MID

Lecture 4

بسم الله الرحمن الرحيم

Pathology Mind Maps

Neurodegenerative disorders-1

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Neurodegenerative disorders

Classic features

- **Progressive loss of neurons**
- **Typically affects groups of neurons with shared functions**
- **Different diseases involve different neural systems, so different symptoms**

Different diseases

Hippocampus and cortex

- Cognitive changes (memory, behavior and language disturbances)
- Dementia
- ALZHEIMER DISEASE (AD)
- FRONTOTEMPORAL DEMENTIA (FTD)
- PICK DISEASE (SUBTYPE OF FTD)

Basal ganglia **movement disorders**

- hypokinesia → PARKINSON DISEASE
- hyperkinesia → HUNTINGTON DISEASE

Cerebellum **ataxia**

- SPINOCEREBELLAR ATAXIA
- FRIEDRICH ATAXIA
- ATAXIA TELANGECTASIA

Motor system **difficulty swallowing and respiration with muscle weakness**

- AMYOTROPHIC LATERAL SCLEROSIS

Details under each branch

Classic features (protein pathology)

Histologic hallmark:

→ accumulation of protein aggregates

Distribution:

- Same protein may aggregate in different diseases
- But at different distribution

Effects of protein accumulation

- Proteins resist degradation
- Accumulate within cells or extracellular space
- Elicit inflammatory response
- Toxic to neurons

Causes of protein accumulation

1. Mutations that alter protein conformation
2. Mutations disrupting processing and clearance of proteins
3. Subtle imbalance between protein synthesis and clearance (genetic or environmental factors)

Common features to many neurodegenerative diseases

Protein aggregates

1. seed the development of more aggregates
2. spread to healthy neurons in Prion-like pattern

No evidence of person-to-person transmission

Activation of the innate immune system

DEMENTIA

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

- **Cognitive changes**
  - **Memory loss**
    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**
- **Psychological changes**
  - **Personality changes**
  - **Depression**
  - **Anxiety**
  - **Inappropriate behavior**
  - **Paranoia**
  - **Agitation**
  - **Hallucinations**

Alzheimer disease

"رَبَّنَا آتِنَا فِي الدُّنْيَا حَسَنَةً وَفِي الْآخِرَةِ حَسَنَةً وَقِنَا عَذَابَ النَّارِ"

Epidemiology

- Most common cause of dementia in older adults
- Incidence increases with age
- 47% in those over 84 years

Types

- **Sporadic** – most cases
- **Familial** – 5–10% – onset before 50

Disease course

- gradual onset

Death

- usually due to infections (pneumonia)

symptoms

Most recognized symptom:

- inability to acquire new memories
- difficulty recalling recently observed facts

As disease advances:

- confusion
- irritability
- aggression
- mood swings
- language breakdown
- long term memory loss
- gradual loss of bodily functions
- death

Pathogenesis

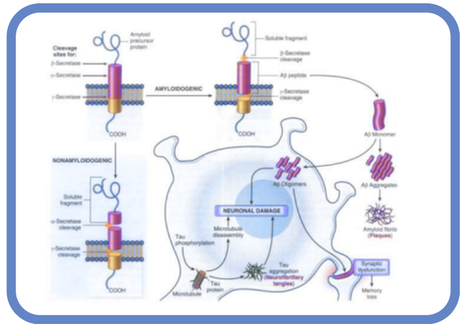
- Accumulation of two proteins (**Aβ amyloid** and **Tau**)
- Plaques (AB amyloid) and neurofibrillary tangles (Tau).
- Leads to neuronal dysfunction, death and inflammation.
- **Plaques** deposit in the neuropil, **tangles** develops intracellularly.
- Aβ generation is the critical initiating event.
- Multiple gene loci contribute to the risk of AD

Role of Aβ

The APP gene is located on chromosome 21, increased risk in down syndrome

Normal pathway

Amyloid precursor protein (APP) is cleaved by α-secretase and γ-secretase, liberating a **nonpathogenic** peptide.



Alzheimer pathway

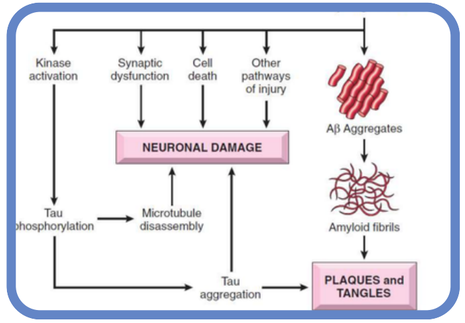
Amyloid precursor protein (APP) is cleaved by

- enzymes B-secretase (βamyloid–converting enzyme, BACE) - γ-secretase

creating Aβ amyloid.

Alzheimer pathway

Mutations in APP or in components of γ-secretase and others.



