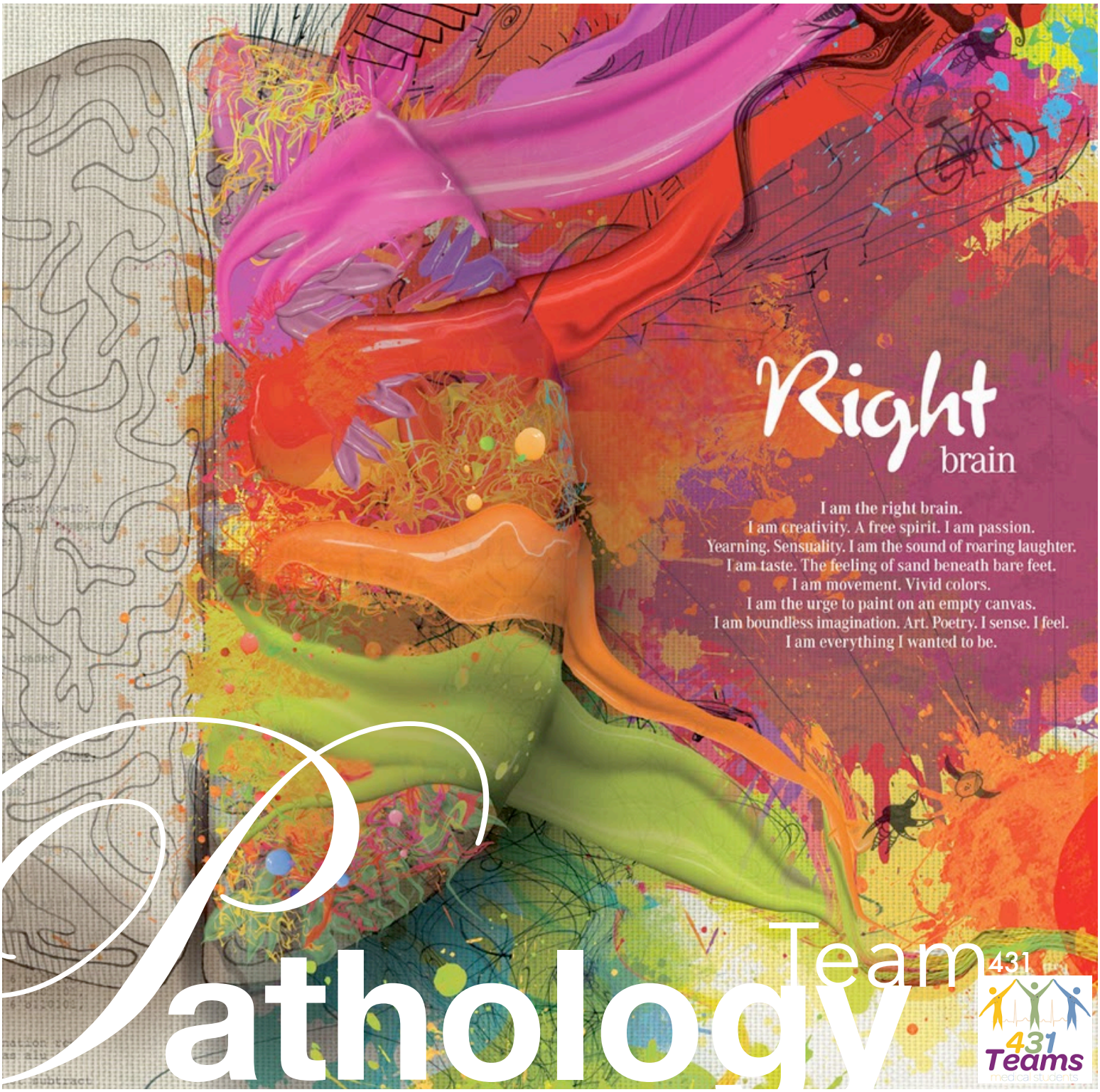


# Pathology Team 431

7/9

## CNS Block


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# Pathology:

# Degenerative Brain Diseases

## Degenerative Brain diseases:

The term "Degenerative" reflects an underlying cellular degeneration of neuronal cells of the brain affecting their normal functioning and transmission ability. {No relation to glial, ependymal nor choroid plexus cells}

Symptoms and manifestations depend on the pattern of involvement of the brain.

