Pathology

437's team work

Lecture (8): Degenerative Brain 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.**
- **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. 6- Hypothesize the possible etiologies of Alzheimer's disease.**
- **List the causes of Parkinsonism. 8- Understand the major clinical and pathological feature of Parkinson disease.**

Degenerative brain disease:

- **What do we mean by "Degenerative" ?** disorders characterized by the **cellular degeneration of subsets of neurons** that typically are related by **function,** rather than by **physical location** in the brain. It is characterized by affecting the type of the cell not location مو شرط تكون الخلايا جنب بعض، المهم ان لها نفس الوظيفة
  - for example : Alzheimer's and Parkinson disease.

- It cause symptoms that depend on the pattern of involvement of the brain:

Hippocampal cortical neurons	•• result in loss of memory, language, insight, and planning, all components of dementia.
Neurons of the basal ganglia	•• result in movement disorders, these may be hypokinetic, as with Parkinson disease, or hyperkinetic, as with Huntington disease.
cerebellum	•• result in ataxia
Those that affect **motor neurons**	•• result in weakness.

although many degenerative diseases have primary targets, other brain regions are often affected later in the course of the illness for example if the neurodegenerative disorder start in the cerebral cortex later on it may involve the basal ganglia or any other region

From Robbins:
-Most neurodegenerative diseases share a pathologic process, **accumulation of protein aggregates**, which serve as a histologic hallmark of specific disorders.
-These aggregates are resistant to degradation by normal cellular processes, they elicit an inflammatory response, and may be directly toxic to neurons.
-Activation of the innate immune system (complement) is a common feature of neurodegenerative diseases.

Dementia It is set of Clinical symptoms

- **What do we mean by "Dementia" ?** 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.**
- It arises during the course of many neurodegenerative diseases; it also can accompany numerous other diseases that injure the cerebral cortex. It can be related to degenerative diseases or can be associated with other non- degenerative diseases
- Dementia is an increasing public health concern as the population ages.
  - Regardless of etiology, dementia is **not** part of normal aging and always represents a pathologic process.

Major cause of dementia	**Examples**
Primary Neurodegenerative Disorders	• **Alzheimer disease.** • Lewy body dementia. • Huntington disease.
Infections	• Prion-associated disorders (e.g. Creutzfeldt-Jakob disease). • HIV encephalopathy (AIDS dementia complex). • Progressive multifocal leukoencephalopathy.
Vascular and Traumatic Diseases	• Multi-infarct dementia. • Global hypoxic-ischemic brain injury. • Chronic subdural hematomas.
Metabolic and Nutritional Diseases	Thiamine deficiency (Wernicke-Korsakoff syndrome). is a degenerative brain disorder caused by the lack of thiamine (vitamin B1). related to alcoholism
Miscellaneous	• Brain tumors. • Neuronal storage diseases. • Toxic injury (e.g. mercury).

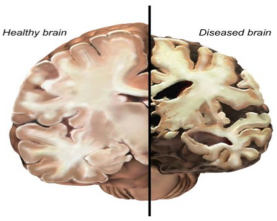
So remember! While Alzheimer's disease is considered as "degenerative"-that is, reflecting an underlying cellular degeneration of neurons in the brain- **not all forms of dementia are degenerative**

Dr.amani's note
Parkinson's patient might have dementia and we call it " lewy body dementia, but NOT ALWAYS .

Alzheimer Disease:

#What is Alzheimer?

It is The most common cause of dementia in the elderly. It usually becomes clinically apparent as **insidious** يبدأ بأعراض خفيفة ثم تسوء impairment of higher **intellectual function**, with alterations in **mood and behavior.** Progress gradually

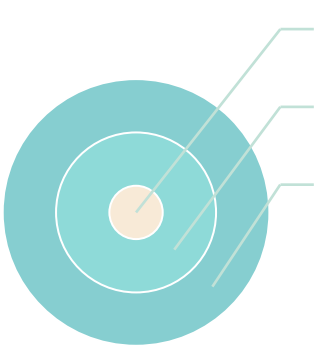


- **Later, there will be severe cortical dysfunction:**
  - Progressive disorientation.
  - Memory loss.
  - Aphasia. Loss the ability to speak
  - Over the next 5 to 10 years, the patient becomes profoundly disabled, mute, and immobile.
- Death usually occurs from **intercurrent pneumonia** or other **infections.**

* **Why the die usually by pneumonia?** because of difficulty in swallowing caused by the disease, an individual inadvertently inhales food particles, liquid or even gastric fluids. ... There they multiply and grow, which leads to **pneumonia**

#Epidemiology :

when considered by age groups, the incidence of Alzheimer disease:



3% for individuals **65 to 74** years old.

