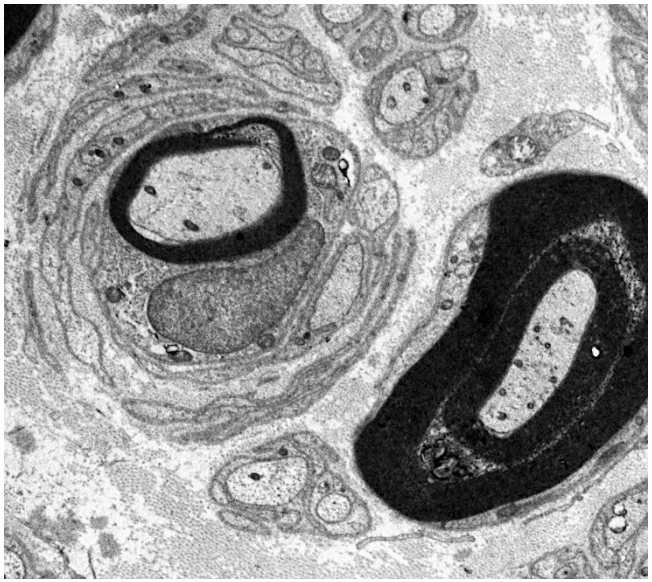
Progressive sensori-motor neuropathy developing over 6 months

Predominantly distal muslce weakness and sensory loss; bilateral foot drop

NCS: demyelinating sensorimotor polyneuropathy







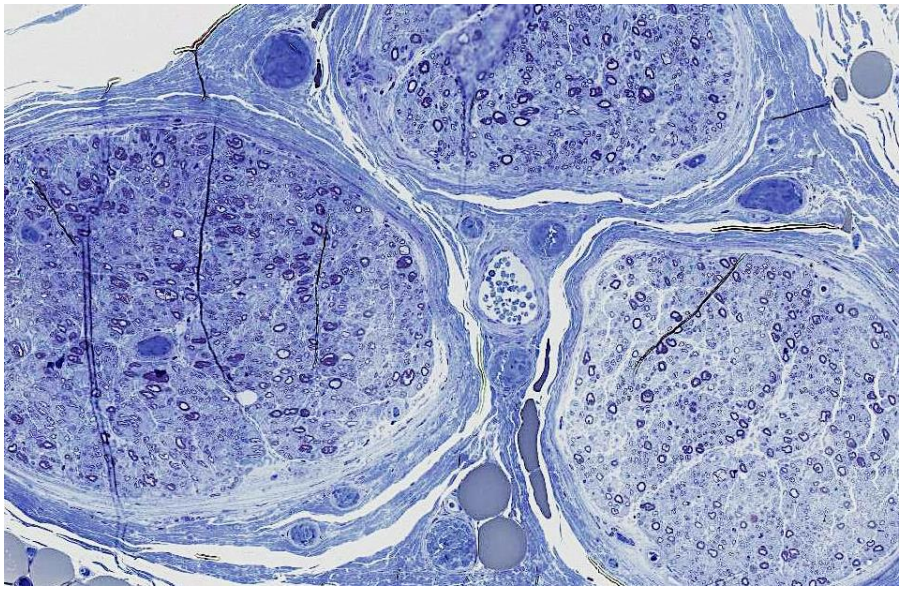
CIDP

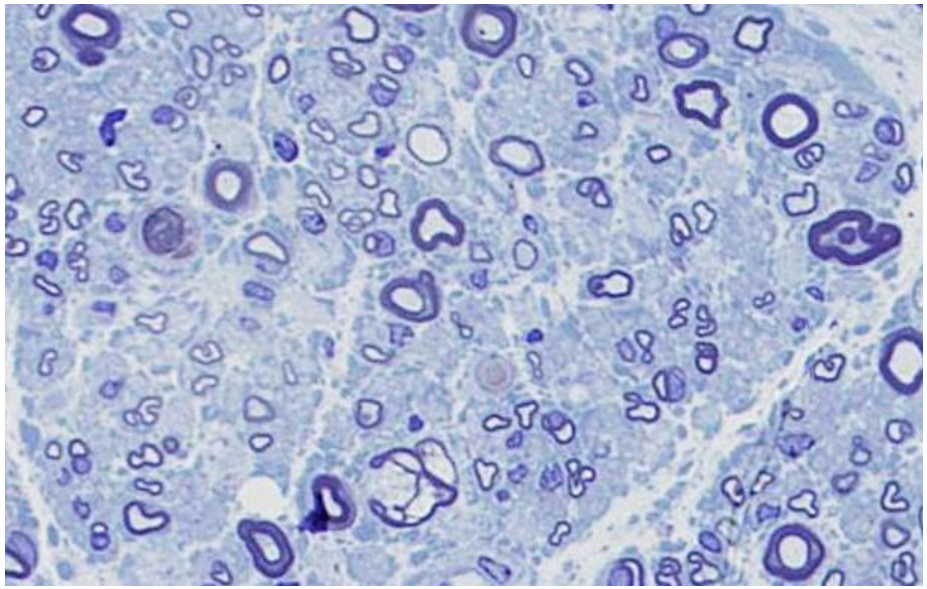
3 Y male; clumsiness, weakness and falls over a week; vomiting 2 days prior to onset of weakness

Symmetric proximal limb weakness; absent DTRs

Raised CSF protein; thickened nerve roots on MRI; NCS – generalised sensorimotor neuropathy; clinically diagnosed with GBS – IvIg

2nd episode in 3 months; repeat NCS – ongoing motor neuropathy, axonal loss and demyelination – further IvIg; poor response





CMT4B1

4 Y male; pes excavatum; delayed motor milestones; weakness with poor balance; frequent falls

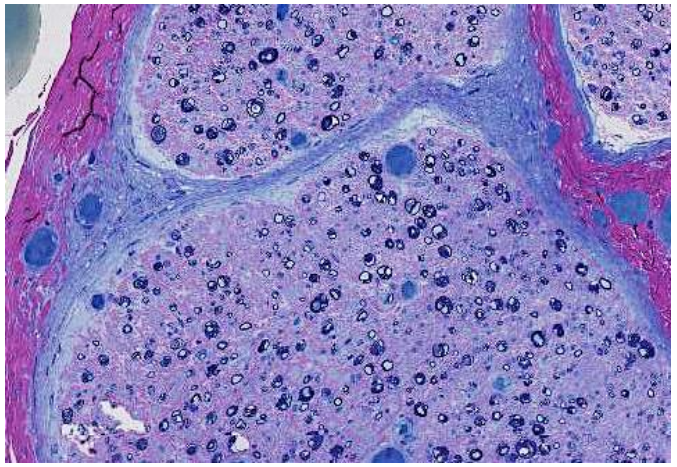
NCS: severe demyelinating sensorimotor neuropathy

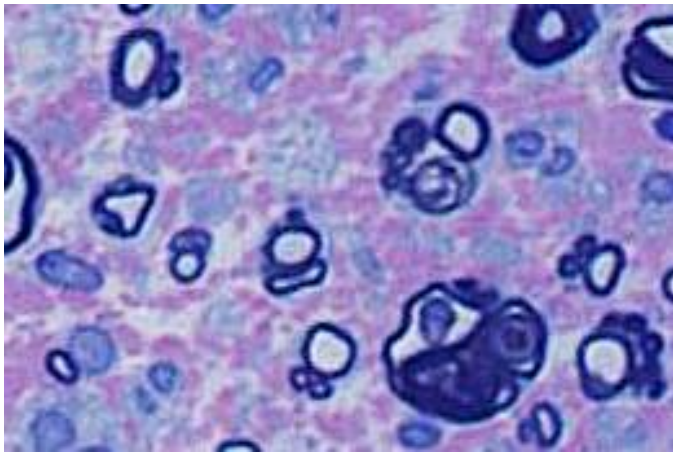
Poor response to Ivlg

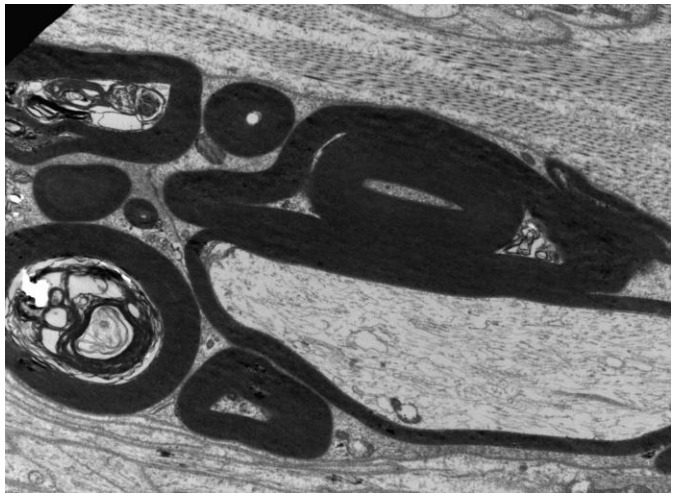
Parental consanguinity

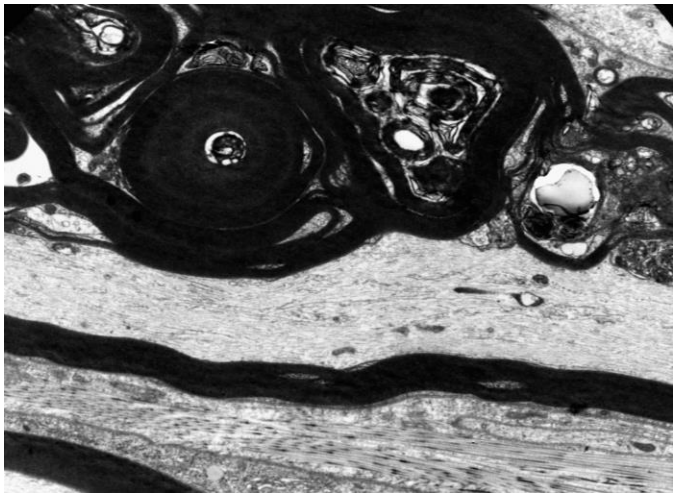
Sural nerve biopsy – severe demyelinating neuropathy with focally folded myelin CMT4B1

