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.
- Hypothesize the possible etiologies of Alzheimer's disease.
- Causes of Parkinsonism.
- Understand the major clinical and pathological feature of Parkinson disease.
- Hypothesize the possible etiologies of Parkinson's disease.

Important note: **Please check out this link before viewing the file to know if there are any additions or changes. The same link will be used for all of our work: Pathology Edit**

Red: Important
Grey: Extra notes

Degenerative: an underlying cellular degeneration of neurons in the brain that cause symptoms depend on the pattern of involvement of the brain.
Dementia: The development of memory impairment and other cognitive deficits with preservation of a normal level of consciousness.

- One of the most important public health issues in the industrialized world.
- There are many causes of dementia
- Regardless of etiology, dementia is not part of normal aging and always represents a pathologic process

Symptoms: Difficulty remembering recent conversations, names or events is often an early clinical symptom; apathy and depression are also often early symptoms. Later symptoms include impaired communication, poor judgment, disorientation, confusion, behavior changes and difficulty speaking, swallowing and walking.

Major causes of dementia	Examples
Primary Neurodegenerative Disorders	Alzheimer disease, Lewy body dementia, Huntington disease
Infections	● Prion-associated disorders (e.g. Creutzfeldt-Jakob disease). A human form of MAd COW ● HIV encephalopathy (AIDS dementia complex) ● Progressive multifocal leukoencephalopathy
Vascular and Traumatic Diseases	● Multi-infarct[1] 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)
Miscellaneous[2]	● 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.

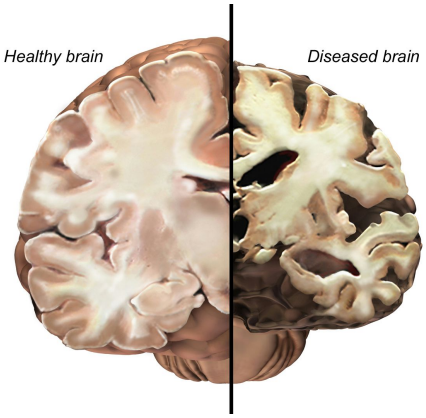
- not all forms of dementia are degenerative.

For further reading..
What is CJD? Creutzfeldt-Jakob disease (CJD) is a rare, degenerative, invariably fatal brain disorder. CJD usually appears in later life and runs a rapid course. Individuals die within 1 year. In the early stages of disease, people may have failing memory, behavioral changes, lack of coordination and visual disturbances. As the illness progresses, mental deterioration becomes pronounced and involuntary movements, blindness, weakness of extremities, and coma may occur.
What is Wernicke-Korsakoff Syndrome? Wernicke's encephalopathy is a degenerative brain disorder caused by the lack of thiamine (vitamin B1). It may result from alcohol abuse, dietary deficiencies, prolonged vomiting, eating disorders, or the effects of chemotherapy. Symptoms include mental confusion, vision impairment, coma, hypothermia, hypotension, and ataxia. ***Korsakoff's amnesic syndrome*-a memory disorder**-also results from a deficiency of thiamine, and is associated with alcoholism. The main features of Korsakoff's amnesic syndrome are the impairments in acquiring new information or establishing new memories, and in retrieving previous memories.

[1] سدادة (failure of blood supply)

[2] different kind of things,odd bunch of things

Alzheimer Disease.



What is Alzheimer's disease?

The most common cause of dementia[3] in the elderly. It usually becomes clinically apparent as insidious impairment of higher intellectual function, with alterations in mood and behavior

Later, there will be severe cortical dysfunction:

- Progressive disorientation
- Memory loss (the destructive pairing of plaque and tangles, start in Hippocampus region. Which responsible for forming memory. loss short-term memory 1st sign of alzheimer)

Hippocampus & memory.

- Aphasia[4] (loss of ability to understand or express 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 Because at the end stages, they become immobile usually always in bed which leads to stagnant > infection > death

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 (the older the patient the more possible to get alzheimer)

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

- 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** & 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
- 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.

