Neurodegenerative disorders

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Red: Doctors' and important notes.
Green: Team notes.

The term "Degenerative":

Reflects an underlying cellular degeneration of neurons in the brain

Symptoms: depend on the pattern of involvement of the brain

Dementia:

Definition:

The development of memory impairment and other cognitive deficits with preservation of a normal level of consciousness

Characteristics:

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

Major causes of dementia with examples:

- **Primary Neurodegenerative Disorders**
  - Alzheimer disease
  - Parkinson disease
  - Huntington disease

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)

- **Infections**
  - Prion-associated disorders (e.g. Creutzfeldt-Jakob disease)
  - HIV encephalopathy (AIDS dementia complex)
  - Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a rapidly progressive neuromuscular disease caused by opportunistic infection of brain cells (oligodendrocytes and astrocytes) by the JC virus (JCV).

Proin: is an infectious agent composed of a misfolded protein so it is neither a viral nor a bacterial infection. In some, which is not understood, prions cause degenerative diseases that are untreatable and usually fatal.

- **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)

So remember! not all forms of dementia are degenerative (it is loss of neurons)

Alzheimer Disease:

- The most common cause of dementia in the elderly

Clinical manifestations:

In the beginning: appear as insidious (progressing gradually) impairment of higher intellectual function, with alterations in mood and behavior

Later: severe cortical dysfunction:

- Progressive disorientation (lose of sense of direction)
- Memory loss
- Aphasia (loss of the ability to understand or express speech)
- Over the next 5 to 10 years, the patient becomes profoundly disabled, mute (can't speak), and immobile (can't move)

Prognosis: death usually occurs from intercurrent pneumonia or other infections

Incidence according to age group:

- 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

Diagnosis:

The combination of clinical assessment and modern radiologic methods allows accurate diagnosis in 80% to 90% of cases. And pathologic examination of brain tissue remains necessary for the definitive diagnosis of the disease.

N.B: A brain biopsy is the only way to confidently diagnose a patient with Alzheimer's.

Types:

- Sporadic: most cases, patients rarely become symptomatic before 50 years of age
- Familial (heritable): at least 5% to 10%, early onset can be seen.

Cause:

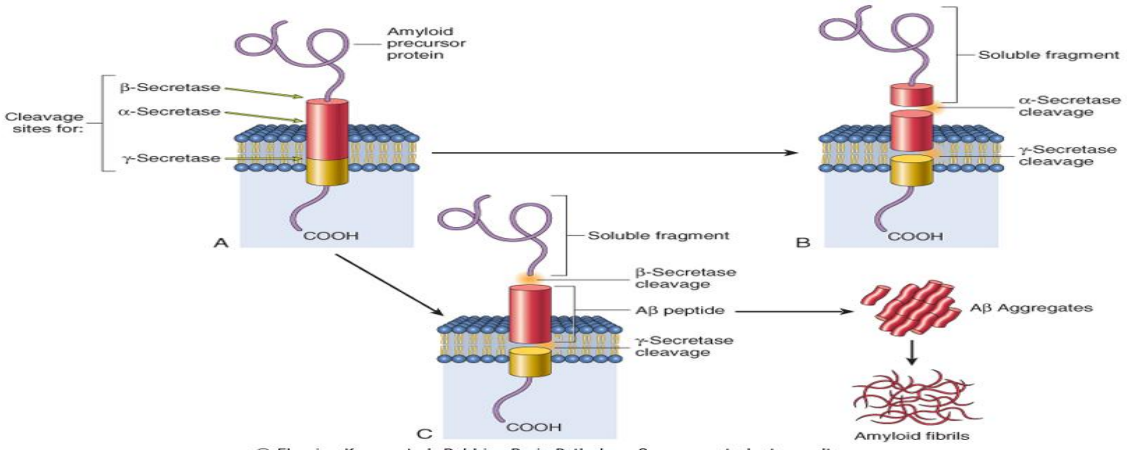
In familial form: the disease indicates that the accumulation of a peptide (β amyloid, or Aβ) in the brain initiates a chain of events that result in the morphologic changes of Alzheimer disease and dementia

Mechanism:

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

1. It can be cleaved by two enzymes, α-secretase and γ-secretase, in a process that prevents formation of Aβ. (The normal process)

2. It can be cut by β-secretase and γ-secretase to generate Aβ. (The abnormal and the Alzheimer associated process)



- Generation and accumulation of Aβ occur slowly with advancing age

- **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

In other genetic diseases: Alzheimer 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)

In sporadic (typical) form: the search for genes is beginning to identify genetic associations that may provide new clues about the pathogenesis of the disease:

- An allele of apolipoprotein, called ε4 (ApoE4), is associated with as many as 30% of cases, and is thought to both increase the risk and lower the age of onset of the disease

- ApoE4 may contribute to the deposition of Aβ, but how it does so is not known

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

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

  Note: Details are not important, just know that late-onset Alzheimer diseases is associated with SORL1

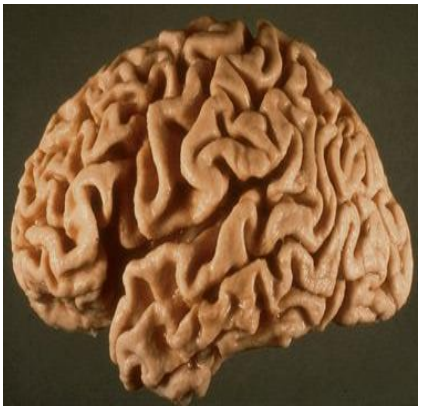
Effect of accumulation of Aβ on neurons and neuronal function:

- 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
- Tau can be detected by silver stain or by other immunostains.