Homozygous MTMR2 mutation in exon 13 –









CMT4F

4 Y male; onset of symptoms around 15 months

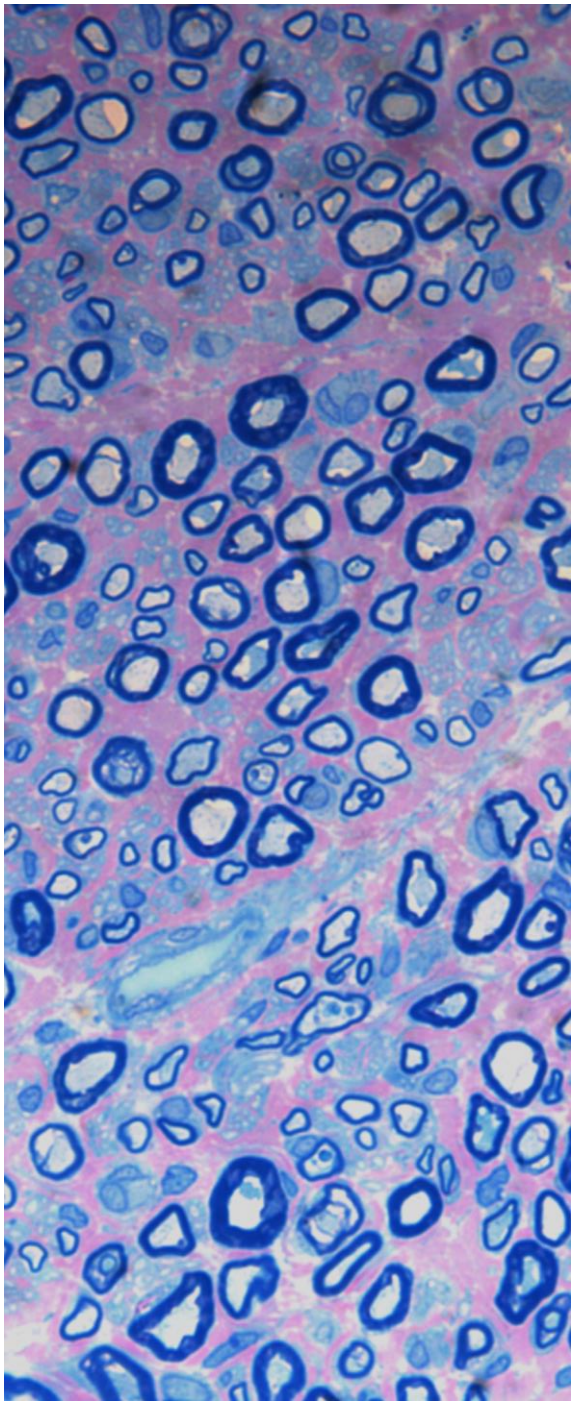
Motor delay; frequent falls; bilateral foot drop; reduced power LL (distal >> proximal)

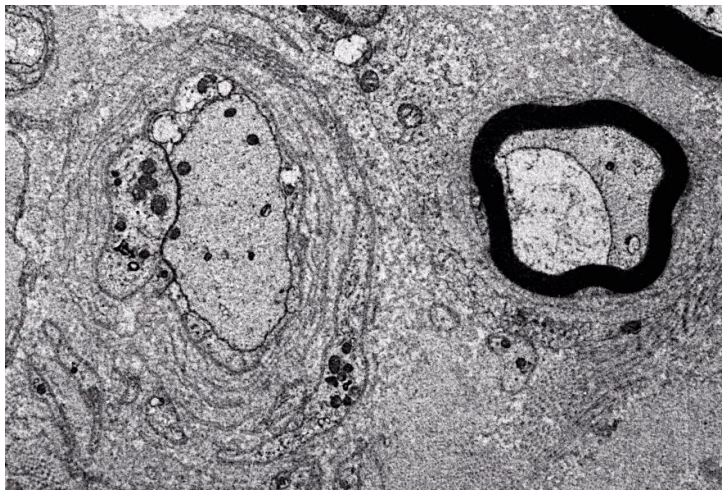
Normal CK; slow NCS

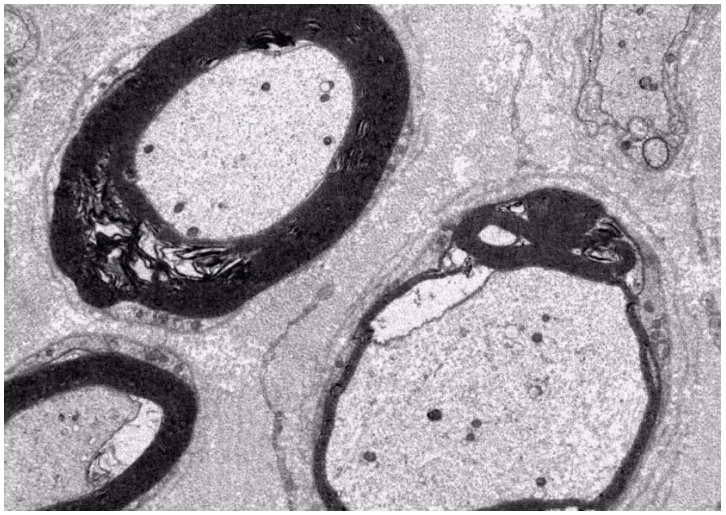
Consanguineous first cousins Bangladeshi parents; 2/4 siblings affected

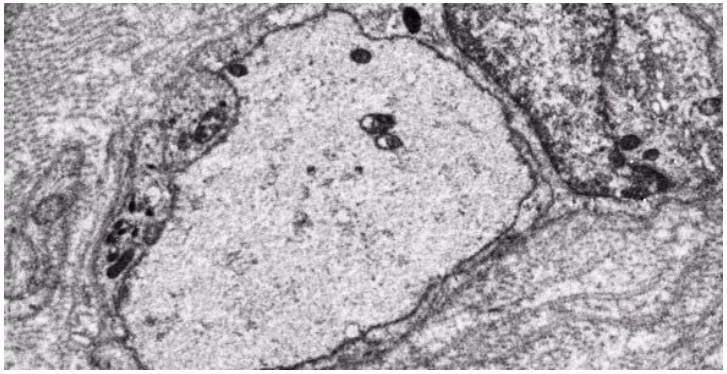
Left sural nerve - Severe demyelinating sensorimotor polyneuropathy;

