Revised & Approved

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08

Pathology

Neurodegenerative diseases

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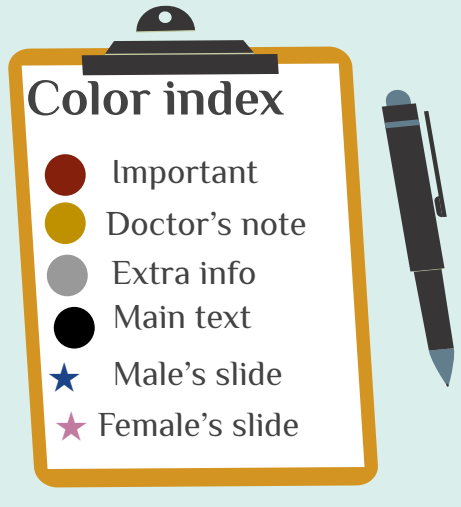


" اللهم لا سهل الا ماجعلته سهلا وانت
تجعل الحزن إذا شئت سهلا "

Objective

01 Explain the basic pathological concepts of neurodegenerative disease, using Alzheimer's and Parkinson disease as a classical example.

02 Know the definition of "dementia" syndrome

03 List the possible causes of dementia

04 Understand the major clinic-pathological features of Alzheimer's disease

05 Hypothesize the possible etiologies of Alzheimer's disease.

06 List the causes of Parkinsonism

07 Understand the major clinical and pathological feature of Parkinson disease

Helpful video

Overview

Degenerative brain disease

- **Dementia (Clinical Syndrome)**
  - **Alzheimer's Disease**
    - Definition
    - Epidemiology
    - Etiology
    - Clinical Features
    - Pathogenesis
    - Pathological Features
- **Parkinsonism (Clinical Syndrome)**
  - **Parkinson's Disease**
    - Definition
    - Epidemiology
    - Etiology
    - Clinical Features
    - Pathogenesis
    - Pathological Features

Introduction

- Neurodegenerative diseases are characterized by progressive loss/**degeneration** **of neurons**, typically affecting group on neurons with **functional** interconnections, rather than by the physical location in the brain.
- ★ They cause symptoms depend on the pattern of involvement of the brain
- ★ Although many degenerative diseases have primary targets, other brain regions are often affected later in the course of the illness.
- A pathologic process shared by most neurodegenerative diseases is the **accumulation of protein** aggregates which serve as histologic hallmarks of specific disorders
- ★ Different diseases tend to involve particular neural systems and therefore have relatively similar presenting signs and symptoms, N.B. that symptoms depend on the pattern of involvement

Cerebral cortical neurons	Result in cognitive changes, often including disturbances of memory, behavior, and language. With time these progress to dementia, as occurs with Alzheimer disease
Neurons of the basal ganglia	Result in movement disorders as with Parkinson disease , and huntington's disease
Cerebellum	Result in ataxia
Motor neurons	Result in weakness

Examples of neurodegenerative diseases

- **Alzheimer's disease**
- **Parkinson's disease**
- Frontotemporal Lobar Degeneration (FTLD)
- Huntington Disease (HD)
- Spinocerebellar Ataxias (SCAs)
- Amyotrophic Lateral Sclerosis (ALS)

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

Dementia الخرف

-A broad term describing a group of related symptoms (syndrome) ,

-Characterized by the development of **memory impairment** begins with recent memory loss and progresses to long term memory loss 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, also can accompany numerous other diseases that injure the cerebral cortex e.g. metabolic disorders, infections or toxins.

-Dementia is an increasing public health concern as the population ages
-Regardless of etiology, Although a major risk factor of dementia is advancing age, it is **not part of normal aging** and always represents a pathologic process

★ Causes of Dementia

01 **Primary Neurodegenerative Disorders**
- Alzheimer disease
- Lewy body dementia
- Huntington disease [1]

02 **Miscellaneous**
- Brain tumors
- Neuronal storage diseases (in childhood)
- Toxic injury (e.g. mercury)

03 **Vascular and Traumatic Diseases**
- Multi-infarct dementia
- Global hypoxic-ischemic brain injury
- Chronic subdural hematomas

04 **Metabolic and Nutritional Diseases**
- Thiamine deficiency (Wernicke-Korsakoff syndrome)

05 **Infections**
- Prion (protein found in brain)-associated disorders (e.g. Creutzfeldt-Jakob disease [2])
- HIV encephalopathy (AIDS dementia complex)
- [3] Progressive multifocal leukoencephalopathy

[1] Is a fatal genetic disorder that causes the progressive breakdown of nerve cells in the brain which causes uncontrolled movements, emotional problems, and loss of thinking ability (cognition).

[2] (CJD) is a universally fatal brain disorder. Early symptoms include memory problems, behavioral changes, poor coordination, and visual disturbances. Later dementia. Is believed to be caused by a protein known as a prion. Caused by eating cow meat.
[3] (PML) is a rare and usually fatal viral disease characterized by progressive damage (-pathy) or inflammation of the white matter (leuko-) of the brain (-encephalo-) at multiple locations (multifocal) .

★ What do you expect in late stage dementia

- Bedbound , requires around the clock care
- Unable to walk or sit up without assistance

- Loss of facial expression
- Unable to speak
- Problem with everyday activity like bathing , dressing

Alzheimer

Video (Osmosis)

Video (Pathoma)

Definition

- Degenerative disease of the cortex
- The most common cause of dementia 60% in the elderly , 2% at 65 years , doubles every 5 years .
- Dementia and parkinsonism are clinical syndromes but Alzheimer disease and Parkinson's disease are the neurodegenerative disease
- While Alzheimer's disease is considered as "degenerative" -that is, reflecting and underlying cellular degeneration of neurons in the brain- not all forms of dementia are degenerative

Epidemiology

- This increasing incidence with age has given rise to major medical, social, and economic problems in countries with a growing number of elderly.

