Pathology of Primary Demyelinating Diseases

GENERAL PROPERTIES OF MYELIN

Normal Myelin

- enhances conduction velocity
- oligodendocytes – **4-50 internodes** – loss causes plaque
- Schwann Cells – **1 internode** – loss causes segmental demyelination in the PNS
- Development
  - PNS 1st, then spinal cord, then brain
  - myelination occurs at different rates in different areas
  - complete by **end of 2nd year of life**
- CNS myelin contains **more lipid** than any other cell membrane

Pathological Myelin

- influx of "foamy" lipid-laden macrophages
- associated with myelin pallor and preservation of axons
- Luxol fast blue – myelin stain used to confirm myelin loss
- Silver Stain – shows integrity of axons
- **1o demyelination –** demyelination occuring by itself
- **2o demyelination –** loss of myelin at the same time as axonal loss and destruction

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PATTERN OF DISSEMINATED PERIVENOUS DEMYELINATION

Acute disseminated encephalomyelitis (ADEM)

- very rare, autoimmune
- usually children (6-10 years of age)
- headache, vomiting, fever, stupor, flaccid paraplegia, and incontinence
- widespread perivenous demyelination and mononuclear inflammatory infiltrates

Acute necrotizing hemorrhagic leukoencephalopathy (Weston-Hurst Disease)

- hyperacute form of ADEM
- in most instance has a fatal outcome in 1-6 days
- perivenous demyelination, vasscular fibrinoid necrosis with hemorrhages, inflammatory inflitrate, high PMNs
- DIFFERENCE FROM ADEM – vascular wall necrosis

Guillain – Barre syndrome

- peripheral nerve segmental degeneration
- severe paralytic illness of short duration
- occurs 1-2 weeks after a banal respiratory infection, flu, or immunization
- rapid onset of flaccidity, areflexic weakness, sometimes with respiratory compromise
- There is a chronic form – chronic inflammatory demyelinating polyneuropathy

PATTERN OF IRREGULAR PATCHES OF DEMYELINATION

Multiple Sclerosis – Chronic Multiple Sclerosis (Classic Type)

- Clinical features
  - **DISTINCT EPISODES OF NEUROLOGIC DEFICITS, SEPARATED IN TIME, ATTRIBUTABLE TO WHITE MATTER LESIONS THAT ARE SEPARATED IN SPACE.**
  - optic neuritis
- Most common demyelinating disorder
- One in 1000 in US
- Most common in young adults < 50 years of age
- CSF: MILDLY INC PROTEIN, **OLIGOCLONAL BANDS**, MILD LYMPHOCYTIC PLEOCYTOSIS
- Risk factors:
  - Women > men
  - **frequency increases with distance from equator and one takes on the relative risk of the environment of which they spent the first 15 years of life**
  - familial
- cellular immunity against myelin components is supported by the presence of CD4+ and CD8+ lymphs in active lesions
- autoimmune mechanisms
- Gross:
  - scattered well-circumscribed "plaques" of gray discoloration of white matter
  - particularly in the white matter adjacent to the lateral ventricles, optic nerves, spinal cord, and brainstem
- In active plaque
  - perivascular and parenchymal inflammation
  - diffuse ongoing demyelination
  - gliosis
- Prognosis: variable

Variants of Multiple Sclerosis

1. **Acute multiple sclerosis**
   - fatal in < 10 months
   - resembles ADEM, no evidence of antecedent infection

2. **Concentric sclerosis (Balo's disease)**
   - rings around BVs
   - seen mainly in Asian countries
   - seen in young individuals
   - death in 3-5 years

3. **Neuromyelitis optica (Devic's disease)**
   - involves the optic nerves and spinal cord

DIFFUSE CONTINUOUS PATTERN OF DEMYELINATION

Leukodystrophies

- DYSmyelinating diseases because they are characterized by abnormal formation of myelin
- almost exclusively occur in children or infants
- the earlier the age of onset, the more likely the severity of the illness
- This group share the following features
  1. symmetric degeneration or failure of myelin formation
  2. lack of inflammation
  3. minimal to mild axonal destruction

Krabbe's Disease

- autosomal recessive
- results from deficiency of galactocerebroside B-galactosidase
- does not result in accumulation of psychosine (a metabolite of galactocerebroside that is toxic to oligodendrocytes)
- Clinical Features
  - rapidly progressing
  - 3-6 mths of age
  - motor signs are chief manifestations
  - 90% of patients die or are chronically vegetative before the age of one year
  - **HYPERIRRITABLE!!**
  - Exaggerated startle response
- Gradual loss of myelin and oligodendrocytes in white matter, as well as myelin loss in peripheral nerves
- Aggregation of multinucleated GLOBOID CELLS around BVs
- spares cortex neurons and axons

Metachromatic Leukodystrophy

- arysulfatase deficiency
- autosomal recessive
- cerebroside sulfate accumulates (as does other sulfatides)
- Four clinical syndromes: congenital, late infantile, juvenile, and adult
  - Juvenile: affects brain primarily
  - late infantile: peripheral nerves
- Myelin loss with sparing of subcortical U fibers
- name of disease derived from the ability of the sulfatides to bind dyes and shift their color

REVIEW

Disseminated perivascular demyelination

1. Acute Disseminated Encephalomyelitis (ADEM) – Central
2. Acute Necrotizing hemorrhagic leukoencephalopathy (AHEM) – Central
3. Guillain-Barre syndrome – Peripheral
4. Chronic inflammatory demyelinating polyneuropathy (CIDP) – paripheral

Pattern of Irregular, patchy demyelination

Chronic and acute relapsing multiple sclerosis

Pattern of diffuse continuous demyelination

1. Krabbe's Disease
2. Metachromatic leukodystrophy