Lecture Seven
Neurodegenerative Disorders

PATHOLOGY TEAM 435

{ ومن لم يذق مرّ التعلُّمِ ساعةً.. تجرع ذلَّ الجهل طوال حياتهِ }

Revised by

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Red: Important. Grey: Extra Notes Doctors Notes will be in text boxes

Objectives:

The student should:

- 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.
- Explain the basic pathological concepts of a neurodegenerative disease, using Alzheimer's disease as a classical example.
- 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.
- Hypothesize the possible etiologies of Parkinson disease.

Background:

Degenerative brain disease is an umbrella term for the progressive loss of structure or function of neurons, including death of neurons. Classical examples on this group of diseases are Alzheimer's disease and Parkinson's disease.

Dementia is a serious loss of cognitive ability in a previously unimpaired person, beyond what might be expected from normal aging. It has many causes. Alzheimer's disease is the most common cause of dementia in people at the age of 65 years and older.

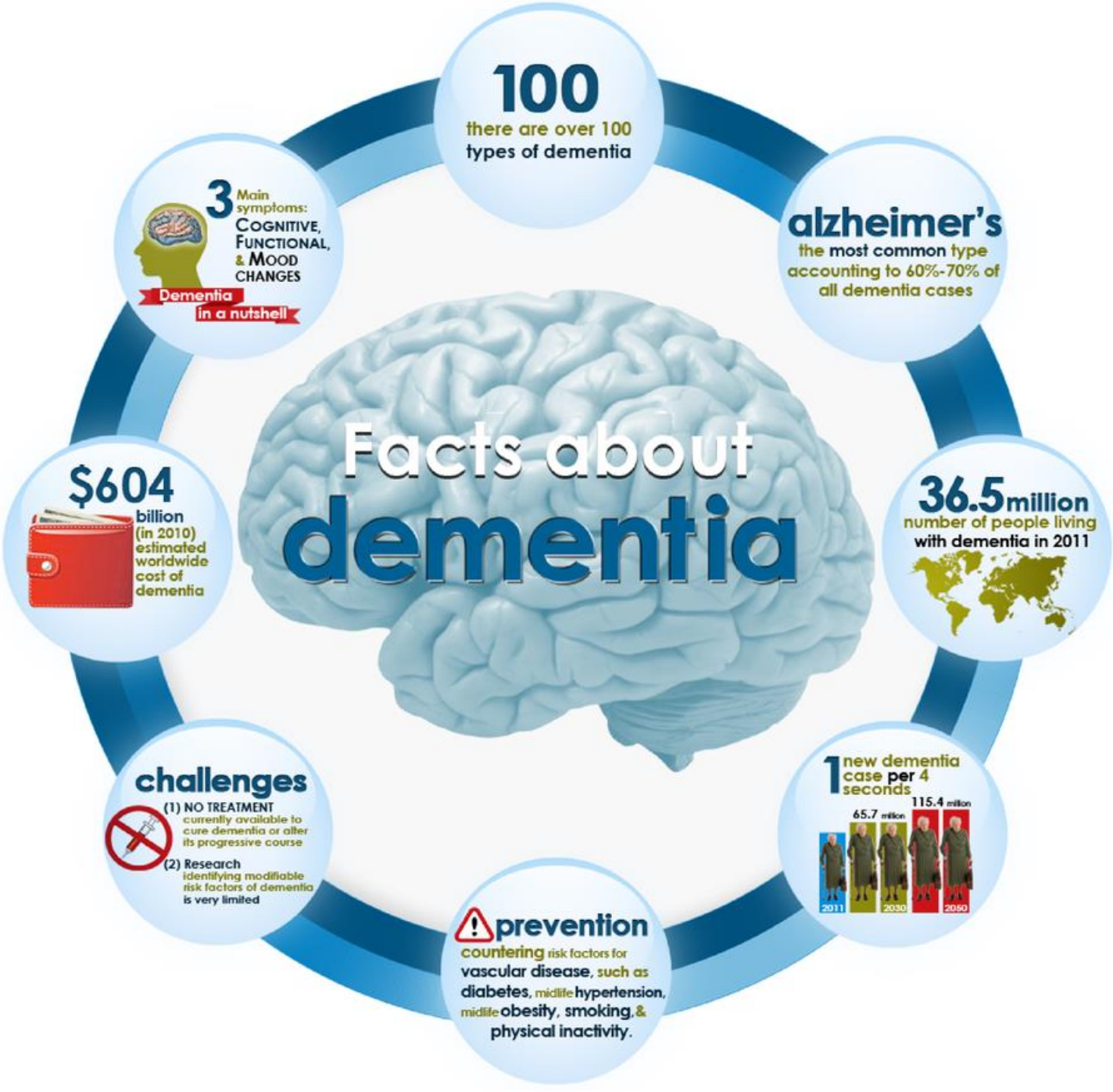
Parkinsonism is a clinical syndrome characterized by diminished facial expression, stooped posture, slowness of voluntary movement, festinating gait, rigidity, and a "pill-rolling" tremor. This syndrome can be seen in a number of conditions that damage to dopaminergic neurons of the substantia nigra or to their projection to the striatum. Idiopathic Parkinson disease is the most common neurodegenerative disease associated with Parkinsonism; the diagnosis is made in patients with progressive Parkinsonism in the absence of a toxic or other known underlying etiology and if they show clinical response to L-DOPA.

