Degenerative diseases of brain stem and cerebellum and parkinsonism

Basal Ganglia

- resting tremor
- postural instability
- festination
- rigidity
- masked facies
- bradykinesia
- dyskinesia
- torticollis
- chorea
- athetosis
- hemiballismus
- akathisia

Cerebellum

- intention tremor
- dysmetria
- dysdiadochokinesia
- hypotonia
- heal to shin
- finger to nose
- rebound
- ataxic gait
- titubation
- nystagmus
- dysmetric saccades

*Basal ganglia lesions produce contralateral signs.*

*Cerebellar lesions produce ipsilateral signs.*

- Most movement disorders produced by cerebellar and basal ganglia pathology disappear during sleep.

Cerebellar and basal ganglia signs are usually not present if the corticospinal tract is damaged.

The cerebellum is the great comparator:

1. It compares cortical willful command with muscle tension, joint position, & tone (via ipsilateral spinocerebellar tracts)
2. Advises the cortex on how much, how many, how fast
3. The motor cortex sends the revised command down the corticospinal tract

- The BASAL GANGLIA are the autopilot for procedural movements. The CEREBELLUM is the refiner of finely controlled movements (particularly of fingers).

**Degenerative brain disease**
- The term “Degenerative“:
- reflecting an underlying cellular degeneration of neurons in the brain
- Cause symptoms that depend on the pattern of involvement of the brain

**Parkinsonism**
- A clinical syndrome characterized by:
- diminished facial expression (masked facies)
- stooped posture
- slowness of voluntary movement
- festinating gait (progressively shortened, accelerated steps)
- rigidity
- "pill-rolling" tremor

**Parkinsonism**
- 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 and toxins
- post-encephalitic parkinsonism (associated with the influenza pandemic)
- **Idiopathic Parkinson disease** *(the most common neurodegenerative disease associated with parkinsonism)*
- other neurodegenerative diseases
- rare: head trauma, stroke

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

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


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

- 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
Clinical Features

- 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.
- Usually progresses over 10 to 15 years.
- Eventually 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.
- 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.

Dementia with Lewy Bodies

- About 10% to 15% of individuals with PD develop dementia.
- Characteristic features are fluctuating course, hallucinations, and prominent frontal signs.
- Some affected individuals have pathologic evidence of AD in combination with the findings of PD.
- In others, the most prominent histologic correlate appears to be the presence of Lewy bodies.
- These inclusions are less distinct than those observed in the brainstem but similarly contain predominantly α-synuclein.
- Immunohistochemical staining for α-synuclein also reveals the presence of abnormal neurites, which contain aggregated protein—called Lewy neurites.

Multiple System Atrophy

- Characterized by the presence of glial cytoplasmic inclusions, typically within the cytoplasm of oligodendrocyte.
• The dominant symptoms can be parkinsonism (MSA-P, historically known as striatonigral degeneration), or cerebellar dysfunction (MSA-C, previously known as olivopontocerebellar atrophy), or autonomic dysfunction (MSA-A, once known as Shy-Drager syndrome).

  **Morphology**
  • In cerebellar forms there is typically atrophy of the cerebellum, including the cerebellar peduncles, pons and medulla while in parkinsonian forms the atrophy involves both the substantia nigra and striatum (especially putamen).
  • Since autonomic symptoms are related to cell loss from the catecholaminergic nuclei of the medulla and the intermediolateral cell column of the spinal cord, there are usually no specific gross findings.
  • Atrophic brain regions show evidence of neuronal loss as well as variable numbers of neuronal cytoplasmic and nuclear inclusions.

  **Pathogenesis**
  • α-synuclein is the major component of the inclusions.
  • no mutations in the gene encoding this protein have been found in patients with MSA.
  • α-synuclein–containing inclusions are found in glial cells, notably oligodendrocytes.
  • The relationship between glial cytoplasmic inclusions and disease is supported by the observation that the inclusions are present in low numbers at earliest stages of MSA and increase in abundance as the disease progresses, although they eventually disappear as cells die in the final stages.

**Huntington Disease**
• Autosomal dominant disease characterized clinically by progressive movement disorders and dementia, and histologically by degeneration of striatal neurons.
• Jerky, hyperkinetic, sometimes dystonic movements involving all parts of the body (chorea)

  **Huntington disease**
  • inherited autosomal dominant disease
  • mutation in gene located in 4p (huntingtin)
  • degeneration of striatum (caudate nucleus and putamen)

  **Morphology**
  • striking atrophy of caudate nucleus, lateral and third ventricles dilatation
  • severe loss of neurons in striatum, gliosis

  **Clinical presentation**
  • onset in the fourth and fifth decade
  • movement disorders: chorea (involuntary jerky movements)
  • cognitive dysfunction progressing to dementia
relentless progressive course of about 15 years, death from intercurrent infection
Morphology.

Macroskopically,
Brain is small and shows striking atrophy of the caudate nucleus
On microscopic examination
Loss of striatal neurons; the most marked changes are found in the caudate
nucleus
Pathologic changes develop in a medial-to-lateral direction in the caudate and
from dorsal to ventral in the putamen.
Both the large and small neurons are affected, but loss of the small neurons
generally occurs first.
Two populations of neurons are relatively spared, the diaphorasepositive neurons
that contain nitric oxide synthase and the large cholinesterase-positive neurons
Fibrillary gliosis
Direct relationship between the degree of degeneration in the striatum and the
severity of clinical symptoms.
Protein aggregates containing huntingtin can be found in neurons in the striatum
and cerebral cortex (Fig. 28-41, inset).

Spinocerebellar Ataxias
Involves cerebellum (progressive ataxia), brainstem, spinal cord, and peripheral nerves.
Pathologically they are characterized by neuronal loss from the affected areas and
secondary
degeneration of white-matter tracts.

Friedreich Ataxia
first decade of life
presents with
- gait ataxia, hand clumsiness and dysarthria
- Deep tendon reflexes are depressed or absent, but an extensor plantar reflex is typically present. Joint position and vibratory sense are impaired.

Morphology.
- Loss of axons and gliosis in the posterior columns, the distal portions of corticospinal tracts, and the spinocerebellar tracts.
- Degeneration of neurons in the spinal cord (Clarke column), the brainstem (cranial nerve nuclei VIII, X, and XII), the cerebellum (dentate nucleus and the Purkinje cells of the superior vermis), and the Betz cells of the motor cortex.

Ataxia-Telangiectasia
- Autosomal recessive
- Early childhood
- Telangiectasias in the conjunctiva and skin; and immunodeficiency
- Cells show increased sensitivity to x-ray-induced chromosome abnormalities
- Cells continue to replicate damaged DNA rather than stopping to allow repair or undergoing apoptosis.

Morphology
- The abnormalities are predominantly in the cerebellum, with loss of Purkinje and granule cells; there is also degeneration of the dorsal columns, spinocerebellar tracts, and anterior horn cells, and a peripheral neuropathy.

Thank You