19% for **75 to 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. So the older the patient the more possible to get Alzheimer .

#how to diagnose alzheimer's?

Although **pathologic examination** of brain tissue remains necessary for the **definitive** diagnosis of Alzheimer disease, the combination of **clinical assessment** and **modern radiologic** methods allows **accurate diagnosis** in 80% to 90% of cases. *Dr. amani : 100% accuracy by pathological features – by autopsy and we cant do it in alive Patient

▪ Pathogenesis overview:

*The story behind Alzheimer's in an easy words:

the cause of Alzheimer disease isn't completely understood but there are two major factors that play arole:

A- plaques:

in the neuronal cell membrane there is a protein called amyloid precursor protein (APP) which play a role in ***neuron growth and repair.*** and like any other protein it will be used then cleaved. APP has 2 pathways.

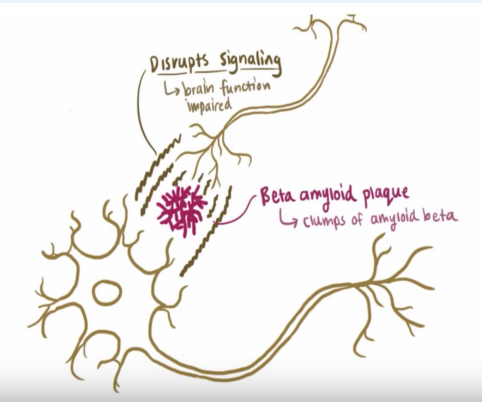
1- APP will be cleaved by **alpha secretase** and **gamma secretase** which will form a soluble complex and won't be accumulated *" normal pathway"*

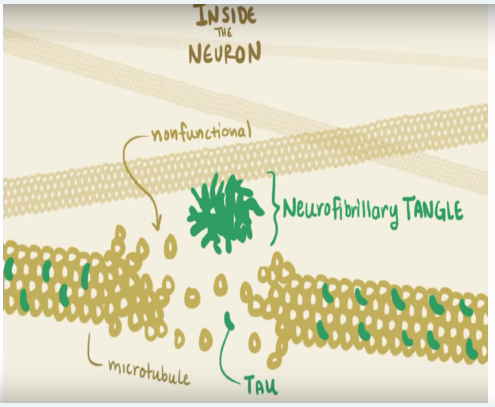
2- APP will be cleaved by **beta secretase** and **gamma secretase** which will form the **beta amyloid (A beta)** => when more are formed it accumulates, becomes toxic and **interferes with function** of neuron and **disrupts signaling** => as they increase they form insoluble oligomers => forming **Beta amyloid PLAQUES*** extracellular *" abnormal pathway"*

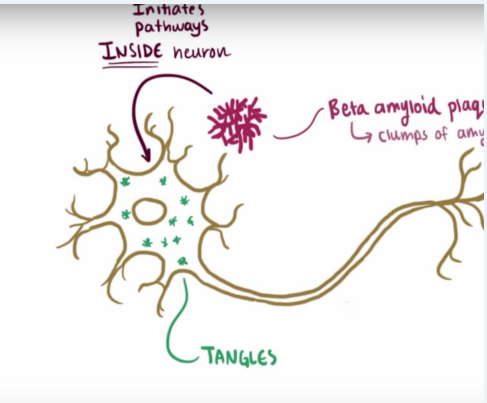
*الـ beta plaques هي نفسها الـ beta amyloid protein بس لما تتراكم ترتبط مع بعضها وتكون بلاكس
* SO TO SUM UP : beta secretase => the enzyme which forms Beta amyloid from APP that causes Alzheimer's.

