Parkinson’s disease: symptoms and age dependency

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Epidemiology of Parkinson’s Disease (PD)

Parkinson’s disease is one of the most frequent neurodegenerative diseases, which mainly affects the elderly. To estimate incidence and prevalence of PD, some problems need to be mentioned. No perfect ante mortem diagnostic test for PD exists and the most reliable diagnostic method is expert neurologic examination at regular time intervals. In autopsy studies, the diagnosis of PD before death has been found to be incorrect in about 24% of cases. Essential tremor may account for 10% - 40% of the false-positive diagnoses of PD. In contrast PD may be misdiagnosed as depression, or in the very elderly, “normal” aging. Other neurodegenerative disorders, like progressive nuclear palsy (PSP) or multiple system atrophy (MSA) may not be distinguished easily from PD early in the course of the disease. Many “atypical” parkinsonian syndromes were only recognised in the past several decades and probably have been classified as PD in early reports.

Incidence and prevalence of Parkinson’s disease

Several studies have been performed to estimate the frequency of PD. The overall incidence is estimated to be 20 / 100 000 per year, and raises to about 1% of persons over 50 years of age and even higher when older. Prevalence of PD varies from 10 to 405 per 100 000 population. This variation may be due to differences in case-finding procedures, in diagnostic criteria, in accessibility of medical services and in the age distribution of populations. Most frequently prevalence is about 100 - 187 per 100 000. As for incidence, prevalence rises almost exponentially after age 50. By the eighth decade, prevalence in Europe and North America is estimated to be between 1000 and 3000 per 100 000 persons. This is confirmed by the Rotterdam Study: prevalence figures were 0.3% for those aged 55 to 64 years, 1.0% for those aged 65 to 74 years, 3.1% for those aged 75 to 84 years and 4.3% for those aged 85 to 94 years. Among women aged 95 to 99 years, prevalence was 5.0%. In some studies an apparent decrease in late life is seen. This is probably due to ascertainment and diagnosis difficulties in this population, rather than an actual decline in disease frequency.

Mortality

In Hoehn and Yahr’s series mortality ratio in patients with primary parkinsonism was 2.9 times that expected in the age-matched population. In a more recent study of parkinsonian patients the overall risk for death, adjusted for age and sex, was 2.0 times that of persons without parkinsonism. Since the introduction of more effective antiparkinsonian medication, especially levodopa, mortality has decreased in younger parkinsonian patients. However in older parkinsonian patients an increase during the last few decades in mortality is found. In the United States between 1962 and 1984, mortality...
decreased for persons younger than age 70, but increased for persons of 75 years and older. This is confirmed by Morens et al., who found that after age 60, PD-associated mortality rates appeared to increase logarithmically. This increase in mortality rate was not attributable to age alone. Increased age-related PD mortality was associated with both absolute age and duration of illness longer than 10 years. Between the ages of 70 and 89 years, parkinsonian patients had a two- to three-fold increase in the risk of dying, corresponding to a mortality ratio of 2.5. In a study of Louis et al., risk of mortality was higher in parkinsonian patients (rate ratio = 2.7) after adjusting for baseline age, years of education, sex, ethnicity and smoking status. It was even higher when PD was combined with dementia (rate ratio = 4.9). In fact dementia is a significant predictor of death in PD. A high baseline score of extrapyramidal signs was most associated with increased risk of mortality among the patients with PD. After subanalysis of the different extrapyramidal signs, severe bradykinesia was the motor manifestation that most highly correlated with increased mortality. The Sydney multicentre study found increased mortality risk among parkinsonian men, whereas this was not significantly different for women, compared to the general Australian population. Predictors of mortality, according to this study, are age at onset and progression rate. Several studies have shown that the effects of levodopa on mortality are apparent in the early years of the disease. In contrast, despite levodopa therapy, mortality is rising in a later stage of the disease. Data from the DATATOP cohort suggests that carefully selected patients with early PD without co-morbidity have normal life expectancy when adequately treated and frequently seen by consulting physicians. For persons with PD diagnosed before the age of 60, they found a relative survival similar to that of the general population, in contrast to people with an older age at diagnosis, who showed a lower relative survival. Pneumonia is the most common cause of death, probably due to immobility and increased risk of aspiration. Death from cerebrovascular disease is increased as well. Some studies have suggested a reduced risk of death from cancer in parkinsonian patients, but other studies did not confirm this.