Once generated:

Aβ is highly prone to aggregation >>>> PLAQUES FORMATION >>> decreased number of synapses >>> synaptic dysfunction >>> memory disruption.

Role of Aβ

Tau is a microtubule-associated protein.

Present in axons in association with the microtubular network.

Hyperphosphorylated Tau loses ability to bind microtubules

→ loss of microtubule stability

→ neuronal toxicity

→ neuronal death

Responsible for neurofibrillary tangles

Tau aggregates spread across synapses

Role of inflammation

Deposits of Aβ elicit an inflammatory response

Cells involved: - microglia - astrocytes

Effect

- clearance of aggregated peptide
- secretion of mediators causing neuronal injury

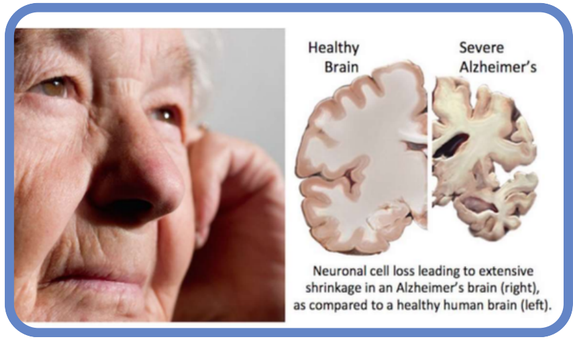
Basis for cognitive impairment

Plaques and tangles appear long **before** cognitive impairment

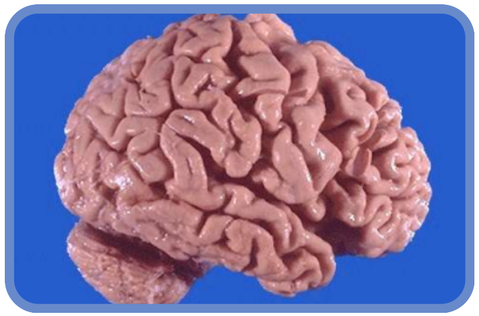
- In familial AD deposition precedes symptoms by 15-20 years
- Large burden of plaques and tangles associated with severe cognitive dysfunction
- Number of neurofibrillary tangles correlates better with degree of dementia than neuritic plaques

Morphology

- **Cortical atrophy**
- **Widening of cerebral sulci**
- **Most pronounced in:**
  - frontal lobes
  - temporal lobes
  - parietal lobes
- **Compensatory ventricular enlargement** (hydrocephalus ex vacuo).



Neuronal cell loss leading to extensive shrinkage in an Alzheimer's brain (right), as compared to a healthy human brain (left).



Mainly in the frontal and parietal regions, characterized by narrowed gyri along with widened sulci.

More marked atrophy seen superiorly and laterally, with sparing of the occipital region.

Progressive cortical atrophy with Alzheimer disease leads to compensatory dilation of the cerebral ventricles known as "hydrocephalus ex vacuo".

Microscopy

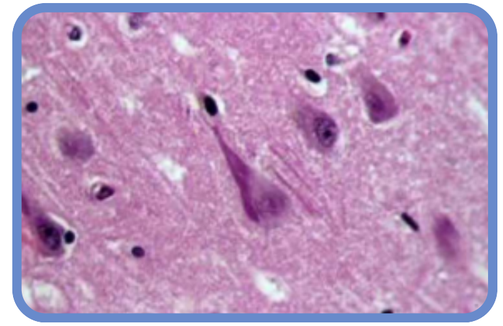
Neuritic plaques

- An extracellular lesion, central amyloid core surrounded by collections of dilated, tortuous, processes of dystrophic neurites.

Location

- hippocampus
- amygdala
- neocortex

(sparing primary motor and sensory cortices until late)

