جامعة الملك سعود
King Saud University

Pathology
Teamwork 438

Lecture 8: Neurodegenerative Diseases

objectives

- Explain the basic pathological concepts of neurodegenerative disease, using Alzheimer's and Parkinson disease as a classical example.
- Know the definition of "dementia" syndrome.
- List the possible causes of dementia.
- Understand the major clinic-pathological features of Alzheimer's disease.
- Hypothesize the possible etiologies of Alzheimer's disease.
- List the causes of Parkinsonism.
- Understand the major clinical and pathological feature of Parkinson disease.

Black: original content
Red: Important
Blue: only found in boys slides

Dark orange: Doctor notes
Grey: Extra/Robbins
Pink: Only found in girls slides

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Editing file

Content

- Diagnosis
- Pathogenesis
- Morphology

- Epidemiology
- Pathogenesis
- Morphology

Parkinson's

Neurodegenerative diseases

ALzheimer's

Causes Of Dementia

Infections

Other causes

Vascular and Traumatic Diseases

Metabolic and Nutritional Diseases

Miscellaneous

Neurodegenerative diseases

- Disorders characterized by progressive loss of neurons that are related by **function**, rather than physical location in the brain.
- **Symptoms:** Depend on the pattern of involvement:

Cerebral cortical neurons	Motor Neurons	Cerebellum	Neurons of Basal ganglia
Result in: Cognitive changes such as loss of memory, language, and planning as with Alzheimer's.	**Result in:** weakness	**Result in:** ataxia	**Result in:** movement disorders as with Parkinson disease.

- Although many degenerative diseases have primary targets, other brain regions are often affected later in the course of disease.

Dementia (Set of symptoms)

- The development of **memory impairment and other cognitive deficits,** severe enough to decrease the affected person's capacity to function at the previous level despite a normal level of consciousness.
- **Dementia may arise during** the course of neurodegenerative diseases and diseases that injure the cerebral cortex.
- Not all forms of dementia are neurodegenerative

Males slides only:

Causes of Dementia	Examples
Primary Neurodegenerative Disorders	• Alzheimer disease. • Lewy body dementia. • Huntington disease.
Infections	• Prion disease. Ex; Cretutzfeldt-Jakob • HIV encephalopathy. • Progressive multifocal leukoencephalopathy
Vascular and Traumatic Diseases	• Multifocal cerebral infarction. • Global hypoxic-ischemic brain injury • Chronic subdural hematomas
Metabolic and Nutritional Diseases	• Thiamine deficiency. (alcoholics) Ex: Wernicke Korsakoff
Miscellaneous	• Neuronal storage diseases. • tumors • Toxic injury (mercury, lead, and others).

Alzheimer Disease

- The **most common cause of dementia** in elderly.
- Usually becomes clinically apparent as an insidious[1] impairment of higher intellectual functions, with alterations in mood and behavior.
- Later leads to severe cortical dysfunction:
  - Progressive disorientation
  - Memory loss[2]
  - Aphasia
  - Over the next 5-10 years, patient becomes extremely **disabled**, **mute**, and **immobile.**
- Death usually occurs from **intercurrent pneumonia** or other infections.
- Infection most commonly in Lung (pneumonia), and bladder (UTI).

Epidemiology

- When considered by age groups, the incidence of Alzheimer disease is:
  - 3% for individuals 65-74 years old
  - 19% for individuals 75-84 year olds
  - 47% for individuals 84+ year olds
- This increasing incidence with age has given rise to major medical, social, and economic problems in countries with a growing number of elderly.

Diagnosis

- Pathological examination of brain tissue is necessary for the definitive diagnosis.
- However, the combination of both **clinical** assessment and **radiological** methods allows accurate diagnosis in 80-90% of cases.

1- Proceeding in a **gradual** way but with **harmful** effects
2- The destructive pairing of plaque and tangles, start in Hippocampus region. Which responsible for forming memory. Loss or short-term memory is the 1st sign of alzheimer.