Peak prevalence when considered by age groups:

65 - 74 yrs	75 - 84 yrs	85 < yrs
3%	19%	47%

Clinical features

Neurologic deficits are not seen early in the disease

Early manifestations: insidious (gradual and subtle development) onset of impaired higher intellectual function (such as thinking, remembering..), memory impairment, and altered mood and behavior

Late manifestations: severe cortical dysfunction occurs with progressive disorientation, memory loss and aphasia (inability to speech)

Over the next 5 to 10 years, the patient becomes profoundly disabled, mute, and immobile.

Death usually occurs from intercurrent pneumonia or other infections due to prolonged time in bed

Etiology

- Most cases are *sporadic *not familial/hereditary
- At least 5% to 10% are familial , early onset
- In general, patients rarely become symptomatic before 50 years of age, but early onset can be seen with some of the heritable forms
- ★ 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

Will be discussed in further detail later in the lecture...

Pathogenesis of Alzheimer

Video

- ★The fundamental abnormality in AD is the accumulation of two proteins **(Aβ and tau)** in specific brain regions, in the forms of **Plaques** and **Tangles**

- The anatomic distribution of these changes (plaques and tangles), which occur roughly in parallel (at the same time), are responsible for the clinical signs and symptoms; they appear to develop well in advance of clinical presentation

1- Plaques

- Plaques is type of extracellular lesion

- Aβ protein is derived from a larger membrane protein known as , amyloid precursor protein (APP) normal protein plays a role in neuronal growth and and repair

- Plaques are deposits of aggregated **Aβ peptides** in the **neuropil** (any area in the nervous system composed of mostly unmyelinated axons, dendrites and glial cell processes that forms a synaptically dense region containing a relatively low number of cell bodies)
- **APP is processed in either of two ways:**

  - **Non- pathogenic (soluble) pathway:** APP is cleaved by two enzymes, **α-secretase and γ-secretase**, in a process that prevents formation of Aβ , (forms other peptide which is non-pathogenic) The cleavage here forms a soluble fragments NO Alzheimer NO amyloid fibrils

  - **Pathogenic (non-soluble) pathway**: APP is cleaved by the enzymes **β-amyloid**–converting enzyme (BACE) and **γ-secretase to generating Aβ proteins** which forms the plaques

- Generation and accumulation of Aβ occur slowly with advancing age

- Aβ generation and accumulation is the critical initiating event for the development of the disease

Effects of accumulated Aβ on neurons and neuronal function

Small aggregates:

- Alter **neurotransmission** -inhibit electrical transport through the neurons-
- Aggregates can be toxic to neurons and synaptic endings

Larger deposits, in the form of **plaques**:

- Lead to neuronal death
- Elicit a local inflammatory response that can result in further cell injury
- May cause altered region-to-region communication through mechanical effects on axons and dendrites.

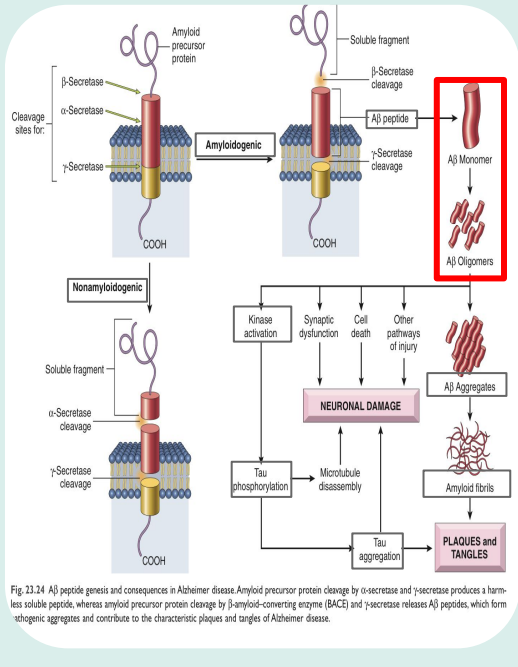


Fig. 23.24 Aβ peptide genesis and consequences in Alzheimer disease. Amyloid precursor protein cleavage by α-secretase and γ-secretase produces a harmless soluble peptide, whereas amyloid precursor protein cleavage by β-amyloid–converting enzyme (BACE) and γ-secretase releases Aβ peptides, which form pathogenic aggregates and contribute to the characteristic plaques and tangles of Alzheimer disease.

Pathogenesis of Alzheimer

2- Tangles

- ★Tangles are aggregates of the **microtubule binding protein tau**, which **develop intracellularly and then persist extracellularly after neuronal death**.

- Mechanism of tau protein is not completely understood but thought that the presence of Aβ leads neurons to activate Kinase enzyme causing **hyperphosphorylation** of the microtubule binding protein **"tau"** resulting in the loss of its ability to bind to microtubules

Just like any other cell, neurons are held together by a cytoskeleton giving the cell its shape, offers support and facilitates movement through 3 main components: microfilaments, intermediate filaments and **microtubules. Tau protein** is an abundant protein in nerve cells performing the of function of stabilizing microtubules. #med437

Effects of accumulated tau on neurons and neuronal function

- 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 also results in neuronal dysfunction and cell death.