Factors causing neurodegeneration:

Trauma, toxins, viruses, bacteria

Fungi can cause reaction and destroy the neurons in the brain tissue

Despite degenerative brain diseases being more common in old people, they are **not** part of normal aging and represent pathological processes.

## Dementia:

The development of memory impairment and other cognitive deficits with preservation of a normal level of consciousness {patient is not comatosed}

Features:

- loss of cognitive functions and memory
- disorientation
- forgetting simple tasks like (getting out of the bed in the morning, having breakfast)

One of the most important public health issues in the industrialized developing world

There are many causes of dementia, that include:

**- Primary (idiopathic) Neurodegenerative Disorders**

- Alzheimer's disease
- Parkinson's disease
- Huntington's disease

Huntington disease is an inherited autosomal dominant disease characterized clinically by progressive movement disorders and dementia, resulting from degeneration of the corpus striatum (caudate and putamen). The movement disorder consists of jerky, hyperkinetic, sometimes dystonic movements known as chorea.

- **Infections**

- Prion-associated disorders

e.g. Creutzfeldt-Jakob disease also called mad cow disease, a degenerative form of brain damage (appears spongy upon imaging) that leads to a rapid decrease of mental function and movement. It is thought to be caused by a strong resistant protein called a prion, that cannot be eliminated by even the strongest of anti-septics. It has an incubation period of up to 30 years. (untreatable and fatal)

- HIV encephalopathy (AIDS dementia complex)
- Progressive multifocal leukoencephalopathy

Deteriorative unstoppable neuromuscular disease caused by opportunistic (immunocompromised host) infection by JC virus affecting numerous different areas in the white matter of the brain

- **Vascular and Traumatic Diseases:**

result of any insidious ischemia

- Multi-infarct dementia
- Global hypoxic-ischemic brain injury
- Chronic subdural hematomas

- **Metabolic and Nutritional Diseases:**

- Thiamine deficiency (Wernicke-Korsakoff syndrome)

- **Miscellaneous:**

- Brain tumors of frontal lobe (the cognitive part of the brain)
- Neuronal storage diseases (deficiency in an enzyme leading to accumulation of the subtrate in the neuron)
- Toxic injury by mercury or lead

Remember that **not** all forms of dementia are degenerative diseaases, may be result of tumors or ischemia ..etc

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## Alzheimer's disease:

The most common cause of dementia in the elderly

Is mostly very stressful and frustrating not on the patient but on the family members and friends surrounding him

Australia is the most common area where Alzheimer's is seen

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

Although we stated above it is not a normal aspect of aging, the incidence of this disease has been proven to increase with increase in age, giving rise to major medical, social, and economic problems in countries with a growing number of elderly. It has become more common nowadays because people are living up to older ages especially in developed countries.

Clinical manifestation:

Beginning:
The disease usually becomes clinically apparent as insidious impairment of higher intellectual function, with alterations in mood and behavior

Later: with severe cortical dysfunction:
- –Lack of cognitive function
- –Progressive disorientation
- –Memory loss (chracterized by forgetting more recent events and remembering very old childhood memories)
- –Aphasia (loss of understanding and ability to speak)
- –Over the next 5 to 10 years, the patient becomes profoundly disabled, mute, and immobile

Prognosis:

As a result of immobility and lack of hygiene patients, death usually occurs from intercurrent pneumonia or other infections

Prevention of Alzheimer's: by keeping your memory working and active & administration of some NSAIDs

Diagnosis:

Usually a combination of:

1. clinical presentation + radiological imaging (allow accurate diagnosis in about 80-90% of cases)
2. pathological examination of brain tissue
3. 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.

Pathogenesis:

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 his 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
2. It can be cut by β-site APP-cleaving enzyme and γ-secretase to generate Aβ

The generation and accumulation of Aβ occur slowly with advancing age.

