Parkinson Disease and Parkinson-Plus Syndromes

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James Parkinson
„An Essay on the Shaking Palsy” (1817)

„It is now recognized, that there are many causes of ‘shaking palsy’ or parkinsonism, with frequent clinical misclassification: even if strict clinical diagnostic diagnostic criteria are used an accuracy of diagnosis of around 80% is to be expected”

Greenfield‘Neuropathology, 7th Ed, 2002
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Parkinson Disease pathology

Substantia nigra

Diminished substantia nigra as seen in Parkinson's disease
Parkinson Disease pathology

- The major neuropathologic findings is a loss of pigmented dopaminergic neurons in the substantia nigra.

- The loss of dopaminergic neurons starts in the ventral lateral substantia nigra.
- Approximately 60-80% of dopaminergic neurons have already been lost before clinical symptoms appear.
Parkinson Disease pathology

- The major neuropathologic findings is a loss of pigmented dopaminergic neurons in the substantia nigra
- and the presence of Lewy bodies.
Lewy bodies

- Lewy bodies within pigmented neurons of the substantia nigra is characteristic for Parkinson Disease
- Lewy bodies also are found in the cortex (Lewy body dementia), nucleus basalis, locus ceruleus, intermediolateral column of the spinal cord, and other areas.
- Post mortem incidental Lewy bodies are found without clinical signs of parkinsonism.
- Incidental Lewy bodies have been hypothesized to represent the presymptomatic phase of PD.
Parkinson Disease pathology

1. The major neuropathologic findings is a loss of pigmented dopaminergic neurons in the (ventrolateral) substantia nigra
2. the presence of alpha-synuclein containing Lewy bodies in the pigmented neurons
3. Globus pallidus, putamen, n. caudatus is unaffected
Parkinson Disease clinical symptoms

- The incidence and prevalence of PD increase with age.
- The average age of onset is approximately 60 years.
- Onset in persons younger than 40 years is relatively uncommon.
- PD is about 1.5 times more common in men than in women.
Parkinson Disease

- PD is one of the most common neurological disorders
- affects approximately 1-2% of population older than 60 years.
- Cardinal features are asymmetrical
  - resting tremor,
  - rigidity,
  - bradykinesia,
  - (and postural instability – not as early sign)
Parkinson Disease epidemiology

- **prevalence**
  100-200/100,000

- **incidence**
  10-20/100,000

- **Sporadic (no increase of incidence among identical twins)**
  environment? Pesticides?

- **Very rare inherited familiar forms monogenic forms**
Parkinson Disease clinical symptoms

- most common initial symptom is resting tremor in an upper extremity.
- Onset of PD is *asymmetric*
- Over time: progressive bradykinesia, rigidity, and gait difficulty
The initial symptoms of PD may be nonspecific and include fatigue and depression.

Some patients complain of aching or tightness in the shoulder region or calf.

The first affected arm may not swing fully when walking (synkinesis is decreased).

Over time, axial posture becomes progressively flexed.

Decreased swallowing may lead to excess saliva and ultimately drool.

Symptoms of autonomic dysfunction are common in the later stage of PD and include constipation, sweating abnormalities, sexual dysfunction, and seborrheic dermatitis.

Sleep disturbances are common.
Parkinson Disease clinical symptoms

- The resting tremor usually begins in one upper extremity and initially may be intermittent.
- The amplitude increases with stress and resolves during sleep.
- During the course of illness the tremor may appear on the other side too, but asymmetry is still present.
The 3 cardinal signs of PD

- **resting tremor** (usual frequency is 3-5 Hz)
- **Rigidity** (increase in resistance to passive movement about a joint)
  - The resistance can be either smooth (lead pipe)
  - or cogwheeling.
- Rigidity can be made more obvious with voluntary movement in the contra lateral limb
- **bradykinesia**
- Of these cardinal features,
  - 2 of 3 are required to make the clinical diagnosis.
  - (Postural instability is the fourth cardinal sign, but it emerges late in the disease, usually after 8 years or more)
The best clinical predictors of PD

- Asymmetry
- Presence of resting tremor
- Good response to dopamine replacement therapy
**Synucleinopathies**
(α-synuclein)

