PATHOLOGY

SHEET NO. 6

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Neurodegenerative diseases affecting the basal nuclei

-The basal ganglia (site 4) have several functions, one of which is controlling and regulating movement, so disorders that involve the basal ganglia will cause movement disorders like hypokinesia in (Parkinson Disease), and hyperkinesia in (Huntington Disease).

Parkinson Disease

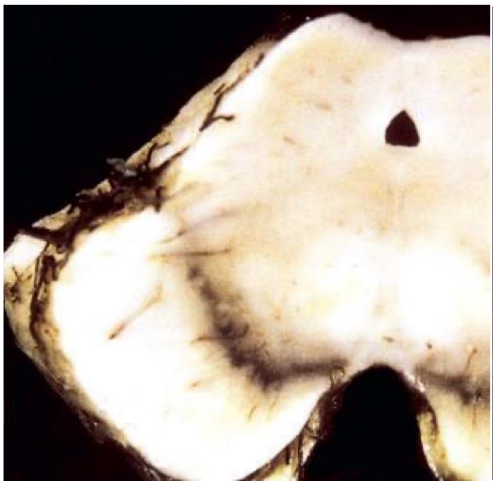
- Parkinson disease (PD) is a neurodegenerative disease marked by a hypokinetic movement disorder that is caused by loss of dopaminergic neurons from the substantia nigra.
- As we discussed before, all neuro degenerative diseases are characterized by accumulation of proteins inside the CNS (but they differ in the type of protein and site of deposition), this accumulation become toxic to the neurons which leads to their death.
- It's the second most common neurodegenerative disorder after Alzheimer's disease.

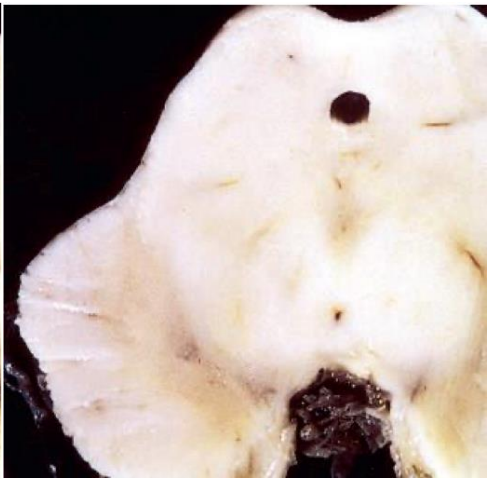
-Parkinsonism is a clinical syndrome: tremor, rigidity, bradykinesia, and instability.

- Parkinsonism: any damage of dopaminergic neurons, which project from the substantia nigra to the striatum (control of motor activity).
- As we know that substantia nigra gives pigmented color (brown) to its site, so the loss of neurons in this area leads to the loss of its pigmentation.
- Parkinsonism: induced by drugs such as dopamine antagonists or toxins that selectively injure dopaminergic neurons (so we should exclude these secondary causes of parkinsonism before diagnosis with Parkinson disease). (Just like Alzheimer's disease)

Pathogenesis

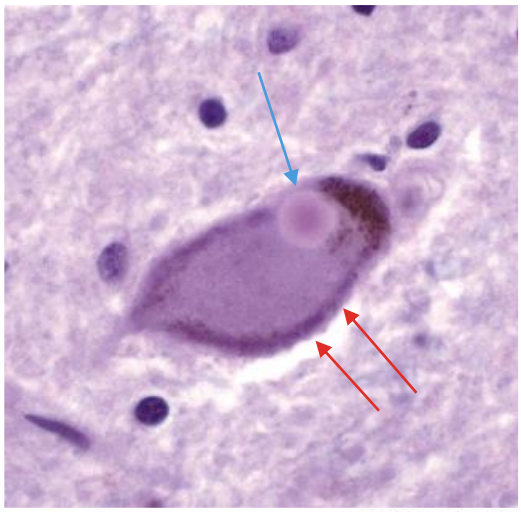
- Protein accumulation and aggregation, mitochondrial abnormalities and neuronal loss in the substantia nigra and elsewhere in the brain.
- Abnormal protein and organelle clearance due to defects in autophagy and lysosomal degradation.
- Clue and diagnostic feature: Lewy body (neuronal inclusions inside the cytoplasm containing *α-synuclein*, a protein involved in synaptic transmission).
- Most cases sporadic(Just like Alzheimer's disease), some are autosomal dominant (mutation of *α-synuclein gene).*