Homozygous periaxin mutation



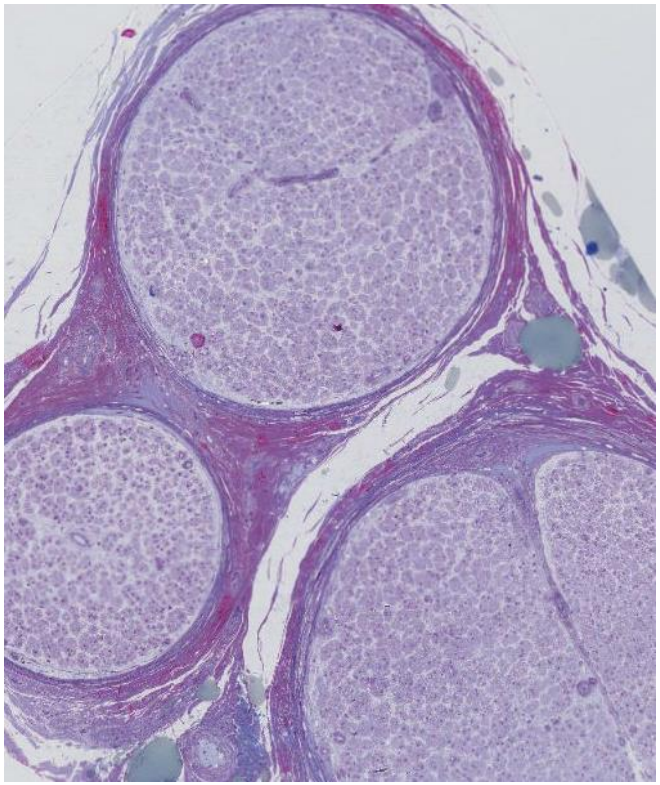


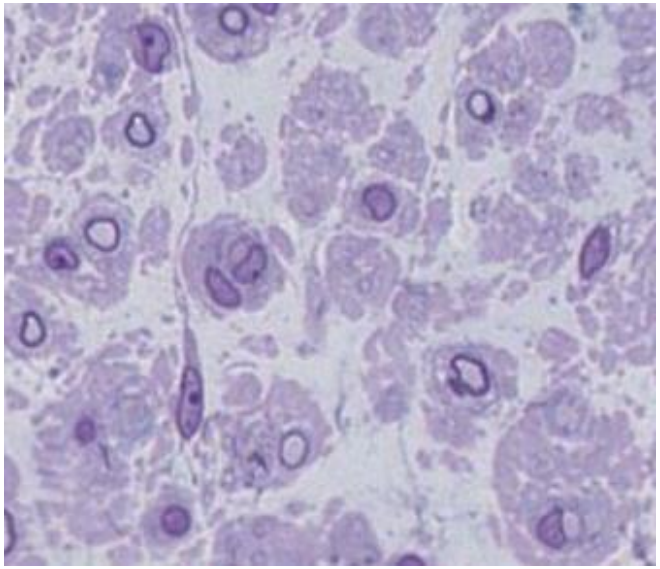


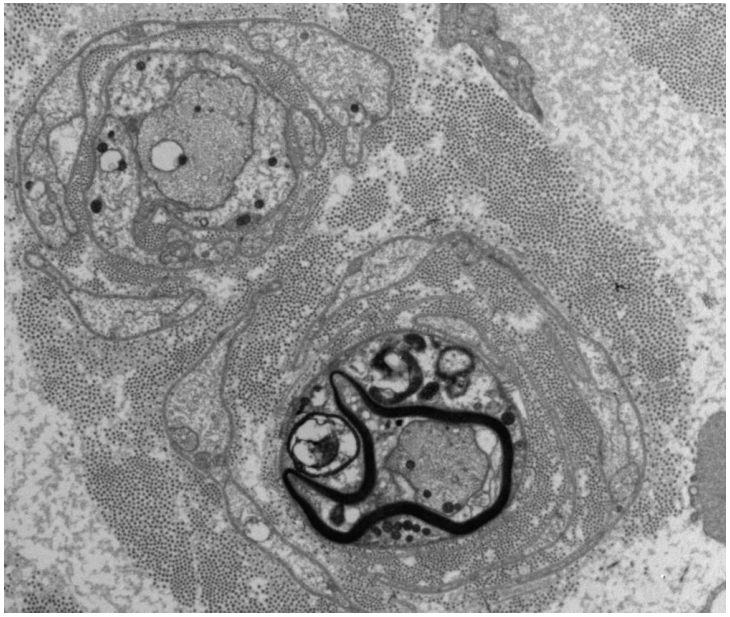


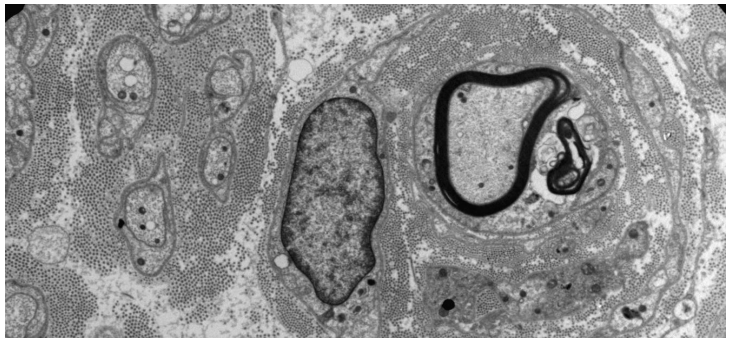
CMT4J

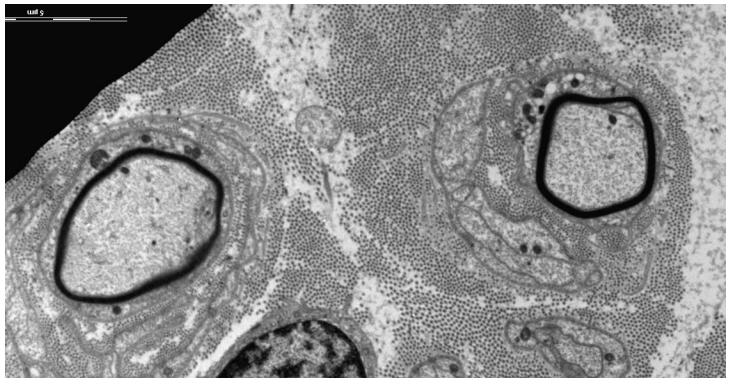
4 Y male at presentation
Motor delay
Severe asymmetric proximal and distal limb weakness
NCS: slowed conduction velocities
EMG: widespread denervation
Left sural nerve – chronic demyelinating neuropathy with prominent Obs
Compound heterozygous mutation in FIG4











Paediatric CMT with inflammation

13 M; 4 m history of clumsy gait, toe walking

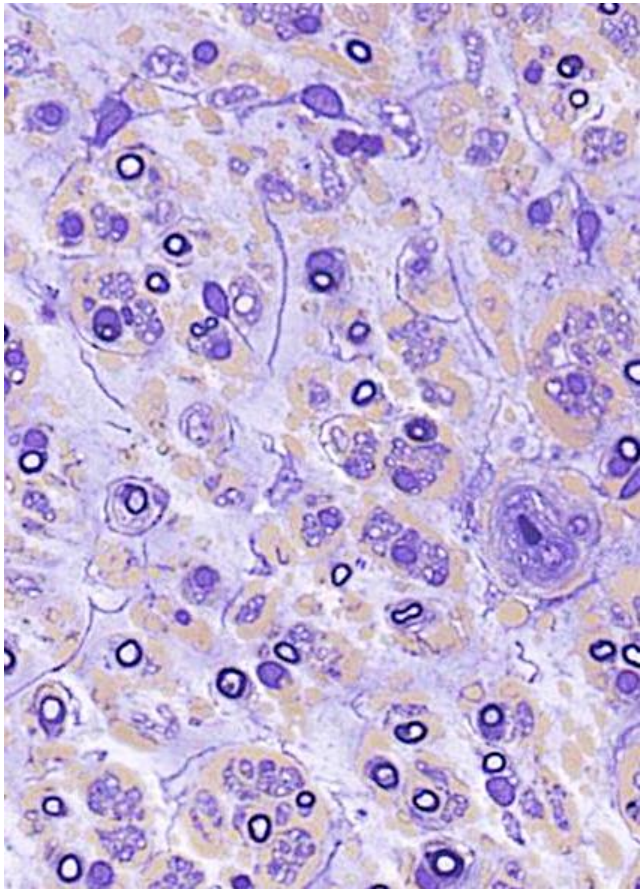
Mild LL muscle weakness; absent reflexes

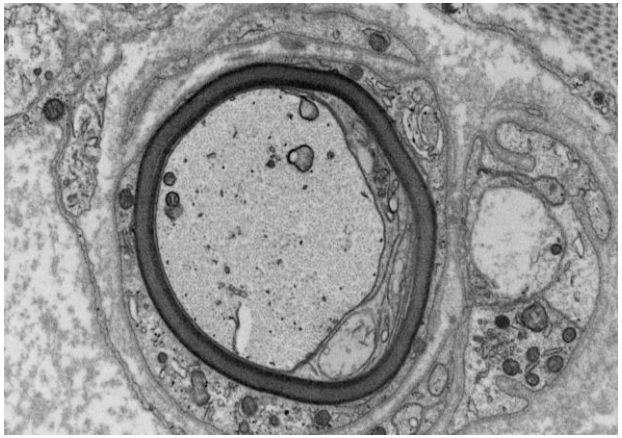
Raised CSF protein

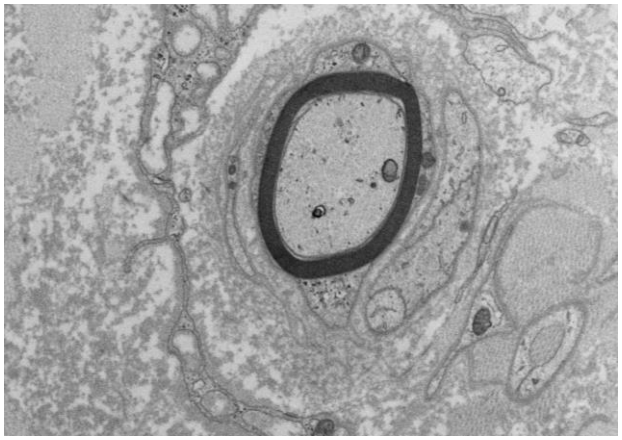
NCS: demyelinating neuropathy

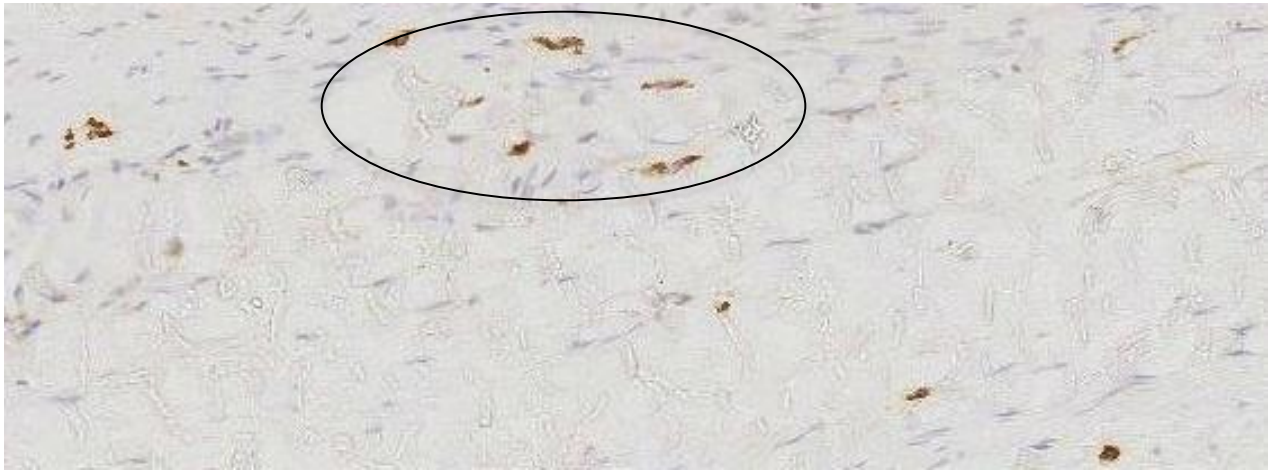
Poor response to treatment

Sural nerve bx– uniform large diameter axonal loss with hypo/demyelination of surviving axons and few onion bulbs; mild inflammation









