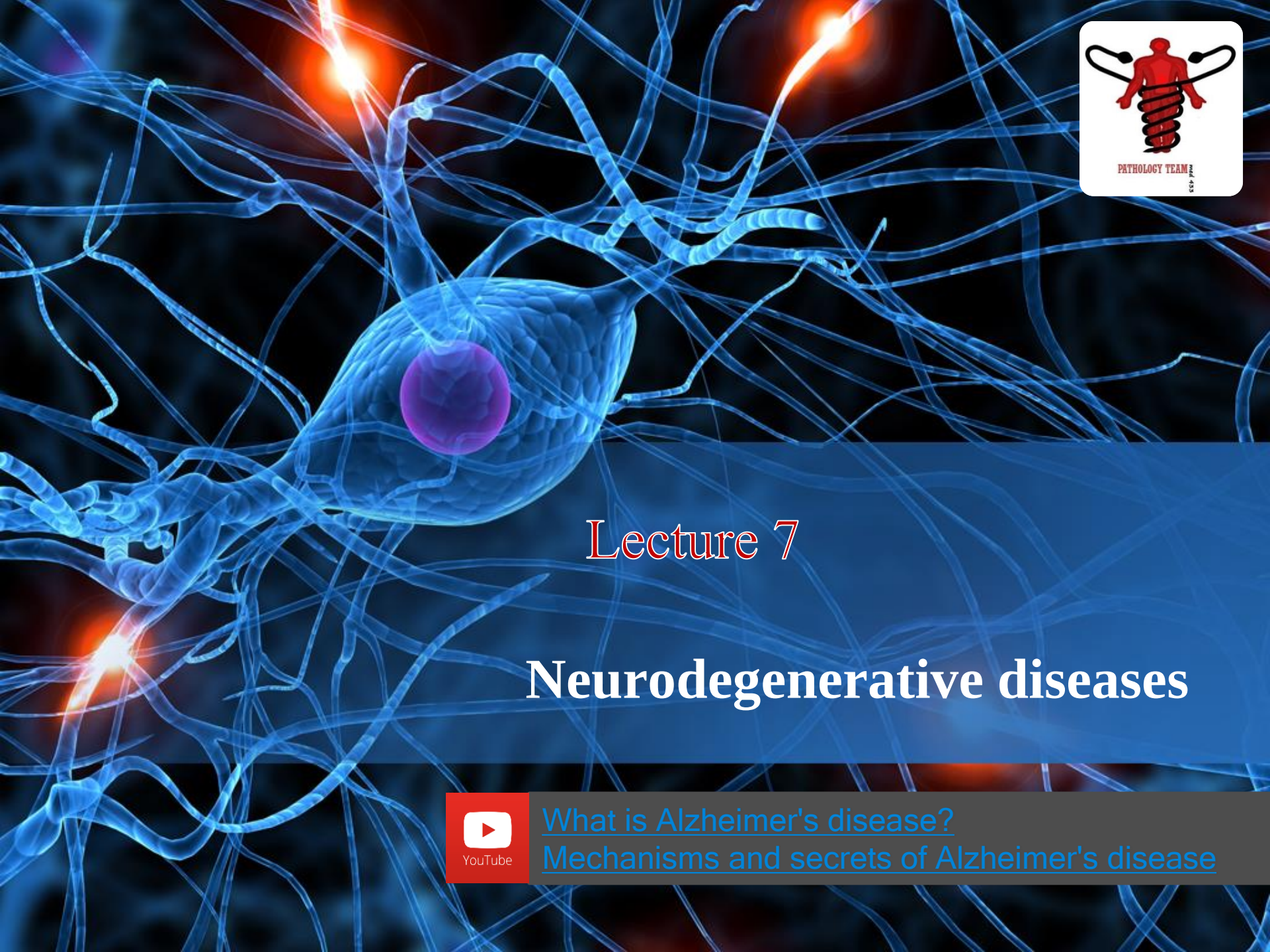


Lecture 7

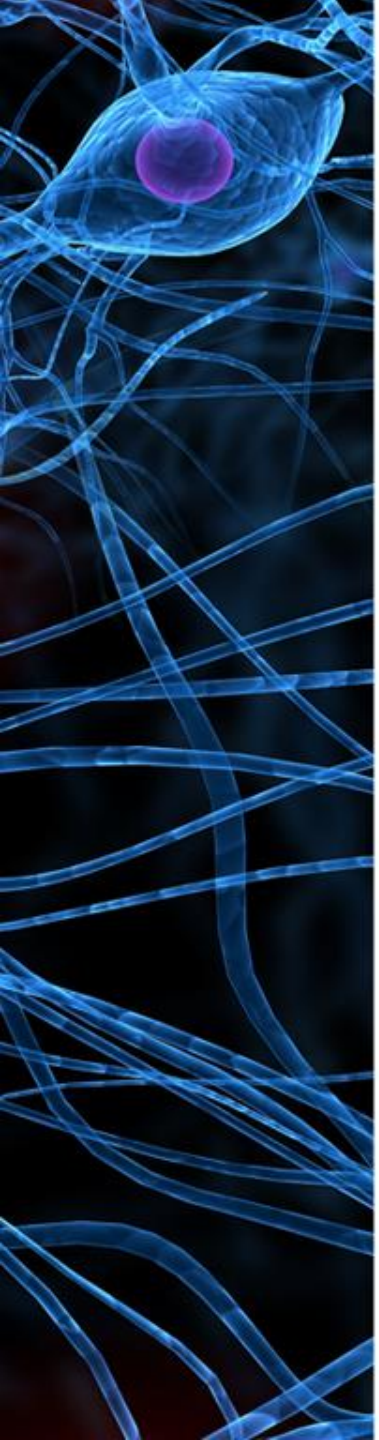
Neurodegenerative diseases

YouTube

What is Alzheimer's disease?
Mechanisms and secrets of Alzheimer's disease

OBJECTIVE

I. Explain the basic pathological concepts of neurodegenerative disease, using Alzheimer's and Parkinson disease as a classical example.
II. Know the definition of "dementia" syndrome.
III. List the possible causes of dementia.
IV. Understand the major clinic-pathological features of Alzheimer's disease.
V. Hypothesize the possible etiologies of Alzheimer's disease.
VI. List the causes of Parkinsonism.
VII. Understand the major clinical and pathological feature of Parkinson disease.
VIII. Hypothesize the possible etiologies of Parkinson disease.



Neurodegenerative diseases:

characterized by progressive loss of structure or function of neurons, including death of neurons.

- Many of these disorders are associated with accumulation of abnormal protein (table)

Disease	Protein	Location
Alzheimer disease	Aβ Tau	Extracellular Neurons
Parkinson disease	α-Synuclein	Neurons

Dementia: is memory loss and other cognitive deficits with normal consciousness.

Note:

- dementia is not part of normal aging and always represents a pathologic process
- **NOT** all forms of dementia are degenerative

Some causes of dementia	
Primary Neurodegenerative disease	Alzheimer disease Lewy body dementia (PARKINSON TYPE) Huntington disease
Infections	Prion-associated disorders (e.g. Creutzfeldt-Jakob disease) 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	Thiamine deficiency (Wernicke-Korsakoff syndrome)
Miscellaneous	1- Brain tumors. 2- Neuronal storage diseases 3- Toxic injury (e.g. mercury)

Alzheimer disease

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

➢ **Symptoms:** Early symptom is short term memory loss (difficulty in remembering recent events). As the disease advances, symptoms can include irritability, mood swings, Aphasia, and long-term memory loss.

➢ **Incidence:**

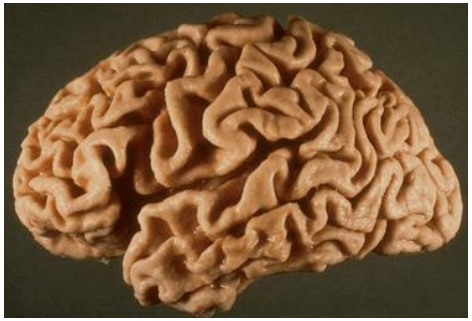
- Increase with aging .
- Most cases are sporadic.
- At least 5% to 10% are familial.
- Sporadic cases rarely present before 50 years of age, but early onset is seen with some familial forms

➢ **Diagnosis:*** based on **clinical manifestations**, and **Radiological methods.**

➢ **Pathogensis of famelial alzheimer :** mentioned in details in biochemistry lecture.