Pathogenesis Of Alzheimer Disease

- **Amyloid β** generation is the critical initiating event for the development of AD.
- Although the exact cause of Alzheimer disease isn't completely understood, there are 2 major players in its progression:

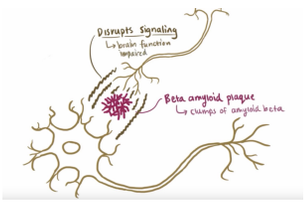
▶ **Plaques:** Deposits of aggregated **amyloid β peptides** (**Aβ**) in the neuropil.

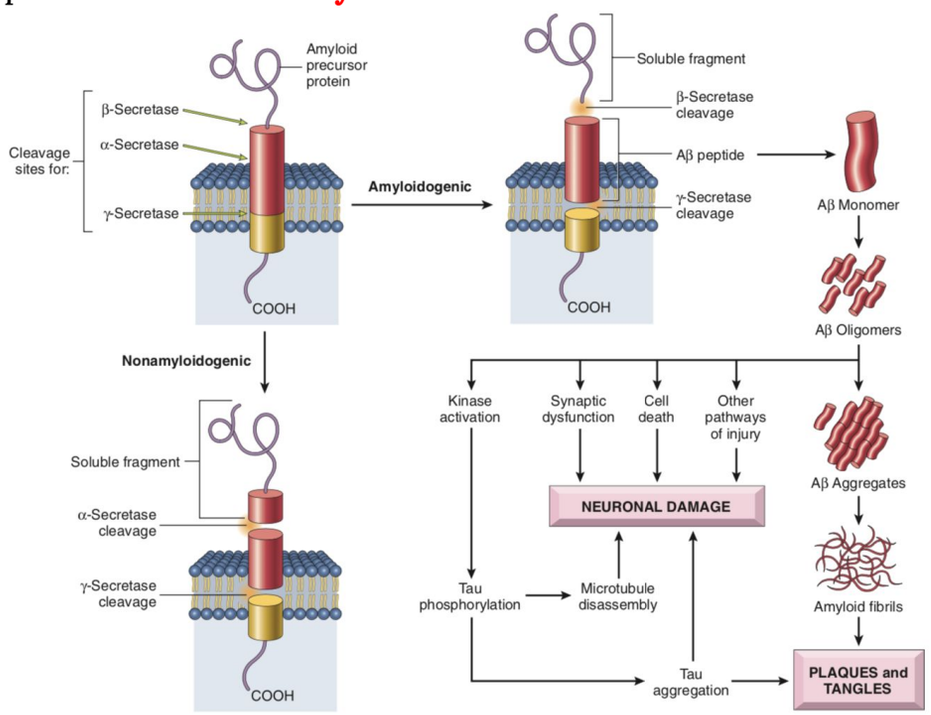
- This **Aβ peptide** is derived from a larger membrane protein known as **amyloid precursor protein (APP)** (located in cell membrane of neurons and plays a role in neuronal growth and repair), and like any other protein it will be used and **cleaved** by 2 pathways:

1 **Normal nonamyloidogenic - nonpathogenic pathway:**
Amyloid precursor protein (APP) cleavage by **α- secretase** and **γ-secretase** produces harmless **soluble peptide.** (a different peptide than Aβ)

2 **Abnormal amyloidogenic - pathogenic pathway:**
Amyloid precursor protein (APP) cleavage by **β-amyloid-converting enzyme (BACE) (β-secretase)** and **γ-secretase** releases **amyloid β peptides (Aβ).**

- When **Aβ** is generated and accumulates, it will become toxic and interfere with functions of neuron (next slide) and **disrupt signaling** → as they accumulate further they form insoluble oligomers "β amyloid plaques" **extracellularly**.