How does β amyloid peptide accumulate in the brain tissue leading to Alzheimer?

- **Mutations** in **APP** (amyloid precursor protein) 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.

Accumulation of Aβ : When Aβ accumulate in the brain over time,it initiate chain of events that result in AD.

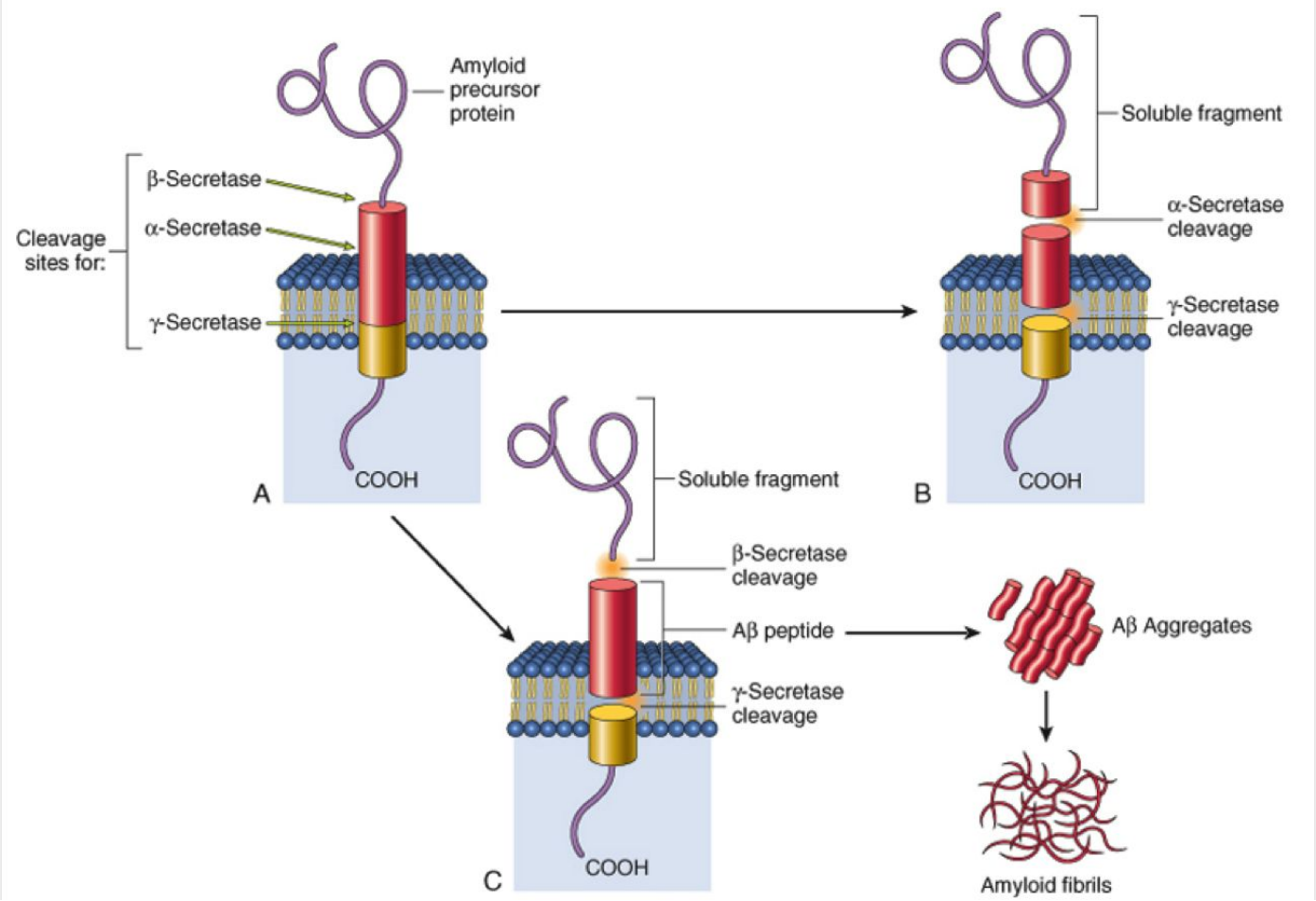
- Aβ his peptide is derived from a larger membrane protein known as **amyloid precursor protein (APP)**, **which is processed in either of two ways:**

