Lecture Seven

Introduction to
Degenerative Brain Disease

432 ***Pathology*** *Team*

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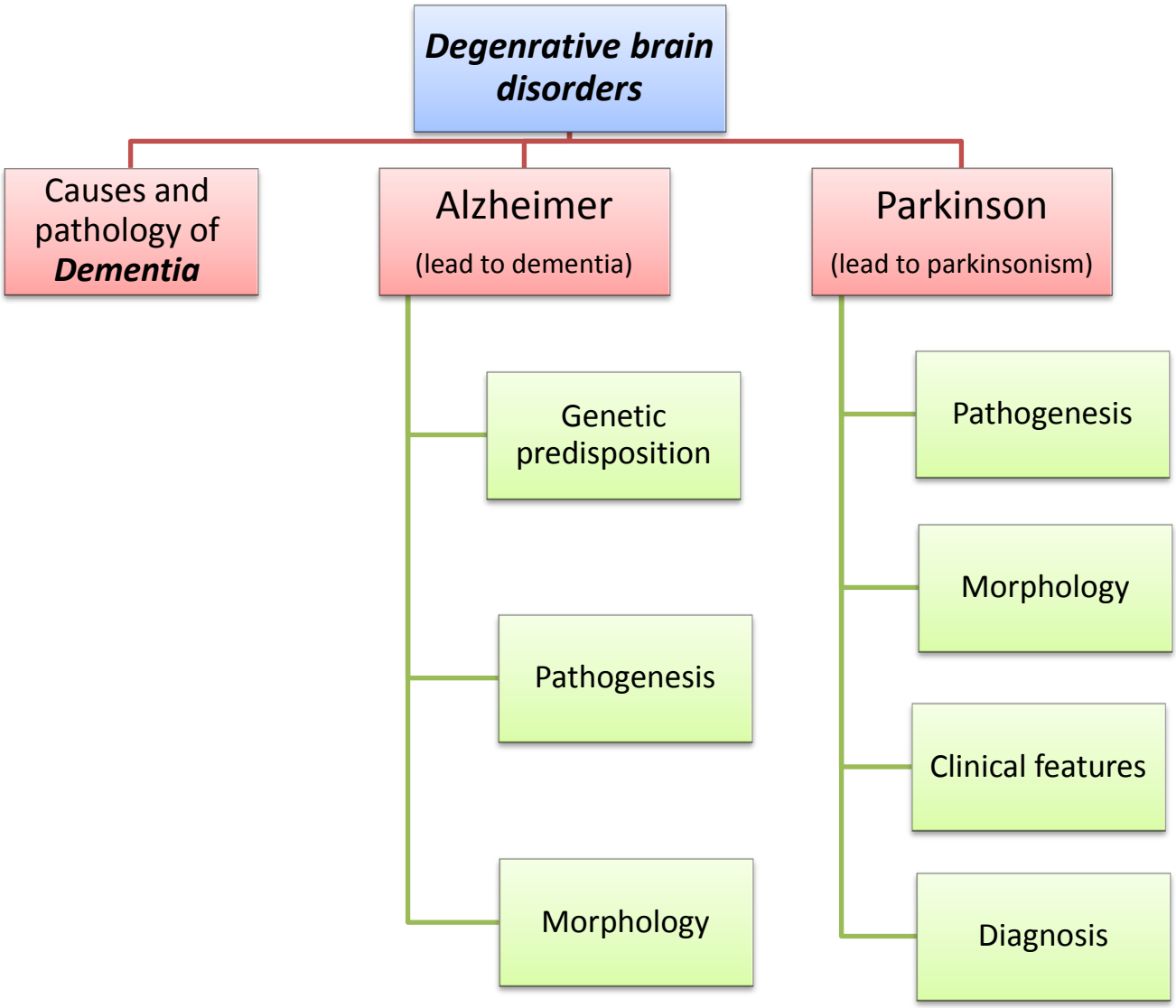
CNS Block

Color Index: female notes are in purple. Male notes are in Blue. Red is important. Orange is explanation.