- Mechanism of of **tangle injury to neurons** remains poorly understood but two pathways have been suggested:

Tangle Injury to Neurons

The microtubule **stabilizing function** of tau protein is **lost**, leading to neuronal toxicity and death

Aggregates of tau protein elicit a **stress response** which persists and eventually leads to cell death

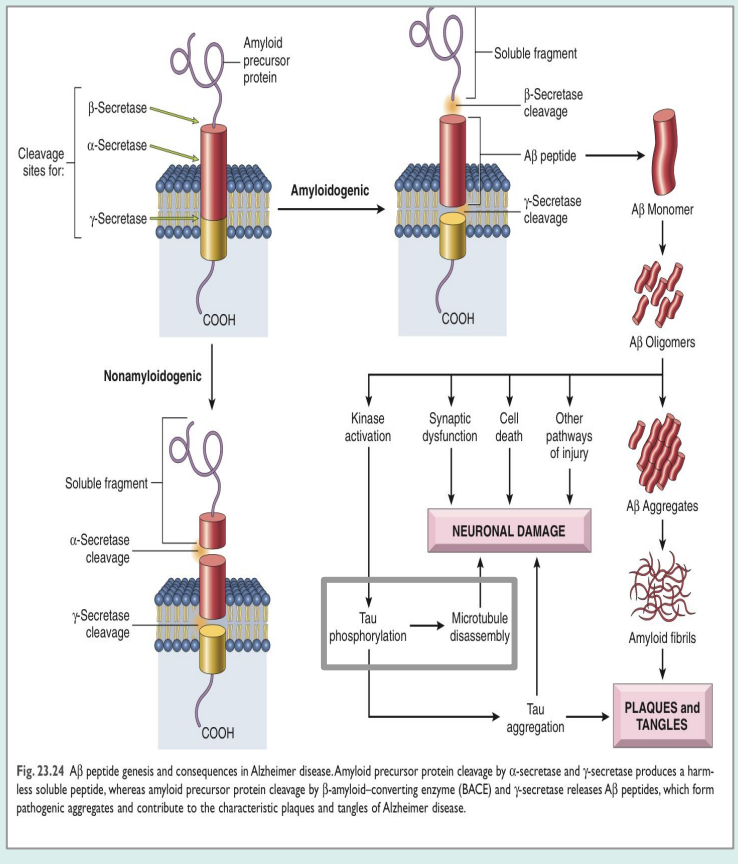


Fig. 23.24 Aβ peptide genesis and consequences in Alzheimer disease. Amyloid precursor protein cleavage by α-secretase and γ-secretase produces a harmless soluble peptide, whereas amyloid precursor protein cleavage by β-amyloid–converting enzyme (BACE) and γ-secretase releases Aβ peptides, which form pathogenic aggregates and contribute to the characteristic plaques and tangles of Alzheimer disease.

To make sure you understood the pathogenesis!
#MED437

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 (normal protein).** 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 that the body can get rid of 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** complex that the body cannot get rid of => forming **Beta amyloid PLAQUES*** extracellular (abnormal pathway)

* Beta plaques are beta amyloid proteins accumulated and formed plaques
* 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"**

Pathological hallmarks of Alzheimer disease include "positive" lesions such as amyloid plaques and cerebral amyloid angiopathy, neurofibrillary tangles.

Forms of Alzheimer

	Sporadic form (most cases, 90-90%)	Familial form (5-10%) of cases
Onset	Late onset Early onset	Early onset (Due to Inheritance of a dominant gene speeding up progression of the disease)
Causes & 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: 1- Early onset | (ApoE4) ε4 , An allele of apolipoprotein: - May contribute to the deposition of Aβ, but how it does so is not known. - Associated with as many as 30% of cases. - it is thought to both increase the risk and **lower the age of onset of the disease**. 2- Late onset | SORL1 gene: - Also recently been found to be associated with **late-onset Alzheimer disease** - 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 Aβ (pathogenic peptide . -Both help formation of Aβ amyloid protein -Early onset sporadic = ε4 (ApoE4) Late onset sporadic = SORL1	Can be caused by several gene mutations: **1- Mutations in** - PSEN-1 gene (on chromosome 14) which encode for presenilin-1 - PSEN-2 gene (on chromosome 1) which encode for presenilin-2 - Both presenilin-1 and presenilin-2 are protein subunits for γ-secretase, mutation in these genes can contribute in increasing the accumulation of Aβ 2- **Down syndrome** (trisomy 21) *extra chromosome 21): - APP gene is found on chromosome 21, meaning that patients with down syndrome have an extra APP gene, therefore AD occurs in almost all patients with Down syndrome who survive beyond 45 years of age due to APP gene dosage effect

Pathological Features

Overview

- ❖ **Plaques** (a type of extracellular lesion) **and** neurofibrillary **tangles** (a type of intracellular lesion) may be present to a **lesser extent** in the brains of elderly nondemented individuals.