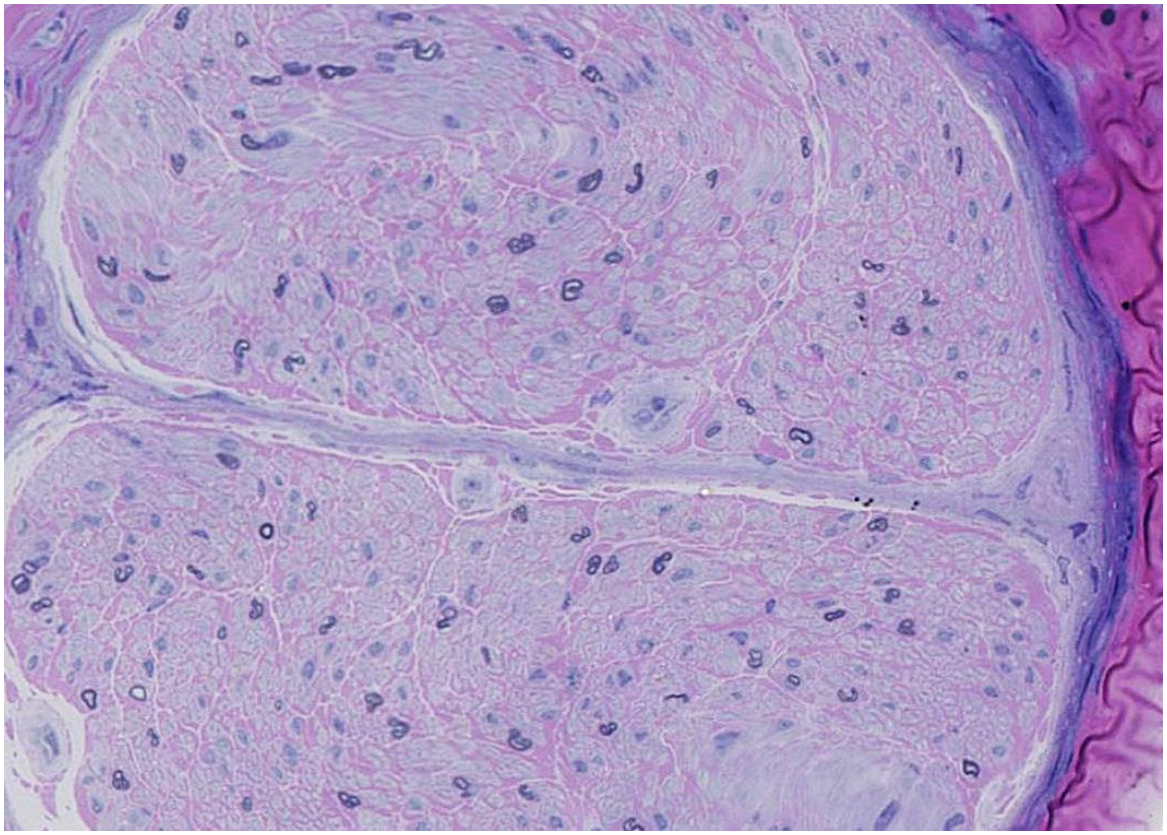
HMSNII

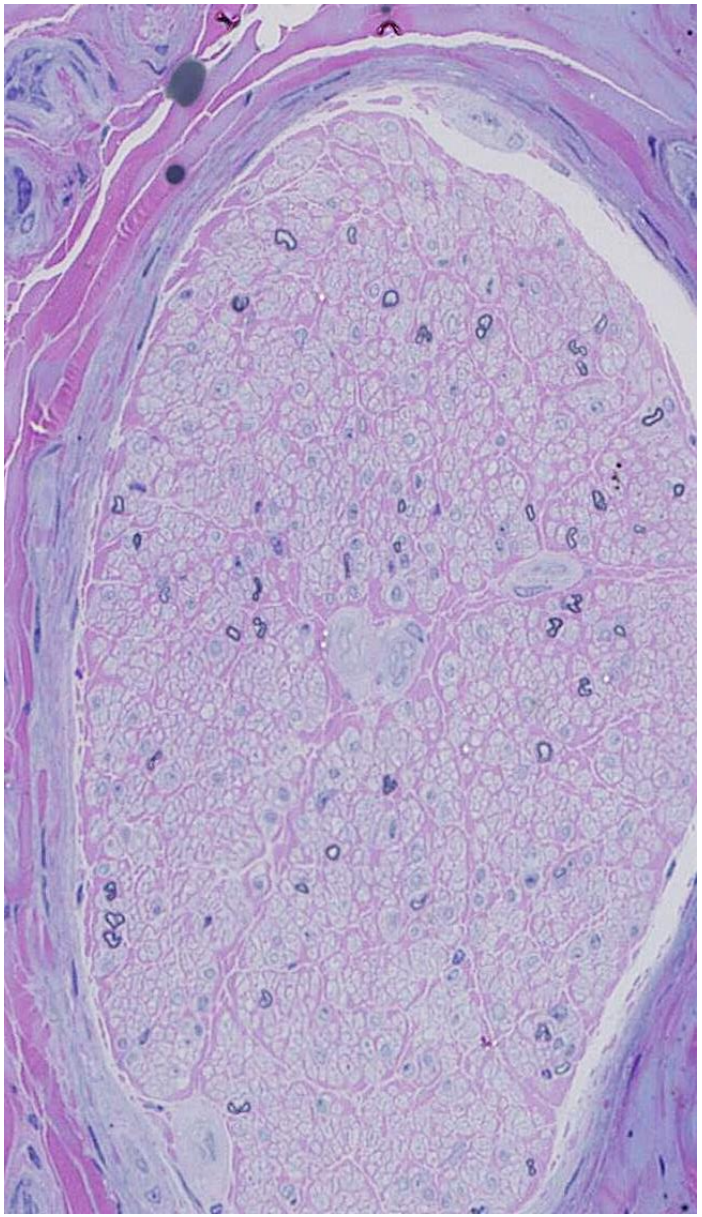
30 Y female

Slowly progressive severe motor sensory neuropathy since childhood

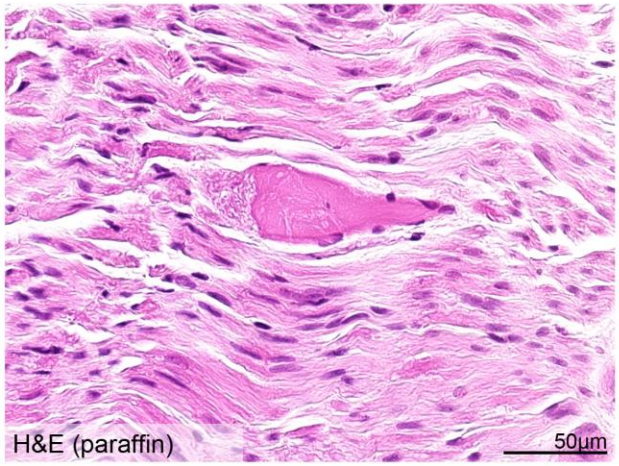
Marked distal lower limb weakness; sensory proprioceptive impairment with ataxia

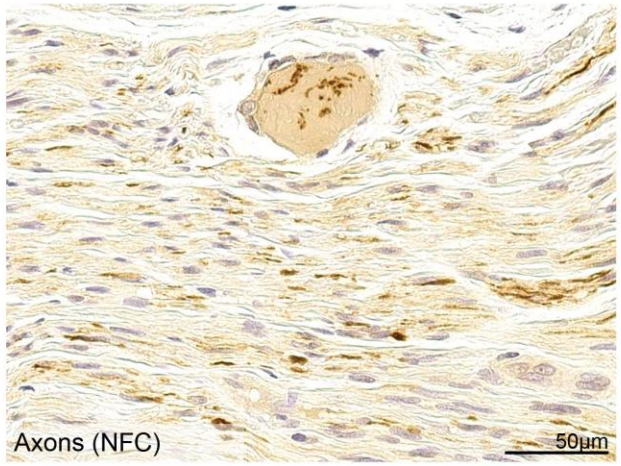
Sural nerve biopsy at 16 Y - severe chronic axonal neuropathy affecting large myelinated fibres without regeneration; no degeneration or demyelination

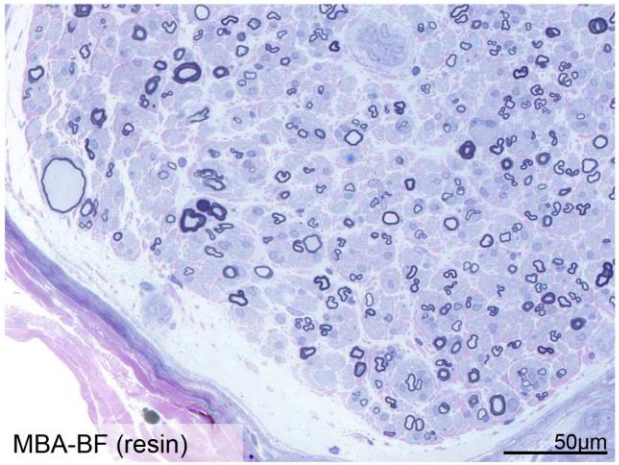


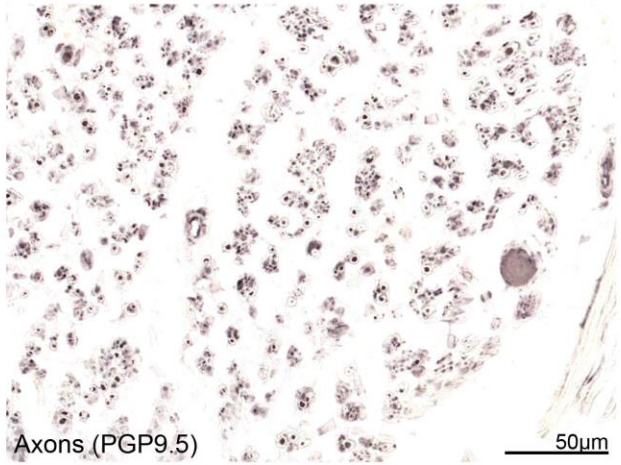


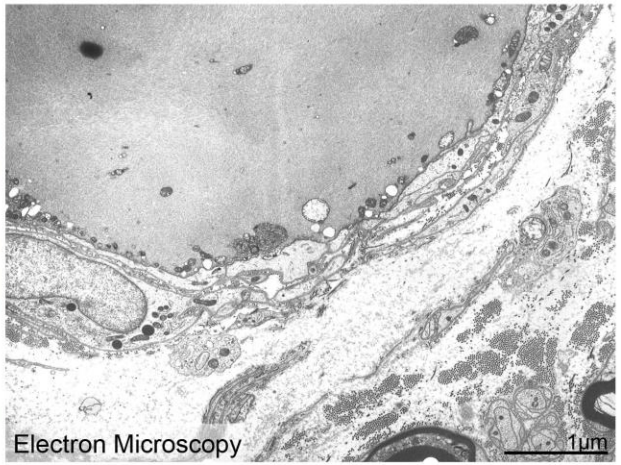
Giant axonal neuropathy (molecularly unclassified)











Adult polyglucosan body disease

A 59 year old Ashkenazi Jewish male presented with progressive left foot weakness, abnormal sensation in the toes, fasciculations, and bladder dysfunction that developed over weeks.

On examination: reflexes were brisk, with asymmetric lower limb proximal and distal weakness and spastic paraparesis.

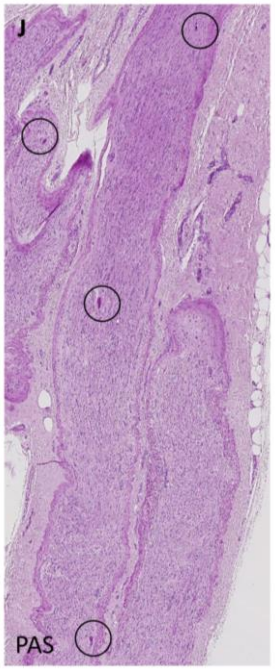
Extensive blood and CSF testing was normal.