Introduction to Degenerative Brain Disease

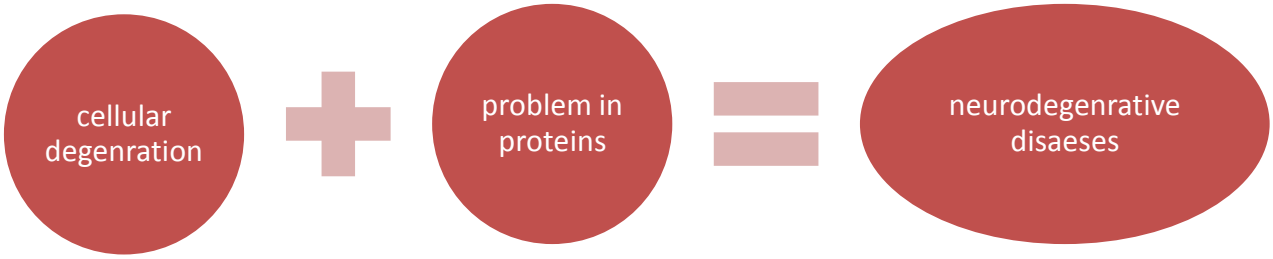
Mind Map:



Degenerative brain disease

The term **Degenerative**:

An underlying cellular degeneration of neurons in the brain. It Causes symptoms that depend on the pattern of involvement of the brain.



I Causes and pathology of dementia:

Dementia is:

1. Development of memory impairment and other cognitive deficits
2. Preservation of a normal level of consciousness
3. It is one of the most important public health issues in the industrialized world.
4. There are many causes of dementia for example (Vitamin deficiency, infection, cardiovascular status)

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.

NOTE: Regardless of etiology, DEMENTIA IS NOT PART OF NORMAL AGING and always represents a pathologic process.

Major causes of dementia:

Primary Neurodegenerative Disorders:	• Alzheimer disease • Parkinson disease • Lewy body dementia • Huntington disease
Infections:	➢ Prion "related to protein"-associated disorders (e.g. Creutzfeldt-Jakob disease), which is also called "mad cow disease", it has long incubation period up to 30 years and it causes a spongy degeneration in the brain. ➢ 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)
Miscellaneous:	• Brain tumors • Neuronal storage diseases • Toxic injury (e.g. mercury)

NOTE: ***Huntington disease (HD)*** is an inherited autosomal dominant disease characterized clinically by progressive movement disorders and dementia, with degeneration of the striatum (caudate and putamen). The movement disorder consists of jerky, hyperkinetic, sometimes dystonic movements (chorea).

Alzheimer Disease

- It is the most common cause of dementia in the elderly

- The disease usually becomes clinically apparent as insidious impairment of higher intellectual function, with alterations in mood and behavior. "At the beginning of the disease the short memory will be impaired but later on everything will be impaired"

- Later, sever cortical dysfunction:
  - Progressive disorientation.
  - Memory loss.
  - Aphasia.
  - Over the next 5 to 10 years, the patient becomes profoundly disabled, mute, and immobile.

- **Death usually occurs** from undercurrents pneumonia or other infections.