B- tangles:

inside the cell there is a protein called **tau** which is present in the microtubules and makes sure it doesn't break apart. somehow the formation of A beta plaques initiate **hyperphosphorylation of tau protein** => aggregation of hyperphosphorylated tau protein inside the cell **" neurofibrillary tangle"**







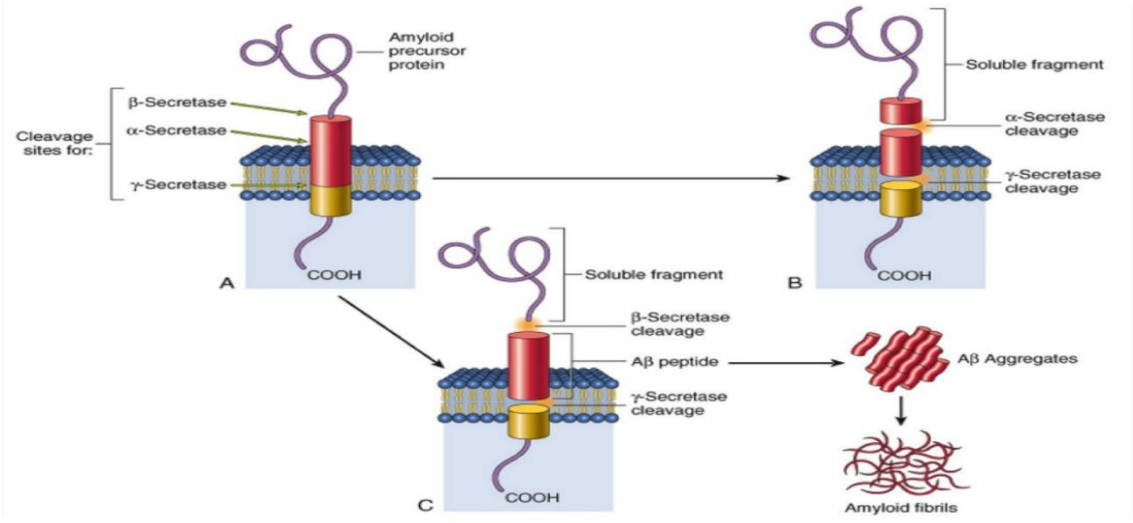
Pathogenesis: Abnormal accumulation of certain proteins

- **Aβ** peptide is derived from a larger membrane protein known as **amyloid precursor protein (APP**), which is processed in either of two ways:

- **The normal pathway :** It can be cleaved by two enzymes, **α-secretase and γ-secretase**, in a process that prevents formation of Aβ. *The cleavage here forms a soluble fragments → NO Alzheimer → NO amyloid fibrils

- **Abnormal pathway :** It can be cut **by β-site** APP-cleaving enzyme or called" **by β-amyloid–converting enzyme (BACE) "**and **γ-secretase** to **generate Aβ** *The Aβ deposits formed by the β, γ-secretase are insoluble, meaning they are not soluble in blood and cannot be secreted in the urine, and will aggregate in the brain!

* هو اصلا بشكل طبيعي موجود على غشاء الخلية APP يحصل له degradation و خلاص يصير soluble ويروح. لكن اذا تغير الانزايم الي يسوي له degradation يخلي الجزء الي كسره insoluble ويتجمع.



#Aβ peptide genesis and consequences in Alzheimer disease نفس الكلام متكرر لكن موجود بالسلايدز

Amyloid precursor protein cleavage **by α-secretase** and **γ-secretase** produces a harmless soluble peptide, whereas amyl**oid 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.

#What are the effects of Accumulation of Aβ on neurons and neuronal function?

- Generation and accumulation of Aβ occur **slowly** with advancing age.

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 mechanical effects on axons and dendrites.

Hyperphosphorylation of tau

•• The presence of Aβ also leads neurons to ***hyperphosphorylate*** the microtubule binding protein ***"tau"***. [1]

From Robbins:
-Aβ is highly prone to aggregation; it first forms **small oligomers**, and these eventually propagate into large **amyloid fibrils**. It is these aggregates that deposit in the brain and are visible as **plaques.**

1* Know more about TAU:

-Just like any other cell, neurons are held together inside by a cytoskeleton; the **cytoskeleton gives a cell its shape**, offers support, and **facilitates movement** through three main components: microfilaments, intermediate filaments, and ***microtubules.*** A special protein called TAU performs the function of **stabilizing microtubules.**

- **In Alzheimer's** : Tau separates from the microtubules causing them to fall apart>> strands of this Tau combine to Form tangles inside the neuron>> disabling the transport system and destroying the cell>> neuron become disconnected from each other and eventually die.

How does this happen? it's thought that Beta amyloid plaque initiates pathway INSIDE the neuron that activates protein kinase -> transfer a phosphate group to TAU -> TAU then change its shape and stops stabilizing the microtubules. -> TAU gets clump and tangled -> leads to the other characteristic finding: **neurofibrillary tangle**.