Key principles to be discussed:

- Neurodegenerative diseases definition.
- The definition and etiology of dementia.
- Alzheimer disease:
    - Definition.
    - Clinical findings including age of onset and progression pattern.
    - Morphologic abnormalities including the gross brain changes, neurofibrillary tangles, and neuritic plaques deposition.
- Parkinsonism: definition and etiology.
- Parkinson disease: definition, epidemiology, pathogenesis and clinicopathological features.

References:

Lecture, First Aid, Kaplan Pathology Lecture Notes, Neuropathology-web.org


100
there are over 100 types of dementia
3 Main symptoms: COGNITIVE, FUNCTIONAL, & MOOD CHANGES
Dementia in a nutshell
alzheimer's
the most common type accounting to 60%-70% of all dementia cases
Facts about
dementia
$604
billion (in 2010) estimated worldwide cost of dementia
36.5million
number of people living with dementia in 2011
challenges
(1) NO TREATMENT
currently available to cure dementia or alter its progressive course
(2) Research
identifying modifiable risk factors of dementia is very limited
1 new dementia case per 4 seconds
65.7 million
115.4 million
2011
2030
2050
prevention
countering risk factors for vascular disease, such as diabetes, midlife hypertension, midlife obesity, smoking, & physical inactivity.

Degenerative brain disease:

The term "Degenerative":

- It's an underlying cellular degeneration of neurons in the brain.
- Causes symptoms that depend on the pattern of involvement of the brain.

Dementia:

It is the development of memory impairment and other cognitive deficits with preservation of a normal level of consciousness. Short term memories are the first to be affected

- Regardless of etiology, dementia is **not** a part of normal aging and always represents a pathologic process.
- One of the most important public health issues in the industrialized world.
- **Characterized by:**
  - Memory loss
  - Apraxia[1]
  - Aphasia[2]
  - Agnosia[3]
  - Impaired judgment
  - They could develop delirium (eg. Patients with Alzheimer disease who develops pneumonia are at high risk of delirium[4]).

We see dementia in industrialized word more than the underdeveloped world

- Could be irreversible (like Alzheimer disease, Huntington disease, pick disease, Creutzfeldt-Jakob disease) Or reversible (like hypothyroidism, vit B12 deficiency, neurosyphilis)

Creutzfeldt–Jakob disease (CJD) is a Neurodegenerative disease that is incurable and invariably fatal. CJD is at times called a human form of mad cow disease

[1] Inability to perform particular purposive actions (loss of learned motor skills)
[2] A communication disorder that results from damage to the parts of the brain that contain language (loss of language skills)
[3] Inability to interpret sensations and hence to recognize things
[4] A serious disturbance in mental abilities that results in confused thinking and reduced awareness of your environment.