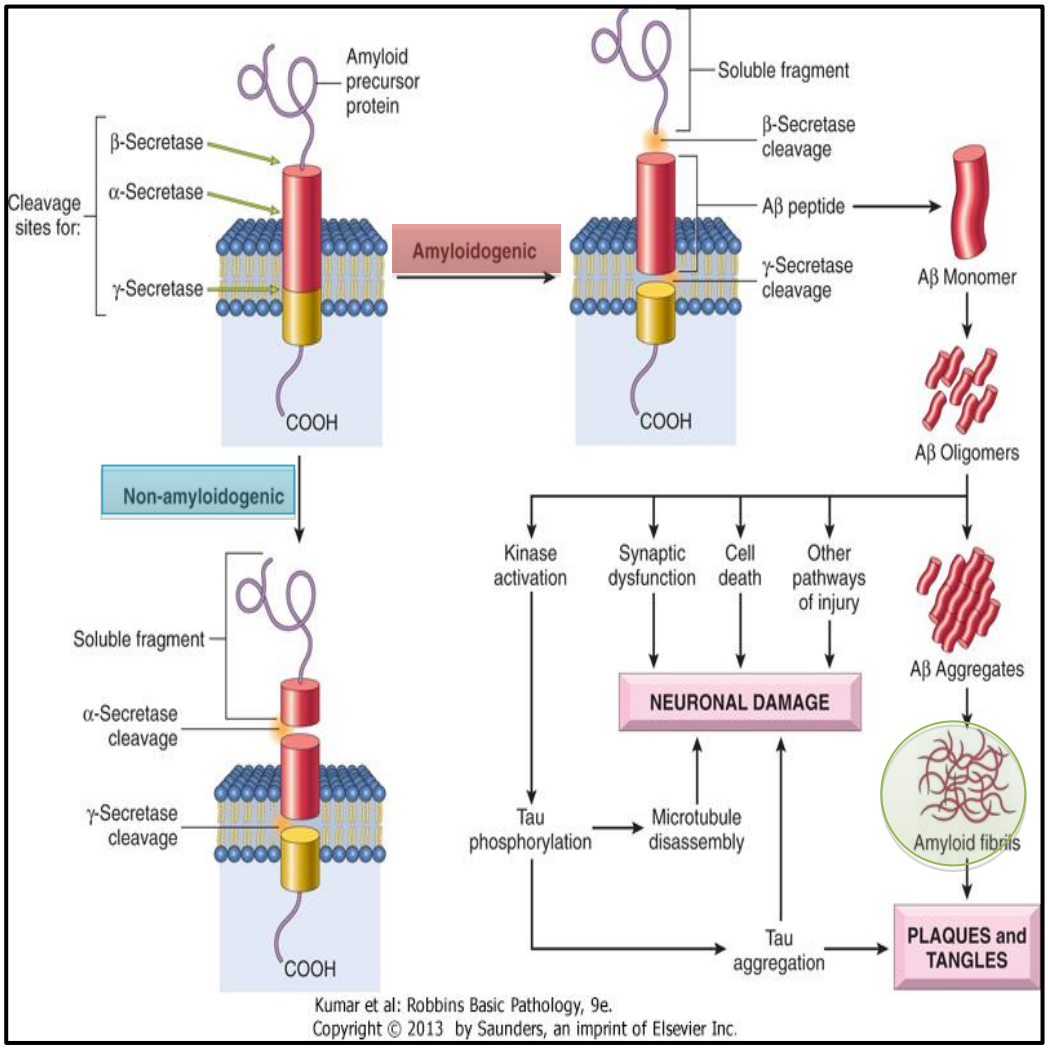
- **When considered by age groups,** the incidence of Alzheimer disease (table). This increasing incidence with age has given rise to major medical, social, and economic problems in countries with a growing number of elderly.

3%	for individuals 65 to 74 years old
19%	for 75 to 84 years
47%	for 85 years or more " 1 in 2 have Alzheimer "

- 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.

- **Most cases are sporadic**; however, at least 5% to 10% are familial type. 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.



Aβ peptide genesis and consequences in Alzheimer disease

- Amyloid size by electronic microscopy (width) = 10 – 12 nanometers
- Beta pleated is the configuration of amyloid protein that make it insoluble

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

Normally

Amyloid precursor protein is cleaved by two enzymes:

- ✓ α-secretase
- ✓ γ-secretase

In a process that prevents formation of Aβ and produces a harmless soluble peptide.

Alzheimer disease

Amyloid precursor protein is cleaved by:

1. β-amyloid-converting enzyme (BACE)
2. γ-secretase

Releases Aβ peptides, which form pathogenic aggregates and contribute to the characteristic plaques and tangles of Alzheimer disease.

Generation and accumulation of Aβ occur slowly with advancing age.

Genetic predisposition:

1) Mutations in APP or in components of γ-secretase (*presenilin-1 or presenilin-2*) lead to early onset **familial *Alzheimer disease*** by increasing the rate at which Aβ accumulates.

2) Alzheimer disease occurs in almost all patients with **trisomy 21 (*Down syndrome*)**-where the gene encoding APP is located-who survive beyond 45 years (due to APP gene dosage effects).

