Parkinson's disease is a movement disorder that is characterized by degeneration of dopaminergic neurons of the substantia nigra, which is a part of the basal ganglia. The disease itself mostly has idiopathic causes and is to be distinguished from the symptomatic and the atypical Parkinsonism. The disease has a chronic-progressive course, whereas the life expectancy of those affected generally corresponds to that of the normal population. In this article, you will gain all the exam-relevant facts concerning epidemiology, etiology, pathophysiology, clinic, diagnosis, and therapy of Parkinson's disease.

Definition of Parkinson's Disease

Parkinson's syndrome includes the clinical triad of rigor, tremor, and akinesia as well as possible postural instability.

On the basis of etiology, one can further distinguish between idiopathic Parkinson's disease, which is synonymous with Parkinson's disease, and an atypical and symptomatic Parkinsonism.

Idiopathic Parkinson's disease or Parkinson's disease is considered a diagnosis of exclusion since no particular cause can be determined.
**Symptomatic Parkinsonism**, however, is triggered by certain identifiable factors. For example in the context of intoxication, manganese or lead may trigger the disease. Another cause of Parkinson’s syndrome is caused by medication, e.g. **neuroleptics**.

Parkinson’s syndrome occurring in the context of other **neurodegenerative** diseases is referred to as **Atypical Parkinsonism**.

### Epidemiology of Parkinson’s Disease

The peak of manifestation of Parkinson’s disease is between ages 40 and 60. Both male and female genders are affected almost equally. Prevalence in 60-year-olds is at approximately 1 % and that of 80-year-olds is at approximately 3 %.

### Etiology of Parkinson’s Disease

#### Etiology of Idiopathic Parkinson’s Syndrome

In most cases, no particular cause can be assigned to idiopathic Parkinson’s disease. However, sometimes there is a familiar accumulation. Yet, this is very rare and is attributed to certain gene loci (Park 1 - Park 11).

#### Etiology of Symptomatic Parkinson’s Syndrome

In the context of symptomatic parkinsonism, there are numerous possible trigger factors, which can be assigned to different superior groups.

Among others, these groups include intoxications, metabolic diseases, inflammations, vascular causes, and medications.

Examples of toxins, which can lead to symptomatic parkinsonism in the context of intoxication are: **manganese**, carbon disulfide, mercury and **MPTP** (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine).

An example of a metabolic disease which can lead to symptomatic parkinsonism is **Wilson’s disease**. One aspect is that disturbed copper excretion leads to an accumulation of copper in the body, including the CNS.

Diseases which can trigger symptomatic parkinsonism usually affect the brain itself. This means that Parkinson’s syndrome is caused by issues related to **encephalitis**.

A vascular disease, which is considered to trigger symptomatic parkinsonism, is **subcortical arteriosclerotic encephalopathy (SAE)**, which presents itself as a progressive atrophy of the brain with simultaneous impairments of cognitive performance.

Medications that modulate dopamine metabolism are especially considered to be possible triggers of symptomatic parkinsonism (see above). Example are **dopamine antagonists** like classical **neuroleptics** and also antiemetics like **metoclopramide**.

Other diseases, which can possibly trigger symptomatic parkinsonism are **normal pressure hydrocephalus**, intracranial **masses** and **traumatic brain injuries**.
In Parkinson’s disease, the lesion is located in the compact part of the **substantia nigra**. Decay of **dopaminergic neurons** and, thus, loss of the inhibitory function of the substantia nigra on the indirect pathway of the **basal ganglia loop** occurs. Via this disinhibition, the indirect pathway is more active and inhibits the thalamus, which results in reduction of movement.

Additionally, degenerative changes occur in the area of the dorsal **vagal nuclei** and peripheral **sympathetic ganglia**. Due to these changes, **autonomous disorders** like bladder dysfunction result (see below).

Typically, the so-called **Lewy bodies** appear in the histopathological specimen. These are usually **hyaline eosinophile** inclusion bodies and occur in the neurons. They are specifically located in the degenerating neurons of the substantia nigra.
In the neocortex, they can be observed at **Lewy body dementia**, which is part of the cortical dementias.