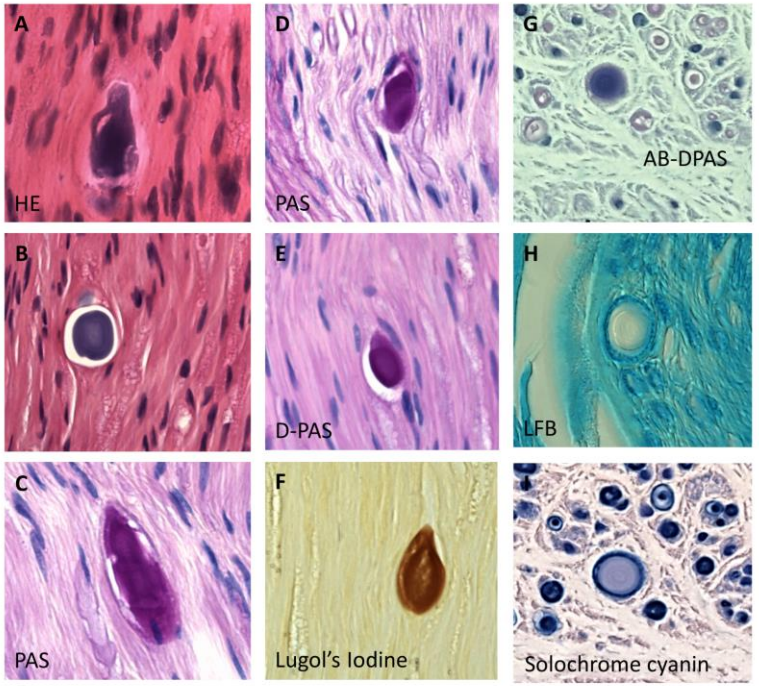
CK was 582 units (38-204).

Neurophysiology: non-length dependent mixed axonal demyelinating neuropathy with slowed conduction.

Glycogen brancher enzyme activity in white cells slightly lower: 26units; range (32-116); reduction not unequivocal as in other cases of GSD IV

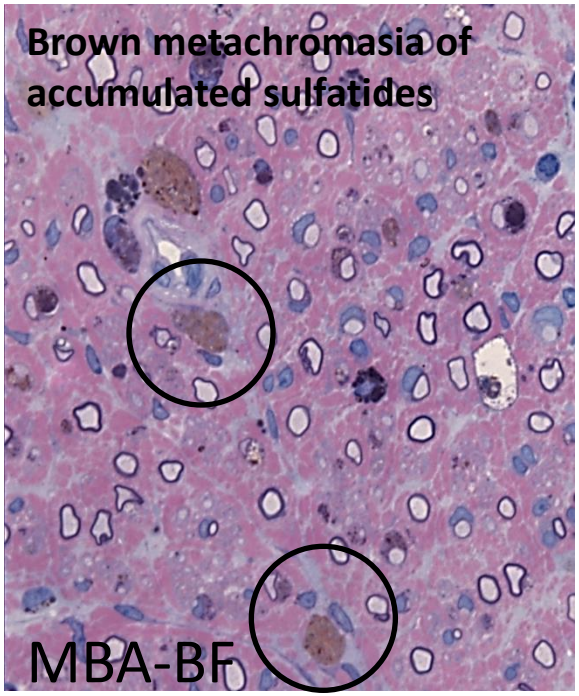
Heterozygous c.986A>C, p.(Ty329Ser) mutation in exon 7 of GBE1; previously described in individuals with APBD in homozygous and heterozygous state

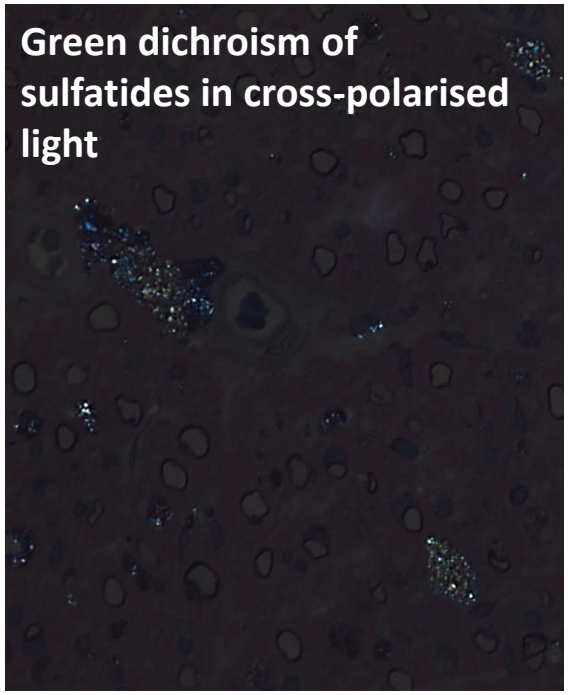


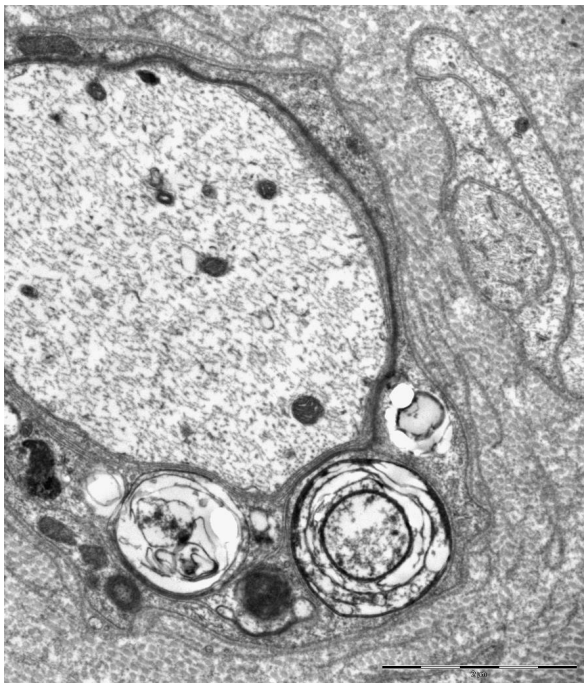


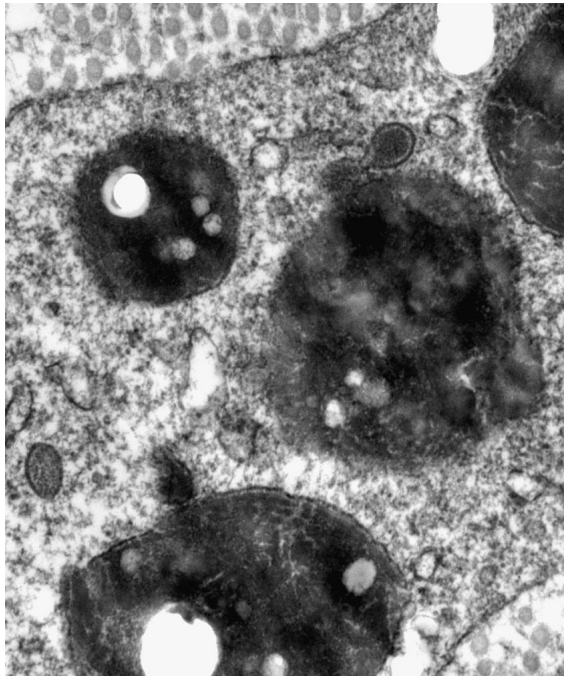
Metachromatic leukodystrophy

F 2.5Y, progressive feeding, motor deterioration from 22m
NCS: demyelinating polyneuropathy with raised CSF protein
Treated in Germany with IvIg and methylprednisolone – no improvement
MRI brain – leukodystrophy and affected BG
Further regression; dystonia
Clinical diagnosis: likely genetic/metabolic, ? Krabbe
White cell enzymes borderline?? ARSA pseudodeficiency
Sural nerve biopsy and genetic testing initiated in parallel
ARSA recessive mutations confirmed

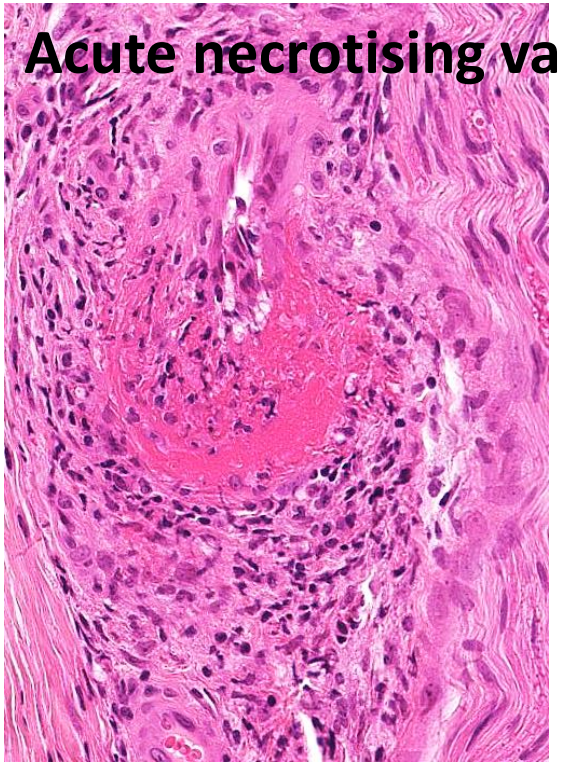


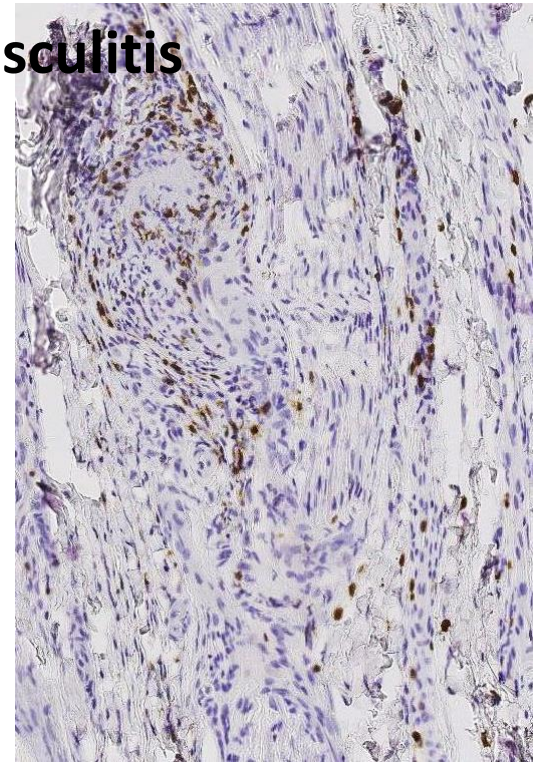






Acute necrotising vasculitis





9 Y old male

Familial cutaneous vasculitis/PAN

Complex history; initial presentation with several weeks PUO; left hemiplegia – resolved