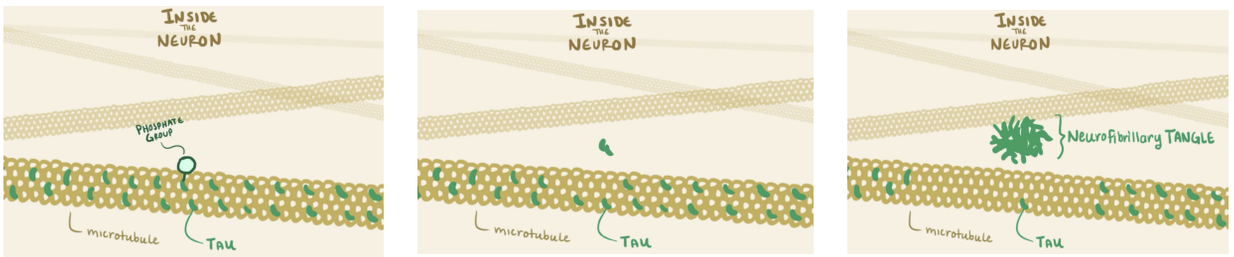




Pathogenesis Of Alzheimer Disease Cont.

Tangles: Aggregates of the microtubule binding protein **tau** which develop **intracellularly** and then persist <u>extracellularly after neuronal death.</u>

- Inside the cell's microtubules are tau proteins which keep the microtubules intact.
- The presence of **β amyloid** plaques play a role in **hyperphosphorylation** of **tau** proteins → changes their shape → tau proteins stop supporting microtubules and start clumping up together → form "neurofibrillary **tangles**" **intracellularly.**
- Tangles are not specific to Alzheimer disease, being found in other degenerative diseases as well.



Effects of Aβ accumulation on neurons and neuronal function:

Small aggregates of Aβ

- Can alter **neurotransmission**, and the aggregates can be toxic to neurons and synaptic endings.

Larger deposits in the form of plaques

- Also lead to **neuronal death**, elicit a local inflammatory response that can result in further cell injury, and may cause altered region-to-region communication through the mechanical effects on axons and dendrites.

Hyperphosphorylation of tau

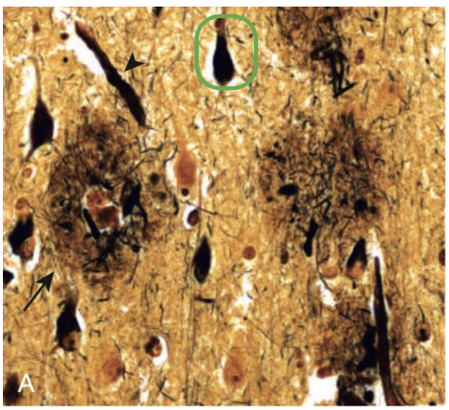
- Tau redistributes within the neuron, from the axon into dendrites and cell body, and aggregates into **tangles.**
- This process also results in **neuronal dysfunction and cell death.**
- The anatomic distribution of these changes, which occur roughly in parallel, are responsible for the clinical signs and symptoms; they appear to develop well in advance of clinical presentation.

Morphology Of Alzheimer Disease Cont.

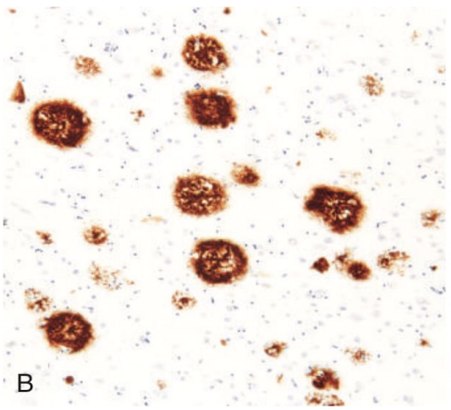
Microscopic Appearance

- There is a fairly **constant pattern** of progression in the brain region involvement in pathological changes:
  - Earliest in the entorhinal cortex → spread through the hippocampal formation and isocortex → then extend into neocortex.
  - Silver staining or immunohistochemistry are helpful in assessing the severity of these changes in the brain.