[3] Dementia is a general term for a decline in mental ability severe enough to interfere with daily life.
[4] Aphasia is a communication disorder that results from damage to the parts of the brain that contain language.

a. It can be cleaved by two enzymes, **α-secretase** and **γ-secretase**, in a process that prevents formation of Aβ.
b. It can be cut by β-site APP-cleaving enzyme and γ-secretase to generate Aβ.

If you didn't understand read this paragraph:

- In normal conditions we have APP (a neuroprotective protein) which is cleaved by *alpha secretase* enzyme and *gamma secretase* (in another place) → and give us a normal protein.
- In alzheimer's *beta secretase* (تحشر نفسها) and cleave APP then gamma comes to cleave it as in normal conditions → as a result beta amyloid is formed → when more are formed it accumulates, become toxic and interfere with function of neuron → as they increase they form insoluble oligomers → **forming Beta amyloid PLAQUEs.**



- Generation and accumulation of Aβ occur slowly with advancing age
- Accumulation of Aβ has several effects on neurons and neuronal function:
  - Small aggregates of Aβ can **alter neurotransmission**, and the aggregates can be **toxic to neurons** and synaptic endings
  - Larger deposits, in the form of **plaques**, also lead to neuronal death, elicit a local inflammatory response that can result in further cell injury, and may cause altered region-to-region communication through mechanical effects on axons and dendrites

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

What is tau protein? Neurofibrillary tangles are made when protein called tau is modified. In normal brain cell Tau stabilize structures critical to the cell internal transport system, nutrients and other cellular cargo(things that are carried) are carried up and down tau structure by microtubules to all parts of neuron.

- In alzheimer disease normal 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.

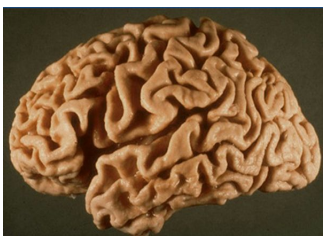
Formation of A β and Neurofibrillary tangles.

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 **ε 4 (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** (apolipoprotein E) may contribute to the deposition of A β , but how it does so is not known.
- Another gene, called ***SORL1***[5] [Sortilin-related receptor, L(DLR class)], has recently been found to also be associated with **late-onset** Alzheimer disease.
    - Deficiency of the **SORL1 protein** may alter the intracellular trafficking [6]of APP, shuttling it to a compartment where the A β peptide is generated by enzymatic cleavage, the net result being **increased generation of this pathogenic peptide**.

- 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 *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 A β generation.



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)

Dr.Hala explanation: The hydrocephalus is not because of increase in CSF circulation, It's because there is a decrease in brain matter, there is a place that should be filled → Hydrocephalus (water in the brain due to vacuo means EMPTINESS).
Other explanation: What is termed "hydrocephalus ex-vacuo" occurs when there is damage to the brain caused by stroke or injury, and there may be an actual shrinkage of brain substance. Although there is more CSF than usual, the CSF pressure itself is normal in hydrocephalus ex-vacuo.

Macroscopic:

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

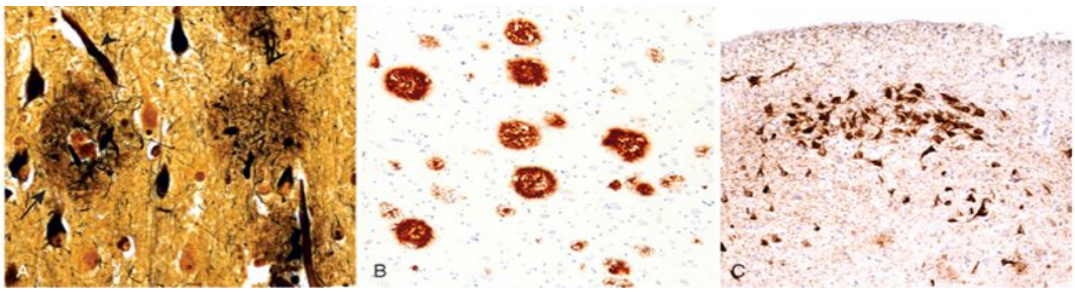
[5] is a protein that in humans is encoded by the SORL1 gene.
[6] transport of proteins and other macromolecules to various destinations inside and outside of the cell.