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:

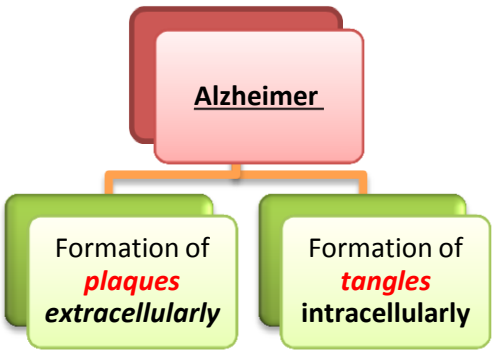
- An allele of ***apolipoprotein,*** called ***ε4 (ApoE4),*** is associated with as many as 30% of cases, and is thought to both increase the risk (of AD by approximately 4 fold) and lower the age of onset of the disease (younger age group of Alzheimer disease) ApoE4 may contribute to the deposition of Aβ, but how it does so is not known.

genes associated with alzheimer disease	
early onset	apoE4
late onset	SORL1

- 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, shuttling it to a compartment where the Aβ peptide is generated by enzymatic cleavage, the net result being increased generation of this pathogenic peptide.

Pathogenesis:

Accumulation of Aβ has several effects on neurons and neuronal function:



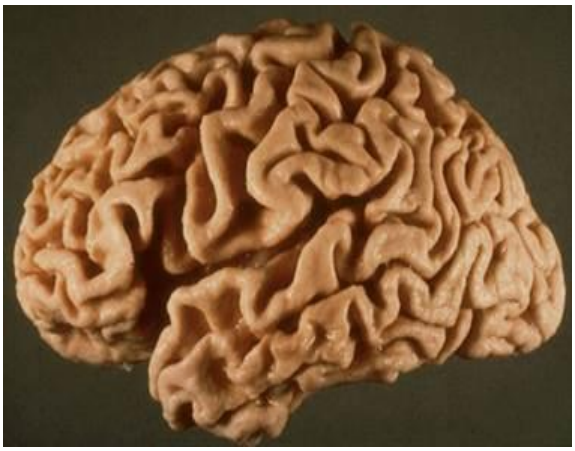
1. Small aggregates of Aβ can alter neurotransmission, and the aggregates can be toxic to neurons and synaptic endings.

2. 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.

3. 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 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:

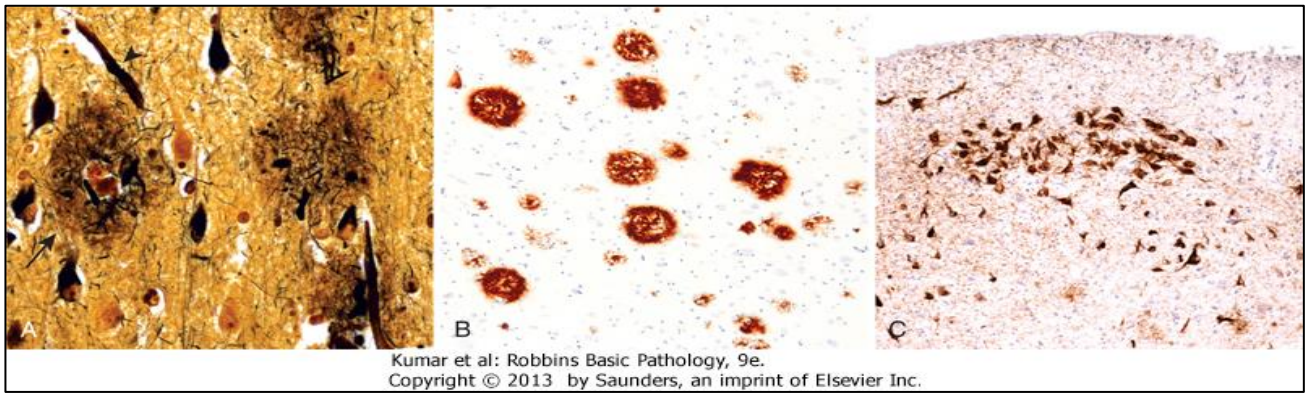


a variable degree of **cortical atrophy** with widening of the cerebral sulci that is most pronounced in the frontal, temporal, and parietal lobes. With significant atrophy, there is **compensatory ventricular enlargement (hydrocephalus ex vacuo).** (When the brain decrease in size, there will be space for the ventricles to increase in size.)