Note: Amyloids are a group of fibrous proteins of various types with a common characteristic; a mutation occurred giving it a misfolded structure making it insoluble and unable to be excreted by the body. It then aggregates via amyloidosis (identified by apple-green appearance when stained by congo-red under polarized light)

Genetic factors:

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.

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)

Genes associated with **typical**, sporadic Alzheimer disease:

Research is beginning to identify genetic associations that may provide new clues about the pathogenesis of the disease:

An allele of apolipoprotein, called ε4 (ApoE4) worsens your prognosis

➔ 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.

The effect of accumulation of Aβ on neurons and neuronal function:

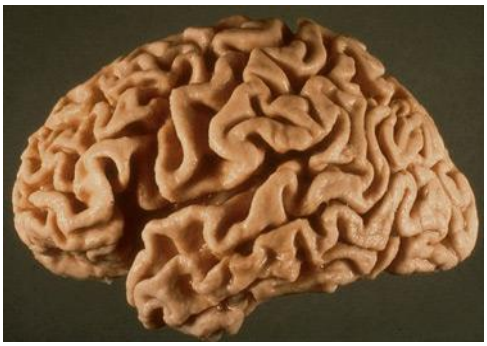
1. Small aggregates of Aβ can alter **neurotransmission**, and the aggregates can be toxic to neurons and synaptic endings. These are intracellular.
2. Larger deposits, in the form of extracellular **plaques**, also lead to neuronal death, elicit a local inflammatory response that can result in further cell injury, and may cause altered region-to-region communication through mechanical effects on axons and dendrites.
3. other:

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, also resulting in neuronal dysfunction and cell death.

Note: Tau is a protein that is found mostly in the CNS, involved in the formation of microtubules, the cellular structures that are concerned mostly with maintaining cell structure.
Tau can be detected by silver stain or by other immunostains.

The anatomic distribution of these changes, which occur roughly in parallel, are responsible for the clinical signs and symptoms; they appear to develop well with the advance of clinical presentation.

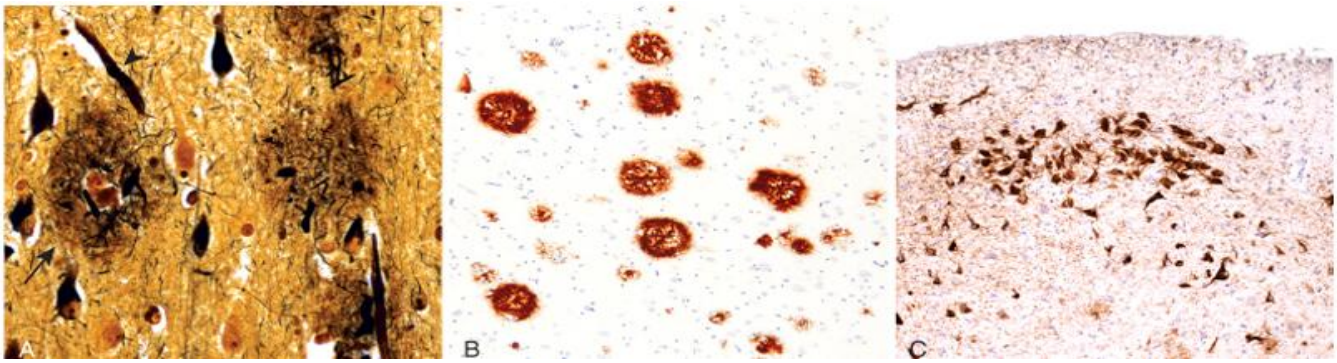
Pathological findings:



1. **Macroscopic:**

- a variable degree of cortical atrophy leading to widening of the cerebral sulci (is most pronounced in the frontal, temporal, and parietal lobes-occipital lobe is spared)

-With significant atrophy, there is compensatory ventricular enlargement (hydrocephalus ex vacuo)




2. **Microscopic:**

•**plaques** (a type of extracellular lesion):

Focal, spherical collections of dilated, tortuous, silver-staining neuritic processes (dystrophic neurites), often around a central amyloid core containing Aβ

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

Will stain congo-red positive as a result of presence of the amyloid core

However, Aβ deposits can also be found that lack any surrounding neuritic reaction, termed *diffuse plaques.* They may indicate an early stage pre-plaque formation.

