وقل رب زدني علماً

النادي الطبي

PERIPHERAL NERVOUS SYSTEM

SUBJECT : Pathology-TABLE

LEC NO. : 3

DONE BY : Sami Alodeh

#كلينيكال_إلا_شحطة

PNS

Pathology Lecture 3

Diseases of Myelin

- Most diseases of CNS myelin do not significantly involve the peripheral nerves, and vice versa

- Loss of myelin interferes with electric impulse transmission along axons

- CNS myelin diseases are separated into two groups:

• Demyelinating diseases: acquired conditions characterized by damage to previously normal myelin, most severe in white matter, with relative preservation of axons in early stages.

• Dysmyelinating diseases or leukodystrophy: myelin is not formed properly or has abnormal turnover.

Myelin Diseases			
Demyelinating diseases (Acquired)			Dysmyelinating diseases (Inherited)
Autoimmune Multiple Sclerosis	Viral ADEM ANHE PML	Metabolic Central Pontine Myelinosis	Leukodystrophy

Multiple Sclerosis

GENERAL FEATURES

- An autoimmune demyelinating disorder characterized by episodes of neurologic deficits, separated in time, that produce white matter lesions separated in space.
- The most common demyelinating disorder - Relatively common (1:1000) - Present at any age (typically 20-40 yrs) (but onset in childhood or > 50 years is rare), F:M: 2:1

Prognosis: - Better in women - Better in patients with 2 or less attacks in the first year

Pathogenesis

- Caused by an autoimmune response directed against components of the myelin sheath.
- Related to genetic susceptibility and largely undefined environmental triggers.

1.Genetic predisposition:

- The incidence is 15-fold higher when the disease is present in a first-degree relative and 150-fold higher with an affected monozygotic twin
- A strong effect of the MHC; HLA-DRB1 - Other genetic loci that are associated with MS: IL-2 and IL-7 receptor genes

2.Immunological mechanisms:

-The disease is initiated by TH1 and TH17 cells that react against myelin antigens and secrete cytokines

- TH1 cells secrete IFN-γ, which activates macrophages, and TH17 cells promote the recruitment of leukocytes

-The demyelination is caused by activated leukocytes and their injurious products - B lymphocytes and antibodies also play a role in the disease.

-These cytokines cause direct damage to oligodendrocytes

3.Environmental factors:

- Infection, viral

Clinical features

- Multiple relapses followed by episodes of remission; typically, recovery during remissions is not complete
- Over time, there is usually a gradual, often stepwise, accumulation of neurologic deficits - In any individual patient, it is difficult to predict when the next relapse will occur
- Unilateral visual impairment is a frequent initial symptom of MS due to optic nerve involvement (optic neuritis, retrobulbar neuritis)
- Involvement of the brain stem produces cranial nerve signs & ataxia & can disrupt conjugate eye movements
- Spinal cord lesions give rise to motor & sensory impairment of trunk & limbs, spasticity, & difficulties with the voluntary control of bladder function
- Changes in cognitive function can be present but are often much milder than the other deficits

Clinical types

•Relapsing remitting MS (RRMS)

Episodic neurologic deficits that may partially or fully resolve but are followed by additional relapses

•Primary progressive MS (PPMS)

Nonepisodic progression of disease from the initial onset of symptoms

•Secondary progressive MS (SPMS)

Typically follows RRMS, where the disease transitions from episodic to continued progression

Investigations

The CSF shows:

-In one-third of cases, there is moderate pleocytosis (increase in WBC count)

-A mildly elevated protein level with an increased proportion of immunoglobulin

- ↑ Oligoclonal IgG bands - There is no oligoclonal band in the serum

MRI: The most accurate test, can show the distribution of lesions across the CNS during active disease

MORPHOLOGY

GROSS

- Plaques are discrete, slightly depressed, glassy-appearing, and gray-tan in color
- Plaques are common near the ventricles and also frequently occur in the optic nerves and chiasma, brain stem, ascending and descending fiber tracts, cerebellum, and spinal cord

MICROSCOPICALLY

The lesions have sharply defined borders

- Active plaques (soft pink):

▪ Contain abundant macrophages stuffed with myelin debris, evidence of ongoing myelin breakdown

▪Lymphocytes also are present, mostly as perivascular cuffs ▪Small active lesions often are centered on small veins.