Causes of Dementia:

Primary Neurodegenerative Disease	Infections	Vascular and traumatic diseases	Nutritional diseases	Miscellaneous
Alzheimer disease	Prion-associated disorders (e.g. Creutzfeldt-Jakob disease)	Multi-infarct dementia	Thiamine deficiency (Wernicke-Korsakoff syndrome)	Brain tumors
Lewy Body dementia	HIV Encephalopathy (AIDS dementia complex)	Global hypoxic-ischemic brain injury		Neuronal storage disease
Huntington disease	Progressive multifocal leukoencephalopathy	Chronic subdural hematoma		Toxic injury (e.g. mercury)

Alzheimer Disease:

While Alzheimer's disease is considered as "degenerative" reflecting an underlying cellular degeneration of neurons in the brain, **not all forms of dementia are degenerative**

- Causes 60% of all cases of dementia.
- It is the most common cause of dementia in people over the age of 65 (elderly).
- Definitive diagnosis of Alzheimer disease, the combination of clinical assessment and modern radiologic methods allows accurate diagnosis in 80% to 90% of cases.

We don't usually do biopsy for Alzheimer because diagnosis is based on clinical, radiological and pathological findings

Epidemiology:

- 3% for individuals 65-74 years old, 19% for 75-84 years, 47% for 85 years or more.
- This increasing incidence with age has given rise to major medical, social, and economic problems in countries with a growing number of elderly.
- Most cases are sporadic[5], but At least 5% to 10% are familial.
- In general, patients rarely become symptomatic before 50 years of age, but early onset can be seen with some of the heritable forms.

[5] Appeared from unknown cause

First symptoms are the loss of short-term memory

Clinical manifestations:

- Has an insidious onset
- 7-8 decades
- Alterations in mood and behavior

Patient of Alzheimer usually die from infections because they're bedridden, hence, their inhalation and expiration is not good so they have secretions and accumulations in the lungs which will induce growth of bacteria and infections

- Progressive memory impairment especially to (recent events)

Later:

It is not normal for old patients to get Alzheimer.

- Severe cortical dysfunction & progressive disorientation.
- Aphasia and apraxia.
- Within 5–10 years patients become muted and bedridden.

Pathogenesis: (Great video that explains the mechanism)