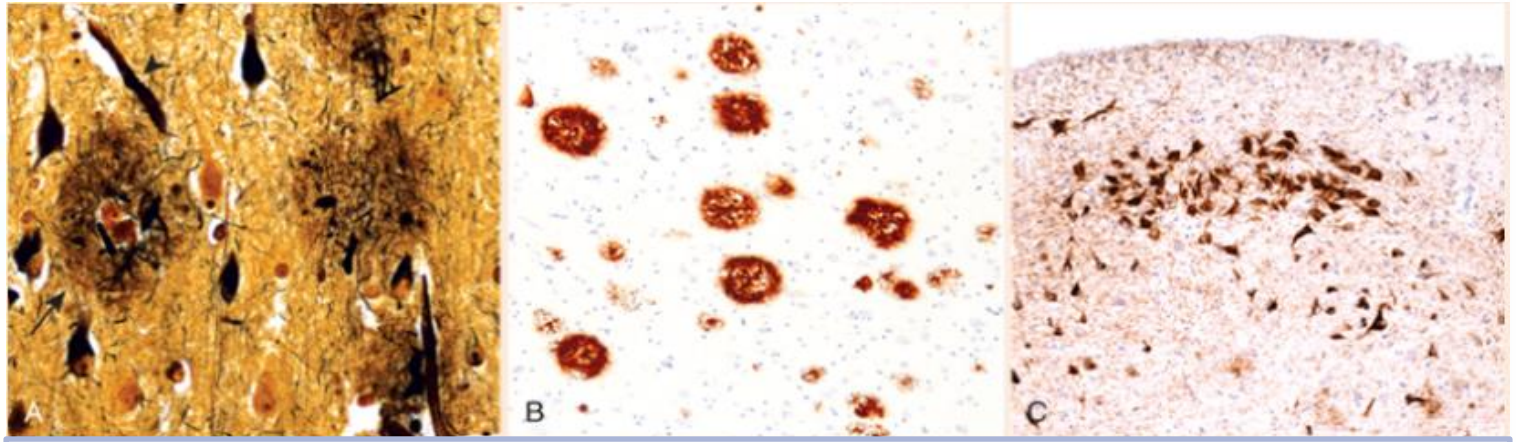
*pathologic examination is definitive diagnosis but the problem is we can take it as an autopsy only.

➢ Morphology



- **Gross:**
- Cortical atrophy
- Widening sulci
- Ventricular enlargement (hydrocephalus ex-vacuo)

- **Microscopic:**



A: Plaques (*arrow*) (extracellular lesion) contain a central core of amyloid and a surrounding region of dystrophic neurites.
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** (intracellular lesion) stained with an antibody specific for tau (it is not specific for the diease).

*plaques and tangles, start in hippocampus, that's why the first symptom is loss of short memory

Parkinsonism

Clinical syndrome characterized by (masked face ,slowness of voluntary movement, festinating gait*,rigidity and "pill-rolling" tremor*).

- Caused by loss of dopaminergic neurons (damage to dopaminergic neurons of the substantia nigra or their projection to the striatum)

- Parkinsonism can be induced by
  I. Drugs (dopamine antagonists).
  II. Post-encephalitic parkinsonism.
  III. Idiopathic parkinson disease (most common).
  IV. Head trauma, stroke (rare).

➢ **Diagnosis parkinson's disease:**

I. Progressive parkinsonism
II. Clinical response to l-dihydroxyphenylalanine (L-DOPA) treatment

- Effect elderly people (6-8 decade)
- Men more than women

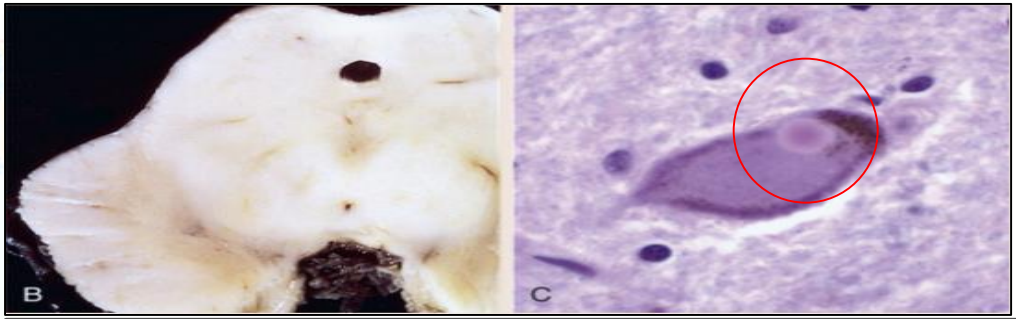
- festinating gait :http://youtu.be/j86omOwx0Hk
- Pill rolling tromer : http://youtu.be/e532YW-Zwf0