▪Axons are relatively preserved but may be reduced in number

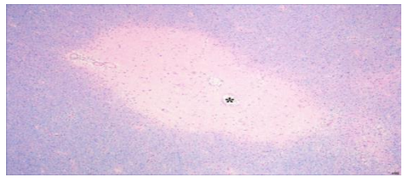
- Inactive plaques (hard grey): quiescent

▪The inflammation mostly disappears, leaving behind little to no myelin, astrocytic proliferation, and gliosis

- Shadow plaques:

- Border between normal and affected white matter representing partial remyelination or incomplete myelin loss

- Luxol fast blue/ periodic acid–Schiff stain for myelin:
section with a well-demarcated area of demyelination centered around a vein



VIRAL

Acute disseminated encephalomyelitis (ADEM)	- Postinfectious or Post-vaccinial autoimmune reactions to the myelin - Occurs after systemic infectious illnesses, such as viral diseases - Not related to the direct spread of infectious agents to the nervous system. Rather, it is believed that immune cells responding to pathogen-associated antigens cross-react against myelin antigens, resulting in myelin damage - Unlike MS, associated with acute-onset monophasic illnesses - Symptoms typically develop 1 or 2 weeks after an antecedent infection and are nonlocalizing (headache, lethargy, and coma), in contrast with the focal findings of MS - Symptoms progress rapidly, and the illness is fatal in as many as 20% of cases; in the remaining patients, there is complete recovery.
Acute necrotizing hemorrhagic encephalomyelitis (ANHE)	A more devastating related disorder, which typically affects young adults and children
Progressive multifocal leukoencephalopathy (PML)	A demyelinating disease that occurs after reactivation of the JC virus in immunosuppressed patients

Neuromyelitis optica (NMO)

- An antibody-mediated demyelinating disease (Antibodies to water channel aquaporin-4) (diagnostic & pathogenic)

- Centered on the optic nerves and spinal cord

- Spinal cord lesions lead to varying degrees of weakness or paralysis in the legs or arms, loss of sensation, and/or bladder and bowel dysfunction

Central pontine myelinolysis

Caused by nonimmune damage to oligodendrocytes, typically after sudden correction of hyponatremia and Acid-base imbalance

◦ Alcohol-induced - Involve the center of the pons

- May result in a rapidly evolving quadriplegia

Pathology:

- Cellular edema, caused by fluctuating osmotic pressures → compression of fiber tracts → demyelination in center of PONS & other areas in brain

Dysmyelinating diseases (leukodystrophy)

GENERAL FEATURES	-Inherited disease caused by abnormal myelin synthesis or turnover -Most are of autosomal recessive inheritance, although X-linked diseases also occur -They are caused by mutations of genes whose products are involved in the generation, turnover, or maintenance of myelin. -Some of these mutations affect lysosomal enzymes, while others involve peroxisomal enzymes; a few are associated with mutations in myelin proteins - Clinically, each disorder of the various leukodystrophies has a characteristic clinical presentation, and most can be diagnosed by genetic or biochemical methods - Affected children are normal at birth but begin to miss developmental milestones during infancy & childhood -There is typically diffuse involvement of white matter, leading to deterioration in motor skills, spasticity, hypotonia, or ataxia		
CLINICAL FEATURES (Distinguish leukodystrophies from demyelinating diseases)	-The leukodystrophies typically present with an insidious and progressive loss of function - Associated with diffuse and symmetric changes in imaging studies - Often begin at younger ages	Examples: - Metachromatic leukodystrophy – Adrenoleukodystrophy - Krabbe disease	
MORPHOLOGY	- Much of the pathologic change is found in the white matter, which is diffusely abnormal in color (gray and translucent) and volume (decreased) - Early, some diseases may show patchy involvement, while others have a predilection for occipital lobe involvement - In the end, nearly all of the white matter usually is affected. - With the loss of white matter, the brain becomes atrophic, the ventricles enlarge, and secondary changes can be found in the gray matter	MICROSCOPICALLY	- Myelin loss is associated with infiltration of macrophages, which often become stuffed with lipids - Some of these diseases also show specific inclusions created by the accumulation of particular lipids.