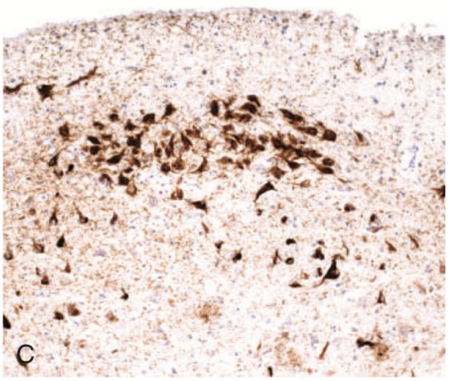
- **Plaques:** Extracellular
  - Focal, spherical collections of dilated tortuous, silver-staining neuritic processes (**dystrophic neurites**)
  - Around a central amyloid core **contains Aβ.**
  - Can be found in the hippocampus, amygdala, & neocortex.
  - Sparing of primary sensory & motor cortex until late stage.
  - Aβ deposits can lack surrounding neuritics, called **diffuse plaques.**
- **Neurofibrillary tangles:** intracellular
  - **Cytoplasmic**, until the cell dies then **become extracellular.**
  - Paired helical filaments, visible as **basophilic** fibrillary structures.
  - Mainly composed of **hyperphosphorylated tau protein.**
  - Displace or encircle the nucleus.
  - Found in:
    - Entorhinal cortex
    - Pyramidal cells of hippocampus
    - Amygdala
    - Basal forebrain



Plaques (arrow) contain a central core of amyloid and a surrounding region of dystrophic neurites (**Bielschowsky** stain).



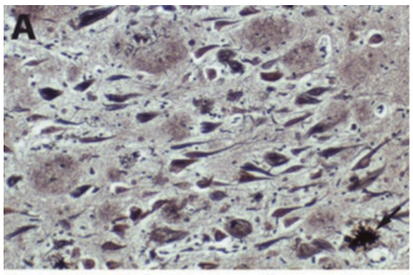
Immunohistochemical stain for Aβ. Peptide is present in the **core** of the plaques as well as in the surrounding region.



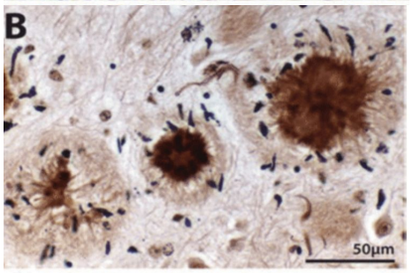
Neurons containing tangles stained with an antibody specific for tau.

Morphology Of Alzheimer Disease Cont.

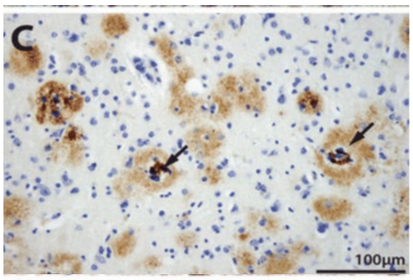
Silver stain



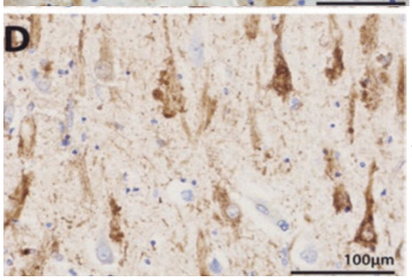
Showing plaques & tangles in the cortex and higher power image of silver positive neuritic plaques.



Amyloid-beta protein in the plaques.



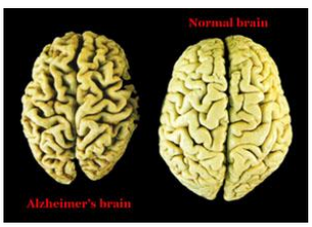
Arrows indicate neuritic plaques.



Hyperphosphorylated tau in tangles

Macroscopic appearance

- Cortical atrophy; widening of the sulci in frontal, temporal, parietal lobes.
- Hydrocephalus ex vacuo (compensatory ventricular enlargement)



Forms of Alzheimer Disease: 2 types

- In general, patients **rarely** become symptomatic before the age of 50, but **early onset** can be seen with some of the **heritable forms.**

Sporadic form (most cases)	**Familial form** (5-10% of cases)
Occur at regular intervals in a population	Occur in a family members
sporadic mutations and environmental risk factors	Inheriting a dominant mutated gene
Late onset	**Early onset**

• **An allele of apolipoprotein (ApoE4)**
  ○ Increased risk of disease
  ○ Lower age of onset
  ○ Deposition of Aβ, unknown mechanism
• **Mutation in SORL1**
  ○ Late onset
	• Mutations in APP or in components of γ-secretase (presenilin-1 or presenilin-2)
	• APP gene is found on chromosome 21
	• Therefore, very common in trisomy 21 **(Down syndrome)** individuals who survive past 45.