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.

There is a fairly constant pattern of progression of involvement of brain regions pathologic changes: Earliest in the entorhinal cortex[7] (entorhinal = interior to the rhinal sulcus) >> then spread through the hippocampal formation >> into isocortex[8] then extend >> neocortex[9]

- **Silver staining** methods or **immunohistochemistry** are extremely helpful in assessing the true burden of these changes in a brain. (to be 100% sure of the diagnosis of Alzheimer disease it has to have a histopathology)

What is immunohistochemistry? Microscopic localization of specific antigens in tissues by staining with antibodies labeled with fluorescent or pigmented material.

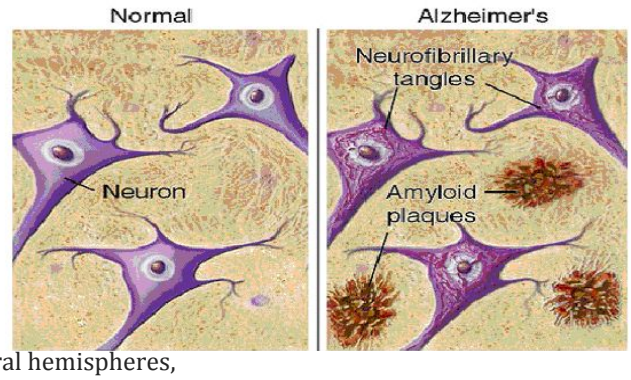


Neuritic plaques: are extracellular deposits of amyloid beta in the grey matter of the brain.

- Focal, spherical collections of dilated, tortuous, silver-staining neuritic processes (dystrophic neurites), often around a central amyloid core {fig.A}
- 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 A β {fig.B}
- A β deposits can also be found that lack any surrounding neuritic reaction, termed ***diffuse plaques.*** (these typically are found in the superficial cerebral cortex, the basal ganglia and cerebellar cortex and may represent an early stage of plaque development).

Neurofibrillary tangles:

- 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. {fig.C}
- Tangles are not specific to Alzheimer disease, being found in other degenerative diseases as well. (note that Degenerative brain diseases are not normal processes in advanced age).



[7] is an area of the brain located in the medial temporal lobe and functic and navigation. The EC is the main interface between the hippocampus

[8] There are two types of cortex in the neocortex – the **true isocortex** ar

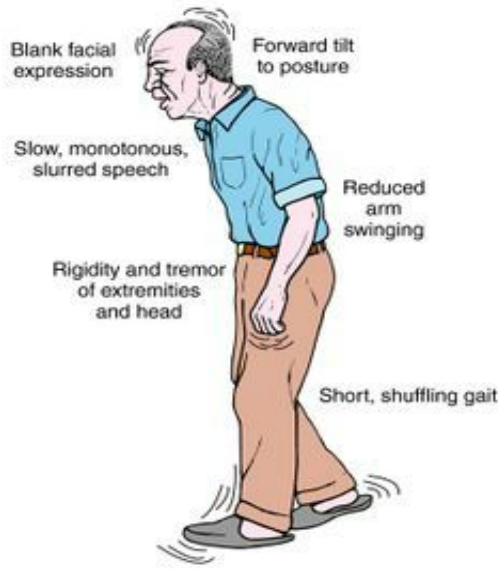
[9] it is the largest part of the cerebral cortex which covers the two cerebral hemispheres,

Note the neurofibrillary tangles as intracellular lesion and the amyloid plaques as extracellular lesion.

Parkinsonism.

