PARKINSON’S DISEASE:
current aspects of ETIOLOGY, DIAGNOSIS and TREATMENT

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### Parkinson’s disease

**Definition**

- **Clinical symptoms:** Neurodegenerative syndrome with chronic, progressive course (hypokinetichyperrigid/tremor-dominant)
- **Pathogenesis:** Degeneration of the nigrostriatal dopamine neurons
- **Etiology:** Idiopathic vs. symptomatic forms

“Involutary tremulous motion, with lessened muscular power, in parts not in action even when supported; with a propensity to bend the trunk forward [...] , the senses and the intellects being uninjured.”

James Parkinson (1817)
Milestones in Parkinson’s research

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1817</td>
<td>J. Parkinson</td>
<td>“Essay on the Shaking Palsy”</td>
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<tr>
<td>1873</td>
<td>Charcot</td>
<td>Description of the clinical picture and first attempts at treatment</td>
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<tr>
<td>1919</td>
<td>Trétiakoff</td>
<td>Discovery of cell degeneration in the substantia nigra as anatomical substrate</td>
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<td>1957</td>
<td>Carlsson</td>
<td>Discovery of dopamine deficiency in the striatum as biochemical substrate (Nobel Prize 2000)</td>
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<td>1979</td>
<td>Davis</td>
<td>Research into the pathological mechanism using the MPTP model</td>
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<tr>
<td>Ongoing</td>
<td></td>
<td>Research into genetic and neuroprotective factors</td>
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## Milestones in therapy - Drug therapy

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>1946:</td>
<td>First synthetic anticholinergics</td>
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<tr>
<td>1961:</td>
<td>Birkmayer &amp; Hornykiewicz - Clinical use of L-dopa</td>
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<tr>
<td>1969:</td>
<td>Schwab - Discovery of the antiparkinson effect of amantadine</td>
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<tr>
<td>1963:</td>
<td>Birkmayer - Clinical use of L-dopa + decarboxylase inhibitor</td>
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<td>1974:</td>
<td>Calne - Introduction of dopamine agonists</td>
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<tr>
<td>1975:</td>
<td>Birkmayer - Use of MAO-B inhibitors</td>
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<tr>
<td>1997:</td>
<td>Introduction of COMT inhibitors to clinical treatment</td>
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Epidemiology – Facts

- In Europe the age-correlated prevalence (per 100,000 inhabitants) is 1.6 (Europarkinson Study, 1997)
- Roughly 1% of all over-65s are affected
- Roughly 25% of Parkinson patients remain undiagnosed
- Average life expectancy is slightly reduced
Age-specific incidence of new cases of Parkinson’s disease

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Incidence (per 100,000 inhabitants)</th>
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<tbody>
<tr>
<td>30-39</td>
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<tr>
<td>40-49</td>
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<tr>
<td>50-59</td>
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<tr>
<td>60-69</td>
<td></td>
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<tr>
<td>70-79</td>
<td></td>
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<tr>
<td>80+</td>
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</tbody>
</table>

- **USA**
- **Iceland**
- **Japan**
- **Estonia**
- **Finland**
Risk factors

- Age
- Positive family history
- Possible: Poisoning with herbicides, pesticides, heavy metals
- Doubtful: Personality
  Living in the countryside

Possible protective factors:
- Consumption of tea and coffee
- Nicotine
Cell degeneration in the substantia nigra

Schneider E.: Diagnostik und Therapie des M. Parkinson [Diagnosis and treatment of Parkinson’s disease], de Gruyter, 1991.
Genetic causes

- **PARK 1**
  Locus: Chromosome 4q21
  Gene product: $\alpha$-Synuclein (Polymeropoulos et al., 1997)

- **PARK 2**
  Locus: Chromosome 6q25
  Gene product: Unknown (Kitada et al., 1998)

- **PARK 3**
  Locus: Chromosome 2p13
  Gene product: Unknown (Gasser et al., 1998)

- **PARK 4 - 10**
Lewy bodies - Microscopic findings

Lewy bodies in a neuron from the substantia nigra in PD

By kind permission of Prof. H. Braak
Center for Morphology, Frankfurt University Hospital

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Lewy bodies - Pathoanatomical cascade model

(Braak et al., 2002)

Stages of Lewy body formation:

I. Dorsal vagal nucleus/olfactory bulb
II. Brain stem/reticular formation
III. Basal prosencephalon/amygdala/substantia nigra
IV. Mesocortex
V. Neocortex - association areas
VI. Neocortex - sensory and motor areas
Oxidative stress

• Disturbed cell homeostasis through:
  - inefficient detoxification
  - impaired mitochondrial function

• Results:
  - increased radical formation
  - reduced ATP production
  - DNA damage
L-Dopa metabolites in the brain

- L-Dopa
  - DDC
- Dopamine
  - MAO-B
  - COMT
- DOPAC
  - COMT
- 3-MT
  - MAO-B
- HVA
Core structures of the basal ganglia