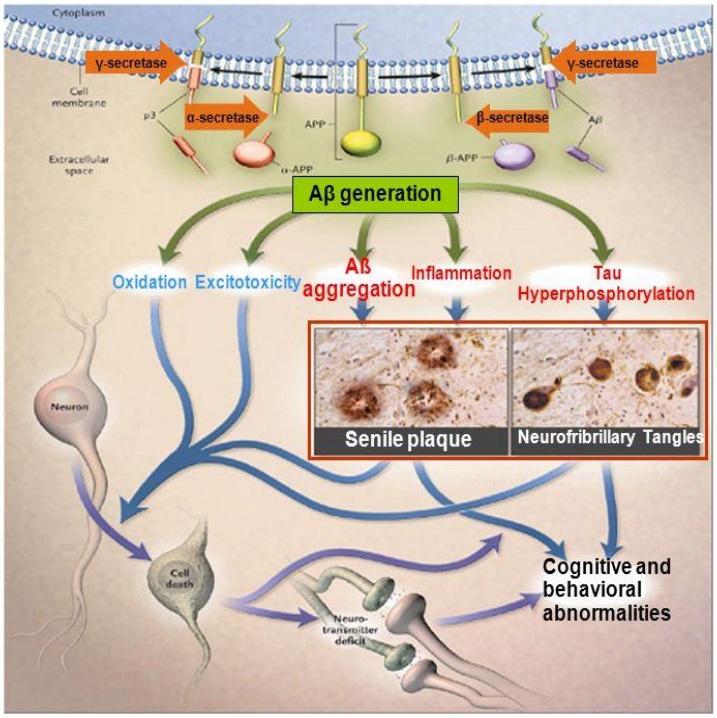
TAU protein :

With this increased level of **phosphorylation** by protein kinase, 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.** " can lead to Apoptosis"

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.

ALZHEIMER'S PATHOGENESIS



Extra from Robbins

Disease	Clinical Pattern	Protein Inclusions
Alzheimer disease (AD)	Dementia	Aβ (plaques) Tau (tangles)
Frontotemporal lobar degeneration (FTLD)	Behavioral changes, language disturbance	Tau TDP43 Others (rare)
Parkinson disease (PD)	Hypokinetic movement disorder	α-synuclein Tau
Huntington disease (HD)	Hyperkinetic movement disorder	Huntingtin (polyglutamine repeat expansions)
Spinocerebellar ataxias	Cerebellar ataxia	Various proteins (polyglutamine repeat expansions)
Amyotrophic lateral sclerosis (ALS)	Weakness with upper and lower motor neurons signs	SOD1 TDP43

#Mutations of Alzheimer :

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

Sporadic form (Most cases)	Familial form(at least 5% to 10% are)
What: occurring at irregular intervals in a population.	**What:** relating to or occurring in a family or its members.
How: by sporadic mutations & environmental risk factors. * تحدث طفره للشخص بدون ما يكتسبها من اهله فمثلا تحدث هذه الطفره من خلال عوامل بيئه	**How:** inheriting a dominant gene (mutated gene). *ينتقل من الاباء للابناء
Late onset	**Early onset** * لأنه اول ما انولد و هذه الطفره مكتسبها من اهله فغالبا تطلع علطول
Example: 1) An allele of apolipoprotein ApoE4, chromosome 19 2) Mutated SORL1	**: Examples** by **Mutations** in ***APP (amyloid precursor*** (1 ***protein)*** **or in** ***components of γ-secretase :*** *presenilin-1*" chromosome 14 " *or presenilin-2* "" chromosome 1 lead to **early** onset **familial** Alzheimer disease* .by increasing the rate at which Aβ accumulates

- 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: بدأ العلماء بالبحث عن اسباب آليات المرض وكيفية حدوثه من جذوره وكانت النتائج كالتالي

1)**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**.

- **How?** ApoE4 may **contribute to the deposition of Aβ**, but how it does so is **not known.** *It helps break down beta Amyloid

2) **Another gene**, called ***SORL1*,*** has recently been found to also be associated with **late-onset** Alzheimer disease

- **How?** Mutation in **SORL1** → Deficiency of the SORL1 protein → may alter the **intracellular** trafficking of **APP**, shuttling it to a compartment where the **Aβ peptide** is generated by enzymatic cleavage, the net result being **increased generation** of this pathogenic peptide.