Parkinsonism is the Syndrome,which is made from group of symptoms.Most cases of parkinsonism are caused by *Parkinson disease*(PD), which is associated with characteristic neuronal inclusions containing α-synuclein. But it's not the only Cause Parkinsonism, it can be due to Drugs or toxins.

It's a clinical syndrome characterized by:



- diminished facial expression (masked facies)
- stooped posture [10](because flexors mostly become stiff before extensors,and most abdominal flexor muscle become stiff)
- Slowness of voluntary movement
- festinating gait [11]
- rigidity
- "pill-rolling" tremor[12](كأنه يسبح)
- Motor disturbance and slowness of voluntary movement > due to damage to dopaminergic neurons of the substantia nigra or their projection to the striatum.

Parkinsonism is induced by:

Anything that would cause Dopamine decrease and Acetylcholine increase.

- Drugs that affect these neurons,particularly dopamine antagonists and toxins. (that selectively injure dopaminergic neurons)
- post-encephalitic parkinsonism (associated with the influenza pandemic)
- *Idiopathic Parkinson disease (most common)*
- *other neurodegenerative diseases*
- *head trauma, stroke (Rare)*

Lewy bodies (in General)

- 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

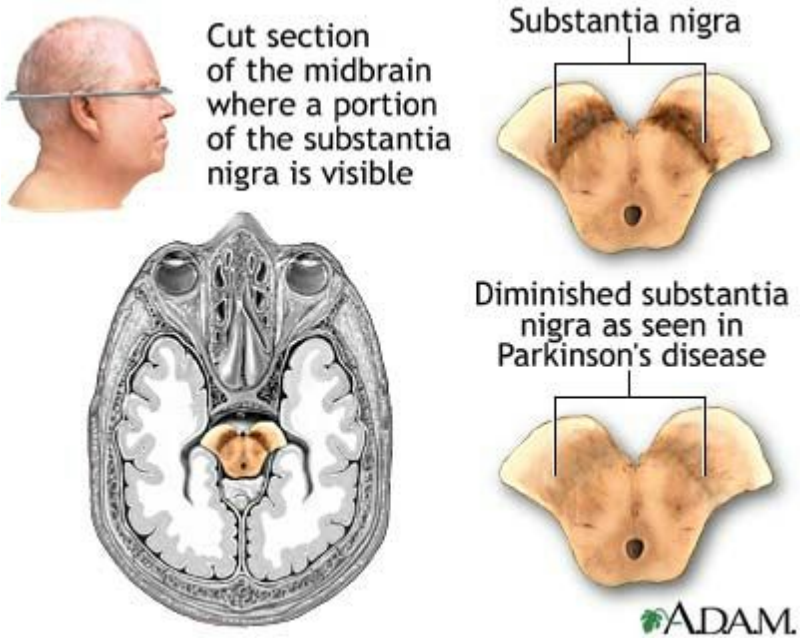
[10] the spine is curved

[11] progressively , accelerated steps

[12] resting tremor of the thumb and fingers

Parkinson's Disease.

- 6-8 decades
- more than 2% in North America develop disease.
- Men more than woman.
- 22/100,000 = crude Prevalence[13] rate in Saudi population



Diagnosis:

- progressive parkinsonism (mainly from history)
- Absence of Toxic or other known underlying etiology.
- Clinical response to l-dihydroxyphenylalanine (l-DOPA) treatment.

(which it increases dopamine level,if the patient's symptoms was relieved>positive> PD)