**Clinic of Parkinson’s Disease**

**Symptoms of Parkinson’s disease**

The typical clinical triad of Parkinson’s disease consists of **akinesia**, **rigor**, and **tremor**. Partially, **postural instability** is considered to be the core symptom. Typically, the tremor is a **resting tremor**, which initially starts on one side. This means that it manifests **asymmetrically**.

**Note:** One-sided onset of symptoms is a characteristic for Parkinson’s disease. It occurs
in this way in 70 % of the cases. The right half of the body is usually more affected.
Depending on the most prominent symptom, one can distinguish between a tremor dominance type, an akinetic-rigid type and an equivalence type. In the latter, the three symptoms of the clinical triad (see above) are roughly equally distinct.

Additionally, the walk of the patients gives the first hint of the disease’s presence. In the context of hypo- or akinesia, small steps and a stooped torso characterize their walk. The arms swing less, usually on one side.

Further symptoms, which can occur before the classical Parkinson’s symptoms, are disorders of REM sleep and impairments of smell either in form of hyposmia or anosmia. There is pain in the shoulder-neck-region, but pain can also occur in the extremities.

**Note:** Muscle stiffness and associated pain in the shoulder-neck-region are common early symptoms, but are not enough to make a diagnosis of Parkinson’s disease.

As the disease progresses further, vegetative symptoms of psychopathological nature such as frontal dementia or depression can occur.

The possible vegetative symptoms include increased salivation (hypersalivation), a mask-like face due to seborrhea, hyperhidrosis, disorders of bladder depletion, obstopation, erectile dysfunction, and disorders of temperature regulation.

# Diagnosis of Parkinson’s Disease

## Parkinson’s disease as a clinical diagnosis

In the case of Parkinson’s disease, the fact that it is a diagnosis of exclusion should be emphasized. A certain diagnosis can only be made during post mortem on the basis of histopathological diagnostic criteria. These include the detection of Lewy bodies and the decay of > 60 % of the neurons of the substantia nigra.

**Note:** Parkinson’s disease is a clinical diagnosis. Its diagnosis is made based on physical examination, medicamentous tests, and instrument-based diagnosis. Possible reversible causes (due to known factors) of Parkinson’s disease (see above) should be excluded.

## Physical examination in the context of diagnostics

The most important element in the context of diagnostics is the physical examination in the course of anamnesis. During anamnesis, questions, especially those concerning the development of the respective symptoms, that is if they are one-sided and in which situations the symptoms occur, should be given a lot of attention.

While conducting clinical examination, the classical triad should be considered. Thus, the examiner should inspect the patient for resting tremors, akinesia, or rigor. Classically, the resting tremor has a frequency of 4 - 7/second and increases during periods of emotional stress or stressful situations.

Rigor can be illustrated by the cogwheel phenomenon and movement of the extremities. This phenomenon is characterized by a stretching resistance, which intermittently suddenly subsides, only to re-occur.

Another hint of existing rigor is the positive head fall test, where by the patient lies on a
couch and the head of the patient is elevated by the examiner. After this, the examiner suddenly releases the head. The head does not fall back onto the couch, but is held in its position.

In clinical examination, hypo- or akinesia presents – for example – an increased turning step count, or a decreased one, as well as absent shuttling of the arms while walking.

Overall, there is a high probability for the diagnosis of Parkinson’s disease after asymmetric onset, positive results after the use of L-DOPA or apomorphin (see below), the absence of further neurological deficits, and the presence of (at least) two of the following symptoms:

- Rigor
- Resting tremor
- Brady- or akinesia
- Disorders of holding and positioning reflexes (e.g. tendancy for propulsion)

Medicamentous testing in the context of diagnostics

A hint for the existence of Parkinson’s disease is an improvement of symptoms after the application of L-DOPA or apomorphin (a dopamine agonist, see below). This improvement should occur in a period of 5 – 15 minutes after the injection of apomorphin.

The L-DOPA test is considered positive if a clinical improvement of approximately 20 % is achieved. For better assessment of clinical improvement, the Unified Parkinson’s Disease Rating Scale (UPDRS) is used.

Opportunities of instrumental diagnostics

In the context of instrumental diagnostics of Parkinson’s disease, imaging of the head is performed using MRI, DaTSCAN™ (dopamine-transporter-scintigraphy), SPECT-examination (imaging of iodine-benzamid-dopamin-receptor-bond), or transcranial sonography.

