Neuropathology. P.2

Demyelinating Diseases

Demyelinating diseases of the CNS are acquired conditions characterized by preferential damage to myelin, with relative preservation of axons.

The clinical deficits are due to the effect of myelin loss on the transmission of electrical impulses along axons.

Demyelinating Diseases

Several disease processes can cause loss of myelin.

destruction of myelin by immunological reactions (multiple sclerosis, infections)

JC virus infection of oligodendrocytes (progressive multifocal leukoencephalopathy)

inherited disorders may affect synthesis or turnover of myelin components (leukodystrophies)

LEUKODYSTROPHIES

- heterogeneous group of inherited diseases

= enzyme defect - disturbances in the formation and preservation of myelin.

CLIN - **psychomotor retardation, progressive dementia, and paralysis**

Metachromatic Leukodystrophy (MLD)

- the most common type leukodystrophy
- AR accumulation of a *cerebroside* (*galactosyl sulfatide*) in the white matter of the brain and peripheral nerves.
- lethal within several years.

-deficiency of ***arylsulfatase A***, a lysosomal enzyme involved in the degradation of myelin.

Krabbe disease

Adrenoleukodystrophy (ALD)

Alexander Disease

LEUKODYSTROPHIES

	Disease classification	Symptoms	Disease Progression	Median Survival
Early onset	Early infantile 0-6 months	Crying/Irritability, feeding difficulties, poor head control, fisted hands, developmental delay	Progressive neurologic deterioration, seizures, psychomotor regression, loss of vision, hearing and voluntary movement	1.5 - 2 years
Early onset	Late infantile 7-36 months	Similar to early infantile	Similar to early infantile but slower progression	9.5 years
Late onset	Juvenile onset 3-15 years	Vision problems, muscle weakness, gait changes, loss of developmental milestones	Variable progression with older patients generally experiencing slower progression	>16 years
Late onset	Adult onset Above 15 years	Gait disturbance, weakness, lower limb hypoesthesia, cognitive regression, spastic paraparesis	Variable progression with older patients generally experiencing slower progression	>33 years

MULTIPLE SCLEROSIS

- chronic demyelinating disease
- autoimmune
- characterized by distinct episodes of neurologic deficits, separated in time
- attributable to white matter lesions that are separated in space.

MULTIPLE SCLEROSIS

It is the most common of the demyelinating disorders

1 per 1000 persons

The disease may become clinically apparent at any age, although onset in childhood or after age 50 years is relatively rare.

Women are affected twice as often as are men.

In most individuals with MS, the clinical course takes the form of relapsing and remitting episodes of variable duration (weeks to months to years) marked by neurologic defects, followed by gradual, partial recovery of neurologic function.

MULTIPLE SCLEROSIS.

Pathogenesis.

- GENETIC FACTORS:
  - – - A genetic predisposition: familial aggregation, increased risk in second- and third-degree relatives of patients with MS.
  - – - Associated with a number of major histocompatibility complex (MHC) alleles - **HLA-DR2**.
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- ♦ IMMUNE FACTORS:
  - – Experimental allergic encephalitis (EAE)
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- INFECTIOUS AGENTS:
  - – vaccinia, mumps, rubella, herpes simplex, and measles
  - – no direct evidence
  - – recently: *JC virus* (replicates in oligodendrocytes)

MULTIPLE SCLEROSIS

Morphology

MS is a white matter disease that is best appreciated in sections of the brain and spinal cord.

Lesions appear as multiple, well-circumscribed, somewhat depressed, glassy, graytan, irregularly shaped **plaques.**

Multiple Sclerosis

Clinical Features:

- **onset** - third or fourth decades
- **abrupt and brief episodes** of clinical progression + periods of relative stability

- **exacerbation** = expression of the formation of additional plaques of demyelination

- ***optic nerves*** → blurred vision or the loss of vision in one eye
- ***brainstem*** → the most troubling early symptoms double vision and vertigo.
- **spinal cord** → weakness legs and sensoric symptoms

- death of respiratory paralysis or urinary tract infections
- survive 20 to 30 years after the onset

Postinfectious and Postvaccinal Encephalomyelitis

= ADEM (acute demyelinating encephalomyelitis)

- foci of perivascular demyelination
    - viral exanthems (e.g., measles, varicella: rubella)
    - between 3 and 21 days after the rash.
    - immunization against smallpox

- Headache, vomiting, fever
- Meningeal signs
- In severe cases → paraplegia, incontinence, and stupor

Central Pontine Myelinolysis

- Rare
- Pons of:
    - malnourished persons
    - alcoholics

Degenerative Diseases

- Symptomatic/anatomic: based on the anatomic regions of the CNS that are primarily affected, which is typically reflected in the clinical symptoms (e.g., neocortical involvement resulting in cognitive impairment and dementia)
- Pathologic: based on the types of inclusions or abnormal structures observed (e.g., diseases with inclusions containing tau or containing synuclein)

- Degenerative diseases may be sporadic or familial.