Just for you to understand: Tau is a protein that is found mostly in the CNS. it is involved in the formation of microtubules, the cellular structures that are concerned mostly with maintaining cell structure (microtubules also have other functions). Phosphorylation of Tau is normal for it to cause an effect, but some disturbances in the process causes the tau to redistribute and aggregate into tangles.

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)



Gross brain shows Wide sulci and atrophied gyri. The occipital lobe here is spared.

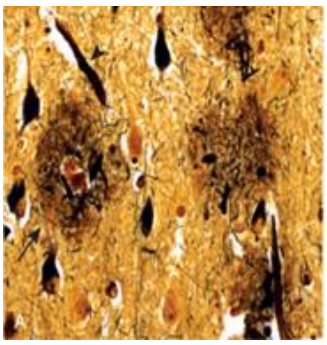
Hydrocephalus ex vacuo: is only a descriptive term. This doesn't mean that the person develops hydrocephalus, but this enlargement is a response to the atrophied brain. This may happen in conditions of dementia and some other neurological

- ***The occipital lobe is usually spared*** ***(not affected).***

Microscopic:

1. ***Neuritic*** **Plaques** (a type of extracellular lesion)

- Focal, spherical collections of dilated, tortuous, silver-staining neuritic processes (dystrophic neurites), often around a central amyloid core
- neurites: refers to any projection from the cell body of a neuron.
- So the neuritic plaques are composed of two parts: β amyloid in the center which that can be stained by congo red, and the dystrophic neurites that can be showed by silver staining. These neurites also contain microglia and astrocytes.



A, Plaques (arrow) contain a central core of amyloid and a surrounding region of dystrophic neurites.

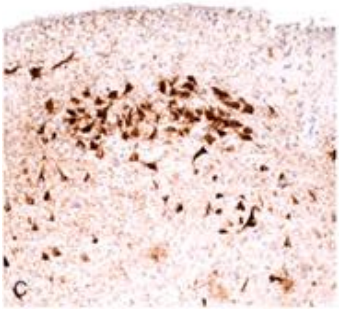
- Congo Red (a type of stain that stains positive to amyloid) will be positive in the center because of the presence of the amyloid protein.

Location: 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
- *These are plaques that have no processes around them. These can be an early phase of plaque formation.*

2. **neurofibrillary tangles** (a type of intracellular lesion)



C, Neurons containing tangles are stained by immunohistochemistry for tau.

- 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

  Location: 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.

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 → 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?

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.

Parkinsonism:

Parkinsonism doesn't equal Parkinson syndrome. Parkinsonism is a clinical presentation that has all these characteristics, and Parkinson's is a specific disease and it is not the only syndrome to show these features.

A clinical syndrome characterized by:

- diminished facial expression (masked faces)
- stooped posture (having the head and shoulders usually bent forward)
- slowness of voluntary movement
- festinating gait (progressively shortened, accelerated steps)
- rigidity
- "pill-rolling" tremor

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

Parkinsonism can be induced by:

- drugs that affect these neurons, particularly dopamine antagonists, psychiatric drugs, and toxins.
- post-encephalitic parkinsonism (associated with the influenza pandemic during world war 1)

Additional info: *a viral infection of the brain that caused a worldwide pandemic of encephalitis lethargica (sleeping sickness) just after World War I resulted in the development of postencephalitic parkinsonism in some survivors, but this has not been reported since 1930.*

- Idiopathic Parkinson disease (the most common neurodegenerative disease associated with parkinsonism)
- other neurodegenreative diseases
- rare: head trauma, stroke

Parkinson's disease:

Diagnosis: There are three clinical criteria for a person to be diagnosed with Parkinson's, which are:

- progressive parkinsonism
- absence of a toxic or other known underlying etiology
- clinical response to l-dihydroxyphenylalanine (l-DOPA) treatment

Incidence:

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

Findings:

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 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 disease:

– which involve genes encoding parkin (an E3 ubiquitin ligase)

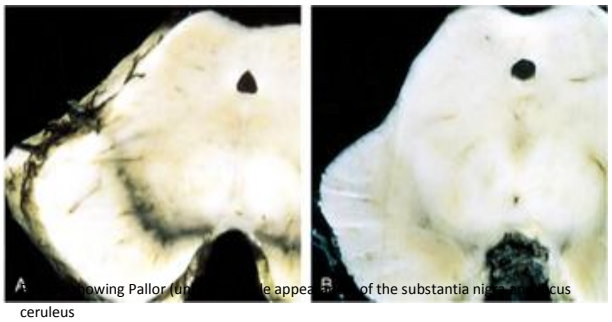
– UCHL-1 (an enzyme involved in recovery of ubiquitin from proteins targeted to the proteasome)

Additional info: The Ubiquitin system is ATP dependent system that is found all tissues and is in involved in protein degradation. The ubiquitin system tags the proteins that are to be degraded. These proteins are then transferred to the proteasome for actual degradation.

So Parkinson's is thought to be caused be abnormal degradation of proteins, which results into accumulation of α-synuclein and then formation of lewy bodies.

Macroscopic:

- pallor of the substantia nigra and locus ceruleus



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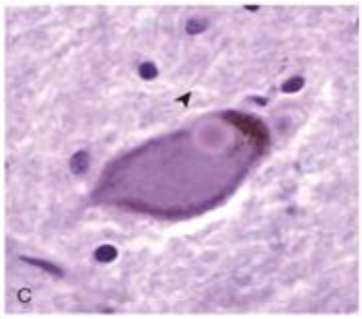
Microscopic:

- loss of the pigmented, 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

***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.

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

Prognosis:

- 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