- ❖ There is a fairly constant pattern of progression of involvement of the brain regions **pathologic changes**:

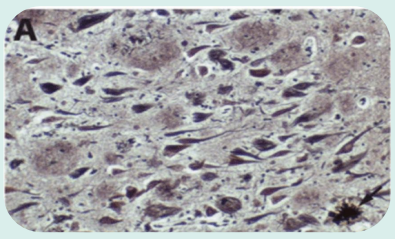
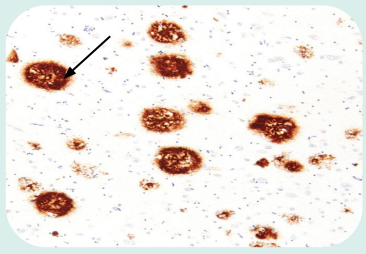
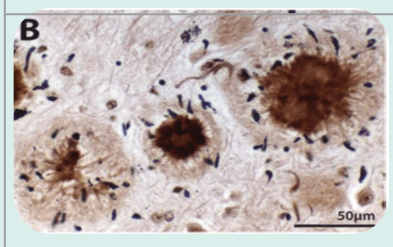
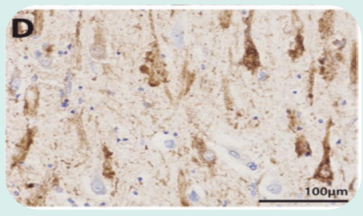
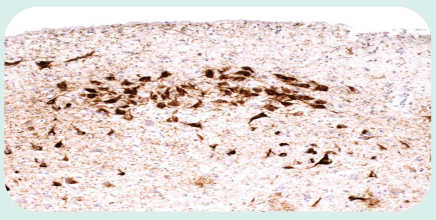
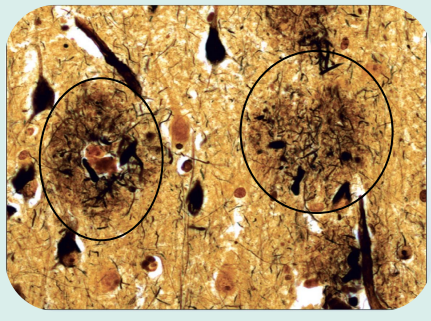
  The earliest occur in the entorhinal cortex → then spread through the hippocampal formation and isocortex →extend into the neocortex.

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

Microscopic

(1)Neuritic plaques (Beta Amyloid Accumulation)

- ❖ Focal, spherical collections of dilated, tortuous, silver-staining neuritic
- ❖ processes (dystrophic neurites) often around a central amyloid core which contains Aβ.
- ❖ 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.
- ❖ Aβ deposits can also lack any surrounding neuritic reaction termed **diffuse plaques.**

Silver staining of cortical brain tissue showing:	Immunohistochemical stain
 ★ Showing plaques and tangles in the cortex and higher power image of silver positive neuritic plaques.	 ★ Immunohistochemical stain for Aβ. Peptide is present in the core of the **plaques** (circle) as well as in the surrounding region.
 ★ Amyloid-beta protein in the plaques	**Bielschowsky stain**
  ★ Neurons containing tangles stained with an antibody specific for tau.	Dendrites (neuritic not diffuse plaques)  ★ **Plaques** (arrow) contain a central core of **amyloid** and a surrounding region of **dystrophic neurites** (Bielschowsky stain)

Pathological Features

Microscopic

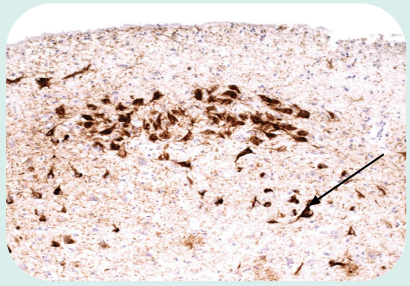
(2) Neurofibrillary Tangles (Tau Accumulation)

- Bundles of **Paired helical filaments**, visible as basophilic fibrillary structures in the cytoplasm of neurons that displace or encircle the nucleus .
- Tangles is (a type of **intracellular** lesion) Cytoplasmic, until the cell dies then become **extracellular** (Displace or encircle the nucleus).
- Tangles can remain after neurons die , becoming a form of an extracellular finding
- A major component of paired helical filament is abnormal hyperphosphorylated forms of the **protein tau**
- Tangles are no specific to alzheimer disease , being found in other degenerative disease as well
- **They are commonly Found in :**

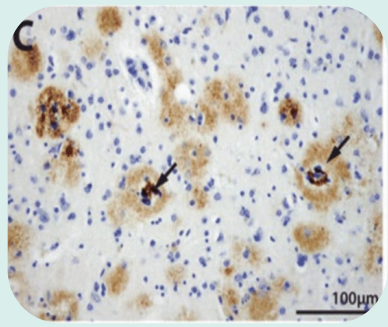
-cortical neuron especially in Entorhinal cortex
-Pyramidal cells of hippocampus
-Amygdala
-Basal forebrain

- Tau and the accumulation of beta-Amyloid are not specific for Alzheimer, but they're a characteristic for Alzheimer disease.

lmmunohistochemistry



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

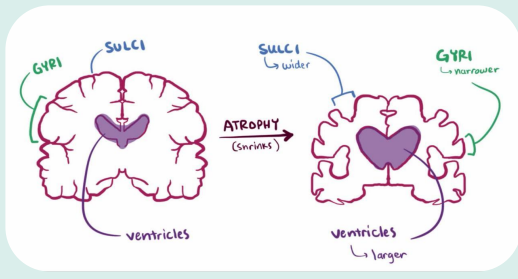


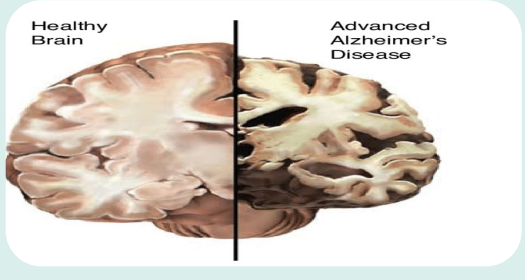
★ Hyperphosphorylated tau in tangles (silver staining)

Macroscopic

- A variable degree of **cortical atrophy** with **widening of the cerebral sulci** that is most pronounced in the **frontal, temporal, and parietal lobes**.