The MRI is primarily used to exclude other possible reversible causes of Parkinsonism, since there are no particular abnormalities in the MRI of Parkinson’s disease.

When examining DaTSCAN™, a decrease in dopamine transporters can be observed in Parkinson’s disease.

SPECT-examination serves for the distinction of multi system atrophy (MSA), which is an atypical Parkinsonism. In the case of Parkinson’s disease, the dopamine-receptor-bond is basically not affected, whereas it is decreased in MSA.

In transcranial sonography, there is evidence of hyperechogenic substantia nigra in the majority of patients suffering from Parkinson’s disease.

Clinical Assessment Scales of Parkinson’s Disease

Besides the Unified Parkinson’s Disease Rating Scale (UPDRS) mentioned above, the Hoehn and Yahr scale can also be used, which classifies Parkinson’s disease on the basis of existing symptoms in stages 0-5.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Symptoms</th>
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<tbody>
<tr>
<td>0</td>
<td>No clinical symptomatic</td>
</tr>
<tr>
<td>I</td>
<td>Unilateral symptomatic; no or only slight impairments</td>
</tr>
<tr>
<td>II</td>
<td>Slight, bilateral symptomatic; no balance impairments</td>
</tr>
<tr>
<td>III</td>
<td>Slight to intermediate impairments with slight holding instability; sustained ability to work (depending on the respective job)</td>
</tr>
<tr>
<td>IV</td>
<td>Full manifestation of the disease including high-degree impairments; standing and walking is, however, possible without help</td>
</tr>
<tr>
<td>V</td>
<td>The patient depends on a wheelchair or is bedridden; and is dependent on the help of others</td>
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Differential Diagnosis of Parkinson’s Disease

Similar diseases such as Parkinson’s disease

The most important differential diagnosis of Parkinson’s disease are the two types of Parkinsonism, i.e. atypical and symptomatic Parkinsonism and the essential tremor.

The atypical Parkinsonism includes multi system atrophy (MSA), progressive supranuclear (PSP, synonym: Steele-Richardson-Olszeski syndrome), corticobasal degeneration, and Hallervorden-Spatz’ disease.

The atypical Parkinsonism can be distinguished from Parkinson’s disease on the basis of the clinical course or the clinical picture. Though the distribution of the symptomatic and atypical Parkinsonism is often symmetric, the disease often progresses more quickly over a shorter period of time, and the reaction to L-DOPA is often weak.

Also, irregular tremor, myokloni, and disorders in the oculomotor system suggest atypical Parkinsonism.

As an important differential diagnosis of Parkinson’s disease, essential tremor often occurs symmetrically and is mostly limited to the upper extremity. The onset of the disease often starts during youthful or early adult age. Essential tremors occur sporadically and are familiarly cumulative (autosomal-dominant inheritance).

In the case of the disease, no further symptoms that would be typical for Parkinsonism, like rigor or akinesia appear. Another difference is that with Parkinson’s disease, there is no resting tremor, but a postural tremor is evident.

Characteristically, it improves after consumption of alcohol and can be treated medically with beta-blockers (e.g. propranolol).

Therapy of Parkinson’s Disease

Treatment of Parkinson’s disease

Therapy of Parkinson’s disease can roughly be divided into a medicamentous and a non-medicamentous form. Non-medicamentous treatment includes symptomatic measures like physiotherapy, speech therapy, and surgical measures.
Surgical measures include deep brain stimulation, which is the implantation of electrodes, which stimulate certain areas of the brain. The main location of stimulation in Parkinson’s disease is the nucleus subthalamicus. Surgical measures should only be considered if medicamentous therapy does not result in sufficient improvement of the symptoms.

For medicamentous therapy of Parkinson’s disease, different medications groups are administered in different doses depending on the patient’s reaction. They include anticholinergics e.g. biperiden, application of L-DOPA, NMDA-antagonists, or COMT-inhibitors (catechol-o-methyltransferase inhibitors).