Microscopic Findings:

- **Plaques** (a type of **extracellular** lesion).
- **Neurofibrillary tangles** (a type of **intracellular** lesion).

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.



Kumar et al: Robbins Basic Pathology, 9e.

Alzheimer disease. **A,** Plaques (*arrow*) contain a central core of amyloid and a surrounding region of dystrophic neurites (Bielschowsky stain). **B,** Immunohistochemical stain for Aβ. Peptide is present in the core of the plaques as well as in the surrounding region. **C,** Neurons containing tangles stained with an antibody specific for tau.

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?

NOTE: **Immunohistochemistry** or **IHC** refers to 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.

Enthorhianl cortex: where memory processing begins, connected with hippocampus, for preporcessing of input signals.

Neuritic plaques (Extracellular):

- Focal, spherical collections of dilated, tortuous, **silver-staining (they will be black and around amyloid)** 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.***

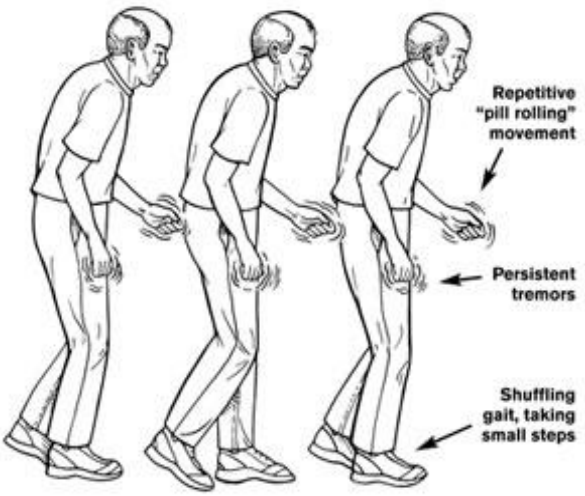
Neurofibrillary tangles (Intracellular):

- 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

Parkinsonism is a clinical syndrome due to number of diseases and it's characterized by:

- Diminished facial expression (masked faces).
- Stooped posture.
- Postural instability.
- Slowness of voluntary movement (Bradykinesia).
- Festinating gait (progressively shortened, accelerated steps).
- Rigidity.
- **Tremor "pill-rolling".**



Motor disturbance may be seen in a number of conditions that damage dopaminergic neurons of the substantia nigra or their projection to the striatum.

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 disease*** *(the most common)*.
- Other neurodegenerative diseases*.
- *Rare: head trauma, stroke*.

Extra Information:

**other neurodegenerative diseases:*

- Multiple system atrophy

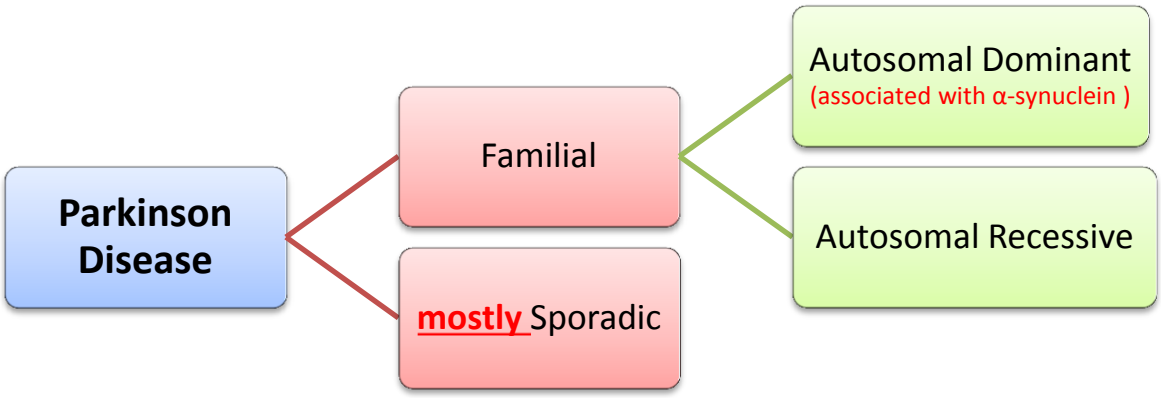
- Progressive supranuclear palsy

- Corticobasal degeneration

Parkinson's disease

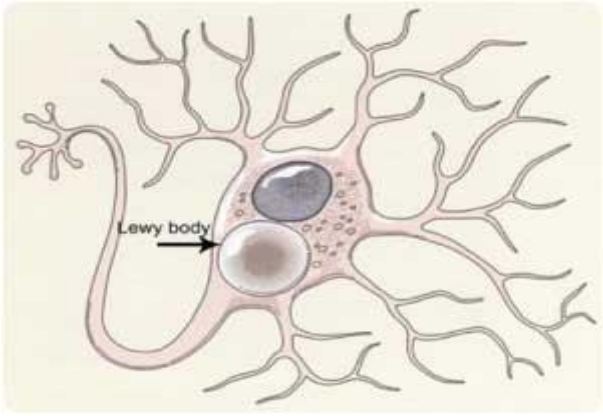
- 6-8 decades.
- More than 2% in North America develop disease.
- Men more than women.
- 22/100,000 = crude prevalence rate in Saudi population.
- Caused by loss of dopaminergic neurons.

Pathogenesis:



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

Even in sporadic cases of Parkinson disease that not caused by mutations in this gene, the diagnostic feature of the disease is the **Lewy body (an inclusion containing α-synuclein).**



NOTE: 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.

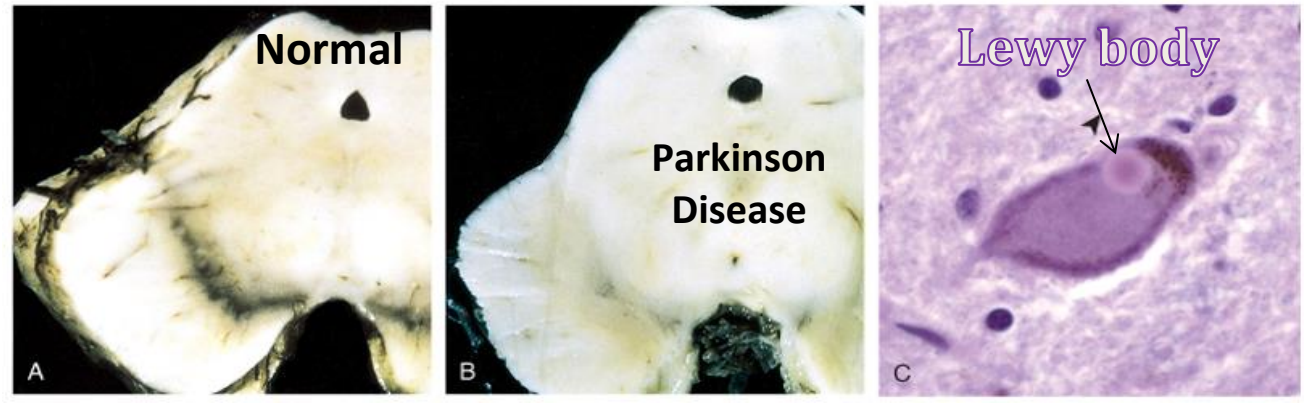
This is supported by the identification of 2 other genetic loci for Parkinson disease:

- **E3 ubiquitin ligase** (encode the proteins parkin).
- **UCHL-1** (an enzyme involved in recycling of ubiquitin from proteins targeted to the proteasome).

(Both involved in protein cycle)

From''Robbins'': ***some forms of familiar PD are associated with mutations in the PARK7 of PINK1 genes, both of which appear to be important for normal mitochondria function.***

Morphology:



Macroscopic finding (pic. B):

- **Pallor**(colorlessness)**of the substantia nigra** and locus ceruleus.

Microscopic findings (pic. C):

- Loss of the pigmented, catecholaminergic neurons in these regions.
- Associated with gliosis.
- ***Lewy bodies* may be found in some of the remaining neurons**.

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.

Clinical features:

- ✓ **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.
- ✓ 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.
- ✓ Usually progresses over 10 to 15 years.
- ✓ 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.
- ✓ **About 10% to 15% of individuals with Parkinson disease develop dementia,** with 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***.