➢ Pathogenesis of Parkinson‘s disease (PD):

- Usually is sporadic, but there are both autosomal dominant and recessive forms of the disease.
- α-synuclein mutations cause autosomal dominant Parkinson’s disease as can gene duplications and triplications
- in sporadic PD, the diagnostic feature of the disease—the Lewy body—is an inclusion containing α-synuclein. (The linkage between α-synuclein and disease pathogenesis is unclear)
- Two other genetic loci for Parkinson disease:

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

➢ Morphology



Macroscopic
Pic B: Depigmented (pallor) substantia nigra in idiopathic Parkinson disease.
Microscopic:
- loss of the pigmented, neurons in these regions
- gliosis
- **Pic C:**Lewy bodies in some remaining neurons

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

➢ Clinical Features:

- PD commonly manifests as a movement disorder .
- usually progresses over 10 to 15 years, eventually producing severe motor slowing to the point of near immobility.
- Usually death result from intercurrent infection or trauma from frequent falls

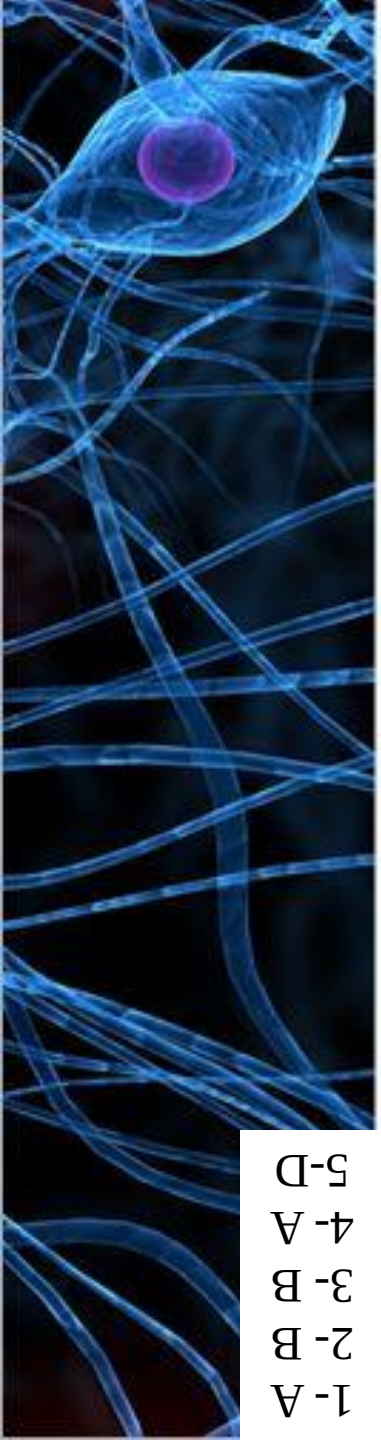
- About 10% to 15% of individuals with Parkinson disease develop dementia,
- When dementia arises within 1 year of the onset of motor symptoms, it is referred to *Lewy body dementia*

Summary from Robbins

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.



MCQs

Q1. Which of the following is not a symptom of Parkinson's disease?

A. Early memory loss
B. Tremors
C. Muscle rigidity
D. An inability to initiate movement

Q2. Most common neurodegenerative disease associated with parkinsonism:

A. ALS
B. Idiopathic Parkinson disease
C. Alzheimer's
D. Huntington's disease

Q3. The causative factor(s) of AD include:

A. Excessive production of pituitary hormone
B. Abnormally folded A-beta and tau protein in brain
C. Decrease in Tryptophan levels
D. None of the above