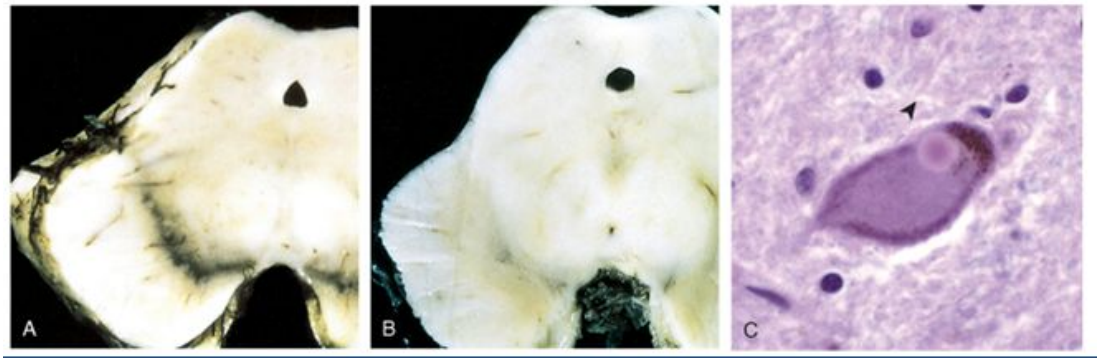
Mutation

While most Parkinson disease is sporadic, there are both autosomal dominant and recessive forms of the disease

- Genetic analysis has identified specific causal mutations, For example α-synuclein[14] mutations cause 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's disease:

- Which involve genes encoding parkin (an E3 ubiquitin ligase)
- UCHL-1 (an enzyme involved in recycling of ubiquitin[15] from proteins targeted to the proteasome)

[13] spread,predominance
[14] a protein that is abundant in the human brain>> mainly at the tips of (neurons) in the presynaptic terminals.
[15] a small regulatory protein that has been found in almost all tissues.



Macroscopic: pallor of the substantia nigra and locus ceruleus**. Fig A&B**

Microscopic:

- loss of the pigmented, neurons in these regions. (loss of dopaminergic neurons in the substantia nigra , nigrostriatal pathway of basal ganglia uses dopamin to initiate movement)
- associated with gliosis
- **Lewy bodies** may be found in some of the remaining neurons. **Fig C**

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**, with the incidence increasing with advancing age.

Dementia :

- Characteristic features of this disorder include a fluctuating[16] 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.***