Regional and racial variation

Estimates of prevalence vary widely depending on geographical location. A Northwest to Southeast gradient is suggested and PD prevalence appears to be highest in Europe and North America, whereas rates in Japan, China and Africa are markedly lower. In the USA PD prevalence is much lower among blacks. Already in 1972, Kessler found a higher frequency of PD for whites compared with blacks. In a survey of PD in New York, age-adjusted prevalence rates were lower for blacks than for whites and Hispanics. Surprisingly however incidence rates were highest among black men, but these incidence rates were otherwise comparable across sex and ethnic groups. By ethnic group, the
cumulative incidence was higher for blacks than for whites and Hispanics, but more deaths occurred among incident black patients. These findings could result from a delay in diagnosis due to limited access to appropriate health services among these people. Some studies however show similar rates for African-American, Asian-American and European-American subjects. In a study among a cohort of American men of Japanese or Okinawan ancestry, epidemiological data are in general in accord with those from Europe and the United States. Incidence data are 5- to 10-fold higher at each age stratum than age-specific incidence figures from China. These findings most likely cannot be explained by methodological differences between Chinese and Western studies alone. However this possibility cannot be ruled out, as the Chinese data have not been verified yet by other studies. Similar findings have been observed in a study in Mississippi, where black men and women have PD prevalence rates more like white men and women than black men and women in Nigeria. These data suggest that risk of developing PD is more a function of environmental factors than racial ones. So different distributions of PD causing factors across populations may contribute to geographic differences in epidemiological findings. These factors could be differences in exposure to causative and protective influences, but also genetic differences in susceptibility to disease. It could be that an environmental agent might only act in genetically susceptible people.

Gender differences
Males tend to have a modestly increased age-adjusted PD prevalence. Male-to-female ratio range from 0.86 (in Japan) to 3.7 (Chinese studies). In a study in New York, age-adjusted prevalence was lower for women compared with men across all ethnic groups. However in another study, age-adjusted incidence did not differ between men and women in all ethnic groups. This is confirmed by the Rotterdam Study in which no significant gender differences in prevalence were found.

Symptoms

Motor symptoms
The classic triad of symptoms of PD consists of tremor, rigidity and hypokinesia. Postural impairment has been called the fourth major symptom of PD. The disease is a slowly progressive disorder and signs and symptoms develop usually over several years. In the early stages of the disease the signs and symptoms may be vague and non-specific in such a way that a reliable diagnosis can not yet be made.

The typical parkinsonian tremor is a 3-6-Hz distal resting tremor. It consists of alternate contractions of agonist and antagonist muscles, including flexors, extensors, pronators and
supinators of the wrists and arms during rest. This may result in a pill rolling movement of the hand. Often the typical parkinsonian rest-tremor starts on one side of the body. In most patients the signs will develop in due course on both sides, but asymmetry will usually persist throughout the disease. The legs or lower jaw may also be involved. The tremor tends to disappear with action. Resting tremor is found in 79% - 90% of patients with PD in clinical studies and in 76% - 100% in autopsy-proven studies. Some patients have little or no resting tremor but a predominant action or postural tremor. Tremor at rest may also be induced by neuroleptic agents.

Rigidity can be present in all four limbs and in the trunk, but mainly affects the arms and is often of the cogwheel type. The increase in tone is fairly equal in flexors and extensors, but slightly more in flexors. It can be diagnosed in 89% - 99% of parkinsonian patients. Bradykinesia means slowness of movements, whereas hypokinesia stands for poverty of movement. Hypokinetic features include facial hypomimia, reduced eye blinking, hypophonic speech and micrographia. There is difficulty in initiating movements, resulting in start hesitation. Rapid repetitive movements are impaired. Bradykinesia is present in 77% to 98% of patients with PD, but it is not unique to PD. It can also occur as a result of other extrapyramidal disorders, such as PSP, MSA, CBD and normal aging. Symptoms can be gravitated by contralateral activation or concentration on mental or physical tasks. Each one of these features can be present for a long time, before others develop. Symptoms usually begin unilaterally or asymmetrical. Later they are bilateral or generalised.