  - **Cortex - Alzheimer´s disease, Pick´s disease**
  - **Expy (BG) - Parkinsonism, Huntington´s disease**
  - **Motor neurons - ALS**

Symptoms of dementia

- Recent memory loss
- Difficulty completing familiar tasks (apraxia)
- Problems communicating (afasia)
- Disorientation
- Mood changes
- Personality changes

Dementia

Degenerative neurological disease - Alzheimer's disease, FTLD, Parkinson's disease, Huntington's disease

Vascular disorders

Infections - HIV, Creutzfeldt-Jakob disease.

Long-time alcohol or drug use

Alzheimer's Disease

- the most common cause of dementia in the elderly

- occur after the age of 50
- a progressive increase in incidence with increasing age

- most cases are sporadic
- 10% of patients - a family history of dementia

Genetic factors:

= genetic abnormalities on chromosomes 21, 19, 14, and 1

1. **Amyloid precursor protein - APP**
   - the breakdown product (**Aβ-amyloid**) = component of both:
     - •the neurofibrillary tangles
     - •senile plaques
     - •within the walls of cerebral blood vessels
   - β-amyloid - toxic to neurons in cell cultures

2. Expression of specific alleles of **apoprotein E (apoE)**
   - ε4 allele of apoE = increased frequency in patients with late-onset AD
   -apoE = involved in the transport or processing of the β-amyloid precursor protein.

3. **presenilins**

4. **TAU protein** - tangles

Clinical features

- progressive impairment of memory and other cognitive functions
- subtle at first (depression)
- cognitive impairment over the course of 5 to 15 years
- complete disorientation and loss of language and other higher cortical functions
- Death - intercurrent bronchopneumonia

Alzheimer Disease

Morphology

Eventually, in 5 to 10 years, the affected individual becomes profoundly disabled, mute, and immobile.

Patients rarely become symptomatic before 50 years of age, but the incidence of the disease rises with age

Prevalence roughly doubles every 5 years, starting from a level of 1% for the 60- to 64-year-old population and reaching 40% or more for the 85- to 89-year-old cohort.

Alzheimer's Disease

Microscopic

• **neurofibrillary tangles** = coarse, filamentous aggregates within the neurons

- neocortex, hippocampus, basal forebrain and brain stem

• **senile plaques** = as aggregates of coarse neurites in the neuropil of the cerebral cortex

- a central amyloid core (β-amyloid)

• **amyloid angiopathy** = β-amyloid deposits in vessels

Alzheimer’s Disease

senile plaques

neurofibrillary tangles

PICK'S DISEASE - FTLD

- Rare presenile dementia - usually presents in 6th-7th decades
- Familial and sporadic occurrence
- Course - 2-10 years

Pathology:

- Circumscribed frontal and temporal lobe atrophy
- **lobar atrophy** or sclerosis,
- Severe neuronal loss and gliosis in atrophic areas
- Argyrophilic cytoplasmic inclusions - Pick bodies
- Typically without senile plaques or neurofibrillary tangles

Creutzfeldt-Jakob disease

Parkinsonism is not a single disease:
= a clinical manifestation of a **disturbance in the dopaminergic pathways connecting the substantia nigra to the basal ganglia**

Parkinsonism

- trauma
- certain toxic agents
- vascular diseases
- encephalitis
- Parkinson’s disease

Parkinson's disease = idiopathic parkinsonism (paralysis agitans)

= degenerative disorder involving the dopamine-secreting neurons of the substantia nigra, as well as the locus ceruleus.

- manifests by the sixth decade
- usually sporadic

MORPHOLOGY.

Macro:

- externally normal or mildly atrophic

- the substantia nigra and locus ceruleus are depigmented

Parkinson's disease

Microscopically

the neuropil in **substantia nigra**

and **locus coeruleus**:

- gliosis

- Lewy bodies = concentrically laminated intracytoplasmic inclusions

Huntington Disease

- hereditary, progressive, fatal disorder involving the ”extrapyramidal” motor system
- characterized by
    1. **involuntary movements (chorea)**
    2. **dementia**
    3. **psychiatric symptoms**
- autosomal dominant trait with complete penetrance

Pathogenesis:

The responsible gene: chromosome 4 (product = huntingtin)
-caused by **trinucleotide repeat expansion** in the Huntington gene:
- in Huntington disease, the number of triplet repeats is increased

- the larger the number, the earlier the onset of disease.
- the molecular pathogenesis of Huntington disease is not fully understood

Huntington Disease

MORPHOLOGY:

Gross

- brain atrophy (less than 1000 g)

-striking atrophy of the caudate nucleus, putamen, and globus pallidus,

Microscopically

- severe loss of neurons within the caudate and putamen,
- accompanied by fibrillary gliosis

Diseases of Motor Neurons

Amyotrophic lateral sclerosis (ALS)

- degenerative disorder involving the upper and lower motor neurons of the pyramidal system
- resultant progressive muscle weakness, atrophy, and spasticity

Pathogenesis of most cases of ALS - unknown

? mutations in the gene coding for the enzyme superoxide dismutase?