3) Alzheimer disease occurs in almost all patients with **trisomy 21 (Down syndrome)** who survive beyond 45 years .

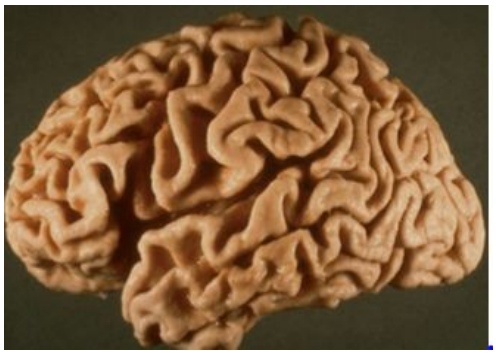
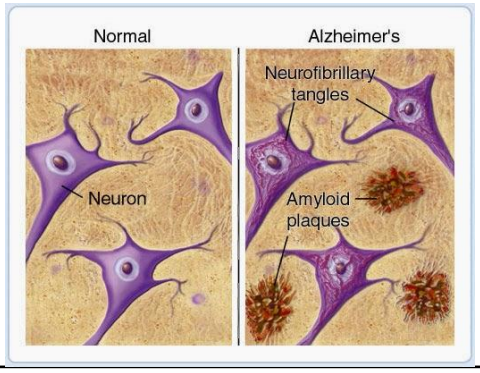
-How? The APP gene is located on chromosome 21.

- (due to APP gene **dosage** effects).

The APP gene is located on chromosome 21., and the risk of AD also is higher in those with an extra copy of the APP gene, such as patients with trisomy 21 (Down syndrome) and persons with small interstitial duplications of APP, presumably because this too leads to greater Aβ generation.

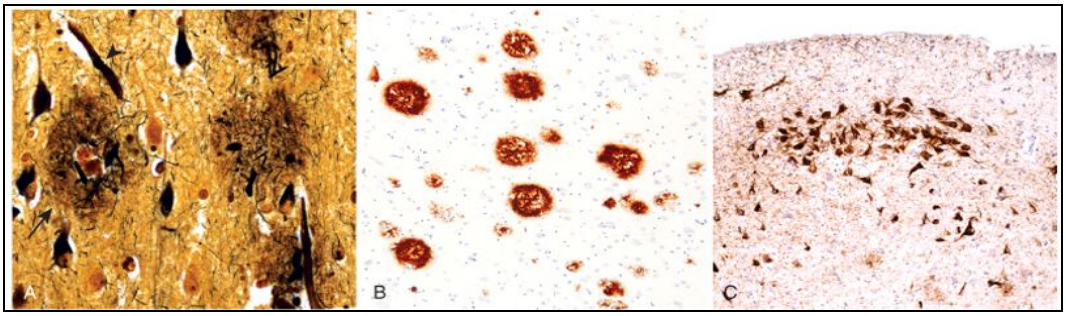
ببساطة لأن الجين المسؤول عن الAPP موجود اساساً بكروموسوم 21 ، ايش مشكلة الداون سندروم ؟ انه عنده زياده كروموسوم ب21 لذلك بيكون من فيه عدد إضافي من نسخ جين App فبتزيد عندهم فرصة حدوث البيتا اميلويد .

Morphology :

Macroscopic:	Microscopic:
-A variable degree of **cortical atrophy** with widening of the cerebral sulci that is most pronounced in the frontal, temporal, and parietal lobes.	**-Plaques** (a type of **extracellular** lesion)
-With significant **atrophy**, there is compensatory **ventricular enlargement (hydrocephalus ex vacuo).**	**-Neurofibrillary tangles** (a type of **intracellular** lesion.
	

- Because these may also be present to a **lesser extent in the brain elderly nondemented** individuals, the current criteria for a diagnosis of Alzheimer disease are based on **combination of clinical and pathologic features**