Diagnosis:

1. Progressive process.
2. Absence of a toxic exposure or other known underlying etiology.
3. Clinical response to L-dihydroxyphenylalanine (L-DOPA) treatment.

Parkinson disease has been targeted for many novel therapeutic approaches, including transplantation , gene therapy , and stem cell injection.

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 (from Robbins Basic Pathology)

Neurodegenerative Diseases:

- Neurodegenerative diseases cause symptoms that depend on the pattern of brain involvement. Cortical disease usually manifests as cognitive change, alterations in personality, and memory disturbances; basal ganglia disorders usually manifest as movement disorders.
- Many neurodegenerative diseases preferentially affect a primary set of brain regions, but other regions can be involved later in the disease course. This evolving process can change the phenotype of the disease over time-as with the appearance of cognitive impairments in people initially affected by the movement disorder of Parkinson disease.
- Many of the neurodegenerative diseases are associated with various protein aggregates, which serve as pathologic hallmarks. It is unclear whether these striking inclusions and deposits are critical mediators of cellular degeneration. Familial forms of these diseases are associated with mutations in the genes encoding these proteins or controlling their metabolism.

Questions from Pathology Recall book

1/ what is meant by degenerative disease?

- one that causes slowly progressive loss of neural function, can occur in CNS as well as peripheral nervous system (PNS).

2/ what is Dementia?

- organic disease of the CNS causing progressive loss of intellectual capabilities

3/What are 2 clinical finding of Alzheimer dementia?

- Slow, progressive loss of intellect
- Deterioration of motor function, including contractures and paralysis

4/what are neurofibrillary tangles?

- intracytoplasmic bundles of filaments, derived from microtubules and neurofilaments

5/where are the tangles found in the brain?

- within neurons, in the cerebral cortex

6/what are senile plaques?

- Also known as neuritic plaques:swollen nerve processes forming spherical foci with a central amyloid protein core.

7/Where are seile plaques commonly located?

- Cerebral cortex
- Amygdala
- Hippocampus

8/What syndrome can exhibit similar findings to Alzheimer dementia?

- Down syndrome in patients who survive to 40 years of age or older.

9/In what other disease can neurofibrillary tangles also be seen?

- Parkinson disease

10/What is the tau protein?

- Normally synthesized in gray matter, it has been shown to have hyperphosphorylation and it accumulates in the tangles and plaques of patients with Alzheimer disease.

11/What is Parkinsonism and what are the associated clinical features?

A group of disorders characterized by

- Resting pill-rolling tremor
- Masked face
- Shuffling gait
- Muscular rigidity
- Slowed movements

12/What is the histology of Parkinson disease?

- Gradual loss and depigmentation of cells in the substantia nigra and locus ceruleus

13/What do the damaged cells characteristically contain?

- Lewy bodies , esinophilic intracytoplasmic inclusions

14/What neurotransmitter is depleted in the corpus striatum?

- Dopamine, because damaged cells in the substantia nigra inhibit neuronal pathways from the substantia nigra to the corpus striatum

15/What therapy can be effective?

- L-dopa, a dopamine precursor

Case 1/ A 62-year-old man is found to have a shuffling gait, a stooped posture, slowness of movement, muscle rigidity, and a pill-rolling tremor at rest. Physical examination finds that he has a "mask-like" facial expretion. The disoreder this individual most likely has is asscoiated with the formation of intracytoplasmic eosinophilic inclusions within neurons that ate located in which of the following areas of the nervous system?

A. Anterior cerebellum
B. Caudate nucleus
C. Geniculate ganglion
D. Substantia nigra

Case 2/ which of the following situations describes a major risk factor for early-onset familiar Alzheimar disease?

A. Expantion of CAG trinucleotide repeats on chromosome 4
B. Ingestion of 1-methyl-4-phenyl-tetrahydrobiopteridine
C. The presence of E4 isotype of apolipoprotein E
D. Mutations in the superoxide dismutase 1 gene

The cases from case files Pathology book

Answers:

- Case 1 / D
- Case 2 / C

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If there is any mistake or feedback please contact us: 432PathologyTeam@gmail.com

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*Good Luck ^_^*