Gait is impaired in patients with PD as well. The patients walk slowly with small shuffling steps. Parkinsonian patients move in a rigid manner and turn en bloc. Their posture is stooped, because of flexion of the shoulders, neck and trunk. In PD the center of gravity is shifted forward. Walking can be hampered by stutter steps, resulting in start- and turn-hesitation, and sudden “freezing”. This phenomenon refers to the patient’s feet stuck to the ground while walking, rendering the patient unable to move with the lower body. It especially happens on turns and in elevators or doorways. Freezing and related phenomena are called motor blocks. It occurs in 32% of parkinsonian patients. Retropulsion refers to the phenomenon that the standing patient if pushed backward, is only able to regain his balance slowly by small and slow steps or even fails to do so and falls. When walking, patients may have problems stopping and legs are preceded by the flexed trunk, resulting in frequent little short steps or propulsive gait. This pattern is characteristic of advanced PD. In the beginning of the disease symptoms are unilateral, affecting only one side. Patients appear to drag a leg when walking and arm swing is decreased at the affected side. In a later stage, when the opposite side is affected as well, steps are short and the feet barely clear the floor. Usually symptoms stay asymmetrical, in contrast to normal aging. In a later stage parkinsonian patients may experience problems of autonomic dysfunction such as constipation, incontinence, hypotension and impotence. If this occurs in an early stage of PD, the diagnosis should be questioned.
Not only motor symptoms may occur. Another abnormality is for example an olfactory disorder. In PD there is an increase of the olfactory detection threshold\(^{70}\), which is probably due to the presence of Lewy bodies in the olfactory bulb and neuronal loss in the anterior olfactory nucleus\(^{14,69}\). Other features include increased saliva production and increased sweating.

None of the 3 major symptoms has enough sensitivity or specificity to diagnose PD. For this reason a scheme has been made for diagnostic classification: The UK Parkinson’s Disease Society Brain Bank clinical diagnostic criteria (see table 1: UK Parkinson’s Disease Society Brain Bank 1993)\(^{15}\).

Table 1

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<tr>
<th>STEP 1 DIAGNOSIS OF PARKINSONIAN SYNDROME</th>
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<tr>
<td>* bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)</td>
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<td>* and at least one of the following:</td>
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<td>- 4 - 6 Hz rest tremor</td>
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<td>- rigidity</td>
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<td>- postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction</td>
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<th>STEP 2 EXCLUSION CRITERIA FOR PARKINSON’S DISEASE</th>
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<td>* history of repeated strokes with stepwise progression of parkinsonian features</td>
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<tr>
<td>* history of repeated head injury</td>
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<td>* history of definite encephalitis</td>
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<td>* oculogyric crises</td>
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<td>* neuroleptic treatment at onset of symptoms</td>
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<td>* more than one affected relative</td>
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<td>* sustained remission</td>
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<td>* strictly unilateral features after 3 years</td>
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<td>* supranuclear gaze palsy</td>
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<td>* cerebellar signs</td>
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<td>* early severe autonomic involvement</td>
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<td>* early severe dementia with disturbances of memory, language and praxis</td>
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<td>* Babinski sign</td>
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<td>* presence of cerebral tumour or communicating hydrocephalus on CT scan</td>
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<td>* negative response to large doses of levodopa (if malabsorption excluded)</td>
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<td>* MPTP exposure</td>
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<th>STEP 3 SUPPORTIVE PROSPECTIVE POSITIVE CRITERIA FOR PARKINSON’S DISEASE</th>
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<td>(three or more required for diagnosis of definite Parkinson’s disease)</td>
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<tr>
<td>* unilateral onset</td>
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<td>* rest tremor present</td>
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<td>* progressive disorder</td>
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<td>* persistent asymmetry affecting side of onset most</td>
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<td>* excellent response (70 - 100%) to levodopa</td>
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<td>* severe levodopa-induced chorea</td>
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<td>* levodopa response for 5 years or more</td>
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<td>* clinical course of 10 years or more</td>
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Non-motor symptoms

In PD there are several other nonmotor clinical features, like dementia, depression and psychotic features.