-Normal substantia nigra

-depigmented substantia nigra in idiopathic Parkinson disease (due to loss of dopaminergic neurons at this site)



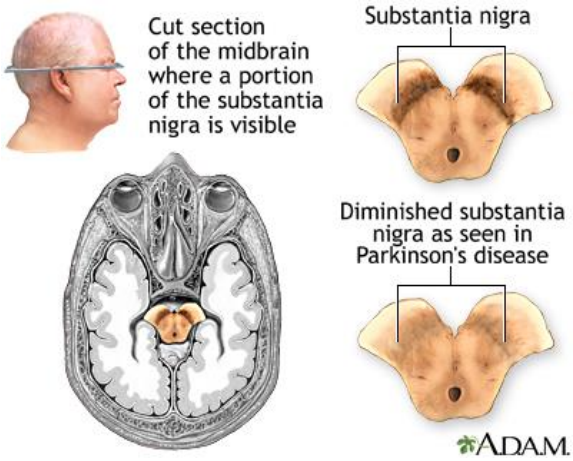
-Reminder, we don't use the histopathology for diagnosis only for studies.

-For Diagnosis we use the clinical presentation after ruling out other diseases.

-Red arrows: Nissl substance.

-Blue arrow: Lewy body.

-Lewy bodies in a neuron from the substantia nigra stain pink and they are amorphous homogeneous rounded to oval inclusions in the cytoplasm of neurons.



Morphology

- Pallor of the substantia nigra and locus ceruleus. (due to loss of pigmentation)
- Loss of the pigmented neurons in these regions.
- Gliosis. (reaction of innate immune system of the body)
- Lewy bodies in neurons (single or multiple, cytoplasmic, eosinophilic, round to elongated inclusions)
- Lewy neurites: dystrophic neurites that also contain aggregated α-synuclein
- Immunohistochemical staining for α-synuclein (for subtle lewy bodies). (appear in brown color under the microscope)
- It's a disease of substantia nigra but with progression changes can appear in: medulla, pons, amygdala, and the cerebral cortex (+Lewy body dementia LBD).
- Lewy body dementia LBD: With involvement of the cerebral cortex, there is typically dementia (loss of cognitive features, memory disturbances, behavioral changes) in addition to the movement disorder.
- IMPORTANT: Parkinson itself does not affect the cognitive features without progression to the cerebral cortex.

Clinical Features

Like all neurodegenerative its gradual not sudden

- Progresses over 10 to 15 years (slow downhill)
- Eventually producing severe motor slowing or near immobility.
- Death due to aspiration pneumonia or trauma from falls caused by postural instability (gait disorder).

Treatment

- Initially respond to L-dihydroxyphenylalanine (L-DOPA), but this treatment does not slow disease progression or reverse morphologic findings .(doesn't affect protein aggregation or neuron loss).
- Over time, L-DOPA becomes less effective (causes dependence). ***(10:00)***
- Another Tx: deep brain stimulation