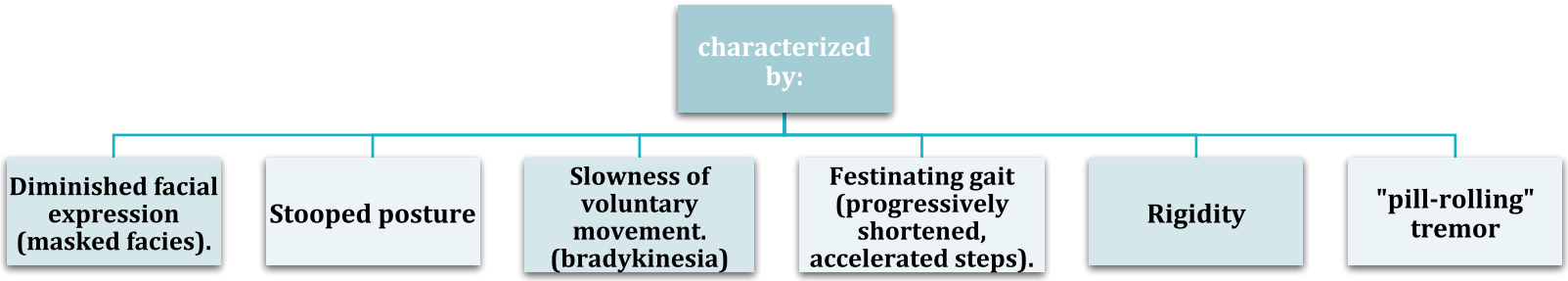
- There is a fairly constant pattern of progression of involvement of brain regions pathologic changes: Earliest in the **entorhinal cortex** → then spread through the **hippocampal formation** and isocortex → then extend into the **neocortex.**
- Silver staining methods or immunohistochemistry are extremely helpful in assessing the true burden of these changes in a brain.
- → *What is **immunohistochemistry**?* Microscopic localization of specific antigens in tissues by staining with antibodies labeled with fluorescent or pigmented material.



Neuritic plaques:	**Neurofibrillary tangles:**
▪ 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***.	▪ Bundles of **paired helical filaments** visible as basophilic fibrillary structures in the cytoplasm of the neurons that displace or encircle the nucleus. ▪ Tangles can remain after neurons die, then becoming a form of **extracellular** pathology. ▪ They are commonly found in cortical neurons, especially in the entorhinal cortex, as well as in other sites such as pyramidal cells of the hippocampus, the amygdala and the basal forebrain. ▪ A major component of paired helical filaments is abnormally hyperphosphorylated forms of the ***protein tau***. ▪ Tangles are **not specific to Alzheimer disease**, being found in other degenerative diseases as well.

Parkinsonism :

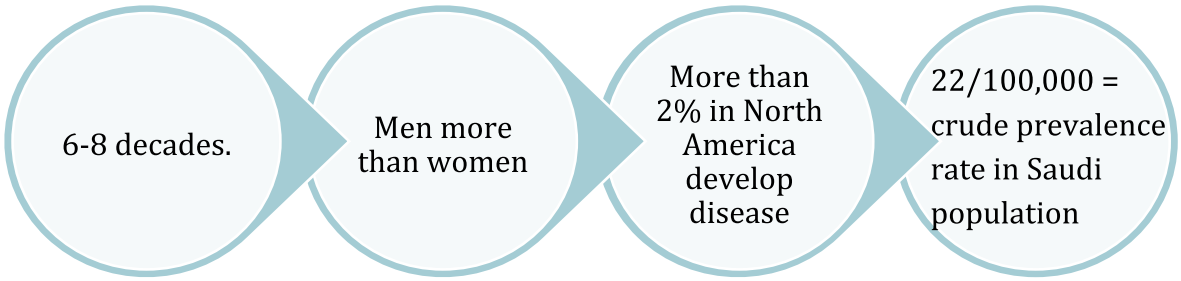
- **What is it ?** It is a long-term **degenerative** disorder of the **central** nervous system that mainly affects the **motor system**. The symptoms generally come on slowly over time.

