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

Synucleinopathies

(alpha-synuclein)

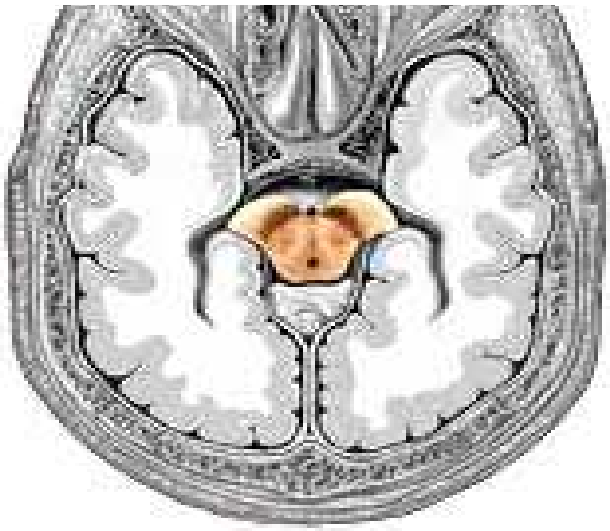
- Parkinson Disease
- Inherited PD (PARK 1-4)
- Cortical Lewy body disease
- „incidental Lewy-body disease”
- Multiple system atrophy (Papp-Lantos inclusion)

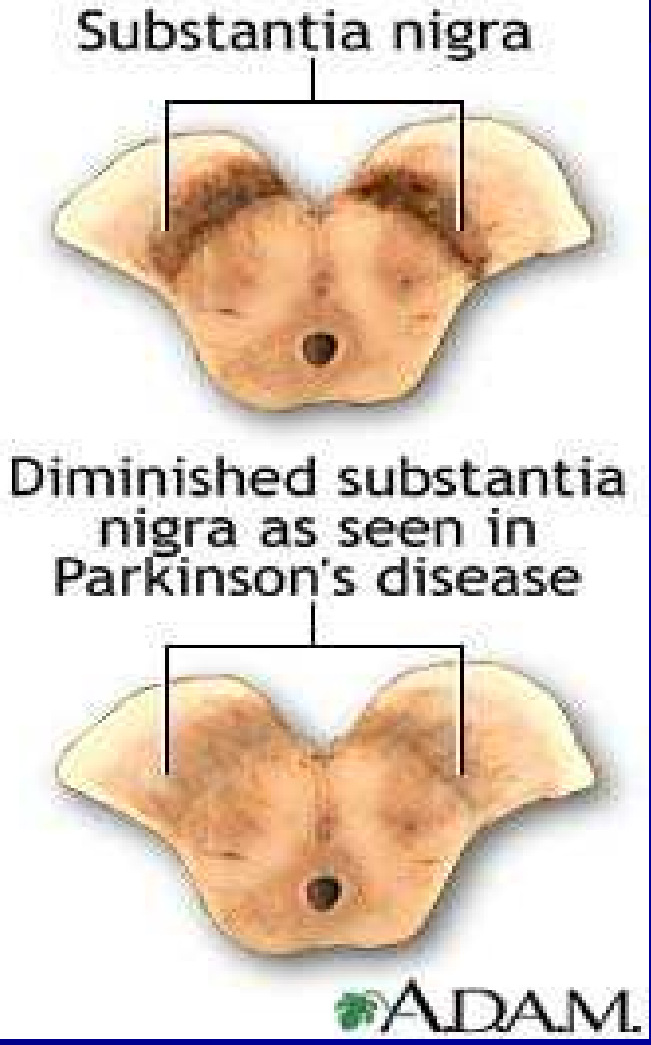
Taupathies

(abnoral phosphorylated tau protein)

- Progressive supranuclear palsy (Steele-Richardson_Olszewski sy.)
- Corticobasal degeneration
- **„variants of frontotemporal demencia parkinsonism linked to chromosome 17”–** tau gene)