- With significant atrophy, there is compensatory ventricular enlargement **(hydrocephalus ex. vacuo)** which is a compensatory increase in CSF volume that result from loss of brain volume not accumulation of fluid.





Diagnosis

- 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 definitive diagnosis of Alzheimer disease, the **combination** of clinical assessment and modern radiologic methods allows **accurate** diagnosis in 80% to 90% of cases.

Parkinsonism

Read more!

Definition

It is a motor disturbance that is seen in a number of conditions that share **damage to dopaminergic neurons of the substantia nigra** or their projection to the *striatum* related to control of movements.

It is a clinical syndrome used to describe a group of neurological problems with **numerous causes** (check etiology). In parkinsonism a person may have **some** but **not all** of the Parkinson's motor symptoms (tremor, bradykinesia, rigidity) and other signs related to an additional condition or cause.

Etiology

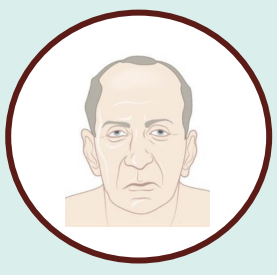
Parkinsonism can be induced by numerous causes such as:

- **Idiopathic**: ex. **Parkinson disease** (**most common** neurodegenerative disease associated with parkinsonism)
- **Drug-induced**: Drugs that affect these neurons, particularly dopamine antagonists and toxins.
- Rare: Head trauma, Stroke
- **Other neurodegenerative diseases**: ex. Multiple System Atrophy (MSA), Progressive Supranuclear Palsy (PSP) and Corticobasal Degeneration (CBD)
- **Infections**: ex. Post-encephalitic parkinsonism (associated with the influenza pandemic).

Symptoms

Parkinsonism is characterized by symptoms such as:

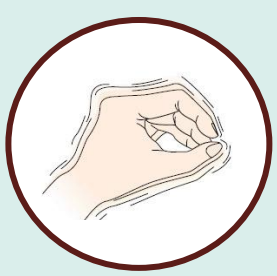
Dr.hisham: very important
(احفظوها صم)



Diminished Facial Expression (Masked Face)

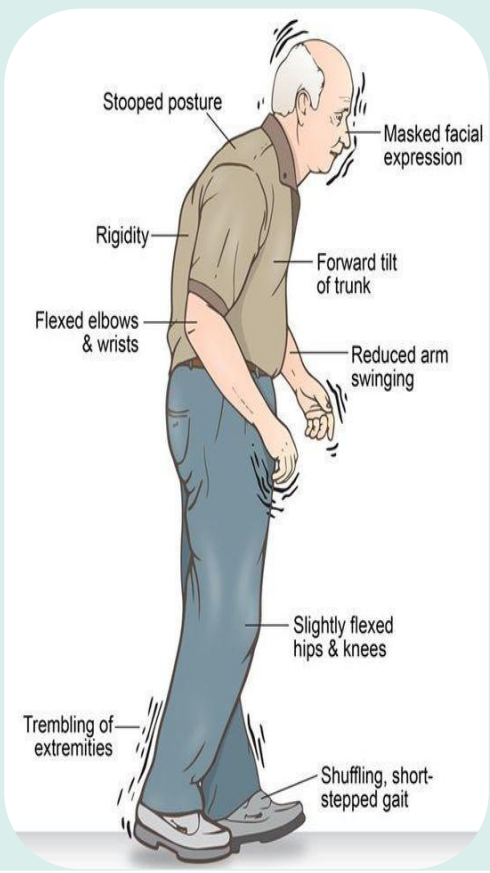
Stooped Posture
(Rounded shoulders & forward lean of the head or whole body)

-Festinating gait (progressively shortened, accelerated steps)
-Slowness of voluntary movement (Bradykinesia)



Pill-rolling tremor
كأن معه مسبحة

Rigidity & instability
(Cogwheel rigidity, major sign of parkinson disease)



Parkinson's Disease

Read more!

Parkinson's Disease

*An example of parkinsonism

Definition

Common, progressive, neurodegenerative disease that involves loss of dopaminergic neurons in the substantia nigra. It may be caused by multiple factors including environmental toxins, infection, genetic predisposition, and aging. (Not understood clearly)

Epidemiology

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

Etiology

While most Parkinson disease is **sporadic**, there are both autosomal dominant and recessive (**hereditary**) forms of the disease. The SNCA gene (alpha-synuclein) has been identified as a risk factor, and gene mutations and multiplications are associated with familial PD, but the majority of cases are sporadic.