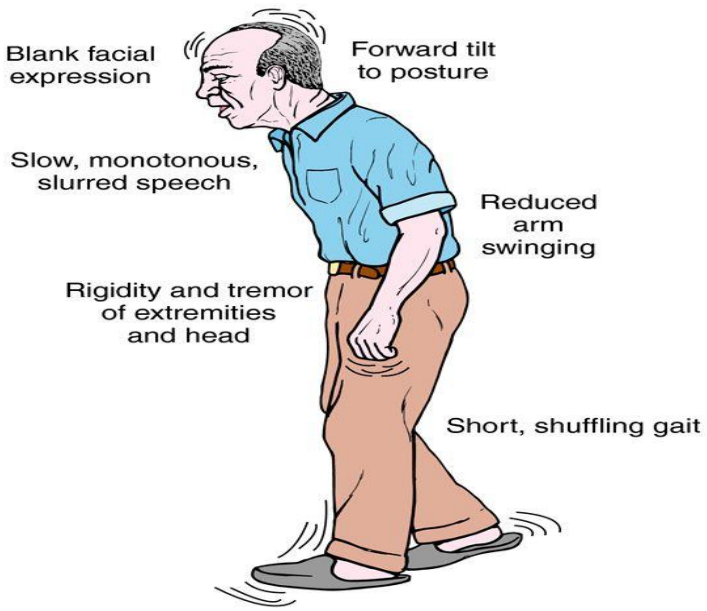


ميل السباية و الإبهام للمس
بعضهم و عمل حركة دائرية

- So, motor disturbance that is seen in a number of conditions that share damage to **dopaminergic neurons** of the **substantia nigra** (in midbrain) or their projection to the striatum (caudate nucleus + putamen).

#Epidemiology of Parkinson's:





Parkinsonism :

Etiology:	**Comment**
Drugs that affect the neurons	Particularly dopamine antagonists and toxins that selectively injure dopaminergic neurons
Post-encephalitic parkinsonism	Associated with the influenza pandemic
Idiopathic Parkinson's disease (PD)	The **most common** neurodegenerative disease associated with parkinsonism
Other neurodegenerative diseases	Multiple system atrophy (MSA), Progressive supranuclear palsy (PSP), Corticobasal degeneration (CBD)
Head trauma – stroke	Rare

Extra from Robbins:

- PD is associated with: characteristic neuronal inclusions containing α-synuclein.
- MSA: α-synuclein aggregates are found in oligodendrocytes.
- PSP and CBD associated with: tau-containing inclusions in neurons and glial cells.

#Diagnosis of Parkinson's Disease :

It's a Progressive parkinsonism.

Absence of a toxic or other known underlying etiology.

Clinical response to **l-dihydroxyphenylalanine (l-DOPA)** treatment
Prodrug of dopamine.

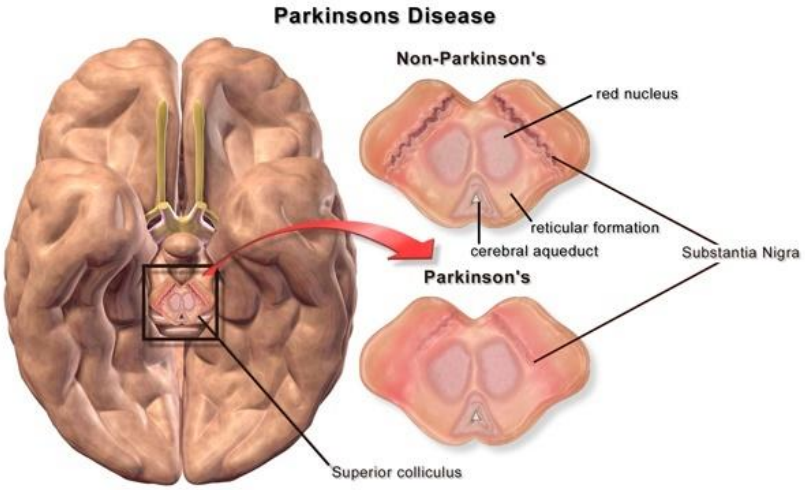
Pathogenesis :

- While most Parkinson disease is sporadic (الأسباب الموجودة بالجدول السابق),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 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 (α-synuclein) 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:

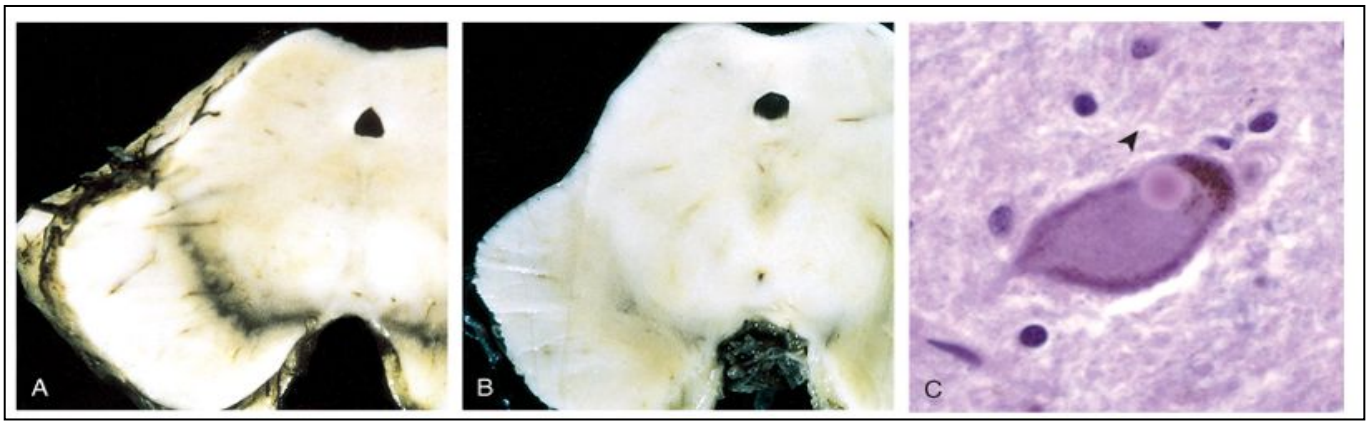
Which involve genes encoding **parkin** (an E3 ubiquitin ligase)