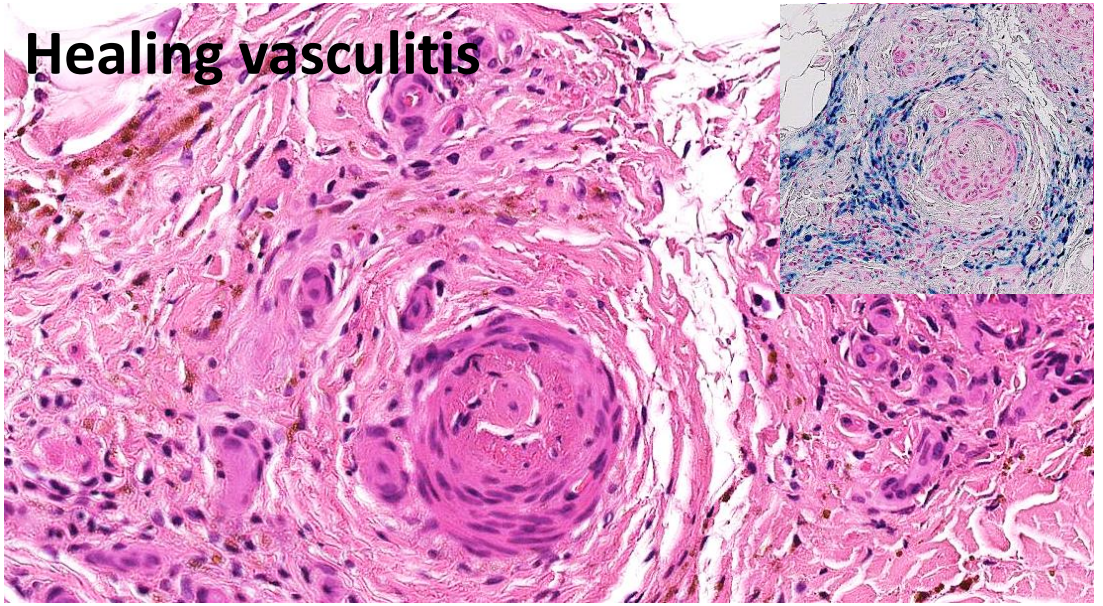
Previously several febrile convulsions

Skin rashes; raised ESR; acute sensorimotor axonal neuropathy

Auto-antibody screen negative

Left sural nerve - necrotising vasculitis

Healing vasculitis



46 M; history of anti-CCP+ nodular RA in remission

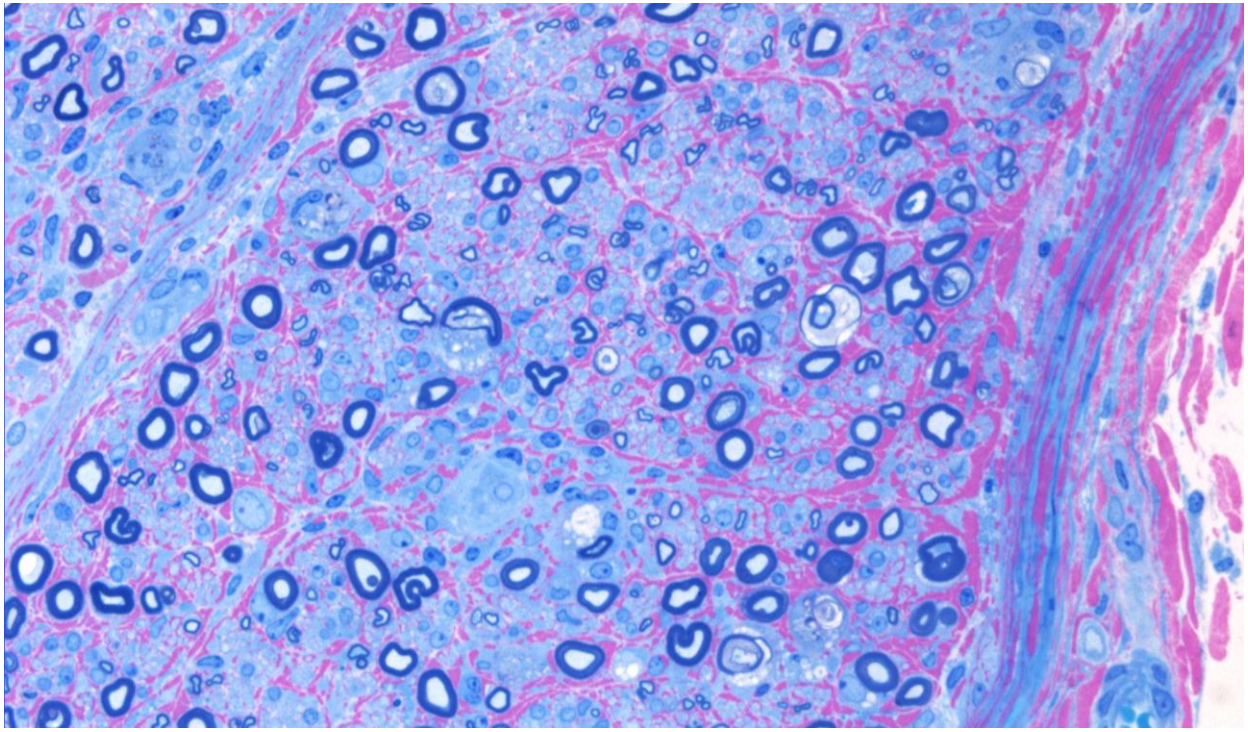
8 mts ago sudden onset of paraesthesia and dysaesthesia over the feet; resolved leaving behind glove and stocking distribution anaesthesia

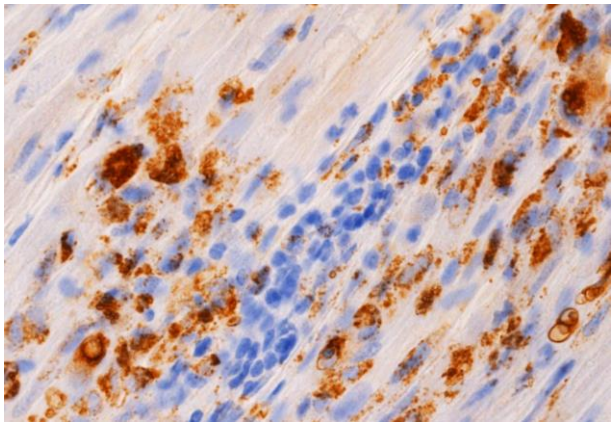
Normal tone, power and reflexes; reduced proprioception on left upto ankle

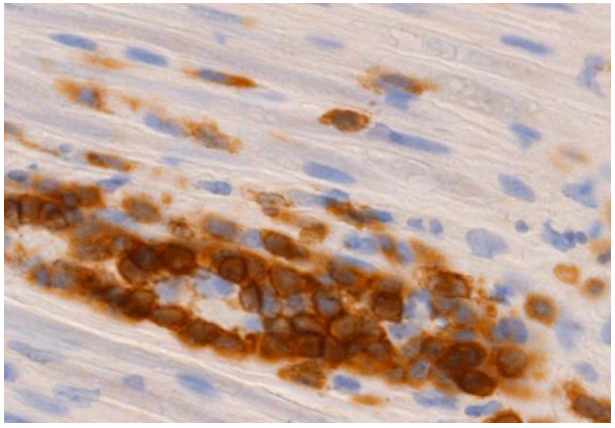
Mild patchy axonal loss with minimal regeneration; neovascularisation with haemosiderin deposition

Small vessel vasculitis

33 male; rapidly progressive tetraparesis; areflexia; increased CSF white cells and proteins; NCS: generalised sensorimotor axonal neuropathy; DD: GBS; AMAN; AMSAN; Sural nerve biopsy – severe acute axonal neuropathy with small vessel vasculitis



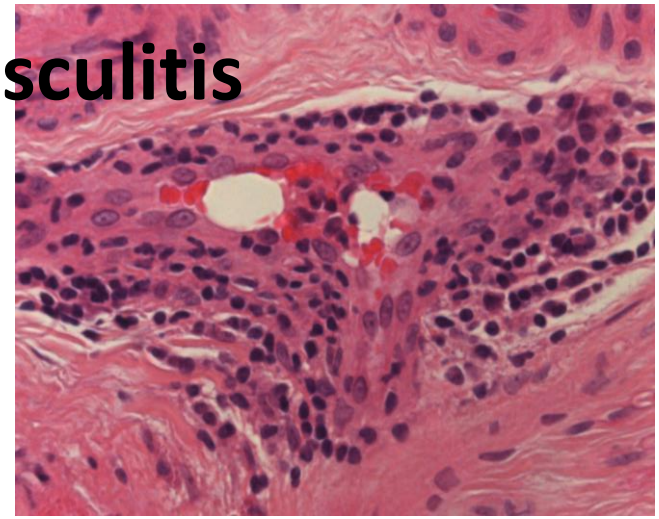


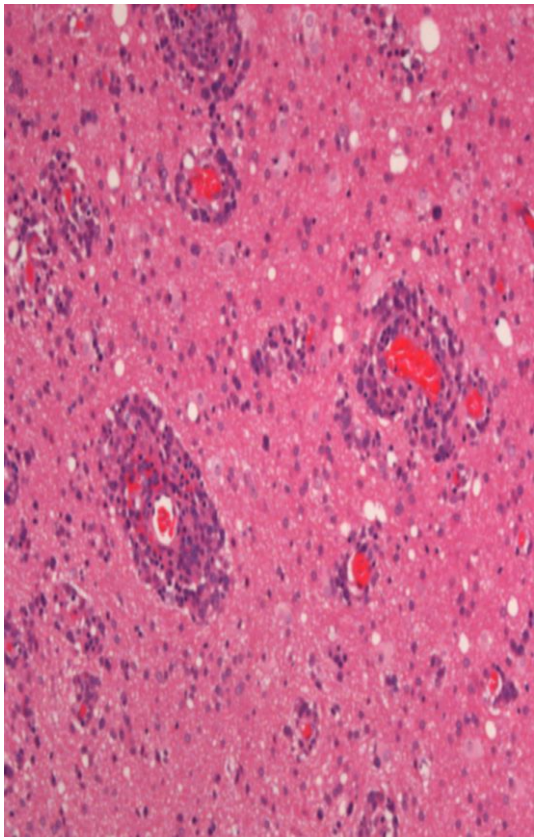


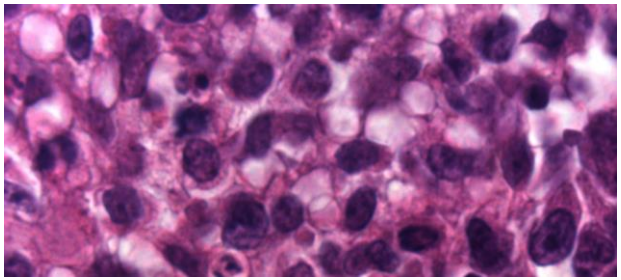
53 F; multiple discrete sequential neurological symptoms; paraesthesia, numbness, weakness of left hand, right Bell's palsy; subsequent pain in the left calf with foot drop; numbness in the right arm, right buttock pain, numbness in the upper left abdomen; ??mononeuritis multiplex; ANA+; full auto-antibody screen negative; Sural nerve biopsy – florid acute axonal neuropathy with small vessel vasculitis - ?? cause