Sporadic Parkinson's: most common, occur in people with no apparent history of the disorder in their family, The cause of these sporadic cases remains unclear.
Hereditary Parkinson's: ~ 15% percent of people with Parkinson disease have a family history of this disorder

Characteristic feature

The characteristic feature of this disorder includes a **fluctuating course** and hallucinations.
Clinically defined by **TRAP**:
Tremor at rest (eg, pill-rolling)
Rigidity
Akinesia/bradykinesia
Postural instability

Diagnosis

The patient **should have all** of the following to diagnose him with parkinson's disease
(1)Progressive parkinsonism
(2) Absence of a toxic or other known underlying etiology
(3) clinical Response to (L-DOPA)
L dihydroxyphenylalanine treatment

Prognosis & Hallmark of Parkinson disease

- ★ It usually progresses over 10 to 15 years
- Disease course 10-25 years
- There is an eventual severe motor slowing to the point of **near Immobility**
- Death is usually the result of intercurrent infection or trauma from **frequent falls** caused by postural instability because it is a motor disturbance .
- About 10% to 15% of individuals with Parkinson disease develop **dementia** , with the incidence increasing with advancing age
- 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

- To date, there is no cure. Treatment is aimed at relieving symptoms. Levodopa is the drug of choice for the symptomatic therapy of Parkinson disease
- 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 due to the resistance generated by the body against it.
- Parkinson disease has been targeted for many novel therapeutic approaches.
- 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

Pathogenesis of Parkinson's Disease

- While most Parkinson disease is **sporadic**, there are both autosomal dominant and recessive (**hereditary**) forms of the disease

- Genetic analysis has identified specific causal mutations like:
  1-**α-synuclein mutations** cause autosomal dominant Parkinson disease
  2-Gene duplications and triplications (not specified)

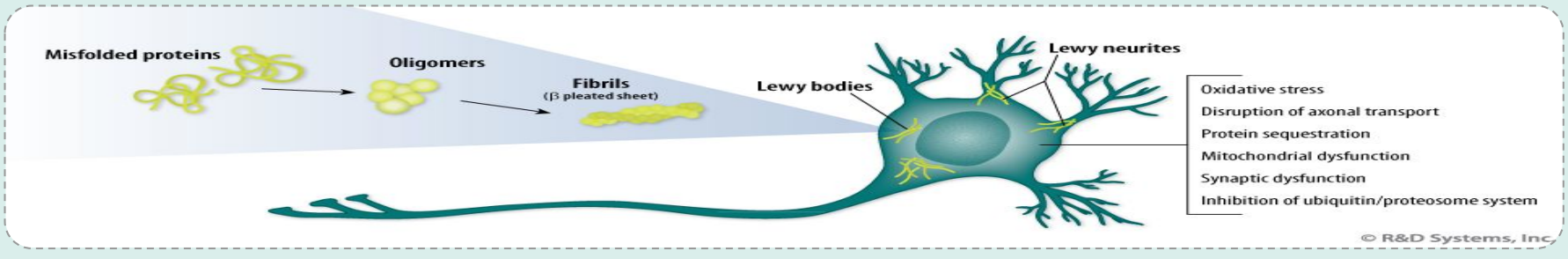
- What is **α-synuclein and what is its involvement in Parkinson's Disease?**
  It is a widely expressed neuronal protein (normally found in neuronal cytosol) that is involved in synaptic transmission and other cellular processes. It shape is normally a wavy-like structure, and in Parkinson's, the alpha-synuclein protein **misfolds** forming a toxic clump or aggregate.
- 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 -Lewy body** = is what we see under microscope & formed by the accumulation of α-synuclein , α-synuclein = is the chemical structure

- How the alterations in sequence or protein levels result in disease is <u>unclear</u>

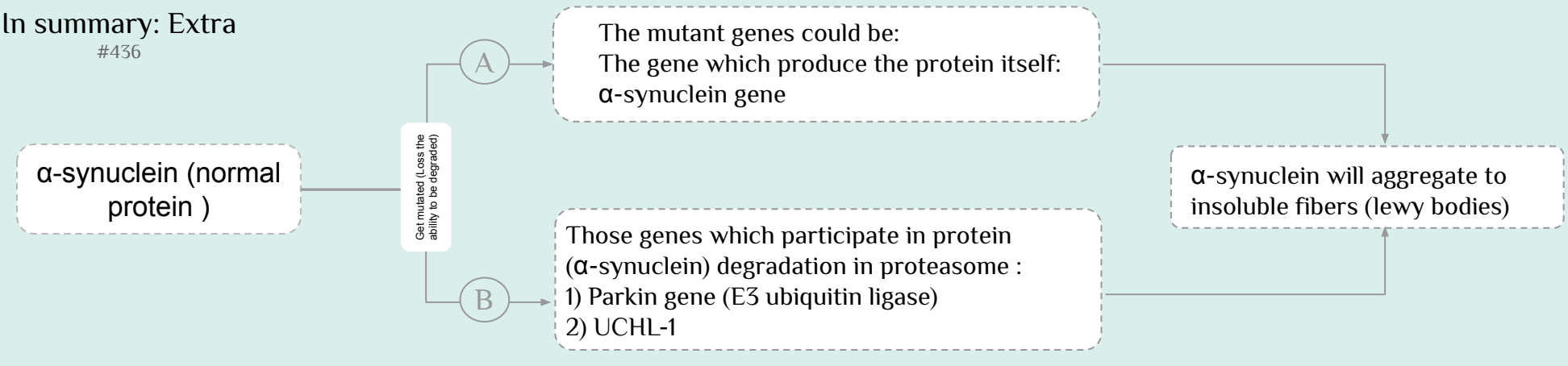
- The presence of α-synuclein in Lewy bodies has suggested that defective degradation of the protein in the [4] proteasome might play a role. A protein complex which degrades unneeded or damaged proteins by proteolysis.