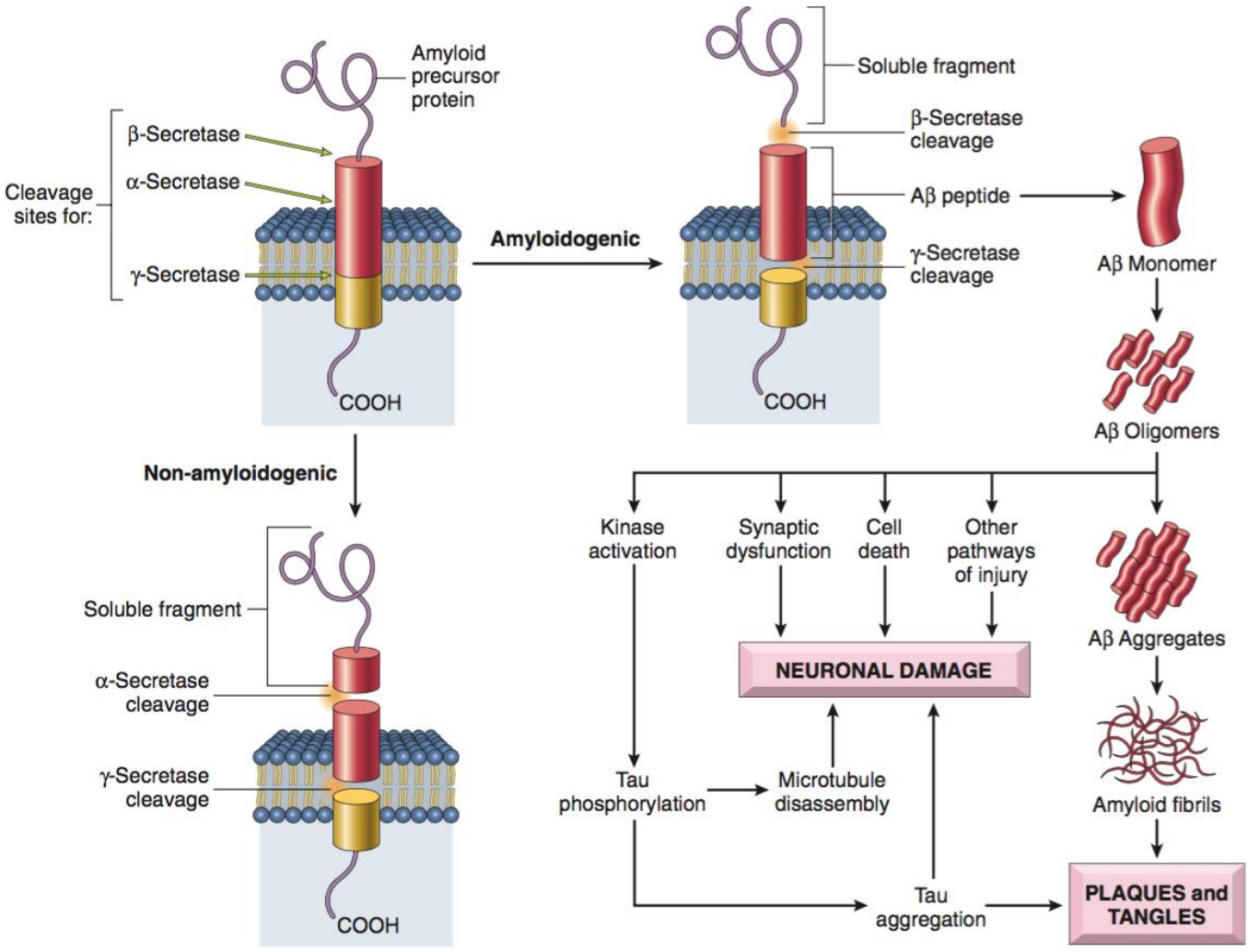


Figure 22–24 Aβ peptide genesis and consequences in Alzheimer disease. Amyloid precursor protein cleavage by α-secretase and γ-secretase produces a harmless soluble peptide, whereas amyloid precursor protein cleavage by β-amyloid–converting enzyme (BACE) and γ-secretase releases Aβ peptides, which form pathogenic aggregates and contribute to the characteristic plaques and tangles of Alzheimer disease.

For better understanding read this page first (It's extra)

AD is driven by two processes:

Extracellular deposition of beta amyloid-Aβ	**Intracellular accumulation of tau protein**.
Both these compounds are insoluble	
The main component of senile plaques	The component of neurofibrillary tangles
Deposition is specific for AD & is primary	Tau accumulation is also seen in other degenerative diseases & is secondary in AD

There are two main lesions in AD:

Senile plaques (SPs**) (also called Alzheimer's plaques)**	**Neurofibrillary tangles (**NFTs**).**
Spherical lesions in the cerebral cortex	Deposits of tau filaments in the neuronal body.
There are 2 kinds of SPs: - **Diffuse Aβ plaques (AβPs)** - **Neuritic plaques (NPs)**.	NFTs develop independently of AB

Diffuse Aβ plaques (AβPs)	**Neuritic plaques (NPs)**.
Spherical exracellular Aβ deposits.	NPs are AβPs containing **degenerating neuronal processes with tau paired helical filaments**
Do not disrupt the neuropil	Contain reactive astrocytes and microglia.
Seen sometimes in large numbers in old, non-demented persons and are not associated with dementia.	Forms a central core or small chunks, has a fibrillary fine structure and is Congo Red positive.

AD develops in 3 stages, transentorhinal, limbic, and isocortical. How?

Analysis of the pattern of NFT and NT deposition shows that these changes appear first in the transentorhinal region of the temporal lobe, lateral to the hippocampus, and then spread to the entorhinal cortex, hippocampus, and association neocortex.

Evidence from familial forms of the disease indicates that the accumulation of a peptide **(β amyloid, or Aβ)** in the brain initiates a chain of events that result in the morphologic changes of Alzheimer disease and dementia.

- **Aβ peptide** is derived from a larger membrane protein known as amyloid precursor protein (APP), which is processed in either of two ways:
  1- It can be cleaved by two enzymes, α-secretase and γ-secretase, in a process that prevents formation of Aβ (Normal)
  2- It can be cut by β-site APP-cleaving enzyme and γ-secretase to generate Aβ (Abnormal)
- Generation and accumulation of Aβ occurs slowly with advancing age.
- The presence of Aβ also leads neurons to hyperphosphorylate the microtubule binding protein "tau".
- With this increased level of phosphorylation, **tau redistributes** within the neuron from the axon into dendrites and cell body and aggregates into "tangles".
- This process 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.
- Mutations in APP or in components of γ-secretase [presenilin-1 (PSEN1)] or [presenilin-2 (PSEN2)] lead to early onset familial Alzheimer disease by increasing the rate at which Aβ accumulates.