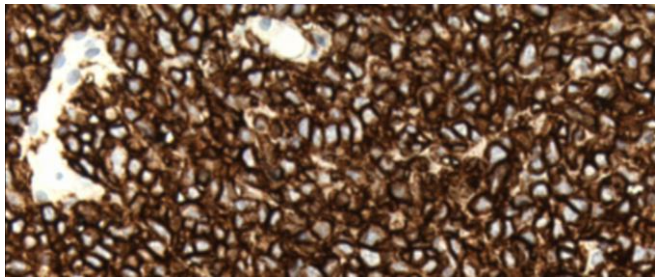
Whole body imaging –FDG avid PET lesion in right breast – biopsy proven diffuse large cell lymphoma; progression to encephalopathy with multiple lesions in the brain – biopsy confirmed DLBCL

Paraneoplastic vasculitis









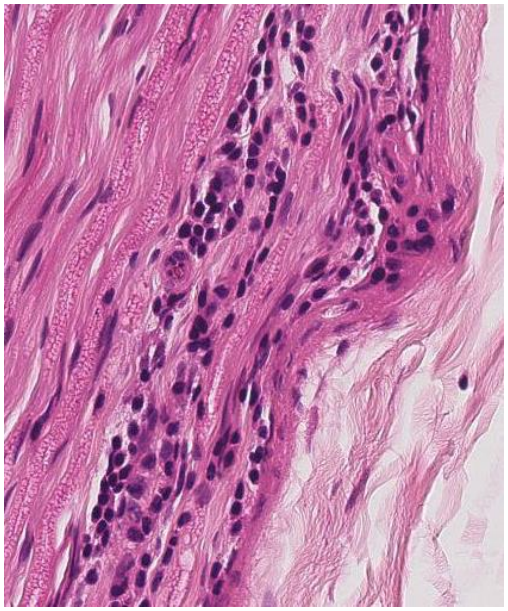
Lymphomatous neuropathy

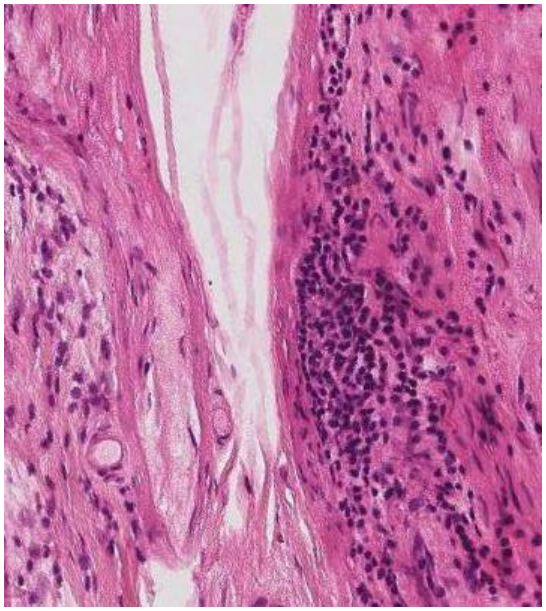
43 M; H/o Waldenstrom's macroglobulinaemia and lymphoplasmacytic lymphoma since 2 years

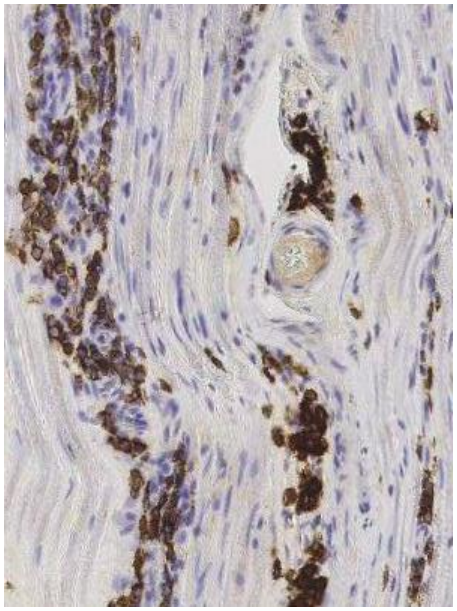
Relapse after treatment; increasing paraprotein

Rapidly progressive numbness and weakness in hands and legs; depressed reflexes

Left sural nerve – diffuse B cell infiltrates; kappa light chain restricted







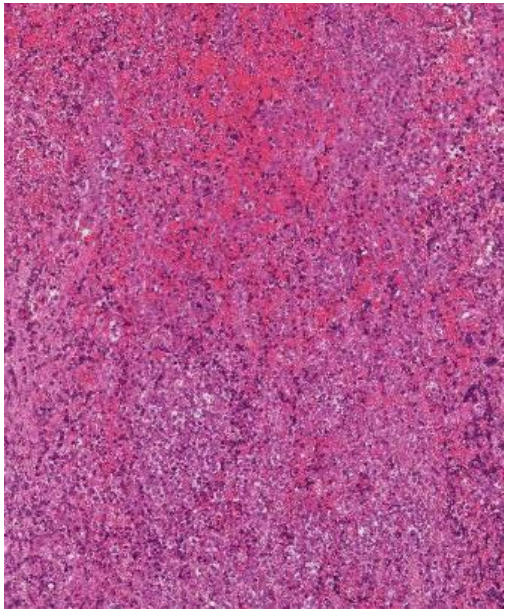
42 M; H/O high grade follicular B lymphoma treated with chemotherapy

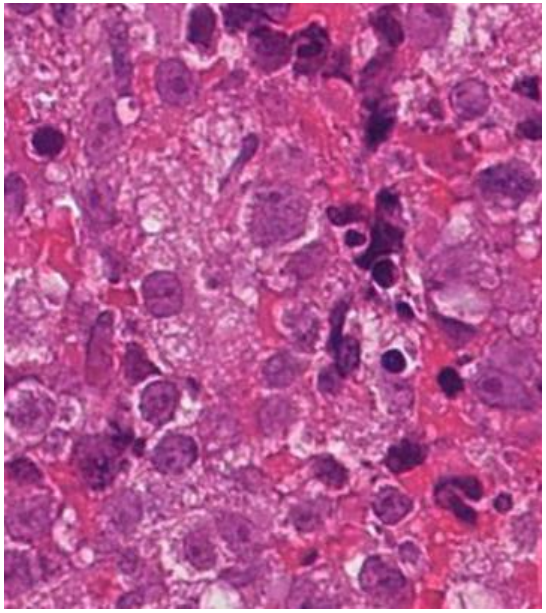
Progressive sciatic nerve lesion – biopsy confirmed neurolymphomatosis; treated with radiation, chemotherapy and autograft

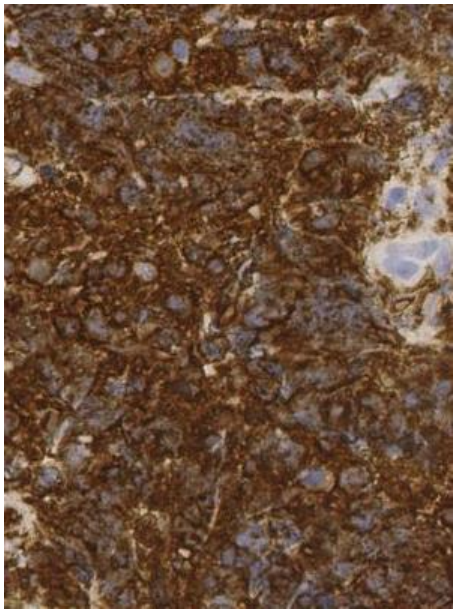
Developed right median sensorimotor neuropathy

Imaging – nodular lesion of the right median nerve at its exit from the axilla

Right median biopsy – neurolymphomatosis (DLBCL) – transformed FL







IgM anti-MAG paraproteinaemic neuropathy

63 M; burning and tingling numbness in toes, hands and over the right thigh

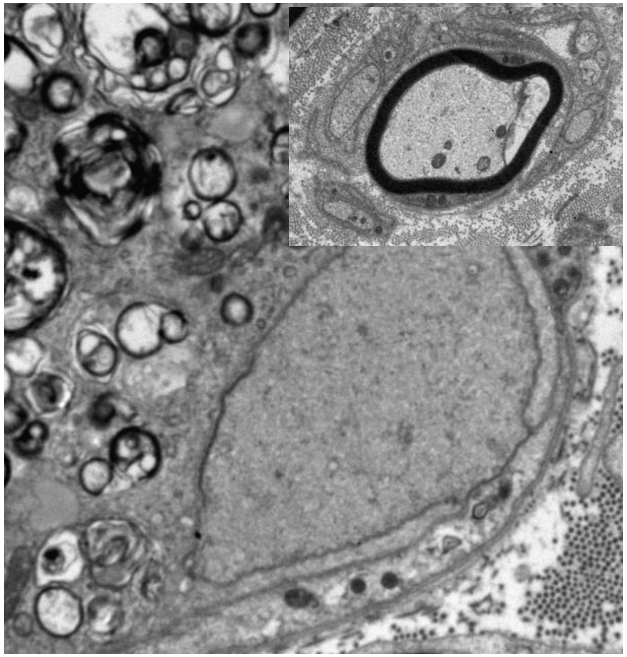
O/E: loss of pin-prick sensation in his toes and thigh; right quadriceps weakness; loss of knee reflexes