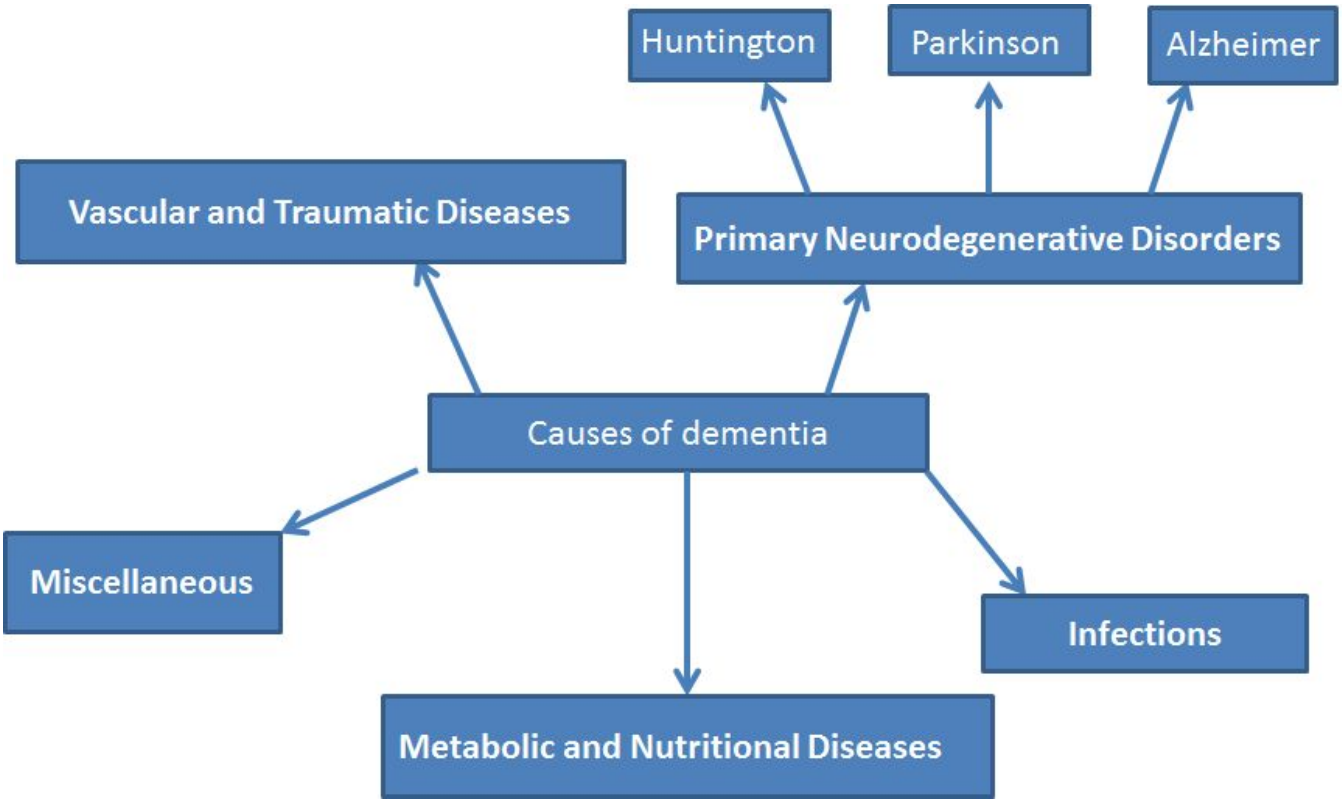
Treatment

-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.

[16] تنبذب

Summary.



SUMMARY

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.

Alzheimer Disease

- The most common cause of dementia
- Most cases are sporadic
- Definition accumulation of a peptide (β amyloid, or A β) in the brain
- A β his peptide is derived from amyloid precursor protein (APP)

Mutations:
A-familial Alzheimer 1-in APP 2-in components of γ -secretase (presenilin-1 or presenilin-2)
B- Sporadic Alzheimer An allele of apolipoprotein, called ε 4 (ApoE4), is associated with as many as 30%

- Alzheimer disease occurs in almost all patients with trisomy 21

Macroscopic:1- cortical atrophy 2-Hydrocephalus ex vacuo
Microscopic: 1- Neuritic plaques.(extracellular) 2- Neurofibrillary tangles. (intracellular)

- Silver staining methods or immunohistochemistry are extremely helpful.

Parkinsonism

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.

Parkinson's disease

Most Parkinson disease is sporadic, there are both autosomal dominant and recessive forms of the disease Genetically.

Mutations:
A-Autosomal dominant 1- α -synuclein mutations 2- gene duplications and triplications
B- Two other genetic loci 1-parkin (an E3 ubiquitin ligase) mutation 2- UCHL

Macroscopic: pallor of the substantia nigra and locus ceruleus
Microscopic: 1- loss of the pigmented neurons 2- gliosis 3- Lewy bodies

Lewy bodies:
Single or multiple, intracytoplasmic, eosinophilic, round to elongated inclusions composed of fine filaments, These filaments are composed of α -synuclein, along with other proteins.

MCQ's.

Note: There can be more than one correct answer.