- Caudate nucleus & putamen
- Substantia nigra
- Globus pallidus
- Tail of the caudate nucleus
- Thalamus
- Striatum
- Caudate nucleus
- Putamen
- Globus pallidus
- Substantia nigra
- Subthalamic nucleus
- Parkinson’s disease
- Pathophysiology
Basal ganglia loops – Physiological state

Cortex

Striatum
- D1 (+)
- D2 (-)

GPe

SNr

GPi

Thalamus

SNC

STN

Glutamate

GABA

Dopamine

Parkinson’s disease
Pathophysiology
Basal ganglia loops - State in Parkinson’s disease

Pathophysiology of Parkinson’s disease involves disruptions in the balance of neurotransmitters, particularly dopamine. The diagram illustrates the key structures and neurotransmitters involved in basal ganglia loops:

- **Cortex**
- **Striatum**
  - D1 (+)
  - D2 (-)
- **SNC**
- **STN**
- **GPe**
- **GPi**
- **SNr**
- **Thalamus**

Key neurotransmitters:
- **Glutamate**
- **GABA**
- **Dopamine**
Development of Parkinson’s symptoms

- Cell death in the substantia nigra
- Dopamine deficiency in the striatum
- Neurotransmitter imbalance (Dopamine deficiency vs. glutamate hyperactivity)
- Dysfunction of the basal ganglia loops
Main symptoms

Parkinson’s disease

 Symptoms

Bradykinesia
Rigor
Tremor
Postural instability
Clinical diagnostic criteria (at least three must be satisfied)

- Unilateral onset of the disease
- Resting tremor and/or at least two of the main symptoms
- Progressive course
- Very good response to L-dopa
- L-Dopa-induced dyskinesia and fluctuations in efficacy
- No atypical signs

Gerlach, Reichmann & Riederer, Springer Verlag, 2003
Accompanying symptoms

Vegetative
- Post-encephalitic seborrhea (seborrhea)
- Sialorrhea
- Digestive disturbances
- Disturbed micturition and potency
- Orthostatic hypotension
- Disturbed thermoregulation

Psychopathological
- Depression
- Bradyphrenia
- Dementia
Exclusion criteria for Parkinson’s disease

- Acute onset
- Oculogyric crises/gaze palsy
- Remission
- Neuroleptics
- Cerebellar symptoms
- Babinski’s sign positive
- Early signs of dementia or autonomic dysfunction
- No response to L-dopa

Gerlach, Reichmann & Riederer, Springer Verlag, 2003
Parkinson Plus syndrome I

- Multisystem atrophy
  - Cerebellar symptoms (disturbances of equilibrium, unsteady gait, coordination disturbances) or
  - Autonomic disturbances (drop in blood pressure, bladder disorders, impotence)

- Progressive supranuclear gaze palsy
  - Postural instability as an early symptom
  - Vertical gaze palsy (upwards or downwards)
  - Unsteady gait
  - Symmetrical symptoms
  - No resting tremor
Parkinson Plus syndrome II

- **Lewy body dementia**
  - Early development of dementia
  - Fluctuating psychotic symptoms
  - Agitation
  - Paradoxical neuroleptic sensitivity

- **Corticobasal degeneration**
  - Dystonia (mainly flexion dystonia of the arm)
  - Irregular, unilateral tremor
  - “Alien limb” phenomenon
  - Cortical sensitivity disturbances
  - Pyramidal tract signs
Secondary (symptomatic) parkinsonism

**Drug-induced:**
- Neuroleptics
- Antihypertensives
- Antiemetics
- Cerebral calcium-channel blockers

**Toxic in origin:**
- Carbon monoxide
- Lead
- Manganese
- Cyanide
- Methanol
- MPTP

**Other etiology:**
- Metabolic
- Postencephalitic
- Traumatic
- Compressive

- Reversible
- Not progressive
- Treatable
Therapeutic options – Drug therapy

- **L-Dopa therapy/dopamine agonists**
  - Dopamine replacement

- **Glutamate antagonist (amantadine)**
  - Inhibition of glutamatergic hyperactivity

- **MAO-B inhibitors**
  - Central inhibition of dopamine breakdown

- **COMT inhibitors**
  - Peripheral inhibition of L-dopa breakdown
Points of attack of drug therapies

- Phenylalanine → Tyrosine → Dopa → Dopamine (DA)
- L-Dopa
- MAO-B inhibitor
- Glutamate antagonist: Amantadine sulfate
- Postsynapse: Glutamate (Glu)

PD Treatment:
- Dopamine agonists
- MAO-B inhibitor
- Glial cell
- Postsynapse

Presynapse: DOPAC

Dopamine (DA)
Therapeutic options - Deep brain stimulation

- Hyperstimulation (120 Hz) in affected regions of the brain:
  - Subthalamic nucleus
  - Globus pallidus
  - Thalamus