Deficiency of the SORL1 protein may alter the intracellular trafficking of APP → Shuttling it to a compartment where the Aβ is generated by enzymatic cleavage → Net result being increased generation of Aβ peptide.

Parkinsonism

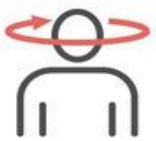
- Parkinsonism is a clinical syndrome characterized by **tremor**, **rigidity**, **bradykinesia**, and **instability**.
- These types of motor disturbances may be seen in a range of diseases that **damage dopaminergic neurons** in the **substantia nigra** or their projections to the striatum.

The Clinical syndrome characteristic

Diminished facial expression (masked facies)

Stooped posture and, slowness of voluntary movement

Festinating gait (progressively shortened, accelerated steps)



Rigidity,bradykinesia and instability

"Pill-rolling" tremor (resting tremor)

Parkinsonism can be induced by:

- **Drugs** that affect these neurons, particularly dopamine antagonists and toxins.
- **Post-encephalitic** parkinsonism (associated with the influenza pandemic).
- **Idiopathic** parkinson's disease (the **most common** neurodegenerative disease associated with parkinsonism).
- Other **neurodegenerative diseases** (later in their course they can affect the dopaminergic neurons). Multiple system atrophy (**MSA**), progressive supranuclear palsy (**PSP**) and corticobasal degeneration (**CBD**)
- Rare: head trauma, stroke

The difference between Parkinson's disease and Parkinsonism

- Parkinsonism is a general term that refers to a group of neurological symptoms similar to those seen in Parkinson's disease such as tremors, slow movement and stiffness.
- Parkinsonism is a syndrome present in other neurological disorders.
- It is often hard to know whether a person has **idiopathic** (meaning "of unknown origins") **Parkinson's disease** or another neurologic disorder that is characterized by parkinsonism.

Parkinson's disease

Epidemiology

- It occurs in the 6th to 8th decades.
- It affects more than 2% in North America.
- It affects **men more than women.**
- The crude prevalence rate in Saudi population if 22/100,000.

Pathogenesis:

While most Parkinson disease is **sporadic**[1], there are both autosomal dominant and recessive forms of the disease.

- Point mutations and duplications of the gene encoding **α-synuclein**, a protein involved in synaptic transmission, cause **autosomal dominant** PD.
- Even in cases not caused by mutations in this gene, the **diagnostic feature of Parkinson disease**, the **Lewy body**, is an inclusion containing α-synuclein.
- How the alterations in sequence or protein levels result in disease is **unclear**.
- The presence of α-synuclein in Lewy bodies has suggested that **defective degradation** of the protein in the proteasome might play a role.
- This is supported by the identification of two other genetic loci for Parkinson disease:
  - Loci which involve genes encoding parkin (an E3 ubiquitin ligase).
  - UCHL-1 (an enzyme involved in recovery of ubiquitin[2] from proteins targeted to the proteasome).

Diagnosis of Parkinson's Disease:

- **Progressive** parkinsonism.
- Absence of a toxic or other known underlying etiology (**idiopathic**).
- Clinical response to L-dihydroxyphenylalanine (**L-DOPA**) treatment.

1- It appears in scattered or isolated instances, means that they do not seem to run in families
2-It is a small regulatory protein found in most tissues that affects proteins in many ways when it binds to them, like marking them for degradation via the proteasome,for this binding between the ubiquitin and the protein, we need many reactions that are catalyzed by diff enzymes one of them is E3 (parkin ligase).

