Neurodegenerative Diseases (1)

Classic Features of Neurodegenerative diseases:

- Progressive loss of neurons.

- Different diseases affect different locations in CNS, so different symptoms.

- The histologic hallmark for ALL neurodegenerative diseases is the **accumulation of protein aggregates**.

  - Same protein may aggregate in different diseases, but at different locations.

  - Protein aggregates can seed the development of more aggregates.

  - Protein aggregates can spread from one neuron to another in Prion-like pattern. (No evidence of person-to-person transmission.

  - Protein aggregates activate the innate immune system.

Neurodegenerative diseases according to the location:

1. Diseases involving the **hippocampus** and **cortex** >>>> cognitive changes (memory disturbances, behavior and language) >>>> dementia >>>>> Alzheimer Disease (AD), Frontotemporal Dementia (FTD), Pick Disease (subtype of FTD)

2. Diseases involving the **basal ganglia** >>>>> movement disorders >>>> hypokinesia (Parkinson Disease) OR hyperkinesia (Huntington Disease)

3. Diseases involving the **cerebellum** >>>> ataxia >>> (Spinocerebellar Ataxia, Friedrich Ataxia, Ataxia Telangiectasia)

4. Diseases involving the **motor system** >>> difficulty swallowing and respiration with muscle weakness >> (Amyotrophic Lateral Sclerosis)

DEMENTIA:

(NOTE: Dementia is not a specific disease by itself, rather it is set of symptoms describes more than one disease)

- Definition: Development of memory impairment and other cognitive deficits severe enough to decrease the person's capacity to function at his previous level despite normal level of consciousness.

  - Cognitive deficit must affect the person's performance in his daily life activities.

  - There is no standard normal cognition, always compared to previous level.

  -NOTE: The consciousness is normal in dementia

- Symptoms of dementia:

1. Cognitive changes
    - Memory loss, which is usually noticed by a spouse or someone else
    - Difficulty communicating or finding words
    - Difficulty reasoning or problem-solving
    - Difficulty handling complex tasks
    - Difficulty with planning and organizing
    - Difficulty with coordination and motor functions
    - Confusion and disorientation
2. Psychological changes
    - Personality changes
    - Depression
    - Anxiety
    - Inappropriate behavior
    - Paranoia
    - Agitation
    - Hallucinations
3. Motor changes (in severe cases)

- Causes of dementia:

- **Neurodegenerative diseases**
- Infections
- Nutritional deficiencies
- Metabolic and endocrine abnormalities
- Drugs
- Subdural hematoma
- Poisons
- Tumors
- Anoxia and ischemia

- Complications of dementia:

1. Inadequate nutrition: Many people with dementia eventually reduce or stop their intake of nutrients.
2. Inability to perform self-care tasks: As dementia progresses, it can interfere with bathing, dressing, brushing hair or teeth, using the toilet independently and taking medications accurately.
3. Personal safety challenges: Some day-to-day situations can present safety issues for people with dementia, including driving, cooking and walking alone.
4. Coma or Death: often from infection

1st Alzheimer Disease (AD)

- Affect cortical neurons.

- Most common cause of dementia in older adults.

- Increase incidence with age.

- Gradual onset.

- Most cases are sporadic, 5-10% are familial (onset before 50)

- Symptoms and Complications:

- The most commonly recognized symptom of Alzheimer is: an **inability to acquire new memories** and difficulty in recalling recently observed facts.
- As the disease advances, the higher intellectual functions start to be impaired.
- Symptoms include: confusion, irritability and aggression, mood swings, language breakdown (Aphasia), long term memory loss, and ultimately a gradual loss of bodily functions.
- Death usually due to infections (pneumonia)

- Pathogenesis:

- Accumulation of two proteins (AB amyloid and Tau) in the form of plaques (by AB amyloid) and neurofibrillary tangles (by Tau) → leads to neuronal cells death and inflammation.

- Plaques deposit in the neuropil (neuropil = extracellularly).

- Tangles develops intracellularly.

- Aβ generation is the critical initiating event for the development of Alzheimer.

- Mutations of the gene encoding the precursor protein for Aβ (PPA) → elevated risk of Alzheimer.

- Mutations of Tau gene do NOT increase risk of Alzheimer.

- Role of Aβ:

- Alzheimer Disease results when the transmembrane protein (Amyloid Precursor Protein APP) is sequentially cleaved by the enzymes β-amyloid–converting enzyme (BACE) (**B-secretase**) and **γ-secretase** creating Aβ.

- Normally, APP can be cleaved by **α-secretase** and **γ-secretase**, liberating a nonpathogenic peptide.

APP ----- (**α-secretase + γ-secretase**) -----> nonpathogenic peptide

APP ----- (**B-secretase + γ-secretase**) -----> Aβ peptide >> **Inflammation** + Aβ amyloid >> **plaques formation** >> **AD**

- Mutations in: (1) APP OR (2) γ-secretase → familial AD.

- The APP gene is located on chromosome 21, so there is increased risk of AD in down syndrome.

- Role of tau:

- Tau is a microtubule-associated protein present in axons of neurons.

- Aβ peptides >> Tau hyperphosphorylation >> Tau aggregation >> cell death (**inflammation**) + **neurofibrillary tangles** >> **AD**.

- Tau hyperphosphorylation >> loses the ability to bind to microtubules >> loss of microtubule stability >> neuronal cell death.

- Tau aggregates can be passed across synapses from one neuron to the next >>> **spread of lesions**.

