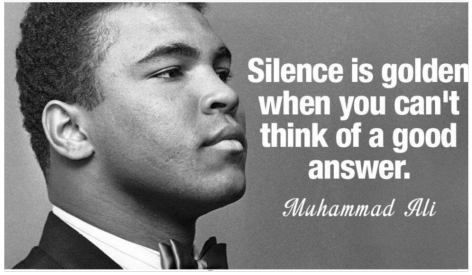
Patho lec 2 summary

Frontotemporal Lobar Degeneration

- Several disorders. (Not a single disease, different diseases with different protein accumulations)
- Preferentially affect the frontal and/or temporal lobes.
- Progressive deterioration of language and changes in personality.
- Clinically, frontotemporal dementias
- **Behavioral and language problems precede memory disturbances, in contrast to AD.**
- The onset of symptoms occurs at younger ages than for AD.
- Neuronal inclusions, which may contain **tau or TDP43. (two forms of disease)**
- *Pick disease (subtype of* FTLD-tau*),* associated with smooth, round inclusions known as *Pick bodies.*

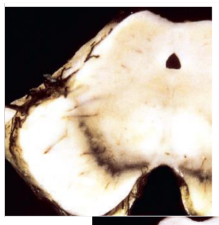
MORPHOLOGY

- Atrophy of frontal and temporal lobes.
- Neuronal loss and gliosis
- In FTLD-tau, the characteristic neurofibrillary tangles, similar to AD .
- Pick bodies.

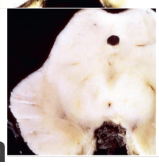


Parkinson Disease (PD)

- A hypokinetic movement disorder that is caused by loss of dopaminergic neurons from the substantia nigra.
- 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).
- Parkinsonism: induced by drugs such as dopamine antagonists or toxins that selectively injure dopaminergic neurons



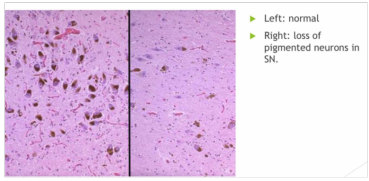
Normal substantia nigra

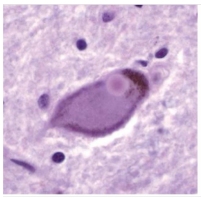


Depigmented substantia nigra in idiopathic Parkinson disease

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 containing *α-synuclein*, a protein involved in synaptic transmission)
- Most cases sporadic, some are autosomal dominant (mutation of *α-synuclein gene)*

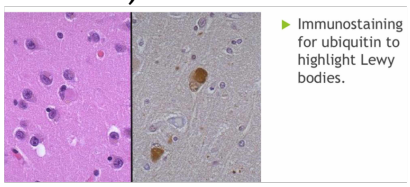




Lewy body in a neuron from the substantia nigra stains pink.

MORPHOLOGY

- Pallor of the substantia nigra and locus ceruleus
- Loss of the pigmented neurons in these regions.
- Gliosis.
- Lewy bodies in neurons (single or multiple, cytoplasmic, eosinophilic, round to elongated inclusions)



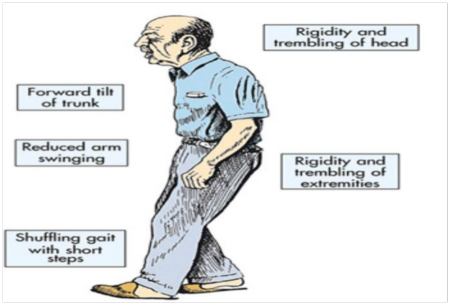
- Lewy neurites: dystrophic neurites that also contain aggregated α-synuclein
- Immunohistochemical staining for α-synuclein (for subtle lewy bodies).
- With progression changes can appear in: medulla, pons, amygdala, and the cerebral cortex (+Lewy body dementia LBD)