•**neurofibrillary tangles** (a type of intracellular lesion)

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 forming the protein **tau**

Tangles are not specific to Alzheimer disease, being found in other degenerative diseases (huntingtons) as well so for diagnosis we must assess the clinical features 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

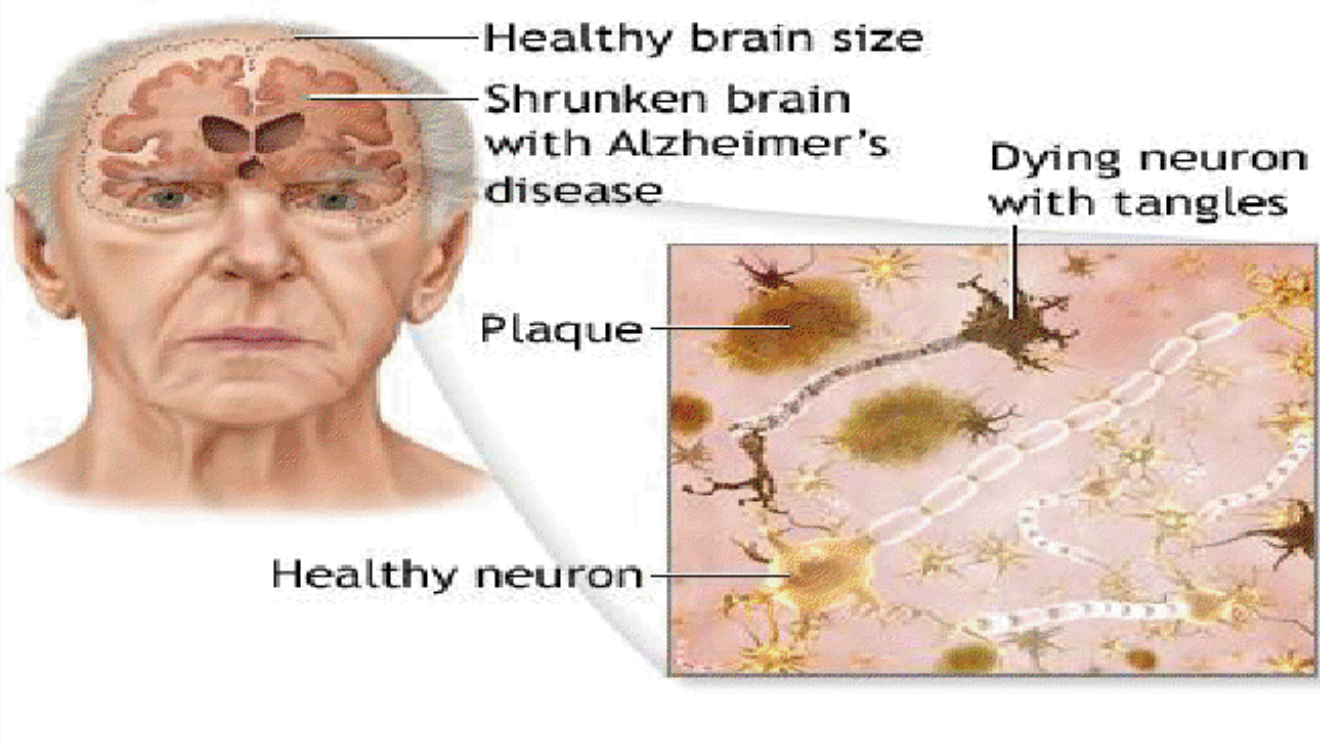
Tests:

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

*What is immunohistochemistry?*
*Microscopic detection of specific antigens in tissues using stains with antibodies labeled with fluorescent or pigmented material (markers).*

There is a fairly constant pattern of progression of involvement of brain regions pathologic changes:

earliest in the **entorhinal cortex** (where the memory process begins) → then spread through the hippocampal formation and isocortex → then extend into the neocortex




## Parkinson's Disease:

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

Clinical manifestations:

- diminished facial expression (masked facies)
- stooped posture
- slowness of voluntary movement
- festinating gait (progressively shortened, accelerated steps)
- rigidity
- "pill-rolling" tremor

Parkinsonism can be induced by:

–*Idiopathic Parkinson disease (the most common neurodegenerative disease associated with parkinsonism)*
–drugs that affect these neurons, particularly dopamine antagonists and toxins
–post-encephalitic parkinsonism (associated with the influenza pandemic)
–other neurodegenreative diseases
–*rare: head trauma, stroke*

• Diagnosis:.