- Role of inflammation:

- Innate immune system responds to **Aβ** and **tau**.

- Deposits of Aβ elicit an inflammatory response from microglia and astrocytes.

- Clearance of the aggregated peptide, and secretion of mediators that cause neuronal injury over time.

- Basis for cognitive impairment:

- tangles Deposits of Aβ and appear long before cognitive impairment (in familial AD, deposition of Aβ and the formation of tangles precede cognitive impairment by as much as **15** to **20** years).

- More plaques and tangles are strongly associated with severe cognitive dysfunction.

- **Number of neurofibrillary tangles correlates better with the degree of dementia**.

- Morphology

- Macroscopically:

1. Narrowed gyri along with widened sulci (Atrophy).

   Most pronounced in the **frontal**, **temporal**, and **parietal** lobes.

   Sparing of the occipital lobe.

2. Compensatory ventricular enlargement (hydrocephalus ex vacuo).

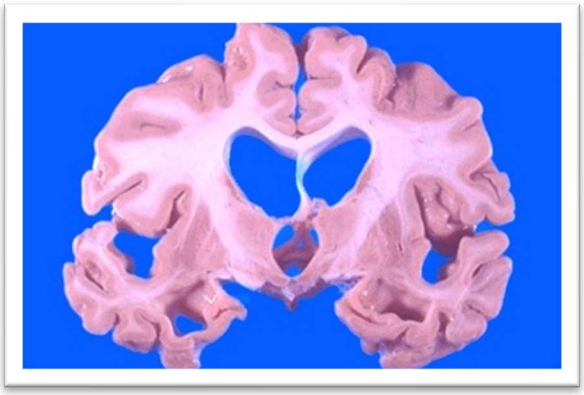

Figure 1: hydrocephalus ex vacuo

- Microscopically (neuropathologic changes):

1. Plaques (an ***extracellular*** lesion): central amyloid core surrounded by collections of dilated, tortuous, processes of dystrophic neurites.

   - Hippocampus and amygdala and neocortex, (**sparing of primary motor and sensory cortices until late**).

2. Neurofibrillary tangles: basophilic fibrillary structures in the ***cytoplasm*** of neurons, displace or encircle the nucleus; persist after neurons die, becoming ***extracellular***.

   - Cortical neurons, pyramidal cells of hippocampus, the amygdala, the basal forebrain, and the raphe nuclei.

2nd Frontotemporal Lobar Degeneration (Frontotemporal dementias)

- Several disorders (not a single disease)

- Symptoms:

- **Behavioral and language problems which precede memory disturbances (in contrast to AD)**.

- The onset of symptoms occurs at younger ages than for AD.

There are neuronal inclusions in FTLDs, which may contain: **Tau** or **TDP43**. (Two forms of disease)

A. Pick disease

(Subtype of FTLD-tau), associated with smooth, round inclusions known as Pick bodies.

B. TDP34 subtype

- NOTE: in FTLD (Pick subtype), Tau accumulation occur in the beginning (not like AD: Aβ >> Tau)

- Macroscopically:

1. Atrophy of **frontal** and **temporal** lobes.

- Microscopically:

- in Pick disease (FTLD-Tau): Neurofibrillary tangles (like AD) and Pick bodies

- Comparison between AD and FTLDs:

- In AD: there is sparing of the frontal lobe, at least at the beginning, so behavioral changes are a late manifestation.

- In FTLD: frontal is affected from the beginning, so patients present with behavioral problems first.

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Summary

Dementia:

- Dementia is not a specific disease by itself, rather it is set of symptoms describes more than one disease.
- The consciousness is normal in dementia.
- Symptoms include: cognitive, psychological, and motor changes.
- Various causes include **neurodegenerative diseases**, infections, and metabolic abnormalities.

Alzheimer's Disease (AD):

- **Sporadic** and Familial.
- Affects cortical neurons and is the most common cause of dementia in older adults.
- Gradual onset, with symptoms such as memory loss, confusion, and language breakdown.
- The most commonly recognized symptom of Alzheimer is: an **inability to acquire new memories.**
- Pathogenesis:
    - APP ----- (**B-secretase + γ-secretase**) -----> Aβ peptide >> **Inflammation** + Aβ amyloid >> **plaques formation** (extracellularly = neuropil) >> **AD**
    - Aβ peptides >> Tau hyperphosphorylation >> Tau aggregation >> cell death (**inflammation**) + **neurofibrillary tangles** (intracellularly) >> **AD**
- Tau aggregates can be passed across synapses from one neuron to the next >>> **spread of lesions**.
- Number of neurofibrillary tangles correlates better with the degree of dementia.
- Mutations in **APP** or **γ-secretase** lead to familial AD.
- Morphological changes Macroscopically include gyri atrophy and ventricular enlargement (hydrocephalus ex vacuo).
- Most commonly affect Frontal, Parietal and Temporal lobes.
- Tau aggregates can be passed across synapses from one neuron to the next >>> **spread of lesions**.

Frontotemporal Lobar Degeneration (FTLD):

- Comprises several disorders with behavioral and language problems preceding memory disturbances.
- Onset occurs at younger ages than AD.
- Inclusions may contain Tau or TDP43 proteins.
- Subtypes include Pick disease (FTLD-Tau) and TDP43 subtype.
- Macroscopic and microscopic changes involve atrophy of frontal and temporal lobes, with neurofibrillary tangles and Pick bodies in Pick disease.