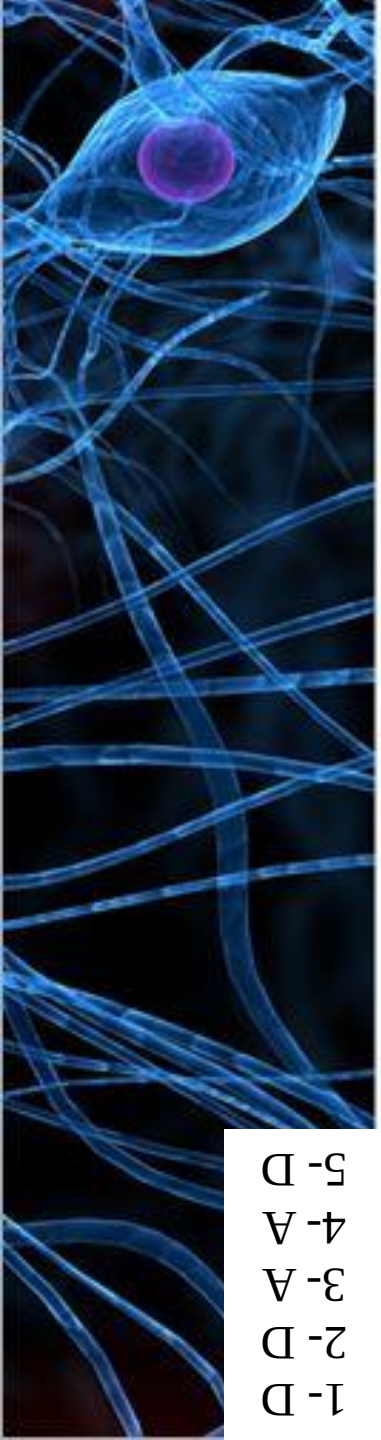
Q4. In Alzheimer's disease, plaques are particularly start in the

A. Hippocampus.
B. Hypothalamus.
C. Brainstem.
D. Thalamus

Q5. Prion disease is a

A. Parasite induced disease
B. Autoimmune
C. Virus induced disease
D. Protein induced disease

1- A
2- B
3- B
4- A
5-D



Q1. Prion disease is a

A. Sporadic
B. Transmitted
C. Inherited
D. All of the above

Q2. A-beta is created when APP is cleaved by

A. The enzyme beta-amyloid
B. The enzyme gamma-secretase
C. The enzyme alpha-secretase
D. A and b

Q3. A-beta is bad because

A. It is insoluble
B. It is soluble
C. Initiate an autoimmune reaction
D. Non of the above

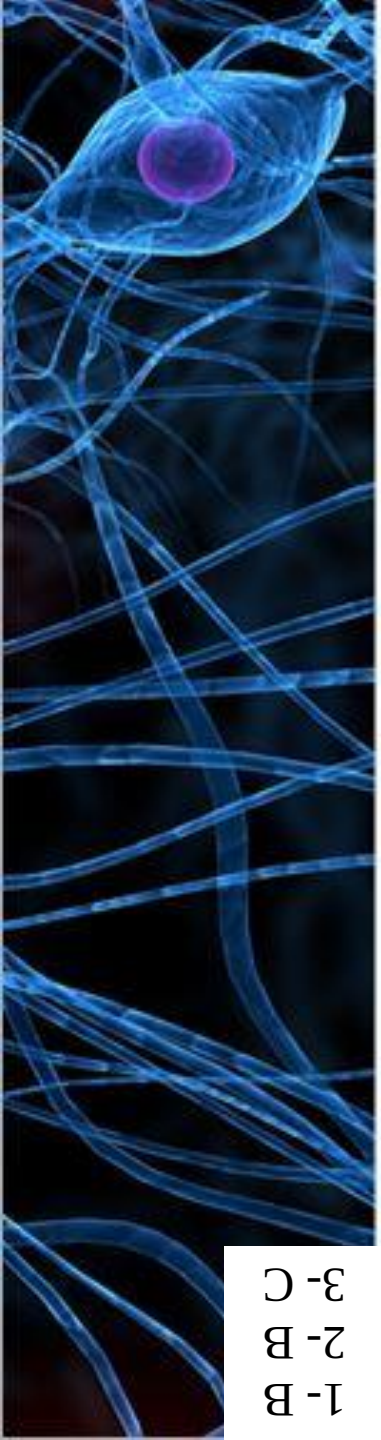
Q4. The onset of AD in down syndrome is

A. Early
B. Late
C. They are not prone to develop AD

Q5. Parkinson's disease is

A. Sporadic
B. Inherited
C. Transmitted
D. A and b

1- D
2- D
3- A
4- A
5- D



Q1. The term "Degenerative" reflects an underlying cellular degeneration of:
A. Neuroglial cells.
B. Neurons.

Q2. All forms of dementia are degenerative.
A. True
B. False

Q3. Which of the following situations describes a major risk factor for early-onset familiar Alzheimar disease?
A. Expansion 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

1- B
2- B
3- C

Done by

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