- The **Pathological hallmark of the disease** is the appearance of Lewy bodies. They are aggregates of misfolded α-synuclein and other proteins (hyaline eosinophilic globules)

- **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 from proteins targeted to the proteasome)



In summary: Extra
#436

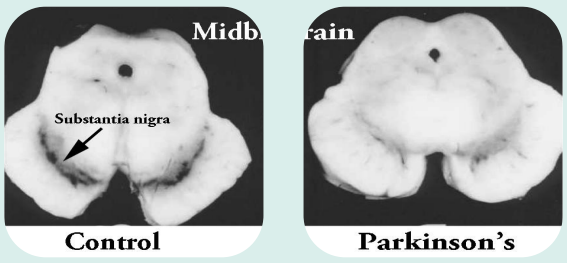


[4] A protein complex which degrades unneeded or damaged proteins by proteolysis.

Pathological Features

Macroscopic

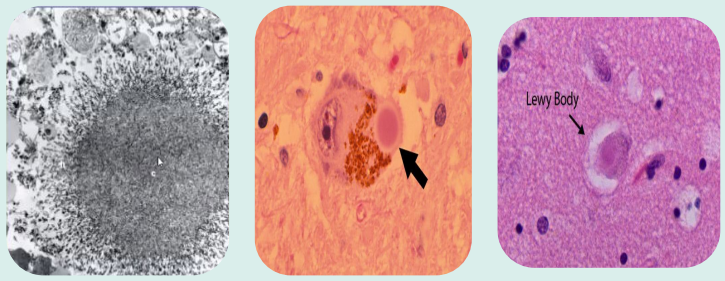
- **Pallor** and depigmentation of the **substantia nigra pars compacta and locus coeruleus** (secondary to loss of dopaminergic neurons).



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

Microscopic

- Loss of the pigmented neurons in these regions
- Gliosis
- **Lewy bodies** may be found in some of the remaining neurons



Lewy Body

01 Single or multiple, intracytoplasmic, **eosinophilic**, round to elongated inclusions that often have a dense core surrounded by a pale halo.

02 Ultrastructurally, Lewy bodies are composed of fine filaments, densely packed in the core but loose at the rim

03 These filaments are composed of α-synuclein, along with other proteins, including neurofilaments and ubiquitin.

04 ★ The other major histologic finding is Lewy neurites (dystrophic neurites) that also contain abnormally aggregated α-synuclein.

QUIZ!

MCQs

01 | Post-encephalitic parkinsonism is associated with:			
A) Influenza	B) Pneumonia	C) TB	D) None of the above
02 | which of the following lead to late onset of Alzheimer:			
A) presenilin-1	B) presenilin-2	C)mutation in SORL1	D) mutation in chromosome 21
03 | A 75 year old female has been suffering from steadily progressing memory loss over the last two and half years. She now needs help with daily activities such as grocery shopping, and cleaning her apartment. A cranial MRI reveals the presence of cortical and hippocampal atrophy, with no other notable findings. What is a possible diagnosis in this patient?			
A)Alzheimer	B) Parkinson's	C)Glioblastoma	D)stroke
04 | A 68 year old male came to the hospital with his eldest son. Over the past 7 months he realised that his father has been losing his balance upon walking. Lately his father's speech became slurred and he lost his facial expressions. What is the possible diagnosis of this patient?			
A) Gliosis	B) Stroke	C) Alzheimer	D) Parkinsonism
05 | which of the following apolipoprotein increase the risk for developing Early ONSET alzheimer			
A) APOE2	B)APOE3	C)APOE4	D)APOC2
06 | What are the genetic loci for Parkinson disease?			
A) E3 ubiquitin ligase	B) UCHL-1	C) APOE2	D) Both A & B

MCQs Answer key	01	02	03	04	05	06
	A	C	A	D	C	D

QUIZ!

MCQs

07 | Parkinson's disease is associated with mutation of which gene:			
A) α-synuclein	B) ApoE4	C) SORL1	D) PSEN-1 gene
08 | Which of the following is a symptom of Parkinsonism?			
A) Tingling	B) festinating gait	C) Nystagmus	D) aphasia
09 | Which type of neurons will be affected in case of parkinsonism :			
A) GABAnergic neurons	B) Serotonergic neurons	C) Dopaminergic neurons	D)stroke
10 | Which one of these enzymes degrades APP and prevents formation of Aβ :			
A) α-secretase and γ-secretase	B) β-site APP-cleaving enzyme and γ-secretase	C) Alzheimer	D) Parkinsonism
11 | Which of the following are the classic pathological features of Alzheimer's disease?			
A) Hirano bodies	B) Lewy bodies	C) Neurofibrillary tangles and senile plaques	D) depigmentation of the substantia nigra
12 | Degenerative brain disease" refers to degeneration of:			
A) Astrocytes	B) Microglial cell.	C) Neurons	D) Both A & B