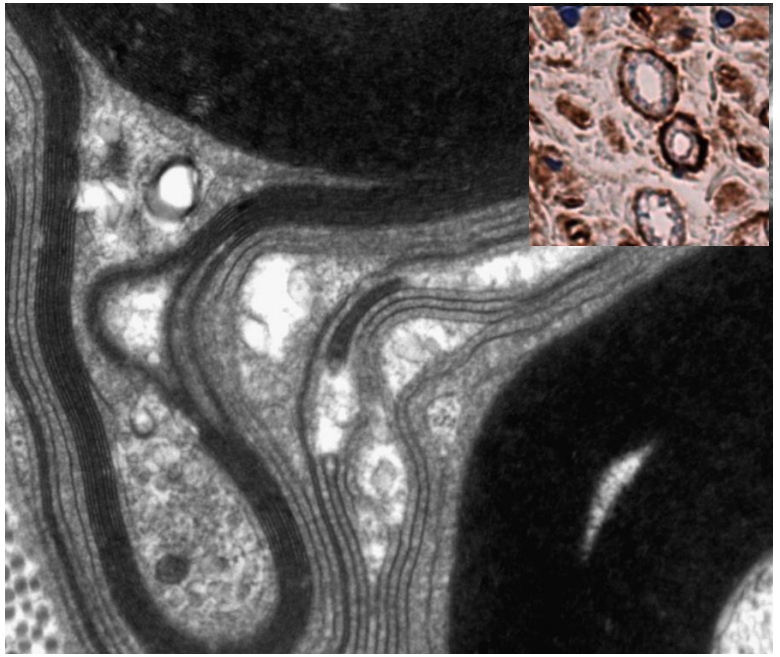
NCS: mixed length dependent axonal and demyelinating sensory polyneuropathy

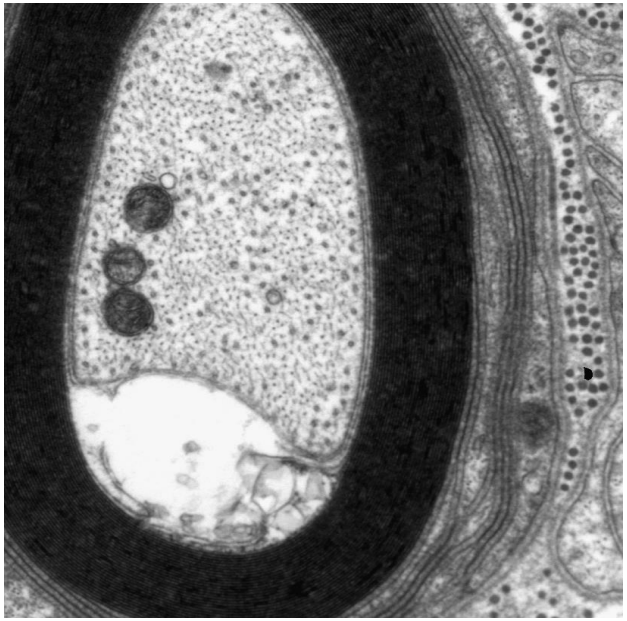
Immunofixation – IgM kappa paraprotein

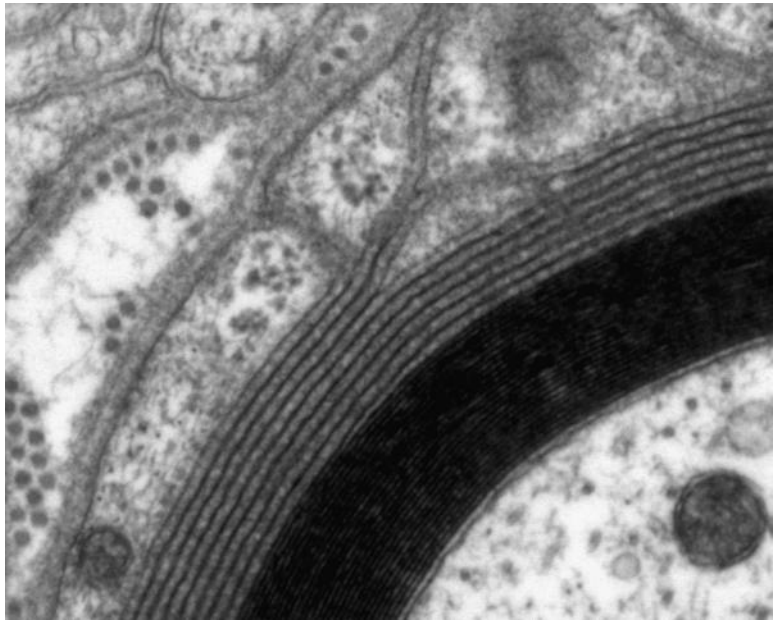
Anti-MAG+

Right sural nerve biopsy – moderately severe neuropathy with axonal loss, frequent WSM and chronic demyelination; mild inflammation



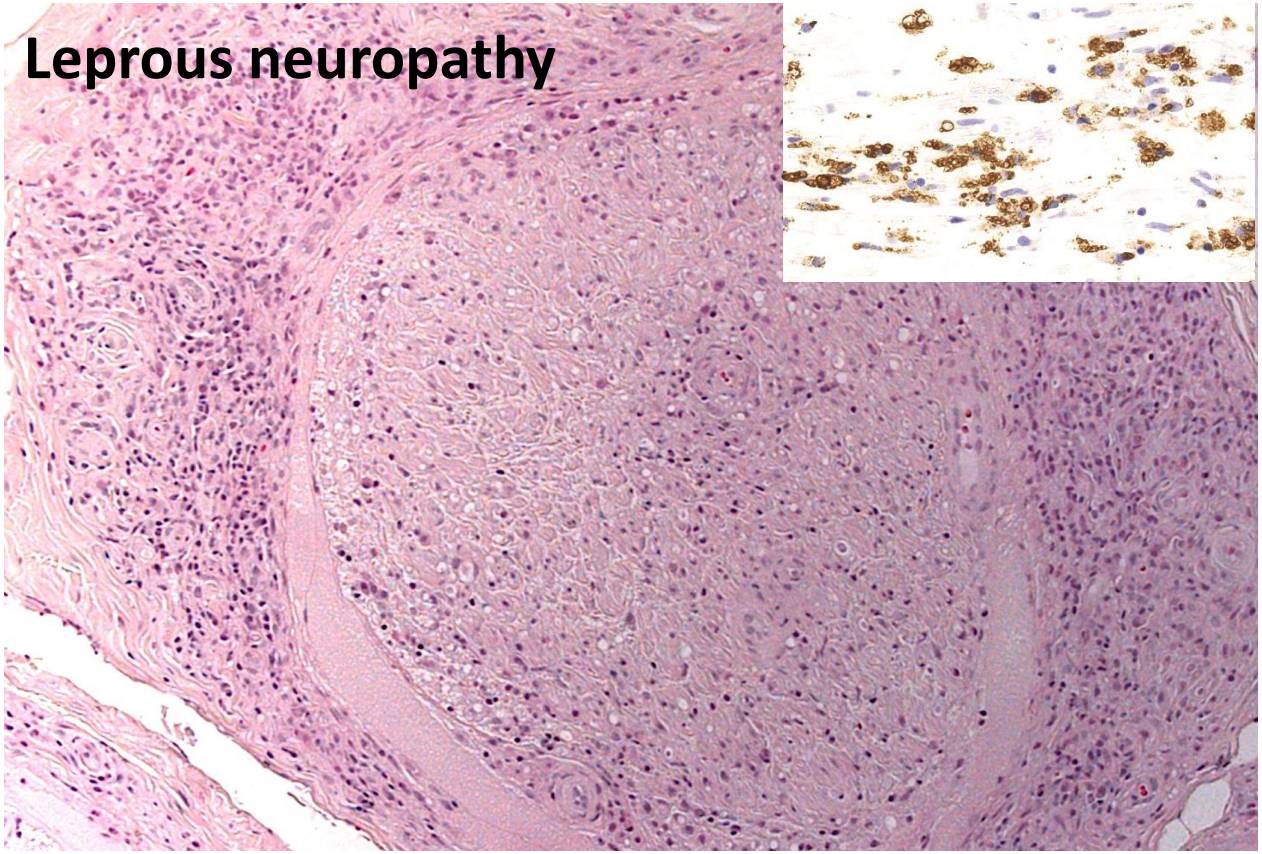


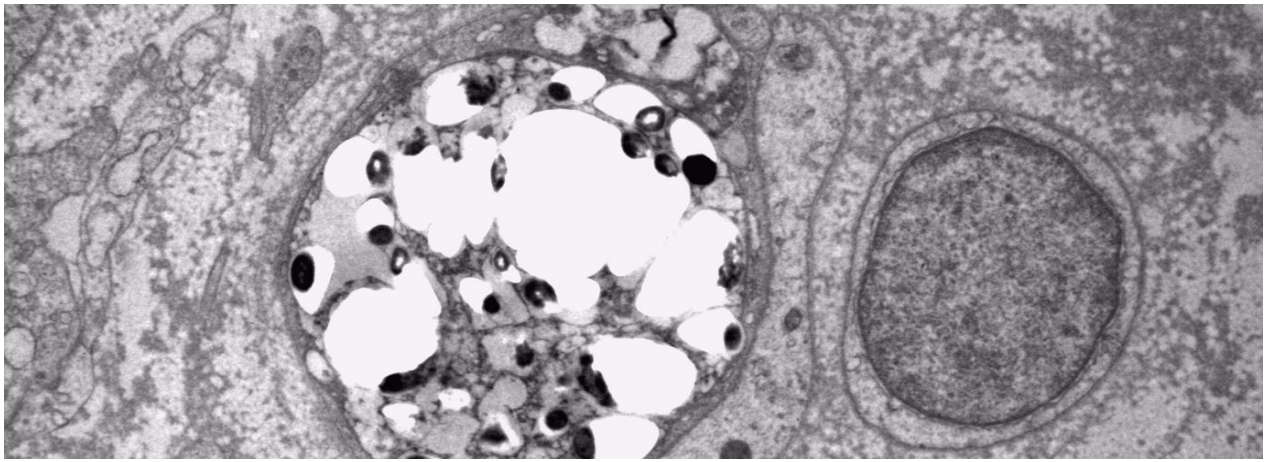




26 Brazilian female; 18 mth history of pain in the right foot with nocturnal cramps followed by left foot involvement
Short stabbing pains in the feet
Patches of numbness over shins
Intermittent pins and needles in the hands
Impaired pin-prick and JPS in the LLs distally; normal tone, power and reflexes
Normal skin; no hypopigmented patches; no thickened nerves – leprosy felt unlikely
Normal inflammatory screen; normal blood glucose; negative for HIV; non-smoker; social drinker; no history of tick bites, tattoos or blood transfusions
NCS: absent SAPs in both legs; borderline in median and ulnar nerves
Sural nerve biopsy – leprous neuropathy
Further review – lepromatous leprosy with positive slit skin smears

Leprous neuropathy





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