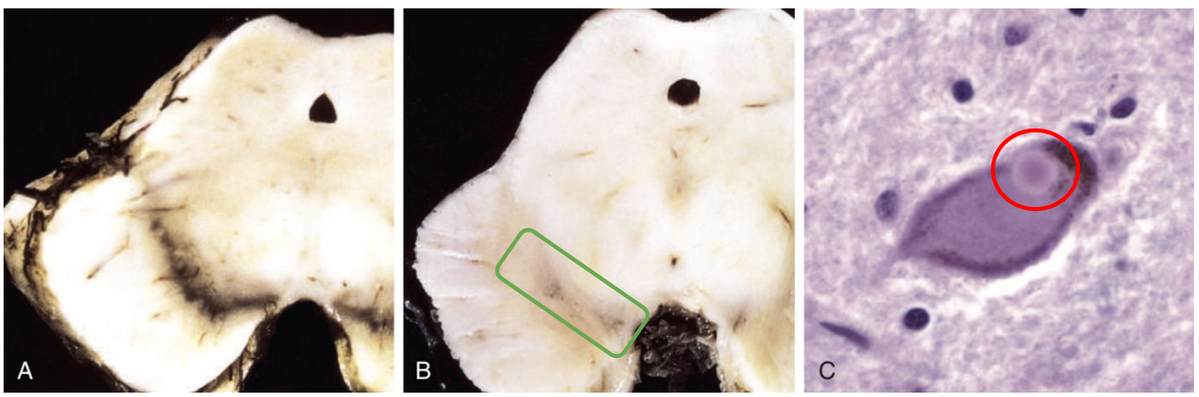
Parkinson's disease

Macroscopic features

- **Pallor** of the **substantia nigra** and locus coeruleus.

Microscopic features

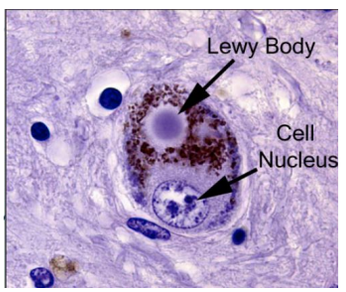
- Loss of the pigmented neurons in these regions.
- Gliosis.
- **Lewy bodies** may be found in some of the remaining neurons. (it's only **intracellular** so if the cell died you will NOT see it).

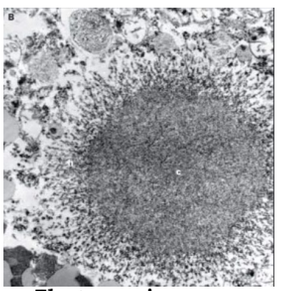


(A) Normal substantia nigra.
(B) **Depigmented** substantia nigra in idiopathic Parkinson disease.
(C) **Lewy body** in a neuron from the substantia nigra stains pink.

Lewy bodies

- Single or multiple, **intracytoplasmic**, **eosinophilic**, round to elongated inclusions that often have a dense core **surrounded by a pale halo.**
- Ultrastructurally, Lewy bodies are composed of fine filaments, **densely packed in the core but loose at the rim.**
- These filaments are mainly composed of **α-synuclein**, along with other proteins, including neurofilaments and ubiquitin.
- The other major histologic finding is **Lewy neurites**, dystrophic neurites that also contain abnormally aggregated **α-synuclein.**





Electron microscope

Parkinson's disease

Clinical features

- It usually progresses over **10 to 15 years.**
- There is an eventual **severe motor slowing** to the point of near immobility.
- Death is usually the result of **intercurrent infection** (Usually pneumonia) or **trauma** from frequent falls caused by postural instability.
- About 10% to 15% of individuals with Parkinson disease develop dementia (At the end of the disease),with the incidence increasing with advancing age.

Dementia in parkinson's

- The characteristic feature of this disorder includes a **fluctuating** course and **hallucinations**.
- While many affected individuals also have pathologic evidence of Alzheimer disease, the dementia in other Parkinson disease patients is attributed to widely disseminated **Lewy bodies in the cerebral cortex.**
- When **dementia arises within 1 year of the onset of motor symptoms**, it is referred to as **Lewy body dementia**[1].