1. progressive parkinsonism
2. absence of a toxic or other known underlying etiology, meaning itt's development is idiopathica
3. clinical response to l-dihydroxyphenylalanine (l-DOPA) treatment

· Parkinsonism is not Parkinson's disease , Parkinsonism is a group of signs and symptoms , but Parkinson's disease is one of Parkinsonism causes

Incidence:

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

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 causes 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, 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:

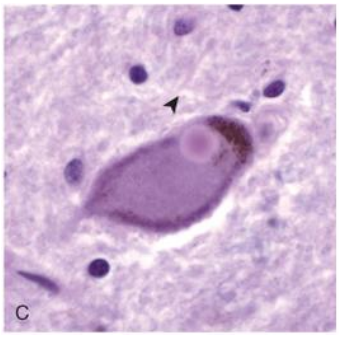
- genes encoding parkin (an E3 ubiquitin ligase)
- UCHL-1 (an enzyme involved in recovery of ubiquitin from proteins targeted to the proteasome)

➔ 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

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 under electron microscope, densely packed in the core but loose at the rim.
-These filaments are composed of α-synuclein, along with other proteins.

Treatment:

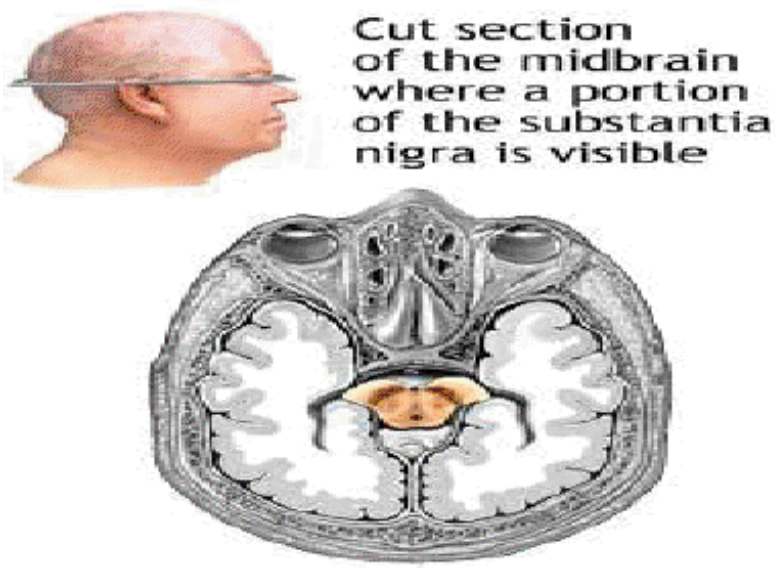
L-DOPA therapy is often extremely effective in symptomatic treatment, but it does not significantly alter the progressive nature of the disease.
Over time, L-DOPA becomes less effective at providing the patient with symptomatic relief and begins to cause fluctuations in motor function on its own.

Research field:

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 for deep brain stimulation

Prognosis:

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
The disease usually progresses over 10 to 15 years with 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.



# Questions:

1. How can a physician diagnose Alzheimer's disease?
    a. Pathological examination of brain tissue
    b. Radiology
    c. Clinical assessment and modern radiology

2. What is the first part of the brain to be affected in case of Alzheimer's disease?
    a. Neocortex
    b. Entorhinal cortex
    c. Optic tract
    d. Hippocampus

3. Of what type is the proteinous core of the inclusions found in Parkinson's disease?
    a. Aβ protein
    b. tau protein
    c. prions
    d. α-synuclein

Answers: 1 C, 2 B, 3 D