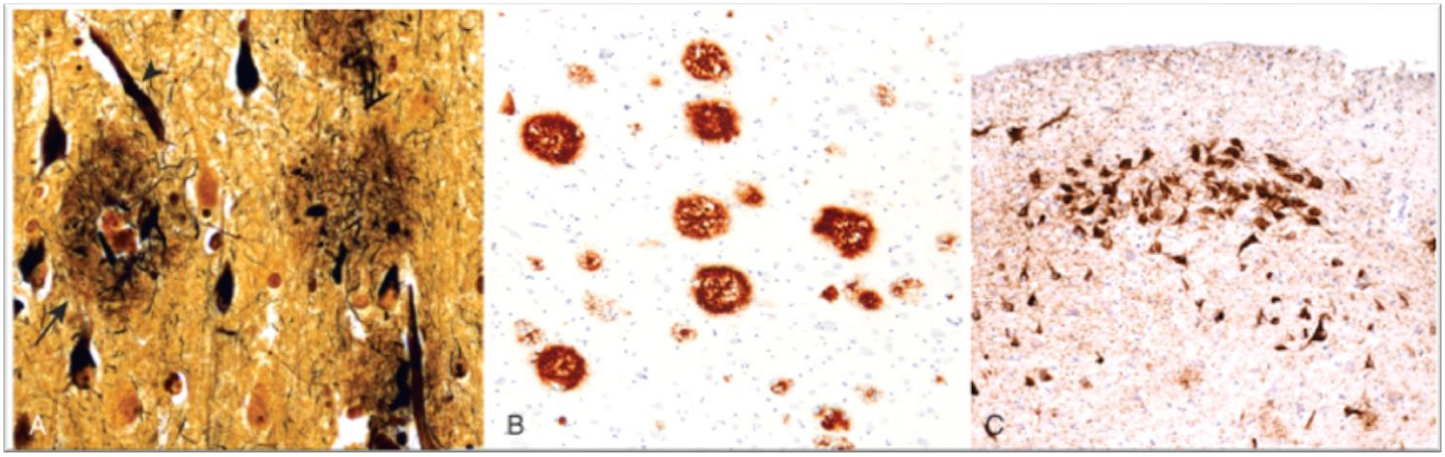
Accumulation of Aβ has several effects on neurons and neuronal function:	
Small aggregation of Aβ	Can alter neurotransmission, and the aggregations can be toxic to neurons and synaptic endings
Larger deposits	Form of plaques, also leads to neuronal death, elicit a local inflammatory response that can result in further cell injury, and may cause altered region-to-region communication through mechanical effects on axons and dendrites

Alzheimer disease occurs in almost all patients with trisomy 21 (Down syndrome) who survive beyond 45 years due to APP gene dosage effects (Because it's where the gene encoding APP is located)

There is a fairly constant pattern of progression of involvement of brain regions pathologic changes:

Earliest in the entorhinal cortex → Spreads through the hippocampal formation and isocortex → Extends into the neocortex.

- Silver staining methods or immunohistochemistry[6] are extremely helpful in assessing the true burden of these changes in a brain.



A. Plaques (*arrow*) contain a central core of amyloid

B. Immunohistochemical stain for Aβ (Plaques)

C. Neurons containing tangles stained with an antibody specific for tau.

Present in some normal individuals but it doesn't mean Alzheimer

Morphology:

Gross	Microscopic
- Atrophy of affected regions. - Thin gyri and wider sulci. - Hippocampus and temporal lobes are markedly atrophic. - Compensatory ventricular enlargement (hydrocephalus ex vacuo)	- Plaques (type of extracellular lesion) - Neurofibrillary tangles (type of intracellular lesion) o Because these may also be present to a lesser extent in the brains of elderly nondemented individuals, the current criteria for a diagnosis of Alzheimer disease are based on a combination of clinical and pathologic features. Although pathologic examination of brain tissue remains necessary for the diagnosis.