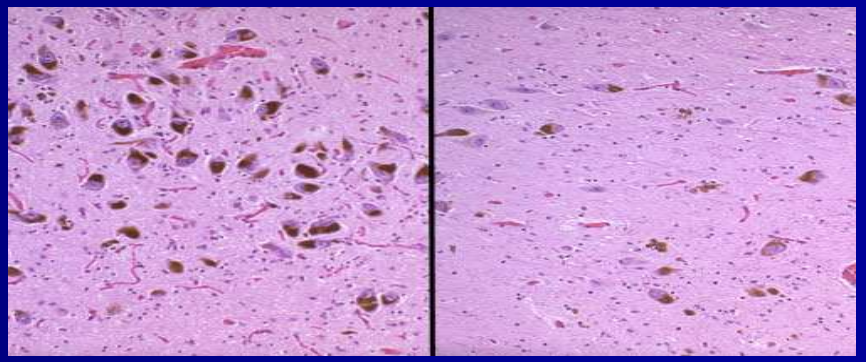
Parkinson Disease pathology





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 sympoms 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 pigmened 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

Parkinson Disease clinical symptoms

- 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

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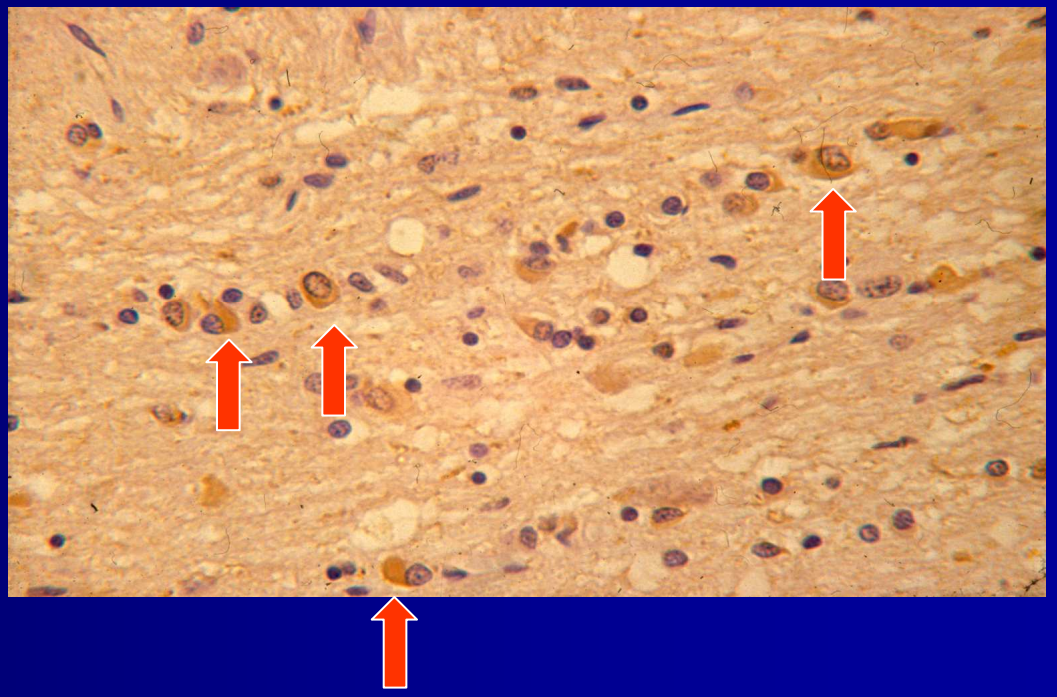
Multiple system atrophy

- 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 degenaration (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

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Progressive supranuclear palsy (PSP) - taupathy

- 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, bradykinesis
- **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, aphaty, 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

Synucleinopathies
(alpha-synuclein)

- Parkinson Disease
- Inherited PD (PARK 1-4)
- Cortical Lewy body disease (dementia, hallucinations)
- „incidental Lewy-body disease”
- Multiple system atrophy (Papp-Lantos inclusion)

Taupathies
(abnoral phosphorylated tau protein)

- Progressive supranuclearis palsy (Steele-Richardson_Olszewski sy.)
- Corticobasal degeneration
- (Parkinsonism) dementia-amyotrophic lateral sclerosis complex
- **„variants of frontotemporal demencia parkinsonism linked to chromosome 17”–** tau gene)

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