The History of Neuropathology

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History

• 1906- Cajal and Golgi awarded Nobel prize for studies of CNS using histological techniques.

• Neuropathology, at this time, evolved from general pathology (which now covers histopathology, forensic pathology, neuropathology, paediatric pathology, cytopathology), but with a strong foot in clinical neurosciences (neurology, psychiatry, neurosurgery).
History

• UK/USA/France- evolved from neurology (Gowers, Jackson, Charcot) and neurosurgery (Cushing, Penfield)

• Germany/Austria- evolved from psychiatry (Nissl, Alzheimer, Freud)

• Spain/Italy- evolved from neurohistology (Cajal, Golgi, Rio-Ortega)
Key names in UK neuropathology

• Alfred Meyer- fled Germany prior to WWII
• Godwin Greenfield- founded British Neuropathological Society 1950 (well before RCPath!!)
• Dorothy Russell- Professor of Morbid Anatomy at the London Hospital (first female head of Pathology Dept. in UK) and expert in neuro-oncology
Early Neurohistology

- Celloidin (nitrocellulose) rather than paraffin sections
- Thick sections, stored in alcohol
- Blocks cut using sledge microtome
Special stains used in neuropathology

- Stains rarely used
  - Gallyas
  - Hortega silver carbonate
  - Holzer
  - Golgi stain
- Stains commonly used
  - Modified Bielschowsky silver stain
  - Luxol fast blue (LFB)
Older stains

Holzer stain

Gallyas stain
Stains still in use

Modified Bielschowsky

LFB stain
Main categories of biopsies

• Surgical neuropathology (neurosurgical/ophthalmic biopsies)
• Neuromuscular biopsies
• Peripheral nerve biopsies
• Post mortem neuropathology
Neurosurgical biopsies

- Intra-operative diagnosis
  - Smear preparations
  - Frozen sections
- Paraffin sections
- Molecular diagnostics
Smear preparations
Molecular neuropathology; Assays available for 1p19q

- **FISH**
  - Fluorescent in-situ hybridisation

- **aCGH**
  - Array comparative genomic hybridisation
FISH

- Test assesses 1p36/1q25 and 19q13/19p13 gene ratios are used to assess the presence or absence of LOH at 1p and 19q.
FISH pros and cons

- Pros: cheap, does not require control DNA
- Cons: limited information, does not detect partial deletions, can be difficult to interpret.
aCGH

• Genome wide differential labelling of somatic and tumour DNA
• Provides an estimate of chromosome number at every locus represented on the array
Array of DNA fragments

Duplication

Deletion

Control DNA

The University of Edinburgh
Edinburgh Neuroscience

Centre for Clinical Brain Sciences
Muscle biopsies

- Muscle biopsies usually sent from:
  - Neurology; undiagnosed myopathy
  - Rheumatology; inflammatory myopathy
Pathological features seen on biopsy

- Changes in fibre shape and size
- Changes in fibre type distribution
- Necrosis and regeneration
- Cellular infiltrates
- Fibrosis
- Structural abnormalities
- Enzyme deficiencies and glycogen/lipid accumulation
Myophosphorylase- enzyme histochemistry
Muscular dystrophies

• These are genetically determined destructive myopathies.
• They are usually progressive.
• Suggestive pathology includes fibre hypertrophy, fibre necrosis, fibre splitting, increased fibrosis.
Immunohistochemistry

- A range of skeletal fibre membrane proteins can be assessed in suspected cases;
  - Dystrophin (C and N terminus, mid-rod domain), merosin ($\alpha_2$ laminin), dysferlin, emerin, $\alpha$-, $\beta$-, $\gamma$-, $\delta$- sarcoglycan, $\beta$-dystroglycan, desmin
Peripheral nerve biopsy

- Few indications for peripheral nerve biopsies
  - Vasculitis
  - Amyloidosis
  - Unknown peripheral neuropathy
An approach to the peripheral nerve biopsy

• Always receive fresh
  – TS and LS paraffin, resin and tissue for teasing
• Paraffin sections
• Semi-thin sections
• Teased nerve fibre preparations (TNF)
• Ultrastructural analysis
Paraffin sections

- H+E
- LFB/CV
- Neurofilament IHC
  - Any evidence of vasculitis?
  - Any abnormal deposits e.g. amyloid?
  - Any obvious structural abnormalities
    - loss of large myelinated axons?
    - Onion bulb formation?
Semi-thin sections

• Greater detail than paraffin sections
• Assessment of fibre types and size
• Regenerative clusters
Teased Nerve Fibres

• Useful in providing information relating to axonal degeneration
Electron microscopy

• EM can be used to demonstrate inclusions within peripheral nerves.
In summary

- Diagnostic neuropathology has come a long way from temperamental stains on thick celloidin blocks, and now requires; tinctorial stains, enzyme histochemistry, immunohistochemistry, molecular diagnostics (FISH, PCR, aCGH, sequencing), resin/plastic sections and electron microscopy, teased nerve preparations etc.