Neurofibrillary tangles first start intracellular then they become extracellular

[6] The process of detecting antigens (e.g. proteins) in cells of a tissue section by exploiting the principle of antibodies binding specifically to antigens in biological tissues.

Neuritic plaques:

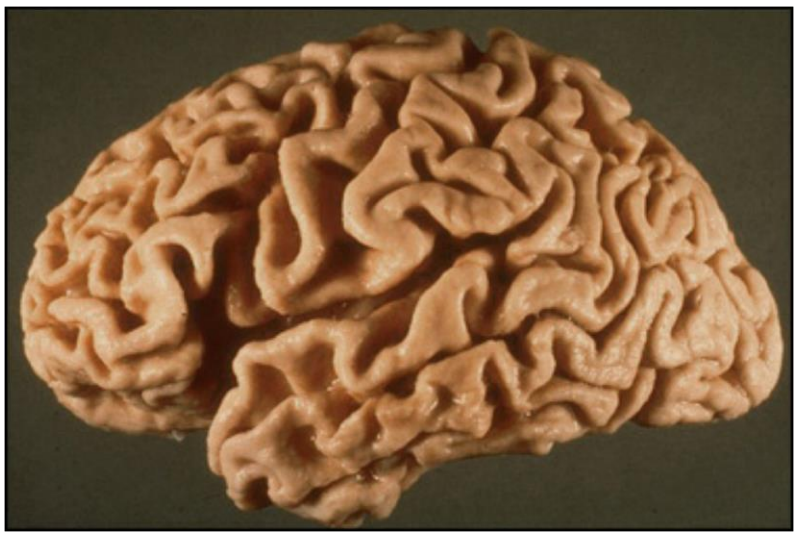
- Focal, spherical collections of dilated, tortuous, silver-staining neuritic processes (dystrophic neurites), often around a central amyloid core.
- Plaques can be found in the hippocampus and amygdala as well as in the neocortex, although there is usually relative sparing of primary motor and sensory cortices until late in the course of the disease.
- The amyloid core contains Aβ.
- Aβ deposits can also be found that lack any surrounding neuritic reaction, termed diffuse plaques.

The Congo red staining is the golden slandered in amyloid

Neurofibrillary tangles:

Bundles of paired helical filaments visible as basophilic fibrillary structures in the cytoplasm of the neurons that displace or encircle the nucleus, mainly composed of abnormally hyperphosphorylated tau forming paired helical filaments (Tangles)

- The presence of Aβ also leads neurons to hyperphosphorylate the microtubule binding protein "tau".
- This process also results in neuronal dysfunction and cell death.
- Tangles can remain after neurons die.
- Commonly found in cortical neurons (pyramidal cells of the hippocampus, amygdala and the basal forebrain)
- Tangles are not specific to Alzheimer disease, being found in other degenerative diseases as well.



Atrophy of gyri and widening of sulci

The main sites which start to shrink is the frontal, partial and temporal parts of the brain

Genes associated with AD (Genetic Risk Factors):

The search for genes associated with typical, sporadic Alzheimer disease is beginning to identify genetic associations that may provide new clues about the pathogenesis of the disease:

- An allele of apolipoprotein, called ε4 (ApoE4), is associated with as many as 30% of cases, and is thought to both increase the risk and lower the age of onset of the disease.
- ApoE4 may contribute to the deposition of Aβ, but how it does so is not known.
- Another gene, called SORL1, has recently been found to also be associated with late-onset Alzheimer disease
    - Deficiency of the SORL1 protein may alter the intracellular trafficking of APP[7], shuttling it to a compartment where the Aβ peptide is generated by enzymatic cleavage, the net result being increased generation of this pathogenic peptide

Parkinsonism:

They respond very well on the dopaminergic drugs at the beginning but then the body stops responding

Motor disturbances that are seen in a number of conditions that share damage to dopaminergic neurons of the substantia nigra or their projection to the striatum.

A clinical syndrome characterized by:

- Diminished facial expression (masked faces).
- Stooped posture.
- Slowness of voluntary movement.
- Rigidity.
- "pill-rolling" tremor. (Shown in the picture)
- Festinating gait (progressively shortened, accelerated steps).

