Summary of mid lectures

Lectures5-7

Multiple sclerosis

- Autoimmune demyelinating disease
- Episodes of neurologic deficits separated in time which are attributed to white matter lesions that are separated in space.
- loss of tolerance of self-proteins in the myelin sheath.
- Genetic and environmental factors play a role in this loss of tolerance.

morphology

- White matter disorder
- Multiple well circumscribed slightly depressed grey tan irregularly shaped lesions= plaques
- **Active plaques**: ongoing myelin breakdown, macrophages containing myelin debris. **Quiescent(inactive plaques**): inflammation disappears leaving behind little or no myelin. Instead there is astrocytic proliferation and **gliosis prominent**

Post infectious demyelination

- Not due to direct effect of the virus
- Pathogen associated antigens cross react with myelin antigens…. Provoke autoimmune response against myelin
- Onset: acute, monophasic

Neuromyelitis optica

- Inflammatory demyelinating disease
- Mainly optic nerve and spinal cord
- Antibodies to **aquaporin-4** are diagnostic
- Previously thought a subtype of MS

Central pontine myelinolysis

- Non immune process
- Loss of myelin in centre of pons, but also can affect other sites.
- Occurs after rapid correction of hyponatremia or after severe osmolar or electrolyte imbalances.
- Edema due to sudden change in osmotic pressure probably is the cause of the damage
- Causes rapid quadriplegia and can cause locked in syndrome

Neurodegenerative diseases

- = Disorders characterized by cellular degeneration of functionally related neurones.
- Many of them related to accumulation of abnormal proteins.

Abnormal protein aggregates in neurodegenerative diseases

- Abnormally aggregated proteins often are directly toxic to neurons. ALL act as prions (spread from one area of brain to another)
- ALSO: There is loss of function m as more and more protein is shunted into the aggregates rather than performing normal physiologic functions.

Alzheimer disease (AD)

- Most common cause of dementia
- Gradual onset of impaired higher intellectual function + altered mood and behaviour.
- Progresses to disorientation , memory loss, aphasia
- Then.. Over 5-10 years, become disabled, mute and immobile
- Death due to infections, mainly pneumonia

pathogenesis

- Alzheimer is caused by accumulation of two proteins: AB amyloid and tau in specific brain regions due to overproduction and decreased removal.
- Both protein aggregates cause neural death and dysfunction.
- The initial event is the AB accumulation.

AB amyloid deposition

-Amyloid precursor protein (APP) is a cell surface protein with a single transmembrane domain

- Point mutations in APP are a cause of familial AD

- APP gene present on chromosome 21.
- Trisomy 21 (Down syndrome) have increased risk of Alzheimer

- AMYLOID CAN ACCUMOLATE IN THE ELDERY WITHOUT CAUSING DEMENTIA

Tau protein

- Tau is a microtubule-associated protein present in axons in association with the microtubular network.
- In AD Tau becomes hyperphosphorylated, and loses the ability to bind to microtubules.

Microscopic changes

- Amyloid plaques and neurofibrillary tangles.
- Plaques are extracellular amyloid deposition ; tangles are intracellular Tau deposition.

Fronto-temporal lobar degeneration (FTLD)

- Heterogeneous group of diseases associated with focal degeneration of frontal and/or temporal lobe.
- Differ from Alzheimer by : changes in personality and language precede memory loss .
- With time.. The disease progresses and dementia occurs.

etiology

- Accumulation of abnormal Tau protein.

Tau in FTLD accumulates in two forms:

- 1. **neurofibrillary tangles**; like those seen in Alzheimer (but in FTLD there is only Tau and no amyloid aggregates)
- 2. smooth inclusions = **Pick bodies**.. This subtype of FTLD is called Pick disease.

Tau protein

- Is a phosphoprotein that interacts with microtubules and stabilizes them.
- When Tau is hyperphosphorylated two changes occur: 1) its ability to bind with microtubules decreases and 2) its ability to aggregate increase.

Parkinson disease

- Parkinsonism: Tremors, rigidity, bradykinesia and instability.
- Caused by damaged dopaminergic neurones that project from substantia nigra
- Parkinsonism can be due to 1) dopamine antagonists , 2) toxins
- 3) Or: can be caused by Parkinson disease (neuro-degenerative disorder)

Parkinson disease
signs and symptoms

- Diminished facial expressions (Masked facies)
- Stooped posture
- Slow voluntary movement
- Rigidity
- Pill rolling tremor
- Festinating gait= progressively shortened accelerated steps.

Clinical features

- Movement disorder.
- Progresses over 10-15 years.. Severe motor slowing
- Death: infections and trauma due to falls (instability)
- Dementia can develop
- If dementia within first year of diagnosis: lewy body dementia.

pathogenesis

- The abnormal accumulation of alpha synuclein is thought to be the main cause of symptom
- Neural inclusions containing alpha synuclein; a protein involved in synaptic transmission.
- These inclusions= Lewy bodies

morphology

- Pale substantia nigra and locus ceruleus
- Loss of pigmented neurones with associated gliosis
- Lewy bodies seen in the remaining neurones in these regions
- Lewy body: intracytoplasmic eosinophilic round to elongated inclusions that have a dense core surrounded by a pale halo

Huntington disease

- Autosomal dominant disease. (no sporadic cases)
- Movement disorder which is chorieform =dancelike Involuntary jerky movements of all parts of the body
- Degeneration of caudate and putamen

pathogenesis

- CAG(cytosine-adenine-guanine) trinucleotide repeat expansions in the gene that encodes huntingtin protein.
- CAG codes for glutamine

- Huntingtin protein is thought to play a role in long term memory storage

Clinical course

- Age of onset:40-50 years of age; related to the length of CAG repeats(more repeats; earlier age of onset)

First symptoms are motor disturbances and choreiform movementsProgressive

- Memory loss can develop and progresses to severe dementia
- Behavioral changes.. Risk of suicide