- Symptom and drug reduction
  - Tremor
  - Hypo-/hyperkinesia
  - L-Dopa-sparing effect

- Invasive, reversible
Therapeutic options - Transplantation

Parkinson’s disease Treatment

TRANSPLANTATION

Decrease in dopaminergic input in the striatum

Dopaminergic reinnervation of the striatum
OTHER MOVEMENT DISORDERS
Movement disorders

- Hyperkinetic
  - Chorea
  - Ballism
  - Tremor
  - Myoclonus
  - Tics
  - Dystonia

- Hypokinetin
  - Parkinsonism: PD and All Parkinsonian Syndromes
DYSTONIA
Dystonia is defined as a syndrome of sustained muscle contractions, frequently causing twisting movements and postures (Fahn 1987). Agonist and antagonist muscles contract simultaneously to produce the abnormal postures of dystonia. Dystonic movements may be slow and continuous, or fast and brief.
Dystonia may be classified by:
- *age of onset,*
- *distribution* and
- *etiology.*

By region of distribution, dystonia is subdivided into *focal,* *segmental,* *hemi-body,* and *generalized* dystonia. Childhood-onset dystonia may begin in a body part, presenting as focal dystonia, but typically becomes generalized, especially if the underlying cause is a genetically-based or metabolic disorder.
CHOREA

• Chorea, from the Greek word meaning dance, describes involuntary, random, abrupt, rapid, arrhythmic, unsustained movements and twitches that seem to flow from one body part to another.
• The timing, direction, and distribution of choreic movements varies from moment to moment, and cannot be predicted by an observer.
chorea
ATHETOSIS

Athetosis, meaning “no fixed position,” describes a pattern of continuous writhing movements.

First coined by Hammond in 1871, the original description of athetosis was “an inability to retain the fingers and toes in any position in which they may be placed.”

Athetosis is often linked with chorea, as in choreoathetosis, to give a sense of its continuous, writhing, twisting aspect. Athetoid movements affect the limbs, especially distally, but also the trunk and cranial structures.
MYOCLONUS

Myoclonic jerks are sudden, brief muscle contractions that produce a simple quick movement. Myoclonic jerks may be repetitive and rhythmic or random and unpredictable.

Myoclonus may occur at rest, with posture-holding, directed movement ("action myoclonus"), or be triggered by external stimuli ("reflex myoclonus"), whether auditory, visual or tactile.
Myoclonus may be classified on the basis of

1. its distribution: focal, segmental, multifocal, or generalized or
2. site of origin: cortex, brain stem, spinal cord
HEMIFACIAL SPASM:
- involuntary tonic or clonic contraction of muscles innervated by 7th cranial nerve
- Idiopathic / vascular compression of facial nerve
- treatment: BTX-A
  - pharmacologic agents
TREMOR

Tremor is a regular, rhythmic oscillation of one or more body parts produced by alternating or synchronous contractions of opposing muscles.

Phenomenologically, tremors are classified according to two main categories:
1. *tremors at rest* and
2. *tremors with action.*
• Rest tremors occur when the affected body part is in complete repose, and fully supported. The classical tremor of parkinsonism is a tremor at rest.
• Action tremors occur with voluntary muscle contractions, and are subdivided into postural, kinetic, task- or position-specific, and isometric tremors
TICS
Tics are repetitive, stereotyped movements or phonations that occur abruptly against a background of normal motor activity and behavior.
Most tics are simple movements, such as an abrupt stereotyped ocular deviation, blink, facial grimace, or shoulder shrug.
Complex tics consist of coordinated patterns of sequential movement.
Tics are purposeless movements that are often preceded by an inner urge or tension that is relieved by allowing the movement to occur.
**WILSON’ S DISEASE**
curable movement disorder
AR, on chr 13q14.3 (Cu transporting ATPase)
failure to excrete Cu --- systemic Cu poisoning
- intestinal absorption is normal
- reduced biliary excretion
- result: increased Cu excretion in urine
initially Cu accumulates in liver
then in brain, eye, kidney, bones and blood tissues.
**Symptoms:** ages of 11-55 year
clinical types: 1. Akinetic-rigid syndrome
2. Generalized dystonic syndrome
3. Tremor+ ataxia+ dysarthria: pseudosclerotic
- **Diagnosis:** 24 hr urine copper excretion
- liver biopsy
- MRI
- genetic study
- **Treatment of Wilson disease**
- D-penicillamine + pyridoxine
- trientine
- Zinc
- BAL?
- **LIVER TRANSPLANTATION**
HUNTINGTON’S DISEASE
- AD, chorea + dementia
- genetic defect: excessive trinucleotide repeat of CAG
- defected protein called huntingtin
- no established therapy
- symptomatic treatment

SYDENHAM’S CHOREA
- beta hemolytic streptococcus induced autoimmune disorder
- between ages of 5-15 years
- outcome is favorable
- prophylactic penicillin therapy prevents recurrences