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

These two are responsible for degradation of **α-synuclein**



#Morphology:



Macroscopic:	Microscopic:
Pallor of the substantia nigra and locus coeruleus. . Fig A&B	• Loss of the pigmented, neurons in these regions. • Associated with gliosis. • **Lewy bodies** may be found in some of the remaining neurons.

#What is 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, including neurofilaments and ubiquitin.
- The other major histologic finding is **Lewy neurites** (neuronal processes)**,** dystrophic neurites that also contain abnormally aggregated α-synuclein.

#Clinical Features:

- 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, the incidence increasing with advancing age.
- 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.**

*Motor fluctuations refer to a decline in the usual benefit from a dose of levodopa. Instead of the smooth, uninterrupted control of symptoms of Parkinson's disease (PD) that levodopa offers early in the disease, symptoms return before the next dose is scheduled, or are only partially controlled by a given dose. Motor fluctuations usually develop gradually, after several years of successful treatment. Most people with PD will eventually experience motor fluctuations as their disease progresses.

- 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.

Summary:

	Alzheimer disease	Parkinson disease
	• Most common cause of **dementia.** • **Most cases** are **sporadic** and **less** are **familial.**	• Associated with **motor disturbance** that share damage to **dopaminergic neurons** of the **substantia nigra** 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	1- **Clinical** assessment. 2- **Radiologic** methods.	1- **Clinical** assessment. 2- Absence of a **toxic** or any **underlying cause.** 3- Clinical response to **L-DOPA.**
Pathogenesis	**Aggregation** of **Aβ** and **Tau** because an **abnormal degradation** of the **APP** (**mutations** in degradation).	Point **mutations** and **duplications** of the gene encoding **α-Synuclein.** **Abnormal degradation** of **α-Synuclein.**
Protein inclusion	1- Aβ. 2- Tau.	α-Synuclein.
Macroscopic features	1- **Cortical** atrophy with **widening** of sulci and **thinning** of gyri. 2- compensatory ventricular **enlargement** (hydrocephalus ex vacuo).	**Pallor** of: 1- Substantia nigra. 2- locus ceruleus.
Microscopic features	1- Plaques (**extra**cellular). ☆ **Neuritic** plaques. Dystrophic neurites around a central amyloid core contain **Aβ.** ☆ **Diffuse** plaques. Contains only **Aβ** deposits. 2- Neurofibrillary tangles (**intra**cellular).	1- **Loss** of the **pigmented**, catecholaminergic neurons in these regions. 2- Gliosis 3- Lewy bodies. (**intra**cytoplasmic). ☆ Lewy **neurites.** Dystrophic neurites contain abnormally aggregated **α-Synuclein.**
Progression	**5 → 10** years.	**10 → 15** years.
Death result of	1- Intercurrent **pneumonia.** 2- Other **infections.**	1- Intercurrent **infection.** 2- **Trauma.**

كل الشكر والتقدير للجهود العظيمة من قبل أعضاء فريق علم الأمراض الكرام:

- قادة فريق علم الأمراض :

- منصور العبرة
- بثينة الماجد

- أعضاء فريق علم الأمراض :

- منيره المسعد
- مجد البراك
- ريناد الغريبي
- غرام جليدان
- رناد الفرم
- ليلى الصباغ
- نورة القاضي
- مها العمري
- غاده الحيدري

Kindly contact us if you have any questions/comments and suggestions:

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- TWITTER: @pathology437

References:

-Slides