[7] Amyloid precursor protein

Can be induced by:

- Drugs that affect these neurons, particularly dopamine antagonists and toxins.
- Post-encephalitic Parkinsonism (associated with the influenza pandemic[8]).
- Idiopathic Parkinson disease (the most common neurodegenerative disease associated with parkinsonism).
- Other neurodegenerative diseases.
- Rare: head trauma, stroke.

Parkinson disease:

Diagnosis:

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

Parkinson **TRAPS** your body: **T**remor (pill-rolling tremor at rest)

Rigidity (cogwheel)

Akinesia (or bradykinesia)

Postural instability

Shuffling gait

Epidemiology:

- 6-8 decades.
- More than 2% in North America develop disease.
- Men more than women.
- 22/100,000 = crude prevalence rate in Saudi population.

Clinical Features

After 10-15 years they may develop Alzheimer

- Usually progresses over 10 to 15 years.
- Eventual severe motor slowing to the point of near immobility.
- About 10% to 15% of individuals with Parkinson disease develop dementia.
- Incidence increases with advancing age.

[8] An epidemic of infectious disease that has spread through human populations across a large region; for instance multiple continents, or even worldwide.

Pathology:

- Mostly sporadic, however, there are both autosomal dominant and recessive forms of the disease.

- Genetic analysis has identified specific causal mutations, For example α-synuclein mutation causes autosomal dominant Parkinson disease as can gene duplications and triplications.

- Even in cases of Parkinson disease not caused by mutations in this gene, the diagnostic feature of the disease - the Lewy body - is an inclusion containing α-synuclein.
    - This is a widely expressed neuronal protein that is involved in synaptic transmission and other cellular processes.

- How the alterations in sequence or protein levels result in disease is unclear

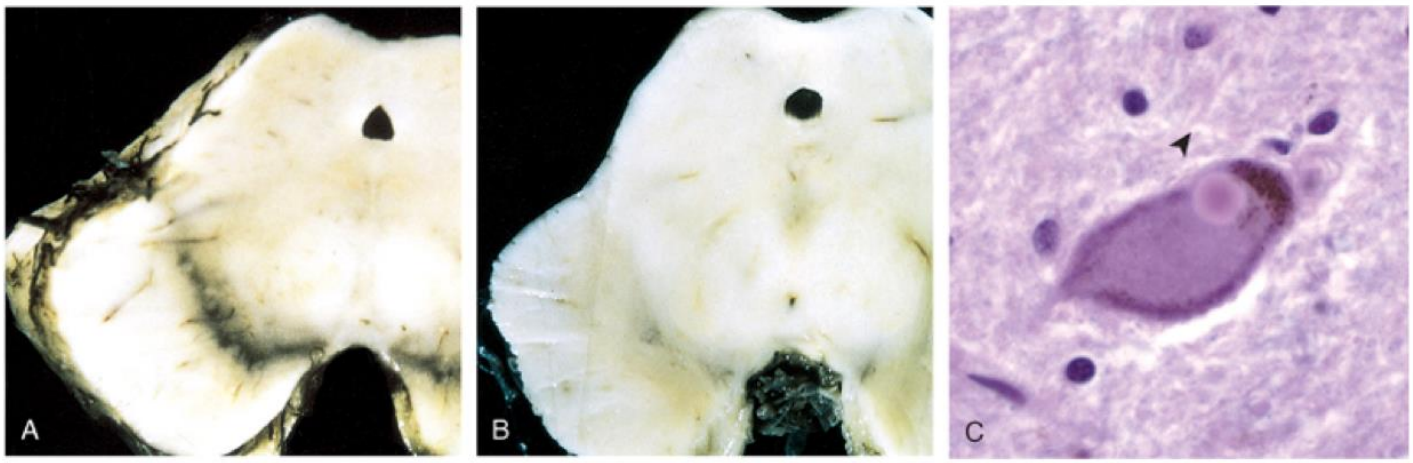
- The presence of α-synuclein in the Lewy bodies has suggested that defective degradation of the protein in the proteasome might play a role

- This is supported by the identification of **two other genetic loci** for Parkinson disease:

    1- Which involve genes encoding parkin (an E3 ubiquitin ligase)

    2- UCHL-1 (an enzyme involved in recovery of ubiquitin from proteins targeted to the proteasome)