1. Late symptoms of AD include all of the following EXCEPT:

A. Behavior problems

B. Loss of Speech

C. Difficulty with self-care

D. Hallucinations

Answer is\ D

2. The greatest risk factor for Alzheimer's is:

A. Exposure to nicotine

B. Gender

C. Age

D. Genetics

E. Head injury

Answer is\ C

3. Hallmarks of Alzheimer's Include:

A. Degeneration of hippocampal and cortical neurons

B. Reduced cholinergic transmission

C. Neuritic plaques

D. Neurofibrillary Tangles

E. Micro Tubules

Answer is
A,B,C,D

4. This mutation leads to the earliest development of AD:

A. APP

B. PS1

C. PS2

D. PS3

E. S3G4

Answer is\ B

5. Tau is present in __ where it stabilizes ___ but loses its abilities when ____

A. Dendrites, microtubules, dephosphorylated

B. Axons, microtubules, hyperphosphorylated

C. Soma, proteins, dephosphorylated

D. Soma, proteins, hyperphosphorylated

Answer is\ B

6. This APOE reduces AD risk:

A. E2

B. E3

C. E4

D. E5

Answer is\ A

7. ApoE4 works by:

A. Necrosis

B. Apoptosis

C. Increasing neurofibrillary tangles

D. Reducing solubility of AB

Answer is\ D

8. Crossword puzzles can reduce risk for AD

A. True

B. False

Answer is\ A

9. NSAIDs can reduce risk for AD:

A. True

B. False

Answer is\ A

10. Opioids can reduce risk for AD:

A. True

B. False

Answer is\ B

11. Parkinson's is:

A. A movement disorder

B. A neurodegenerative disorder

C. An airborne pathogen

D. Curable

Answer is\ A, B

12. Symptoms of Parkinson's include all of the following except:

A. Tachykinesia

B. Rigidity

C. Resting tremor

D. Postural instability

E. Bradykinesia

Answer is\ A

13. Parkinson's may change a person's handwriting and speech:

A. True

B. False

Answer is\ A

14. The basal ganglia includes:

A. Amygdala

B. The striatum

C. The globus pallidus

D. Subthalamic nuclei

E. Substantia Nigra

Answer is\ B, C, D, E

15. The substantia nigra provides ___ for the striatum

A. GABA

B. 5HT

C. Dopamine

D. Glutamate

Answer is\ C

16. The striatum delicately balances ____ and ____

A. GABA, Glutamate

B. DA, Ach

C. 5HT, DA

D. Ach, nicotine

Answer is\ B

17. Parkinson's is associated with:

A. Somal spheres

B. AB plaques

C. Neurofibrillary Tangles

D. Lewy Bodies

Answer is\ D

18. Alpha synuclein:

A. Can lead to early PD

B. Is not dangerous if duplicated

C. Is the main component of lewy bodies

D. Clearly works in 5HT trafficking

Answer is\ A, C

19. Dementia with Lewy Bodies is associated with:

A. Lewy bodies in the brain

B. Lewy bodies in the nasal cavity

C. Hallucinations

D. Impaired balance

E. Improved coordination

Answer is\ A, C, D

20. PD is common among people with:

A. Long term exposure to copper, lead, iron, or manganese

B. Long term exposure to hot springs

C. Long term exposure to sun

D. Long term exposure to cold

E. Long term exposure to coal

Answer is\ A

21. L-Dopa works to:

A. Encourage DA breakdown

B. Prevent DA breakdown

C. Inhibit DA production

D. Increase DA production

Answer is\ D

22. L-Dopa degradation is blocked by:

A. MAO inhibitors

B. COMT inhibitors

C. Tricyclic antidepressants

D. SSRIs

Answer is\ B

23. This turns L-dopa into DA

A. Vitamin C

B. Vitamin D

C. Vitamin B6

D. Vitamin B12

E. Vitamin K

Answer is\ C

24. L-Dopa works best:

A. Alone

B. With carbidopa

C. With dope (cannabinoids)

Answer is\ B

25. L-Dopa can lead to psychosis, which can be treated with:

A. Typical antipsychotics

B. Atypical antipsychotics

C. Haloperidol

D. Clozapine

E. Clonazepam

Answer is\ B

26. Conventional antipsychotics ___ while nonselective MAOIs ____

A. Block dopamine receptors, promote vasoconstriction

B. Block dopamine receptors, promote vasodilation

C. Break down L-dopa, promote vasoconstriction

D. Break down L-dopa, promote vasodilation

Answer is\ A

27. DA agonists:

A. Pramipexole

B. Bromocriptine

C. Need to be metabolized

D. Are metabolized in the periphery

E. Have no side effects

Answer is\ A, B

28. Anticholinergics:

A. Enhance responses to L-dopa

B. Include amantadine

C. Include atropine

D. Include benztropine

Answer is\ A, C, D

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فتون سالم
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روان غندور
أسماء الرصيص

حسين الكاف
خالد الدريبي
فيصل أبو نهية
عبدالرحمن النعيم