Overall, medicamentous therapy aims to balance a relatively high overshoot of acetylcholine compared to reduced amounts of dopamine.
The determination of when therapy should start depends on the biological age of the patient. At an age of < 70 years, therapy should be begun with dopamine agonists. At patients > 70 years old, the application of L-DOPA is recommended (guideline Parkinson [September 2012] of the German Society for Neurology).

Overall, the respective therapy scheme has to be chosen for each individual patient depending on the dominating symptoms.

Thus, use of anticholinergics like e.g. biperiden are mainly used for patients suffering from vegetative symptoms and tremor. When applying anticholinergics, one should consider contra-indications like existing prostate hyperplasia or glaucoma.

The dosage of L-DOPA intensifies symptoms like akinesia and rigor. During long-term administration of L-DOPA, a positive effect on the tremor is realized. To avoid peripheral side effects of dopamine, like nausea or a drop in blood pressure, the simultaneous application of a dopa-decarboxylase inhibitor (e.g. benzerazid, carbidopa) is recommended.

In the periphery, it inhibits the conversion of L-DOPA to dopamine, whereas the conversion in the CNS is not affected since the dopa-decarboxylase inhibitor cannot pass the blood-brain barrier.
In the context of the administration of L-DOPA, one also has to consider that dosage over several years can lead to a regular loss of its effect in as short as 2-3 hours after ingestion of L-dopa (end of dose akinesia). Also, the so-called on-off-phenomenon can occur. This means that there is severe fluctuation of symptoms over the course of the day.

Single doses which are frequently administered and spread out over the course of the day or the application of depot or controlled-release preparations should be used if these effects occur. Additionally, duodenal infusions via a percutaneous tube are used.

**Note:** The effects of long-term therapy with L-DOPA explains the reasons as to why the application of L-DOPA is recommended for patients > 70 years. In patients < 70 year, it is recommended to start monotherapy with dopamine agonists. E.g., pramipexol or ropinirol are approved for monotherapy. These two substances are non-ergot-preparations, which are preferred to ergot-preparations since the latter can lead to side effects like fibrosis of the cardiac valves.

Examples for the group of ergot-preparations are bromocriptin, cabergolin, lisurid, or pergolid.

**Note:** Due to their side effects, ergoline dopamine agonists are not considered as first-resort medicines.

Monoaminoxidase-B-inhibitors inhibit the further degradation of dopamine, making it available for a longer period of time. This way, either the dose of L-DOPA can be decreased in combination with a decarboxylase inhibitor or a lower level of fluctuation of symptoms can be reached.

The effect of the group of catechol-o-methyltransferase inhibitors (e.g. entacapone, tolcapone) also depends on the inhibition of dopamine degradation.

**Prognosis of Parkinson’s Disease**

Of the three types of Parkinson’s disease, the tremor dominance type has the best prognosis, where the smallest therapeutical influence on symptoms is observed.

Under therapy, life expectancy is almost equal to that of the normal population. On average, care dependency sets in 20 years after the onset of the disease.

**Review Questions**

The answers can be found below the references.

1. **Which statement concerning the etiology of Parkinson’s syndromes is not correct?**
   - A. The cause of idiopathic Parkinson’s syndrome is not known.
   - B. Symptomatic Parkinsonism can be triggered by Wilson’s disease.
   - C. Neuroleptics can trigger symptomatic Parkinsonism.
   - D. Atypical Parkinsonism is triggered by the occurrence of other neurodegenerative diseases.
   - E. In cases of encephalitis, Parkinsonism often occurs.

2. **Which statement concerning the clinic of Parkinson’s disease is not correct?**
   - A. The typical triad consists of rigor, tremor, and akinesia.
The tremor is a holding tremor, which mostly manifests symmetrically.
C. In the course of the disease, vegetative symptoms can occur.
D. The symptoms typically begin single-sided.
E. In the course of the disease, dementia can occur.

3. Which statement is correct concerning the diagnosis of Parkinson’s disease?

A. The diagnosis of Parkinson’s disease can only be made after post mortem.
B. In the physical examination, the pocket-knife-phenomenon can often be observed.
C. Non-response to L-DOPA suggests Parkinson’s disease.
D. A MRI scan does not indicate any particular abnormalities in Parkinson’s disease.
E. Typically, the head-fall test is negative.

References


**Correct answers:** 1E, 2B, 3A

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