MCQs Answer key	07	08	09	10	11	12
	A	B	C	B	C	C

Summary

	Alzheimer Disease	Parkinsonism
characterized	❖ Impairment of higher intellectual function ❖ Alterations in mood and behavior. ❖ Progressive disorientation. ❖ Memory loss. ❖ Aphasia. ❖ The next 5 to 10 y the patient becomes profoundly disabled, mute, and immobile. ❖ Cause of death is pneumonia and infections	❖ Diminished facial expression (masked facies). ❖ Stooped posture. ❖ Slowness of voluntary movement. ❖ Festinating. ❖ Rigidity. ❖ "pill-rolling" tremor.
Pathogenesis	❖ Accumulation of a peptide (β amyloid, or Aβ), due to the cleavage of APP by the β and γ-secretase	❖ The presence of α-synuclein in the Lewy bodies
Protein inclusion	❖ Aβ ❖ Tau	❖ α-synuclein
Mutations	❖ In APP or in components of γ-secretase (presenilin-1 or presenilin-2). ❖ Patients with trisomy 21 (Down syndrome). ❖ An allele of apolipoprotein, called ε4 (ApoE4), ❖ Another gene, called SORL1.	❖ α-synuclein mutations. ❖ Parkin (an E3 ubiquitin ligase). ❖ UCHL-1.
Morphology	❖ Macroscopic: 1-Atrophy in gyri with widening of the cerebral sulci. 2- Ventricular enlargement (hydrocephalus ex vacuo). ❖ Microscopic: 1- Plaques (a type of extracellular lesion) 2- Neurofibrillary tangles (a type of intracellular lesion)	❖ Macroscopic: Pallor of the substantia nigra and locus ceruleus. ❖ Microscopic: 1- Loss of the pigmented, neurons in these regions. 2- Associated with gliosis. 3- Lewy bodies may be found in some of the remaining neurons
Death result in	❖ Inter current pneumonia ❖ Othrt infection	❖ intercurrent infection ❖ trauma

Summary

There is some extra info in this summary

A 78-year-old woman is brought to your clinic by her son and daughter. They tell you that she has been very **forgetful lately** and has twice wandered out of her house and gotten lost, requiring the police to bring her back. Upon speaking with the woman, you note that her short-term memory is compromised and that she has trouble finding the words to express what she wants to say. An MRI of the brain does not reveal any evidence of a stroke. You suspect that a biopsy of this woman's brain would reveal **neuritic plaques and neurofibrillary tangles**.

Alzheimer Disease

Etiology and Epidemiology	**Etiology unknown**, but theories involve abnormal expression of amyloid gene resulting in **increased Aβ protein**, **Familial Alzheimer disease** involves **mutations in amyloid precursor protein (APP) gene on chr 21**, mutations in presenilin genes (chr 1,14), and the d4 allele of apolipoprotein E (chr 19). Affects 50% of people > 85 years old
Pathology	Gross: **Cortical atrophy of brain with widening of sulci** and ventricles Microscopic: Neurofibrillary tangles composed of tau protein within cytoplasm that displace nucleus; neuritic plaques (spherical cluster with Aβ protein core and peripheral astrocytes); amyloid angiopathy; Hirano bodies (eosinophilic bodies in hippocampal cells); granulovacuolar degeneration (cytoplasmic vacuoles in hippocampal cells)
Clinical Manifestations	**Dementia** presenting with progressive memory disturbances, disorientation, aphasias, visuospatial deficits, loss of motor skills or incontinence
Treatment and Prognosis	Donepezil (acetylcholinesterase inhibitor) to slow progression Progressive disease with no cure
Notes	Pick disease also causes dementia, but tends to affect women more than men. Histopathologically, it is characterized by cortical atrophy of the frontotemporal lobes and Pick bodies (cytoplasmic inclusion bodies made of neurofilaments).

Summary

There is some extra info in this summary

A 64-year-old man presents to your neurology clinic complaining of unsteadiness. As you obtain a history from this patient, you notice that he has **expressionless facies** and a **pill-rolling tremor at rest**. Physical examination reveals a **shuffling gait**, **rigidity** in response to passive movement, and **bradykinesia**. You suspect that the neurons of his substantia nigra may contain Lewy bodies and you prescribe levodopa to treat his symptoms.

Parkinson Disease

Etiology and Epidemiology	. **Etiology unknown** Usually presents in people over the age of 50
Pathology	Gross: **Pale substantia nigra** and **locus ceruleus** Microscopic: **Loss of pigmented dopaminergic neurons in substantia nigra** with gliosis; **Lewy bodies** (eosinophilic, intracytoplasmic inclusion bodies) in substantia nigra neurons Pathophysiology: Loss of dopaminergic input to the striatum results in loss of stimulation of the basal ganglia motor circuit
Clinical Manifestations	Symptom constellation of **pill-rolling tremor, bradykinesia, shuffling gait, rigidity, postural instability**, and **expressionless facies** (all together known as parkinsonism) Of patients with Parkinson disease, 10%–15% develop dementia
Treatment and Prognosis	Pharmacologic therapy (amantadine, anticholinergics, levodopa, dopamine agonists, MAO-B inhibitors)
Notes	Other causes for parkinsonism include repeated trauma (as with boxers), drugs (especially MPTP), postencephalitic parkinsonism (observed after the influenza pandemic in the early 1900s), and Shy-Drager syndrome (parkinsonism with orthostatic hypotension and autonomic dysfunction).

"اللهم علمنا ماينفعنا ، وانفعنا بما علمتنا وزدنا علما يارب العالمين"

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Special thanks to #436 , and #437 pathology teams

Any future corrections will be in the editing file , Click

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- Member
- Note taker
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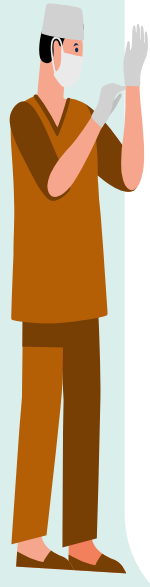

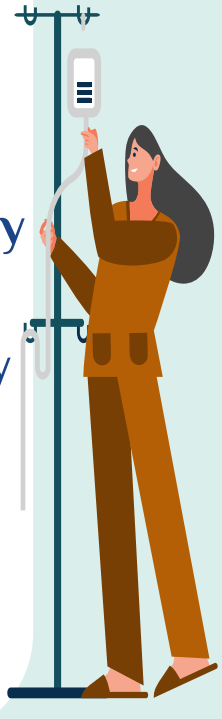

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