- Parkinson Disease
- Inherited PD (PARK 1-4)
- Cortical Lewy body disease
- "incidental Lewy-body disease"
- Multiple system atrophy (Papp-Lantos disease)

**Taupathies**
(abnormal phosphorylated tau protein)

- Progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome)
- Corticobasal degeneration
- "variants of frontotemporal demencia parkinsonism linked to chromosome 17"—tau gene)
Multiple system atrophy

- Prevalence: 4.4/100,000 (UK)
- Duration of illness: 1-18 years (average: 6.2 years)
- (PD prevalence: 100-200/100,000)
Multiple system atrophy

- Papp-Lantos inclusions in oligodendrocytes

- It has been Discovered in Budapest by Gallyas silver impregation (M. I. Papp, 1986)
Multiple system atrophy:
Papp-Lantos body
(oligodendrocytes)

- Papp M.I., Komoly S (Clin Neuropath 1988, 7:195) "Filamentous glial cytoplasmic inclusion in the CNS of patients with various combinations of"
- striatonigral degeneration (snd)
- olivopontocerebellar atrophy (opca),
- and Shy-Drager syndrome (sds)

"primer autonome failure" severe orthostatic hypotension-
Multiple system atrophy (MSA)

- **MSA-C**: oliva inferior olive, pontin nuclei, cerebellar hemisphere, vermi
- **MSA-P**: putamen, caudate nucleus, globus pallidus
- early-at beginning:
  - autonome symptoms,
  - postural instability
Multiple system atrophy: clinical symptoms

- 89% parkinsonism (akinetic-rigid symptoms, axial instability with frequent falls)
- Poor response to dopamine replacement therapy
- 78% autonome dysfunctions
  orthostatic hypotension, incontinence, impotence
- 61% pyramidal signs (Babinski)
- 55% cerebellar symptoms
  nystagmus, trunk-, limb-ataxia, intention-tremor, ataxic speech
**Synucleinopathies**  
(alpha-synuclein)

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Progressive supranuclear palsy (PSP) - tauopathy

- Described by Steele, Richardson, Olszewski 1964
- Prevalence: 1/100 000 (UK)
- Male : female = 2:1
- Progressive course, average duration: 5.3 years
- Onset: over 40 years, (typically in 6-7 decades)
Progressive supranuclear palsy (PSP) - major clinical symptoms

- **Postural instability, frequent falls** *(early in course of illness)* freezing, axial rigidity, bradykinesia

- **Impaired vertical gaze** (downwards) (which can be overcome by vertical doll's-eyes maneuvers.)

- apraxia of eyelid opening or closure

- dysarthria, dysphagia

- Frontal lobe symptoms
  - echolalia, palilalia, perseveration, aphyta, dementia
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Corticobasal degeneration (taupathy)

- Asymmetric frontal, parietal premotor cortex atrophy

tau positive astrocyte plaques
Corticobasal degeneration: clinical symptoms

- Rare disorder, onset in 6-7. decade, survival: 5-10 years progressive course

  **Cortical** (parietal): - apraxia,
  - cortical sensory loss
  - „alien hand”

  **Motor signs:**
  - akinetic-rigid sy, no response to L-DOPA
  - dystonia
  - myoclonus
  - chorea
  - postural/kinetic tremor
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Clinical clues suggestive of Parkinson-plus syndromes

- Lack of response to levodopa/carbidopa or dopamine agonists in the early stages of the disease
- Early onset of dementia
- Early onset of postural instability
- Early onset of hallucinations or psychosis with low doses of levodopa/carbidopa or dopamine agonists
- Ocular signs, such as impaired vertical gaze, blinking on saccade, square-wave jerks, nystagmus, blepharospasm, and apraxia of eyelid opening or closure
- Pyramidal tract signs not explained by other cause (such stroke, MS etc)
- Autonomic symptoms (postural hypotension and incontinence early in the course of the disease)
- Prominent motor apraxia, alien-limb phenomenon
- Marked symmetry of signs in early stages of the disease
- Axial symptoms more prominent than affection of extremities