Treatment

- **L-DOPA** therapy is often extremely effective in symptomatic treatment, but it does not alter the progressive nature of the disease.
- Over time, L-DOPA becomes less effective at providing the patient with symptomatic relief and begins to cause **fluctuations** in motor function on its own.
- Current neurosurgical approaches to Parkinson disease include the placement of lesions in the extrapyramidal system to compensate for the loss of nigrostriatal function or placement of stimulating electrodes - deep brain stimulation.

1- Because its the widespread of lewy bodies that destroys almost all neurons.

Summary

	Alzheimer disease	Parkinson disease
	- **Most common cause of dementia** - Most cases are sporadic and less familial.	- Associated with motor disturbance that share damage to **dopaminergic neuron of the SN** or their projection to the striatum. - Most cases are sporadic and less are familial.
Age group	Start at 60-70 years and the risk increase with aging 80-85 years.	60-80 years
Diagnosis based on	- Clinical assessment. - Radiological methods.	- Progressive parkinsonism. - Absence of a toxic or any underlying causes. - Clinical response to L-DOPA.
Pathogenesis	Accumulation of two proteins (**Aβ and tau**) in specific brain regions, in the forms of **plaques and tangles**, respectively.	- Point mutations and duplications of the gene encoding **α-synuclein** - Abnormal degradation of α-synuclein
Protein inclusion	**Aβ** **Tau**	**α-synuclein**
Macroscopic features	- Cortical **atrophy** with widening of sulci and thinning of gyri. - Compensatory ventricular enlightenment (hydrocephalus ex vau)	**Pallor** of: - SN - locus coeruleus
Microscopic features	1- **Plaques** → extracellular. • **Neuritic plaques** (Dystrophic neurites around a central amyloid core contain Aβ) • **Diffuse plaques** (Contain only Aβ deposits) 2- Neurofibrillary **tangles** → intracellular	- Loss of the pigmented, catecholaminergic neurons in these regions - Gliosis - **Lewy bodies** (intracytoplasmic) • **Lewy neurites** (Dystrophic neurites contain abnormally aggregated α-synuclein)
Progression	5-10 years	10-15 years
Death result of	- Intercurrent pneumonia - Other infections	- Intercurrent infection - Trauma

Quiz

Q1: What is the most important cause of dementia?

A) Parkinson disease
B) Aging
C) Alzheimer disease
D) Chronic meningitis.

Q2: 64 old man patient with diabetes present with tremor, dysarthria and akinesia, which of the following structure is most likely affected?

A) Thalamus
B) Substantia nigra
C) Corpus callosum
D) Limbic system

Q3: A 65 years old female who is known to have dementia, she died due to a cardiorespiratory disease. A biopsy from her brain showed lewy bodies, which of the following will be positive in her case?

A) Tau protein
B) Alpha synuclein
C) Presenilin
D) gamma secretase

Q4: Which of the following is the critical initiating event for the development of AD:

A) Hyperphosphorylation of the microtubule binding protein tau.
B) Amyloid β hyperphosphorylation.
C) Amyloid β excretion.
D) Amyloid β generation.

Q5: An 80 year old man was referred to the neurology clinic because of progressive intellectual deterioration that included loss of recent memory. Which ONE of the following abnormalities is likely to be seen in this man's cerebral cortex?

A) Depigmentation of locus coeruleus
B) Degeneration of lateral corticospinal tracts
C) Neurofibrillary tangles within neurons
D) Lewy bodies

Q6: Which ONE of the following enzyme cleavage sequences would lead to Aβ production from the amyloid precursor protein?

A) α-secretase and then γ-secretase
B) β-secretase and then γ-secretase
C) γ-secretase and then α-secretase
D) γ-secretase and then β-secretase

Q7: A patient is suspected to have Alzheimer's disease. Which of the following will be hyperphosphorylated?

A) Amyloid B40
B) Amyloid precursor protein
C) Apolipoprotein E
D) Tau protein

1-C 2-B 3-B 4-D 5-C 6-B 7-D

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Thank you