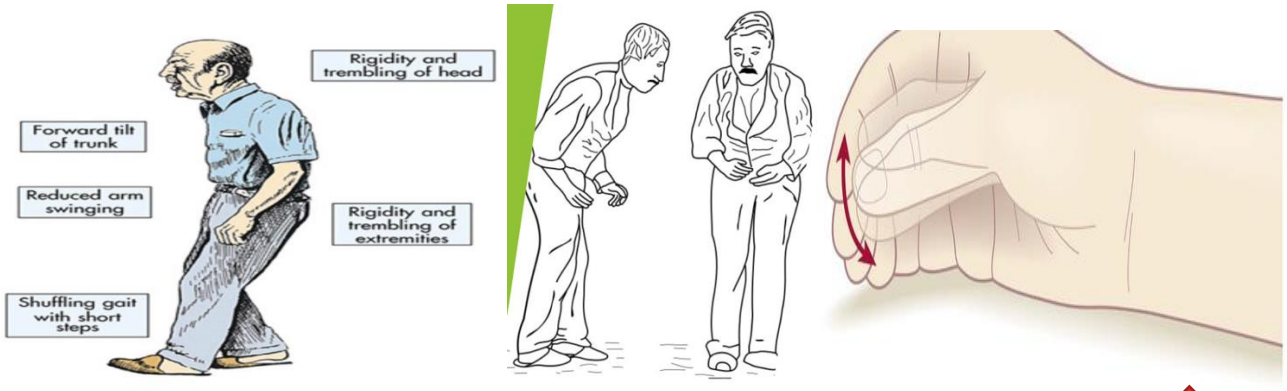
SYMPTOMS

Everything is slowed down.

- **Tremor:** involuntary shaking, usually at rest and disappears with movement, begins in a limb, often in the hands or fingers. Patients might rub their thumb and forefinger back-and-forth (pill-rolling tremor.)

Elaboration from the doctor: The kind of tremor in Parkinson's is a coarse tremor or pill-rolling tremor (they are two different tremors). We have two types of tremors coarse and fine. Fine tremors we can't see it unless the patient stretches their hand, and it is mild like in hyperthyroidism, stress and sometimes familial. Coarse tremors on the other hand are very apparent.

- **Slowed movement (bradykinesia) :** steps may become shorter, difficult to get out of a chair. Patients drag their feet as they try to walk.(Shuffling , festinating gate). (like a robot)
- **Rigid muscles:** The stiff muscles can be painful and limit the range of motion.
- **Impaired posture and balance:** stooped posture (leaning forward), and balance problems.
- **Loss of automatic movements.:** decreased ability to perform unconscious movements, including blinking, smiling (masked face) or swinging arms during walking.
- **Speech changes:** Patients might speak softly, quickly, slur or hesitate before talking.
- **Writing changes:** It may become hard to write.(due to rigidity and slowed movement).
- **Diminished facial expressions** (Masked facies).
- **Stooped posture.**
- **Slow voluntary movement.**
- **Rigidity.**
- **Pill rolling tremor.**
- **Festinating gait= progressively shortened accelerated steps.**



Pill rolling tremor

We can consider Parkinson's as a triad:

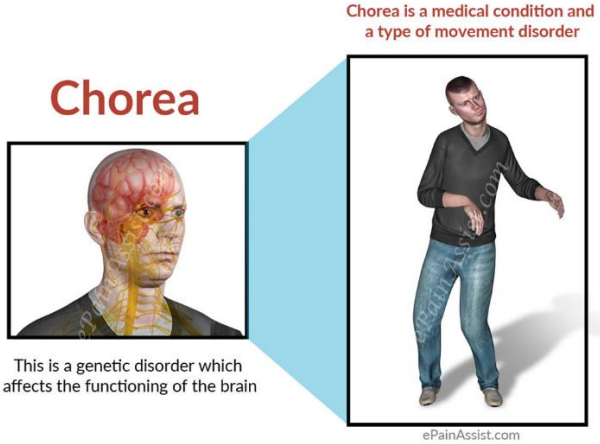
We have main features:

And other motor features:

Huntington Disease

It is the opposite of Parkinson's it is characterized by hypermotility or mobility. Choreiform dancing movements of the whole body (from the head to the limbs and trunk) called chorea