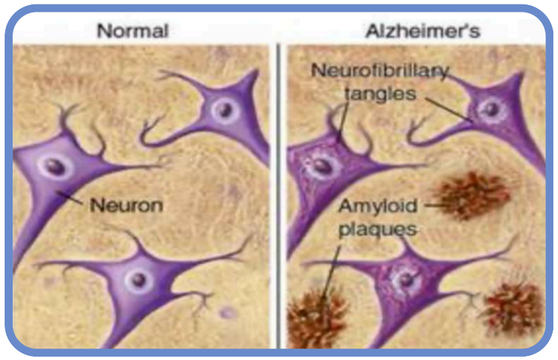


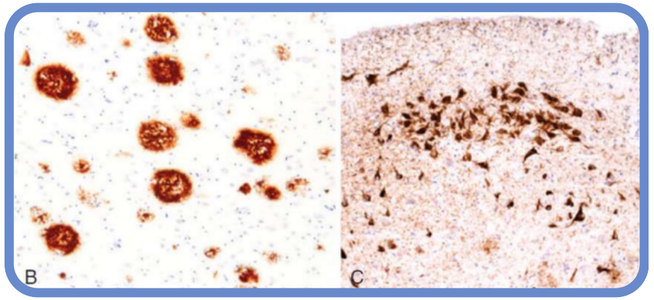
NEUROFIBRILLARY TANGLES

The amyloid core contains Aβ

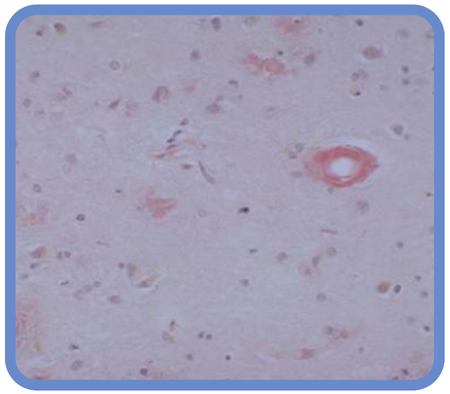
Neurofibrillary tangles

- 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.
- Contains hyperphosphorylated tau.





Plaques and tangles



Congo red stain for amyloid core of plaques.

Clinical features

Slow relentless progression (>10 years)

Early

- forgetfulness
- memory disturbances

Progression

- language deficits
- loss of mathematical skills
- loss of learned motor skills

Late stage

- incontinent
- mute
- unable to walk

Terminal event

- pneumonia

Early intervention

- drugs or antibodies to clear Aβ amyloid
- prevent Tau alterations

Biomarkers for detection

- imaging methods
- CSF studies: phosphorylated Tau and reduced Aβ in CSF

Frontotemporal Lobar Degeneration

اللهمَّ أَنْتَ رَبِّي لا إِلَهَ إلا أَنْتَ،خَلَقْتَنِي وَأَنَا عَبْدُكَ، وأَنَا عَلَى عَهْدِكَ ووعْدِكَ مَا اسْتَطَعْتُ، أَعُوذُ بِكَ مِنْ شَرِّ مَا صَنَعْتُ،أَبُوءُ لَكَ بِنِعْمَتِكَ عَلَيَّ،وَأَبُوءُ لَكَ بِذَنْبِي،فَاغْفِرْ لِي،فَإِنَّهُ لا يَغْفِرُ الذُّنُوبَ إلا أَنْتَ

Definition

- Heterogenous group, preferentially affect the frontal and/or temporal lobes.
- Behavioral and language problems precede memory disturbances, in contrast to AD.
- The onset of symptoms occurs at younger ages than for AD.

Types according to neuronal inclusions

1-FTLD-tau.

2-FTLD-TDP43: also deposited in ALS.

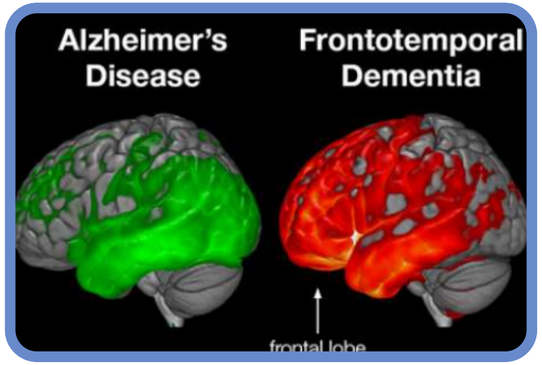
Clinical comparison with AD

FTLD:

- frontal lobe affected early
- behavioral problems first

AD:

- frontal lobe spared early
- behavioral changes appear later



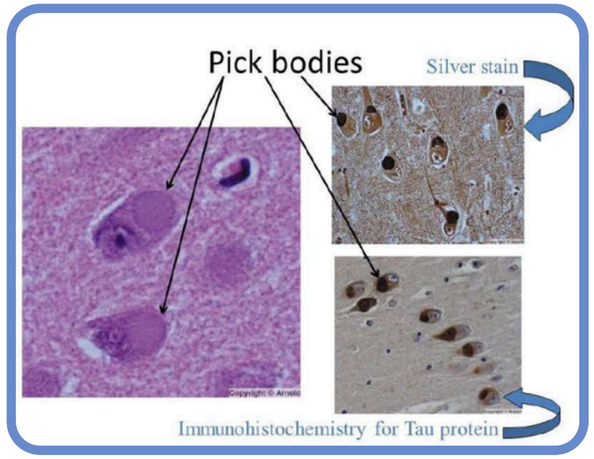
Morphology

- Atrophy of frontal and temporal lobes.
- Neuronal loss and gliosis

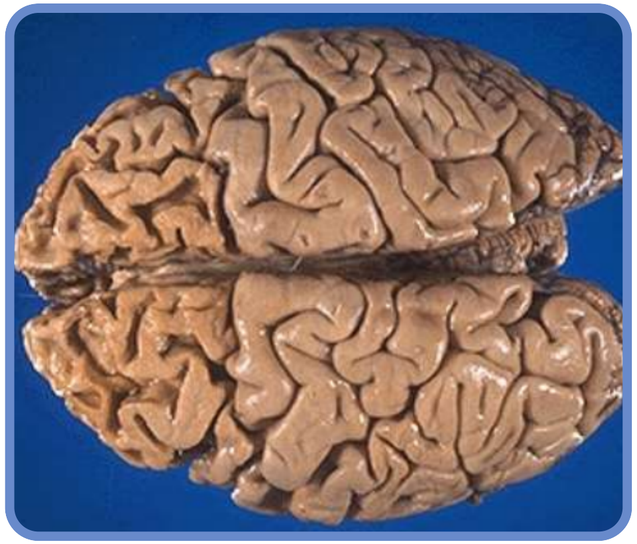
- In FTLD-tau: neurofibrillary tangles like in AD.
- In FTLD-TDP43: cytoplasmic inclusions.

Pick disease

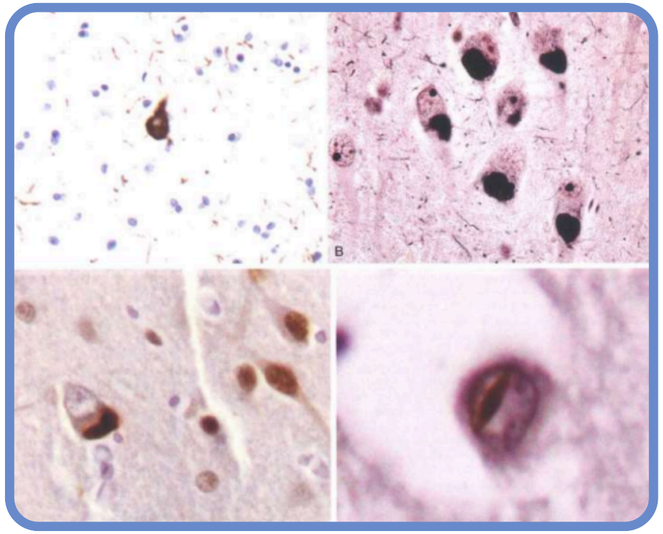
- Pronounced and asymmetric atrophy of frontal and temporal lobes with sparing of posterior two thirds of superior temporal gyrus.
- **Pick bodies :** round oval cytoplasmic filamentous inclusions stain strongly with silver stain.



Very marked frontal lobe atrophy and temporal lobe atrophy



Frontal lobes are markedly thinned



This file contains the lecture material presented through mind maps to make the information clearer, more organized, and easier to follow. It is designed to simplify studying and make revision more effective.

We truly hope you find it beneficial.
If it helps you in any way, please remember us in your prayers.

Best of luck in your studies💙!

اللهم اجعل أجر هذا العمل صدقة جارية عن روح **عمر عطيه عوده المرابي**

- اللَّهُمَّ اغْفِرْ له وَارْحَمْهُ، وَاعْفُ عنْه وَعَافِهِ، وَأَكْرِمْ نُزُلَهُ، وَوَسِّعْ مُدْخَلَهُ، وَ اغْسِلْهُ بمَاءٍ وَثَلْجٍ وَبَرَدٍ، وَنَقِهِ مِنَ الخَطَايَا كما يُنَقّى الثَّوْبُ الأبْيَضُ مِنَ الدَّنَسِ.
- اللَّهُمَّ أبدله داراً خيراً من داره، وأهلاً خيراً من أهله، وأدخله الجنّة، وأعذه من عذاب القبر ومن عذاب النّار.
- اللهمّ يمّن كتابه، ويسّر حسابه، وثقل بالحسنات ميزانه، وثبّت على الصراط أقدامه، وأسكنه في أعلى الجنات، بجوار حبيبك محمد صلّى الله عليه وسلم.
- اللهم اغفر لحينا وميتنا وشاهدنا وغائبنا وصغيرنا وكبيرنا وذكرِنا وأنثانا اللهم من أحييته منا فأحيِه على الإسلام ومن توفيته منا فتوفه على الإيمان اللهم لا تحرمنا أجره ولا تضلنا بعده.
- اللهم اغفر له وارفع درجته في المهديين، واخلفه في عقبه في الغابرين، واغفر لنا وله يا رب العالمين، وافسح له في قبره، ونوّر له فيه.
- اللَّهُمَّ أنزل على أهله الصّبر والسلوان وارضهم بقضائك.

اللهم لا تفجعنا بأنفسنا ولا أهلنا ولا أحبتنا، اللهم أعوذ بك من فواجع الأقدار ومن مصائب الدنيا وتقلب حوادثها، اللهم إنا نخاف الفقد فلا تحملنا ما لا طاقة لنا به.