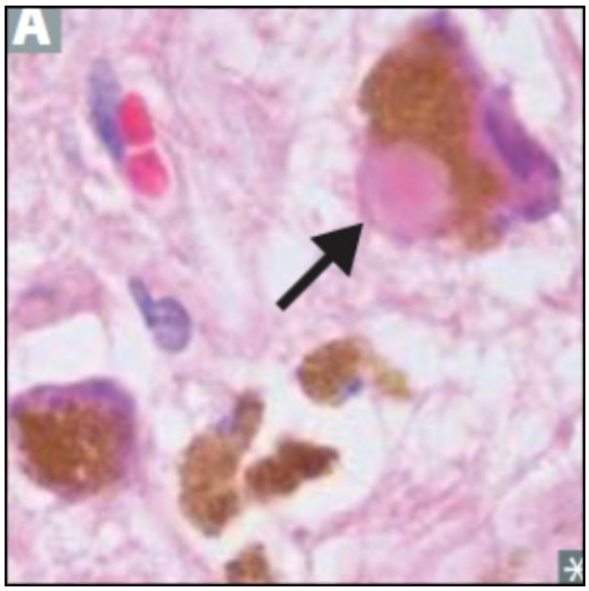
Morphology:



Gross	Microscopic
Pallor of the substantia nigra[9] and locus ceruleus (B)	Loss of the pigmented neurons in these regions. – Associated with gliosis. – Lewy bodies may be found in some of the remaining neurons (C)

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 composed of α-synuclein, along with other proteins



[9] Black

Dementia associated with Parkinson disease:

- Characteristic features of this disorder include 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 Lewy body dementia.

Treatment & Progression:

- L-DOPA therapy is often extremely effective in symptomatic treatment, but it does not significantly 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.
- Death is usually the result of intercurrent infection or trauma from frequent falls caused by postural instability. (Stagnant → infection → death)
- Parkinson disease has been targeted for many novel therapeutic approaches.
- Currently used 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

Novel therapy is a surgical therapy, in which they stimulate electrodes deep in the area affected

Take home messages:

- Neurodegenerative diseases cause symptoms that depend on the pattern of involvement of the brain.
- Diseases that affect cerebral cortex primarily (e.g., Alzheimer disease) are more likely to cause cognitive change, alterations in personality and memory disturbance.
- Accumulation of the Aβ peptide, derived from amyloid precursor protein, is central to the pathogenesis of Alzheimer disease.
- Dementia is a non-specific illness syndrome that has many causes.
- Diseases that affect basal ganglia (e.g. Parkinson disease) have motor symptoms as prominent clinical features.
- Parkinson disease is caused by loss of dopaminergic neurons.
- Parkinsonism is not Parkinson's disease.
- Parkinson's disease is associated with abnormal aggregation of proteins, which may lead to loss of function or may trigger apoptosis. Familial forms are associated with mutations in the genes encoding these proteins.

Check Your Understanding

True or False:

1- APOE4 decreases the risk of onset of Alzheimer disease.
2- Slow, progressive loss of intellect is a clinical finding of Alzheimer dementia.
3- Neurofibrillary tangles can be seen in Parkinson disease.
4- All forms of dementia are degenerative.

1:F 2:T 3:T 4:F

MCQs:

1- Mutation of which protein leads to the earliest development of Alzheimer disease?
A- Ps1
B- APP
C- A-crystallinPs2

2- The APP gene is located in chromosome?
A. 17
B. 20
C. 21
D. 19

3- Which of the following reduces Alzheimer disease risk?
A- E2
B- E1
C- APoE4
D- A&C

4- The main component of neurofibrillary tangles is?
A. Ubiquitin
B. Beta Amyloid
C. Tau protein
D. Synuclein

5- Symptoms of Parkinson disease include all the following except?
A. Tremor
B. Bradykinesia
C. Rigidity
D. Hallucination

6- The earliest changes in Alzheimer disease are usually found in the:
A. Hippocampus
B. Entorhinal cortex
C. Amygdala
D. Association cortex

1:A 2:C 3:A 4:C 5:D 6:B

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قال صلى الله عليه وسلم: {من سلك طريقًا يلتمس فيه علمًا سهَّل الله له بهِ طريقًا إلى الجنة}

دعواتنا لكم بالتوفيق