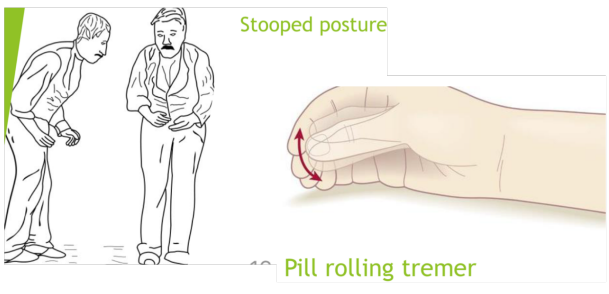
Clinical Features

- Progresses over 10 to 15 years
- Eventually producing severe motor slowing or near immobility.
- Death due to aspiration pneumonia or trauma from falls caused by postural instability.
- Initially respond to L-dihydroxyphenylalanine (L-DOPA), but this treatment does not slow disease progression or reverse morphologic findings
- Over time, L-DOPA becomes less effective
- Another Tx: deep brain stimulation

SYMPTOMS

- **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.)
- **Slowed movement (bradykinesia) :** steps may become shorter, difficult to get out of a chair. Patients drag their feet as they try to walk.(Shuffling عم بشحط حاله شحط , festinating gate)
- **Rigid muscles (rigidity):** The stiff muscles can be painful and limit the range of motion.
- **Impaired posture and balance.** stooped posture (leaning forward)مشان يحاول يثبت نفسه, and balance problems





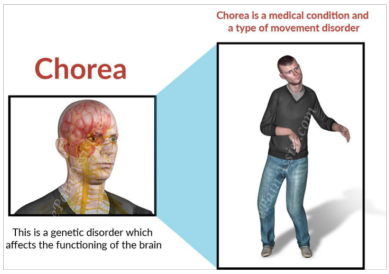
- **Loss of automatic movements.:** decreased ability to perform unconscious movements, including blinking, smiling or swinging arms during walking
- **Speech changes.** Patients might speak softly, quickly, slur or hesitate before talking.
- **Writing changes.** It may become hard to write
- Diminished facial expressions (Masked facies)
- Slow voluntary movement (to get out of the chair..everything is slowed down).

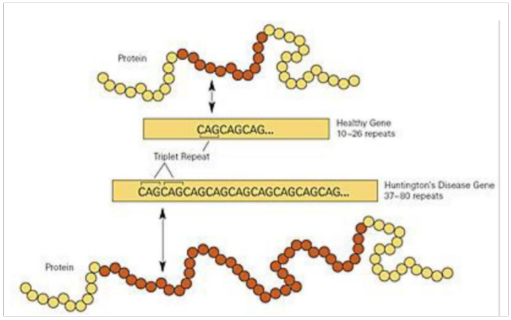
Huntington Disease

- Autosomal dominant movement disorder associated with degeneration of the striatum (caudate and putamen)
- 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 trinucleotide 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 results in earlier-onset disease.
- Mutant protein is subject to proteolysis >>> fragments can form large intranuclear aggregates >>> toxic
- Age of onset:40-50 years; related to the length of CAG repeats (more repeats; earlier age of onset)



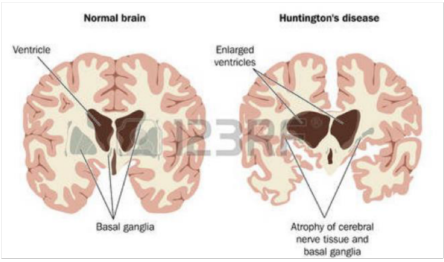


Morphology:

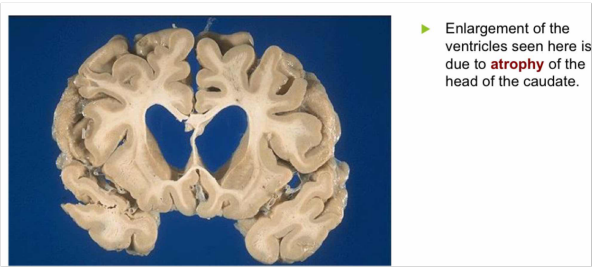
- Brain is small
- Striking atrophy of the caudate nucleus and the putamen
- Atrophy of globus pallidus
- Dilated lateral and third ventricles
- Severe loss of neurons from affected regions of the striatum + gliosis
- Spiny neurons that release γ-aminobutyric acid (GABA), enkephalin, dynorphin, and substance P are especially sensitive, disappearing early.
- Intranuclear inclusions (aggregates of ubiquitinated huntingtin protein)

Test yourself!

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



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