بسم الله الرحمن الرحيم
Pathogenesis of Demyelinating Diseases

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PRIMARY DISEASES OF MYELIN

Within the CNS,

- Axons are tightly ensheathed by myelin.
- Myelin serves as an electrical insulator to allow rapid propagation of impulses.
- Myelin consists of multiple layers of the specialized plasma membrane of oligodendrocytes.
- Myelinated axons are the dominant component in the white matter*
- Most diseases of myelin are primarily white matter disorders
The myelin in PN is similar to the myelin in the CNS, but has several important differences:

**what are they???

The natural history of demyelinating diseases is determined, in part, by:

- The limited capacity of the CNS to regenerate normal myelin.
- The degree of secondary damage to axons that occurs as the disease runs its course.
In general, diseases involving myelin are separated into two broad groups:

- Demyelinating diseases of the CNS.
- Dysmyelinating diseases of the CNS.
Demyelinating diseases of the CNS are:

- Acquired conditions.
- Characterized by damage to previously normal myelin.
- Diseases in this group:
  - Multiple sclerosis (MS) (The most common) (immune-mediated injury).
  - Progressive multifocal leukoencephalopathy (viral infection of oligodendrocytes)
  - Injury caused by drugs and other toxic agents.
Multiple Sclerosis

- **MS** is an *autoimmune demyelinating* disorder.
- Characterized by distinct episodes of neurologic deficits, separated in time, attributable to *white matter lesions* that are separated in space.
- It is the most common of the demyelinating disorders.
- Age, young adult
- Women : men 2:1
- The illness shows relapsing and remitting episodes of neurologic deficits.
Multiple Sclerosis

✓ Pathogenesis

✓ The lesions of MS are caused by an immune response that is directed against the components of the myelin sheath.

✓ the pathogenesis of this disease involves both genetic and environmental factors

✓ 15-fold higher in a first-degree relative, 150-fold higher with an affected monozygotic twin.

✓ Genetic linkage of MS susceptibility to the HLA-DR2 extended haplotype
Multiple Sclerosis

**Morphology**: MS is a white matter disease.

- **Grossly**: characterized by **plaques** a multiple, well-circumscribed, slightly depressed, glassy, gray-tan, irregularly shaped lesions.

- The size of lesions varies, from small foci to confluent plaques.

- The lesions often have sharply defined borders.

- **Plaques commonly occur adjacent to the lateral ventricles**
Multiple Sclerosis (Morphology conte)

✓ Microscopic:

✓ The lesions have sharply defined borders at the microscopic level.

✓ In an active plaque there is evidence of ongoing myelin breakdown with abundant macrophages containing myelin debris.

✓ Lymphocytes and monocytes are present, mostly as perivascular cuffs.

✓ Small active lesions are often centered on small veins.

✓ Axons are relatively preserved, although they may be reduced in number.
Multiple Sclerosis (Morphology conte)

Microscopic: inactive plaques,

✓ plaques become quiescent, the inflammation mostly disappears, leaving behind little to no myelin.

✓ Instead, astrocytic proliferation and gliosis are prominent.

shadow plaques, (incomplete myelin loss or partial remyelination.)
Multiple Sclerosis

Clinical Features:

- Commonly there are multiple episodes of new symptoms (relapses) followed by episodes of recovery (remissions).
- Typically the recovery is not complete.
- The consequence of disease is the gradual, often stepwise, accumulation of increasing neurologic deficits.
**Multiple Sclerosis**

**Clinical Features:**

- Unilateral visual impairment is a frequent initial manifestation of MS.
- Involvement of the brain stem produces cranial nerve signs and ataxia, and can disrupt conjugate eye movements.
- Spinal cord lesions give rise to motor and sensory impairment of trunk and limbs, spasticity, and difficulties with the voluntary control of bladder function.
- Changes in cognitive function can be (milder)
Multiple Sclerosis

✓ The CSF in MS patients shows:
  • a mildly elevated protein level.
  • an increased proportion of $\gamma$-globulin.
  • in one-third of cases there is moderate pleiocytosis.

✓ When the immunoglobulin is examined further, most MS patients show oligoclonal bands (a marker for disease activity)

✓ MRI can show the distribution of lesions across the nervous system during active disease.
Other Acquired Demyelinating Diseases

• Immune-mediated demyelination can be found after a number of systemic infectious illnesses.

• There are two general patterns of post-infectious pathology (unlike MS, they are monophasic illnesses with relatively abrupt onset)
Other Acquired Demyelinating Diseases

- **Acute disseminated encephalomyelitis,**
  - a week or two after infection. Diffuse, acute, with a fatal outcome

- **Acute necrotizing hemorrhagic encephalomyelitis:**
  - is a more devastating related disorder, which typically affects young adults and children.
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- Demyelinating diseases of the CNS.
- Dysmyelinating diseases of the CNS.
PRIMAR Y DISEASES OF MYELIN

Dysmyelinating diseases of the CNS. *(leukodystrophy)*:

- Myelin is not formed properly or has abnormal turnover kinetics.
- Dysmyelinating diseases are associated with *mutations* affecting the synthesis or degradation of proteins or myelin lipids required for formation of normal myelin.
Leukodystrophies

Morphology:

✓ Much of the pathology of leukodystrophies is found in the white matter.

✓ which is diffusely abnormal in color (gray and translucent) and volume (decreased).

✓ nearly all of the white matter is usually affected.

✓ With the loss of white matter, the brain becomes atrophic, the ventricles enlarge.

✓ Myelin loss is common across the leukodystrophies, often with macrophages stuffed with lipid
Leukodystrophies

✓ Clinical Features:

✓ Affected children are normal at birth but begin to miss developmental milestones during infancy and childhood.

✓ Diffuse involvement of white matter leads to deterioration in motor skills, spasticity, hypotonia, or ataxia.

✓ In general, the earlier the age at onset, the more severe the deficiency and clinical course
THE END