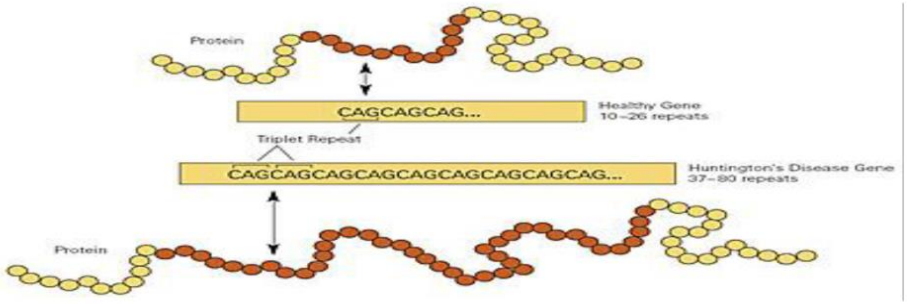
- Autosomal dominant (so it's a familial disease not sporadic like Parkinson) movement disorder.
- Associated with degeneration of the striatum (caudate and putamen) as a result of protein accumulation.
  Note: Caudate and Putamen are also part of the basal ganglia.
- Involuntary jerky movements of all parts of the body; writhing movements of the extremities.
- Progressive, death after an average 15 years
- Early cognitive symptoms (forgetfulness and thought and affective disorders, severe dementia).



Pathogenesis

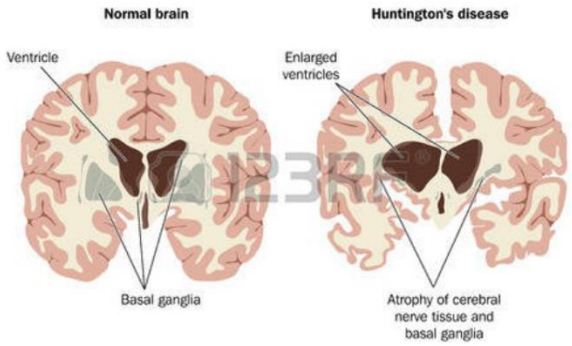
- CAG trinucleotides repeat expansions in huntingtin protein gene located on 4p16.3 (Polyglutamine)
- Normal alleles contain 11 to 34 copies of the repeat.
- Disease-causing alleles, number of repeats is increased (may be hundreds)
- Larger numbers of repeats result in earlier-onset disease.
- Mutant protein is subject to proteolysis >>> fragments can form large intranuclear aggregates (not in the cytoplasm)>>> toxic>>>loss of neurons
- Age of onset:40-50 years; related to the length of CAG repeats (more repeats; earlier age of onset)

  Explanation: CAG are repeats of nucleotides on Chromosome 4, as we know every 3 nucleotides encodes for an amino acid, CAG encodes for glutamine, and the resultant protein is called Polyglutamine, its present normally and the CAG repeats vary in number from 11 to 34 copies. When the number of copies become 35 or more the disease happens, some people have forties some have fifties some have hundreds, the more the number of repeats the longer the protein the earlier the age of the onset of disease.



Morphology

- Brain is small (atrophic brain) ***(20:00)***
- Striking atrophy of the caudate nucleus and the putamen
- Atrophy of globus pallidus
- Dilated lateral and third ventricles secondarily (like Alzheimer's but at small age)
- Severe loss of neurons from affected regions of the striatum + gliosis
- Spiny neurons that release γ-aminobutyric acid (GABA), enkephalin, dynorphin, and substance P are especially sensitive, disappearing early.
- Intranuclear inclusions (aggregates of ubiquitinated huntingtin protein)



Some questions from the doctor:

1) Several members of a large family are affected by the onset of decreasing mental function and motor coordination when they reach middle age. Their extremity movements are marked by choreoathetosis. Genetic testing reveals increased trinucleotide CAG repeats. Which of the following intracranial structures is most likely to appear grossly abnormal with radiologic imaging of these affected persons?

A. Caudate nucleus
B. Midbrain
C. Temporal lobe
D. Locus ceruleus
E. Spinal cord

2) A 66-year-old man is finding that he has more difficulty getting up and moving about for the past year. He is annoyed by a tremor in his hands, but the tremor goes away when he performs routine tasks using his hands. His friends remark that he seems more sullen and doesn't smile at them, but only stares with a fixed expression on his face. He has not suffered any loss of mental ability. Which of the following conditions is he most likely to have?

A. Amyotrophic lateral sclerosis (ALS)
B. Huntington disease
C. Parkinson disease
D. Niemann-Pick disease
E. Tuberous sclerosis

1)A 2)C