Dementia

In 20 to 40% of patients with PD cognitive impairment develops and the risk of dementia in non-demented PD patients is almost twice that of age-matched non-demented elderly controls. Prevalence however is estimated to be 10.9%. Here it needs to be considered that PD patients with dementia have a shorter life expectancy. Dementia in PD is characterized by a severe dysexecutive syndrome without instrumental disorders like aphasia, apraxia or agnosia.

In several studies the influence of age at onset on the presentation and course of PD has been demonstrated. Young onset patients have little cognitive impairment even after a disease duration of over 20 years. Dementia mainly develops in patients with onset after 70 years. In this cohort of patients prevalence of dementia is more than twice that of younger patients. Usually it develops after several years of disease duration. This in contrast to diffuse Lewy body disease, where cognitive deficits occur very early (less than 2 years) or even precede motor symptoms. Other risk factors for developing dementia in PD are lack of education and severe motor deficits (UPDRS motor scores above 24). Cognitive deficits however are usually less prominent than motor symptoms.

Depression

Depression is estimated to occur in 30 - 60% of patients with PD at some point during the disease. It has been suggested that there is a natural tendency for chronic, disabling diseases to induce depression. However it appears that the prevalence of depression in patients with PD is higher than in other chronic disorders. Besides, the depression is unrelated to the severity of motor symptoms and depression can continue despite improvement in motor symptoms after L-dopa therapy. It is possible that depression precedes the motor symptoms of PD. There are some similarities between clinical and biochemical changes in PD and depression. Clinical similarities include akinesia and psychomotor retardation, while biochemical similarities include dysfunction in dopaminergic, noradrenergic and serotonergic systems. Reduced serotonergic function is associated with psychomotor retardation, reduced noradrenergic function with bradyphrenia and reduced dopaminergic function with extrapyramidal symptoms, cognitive slowing and more severe symptoms of depression.
**Psychotic features**

Psychotic symptoms may either be a manifestation of the disease itself, or it may be the result of therapy with dopaminergic agents\(^2^5\). Psychosis may also occur as a reaction to the disease and functional impairment ("reactive psychosis") as well, although this is probably a rare condition. About 30% of parkinsonian patients, treated with levodopa, have experienced psychotic symptoms and the lifetime prevalence may approach 50%. Visual hallucinations are most common and the images are usually fully formed human or animal figures. Usually insight is preserved\(^2\).

**Pathology findings**

The most prominent lesion in PD is the degeneration of neuromelanin-containing neurons in the pars compacta of the substantia nigra, which at post-mortem inspection turns visibly pale. Also selected aminergic brain-stem nuclei (catecholaminergic and serotoninergic), the cholinergic nucleus basalis of Meynert, hypothalamic neurons, small cortical neurons (particularly in the cingulate gyrus and entorhinal cortex), olfactory bulb, sympathetic ganglia and parasympathetic neurons may be involved in this progressive degenerative process.

Not all dopaminergic neurons are equally susceptible. Within the substantia nigra pars compacta, neuronal loss appears to be greatest in the ventrolateral part, followed by the medial part and the dorsal part\(^2^4\). This has been confirmed by Damier and coworkers\(^1^3\). It results in a regional loss of striatal dopamine\(^5^0\). The nigrostriatal dopaminergic neurons which project to the putamen are more affected than those which project to the caudate nucleus and nucleus accumbens. The latter one is believed to be responsible for akinesia and rigidity. This pattern of cell loss seems to be rather unique to Parkinson’s disease and is different of the pattern seen in normal aging. Neuronal loss of the medial nigral cells, with enhanced involvement of projections to the caudate nucleus, could result in more cognitive symptoms. Another possible clinical-pathological correlation may be based on degenerative changes of the olfactory bulb, causing anosmia. Autonomic dysfunction may be the result of lesions in the sympathetic and parasympathetic ganglia or degeneration in the intermediolateral columns of the spinal cord\(^7^5\). Some believe that dementia in PD may be the result of cell loss in the nucleus basalis of Meynert\(^7^7\).

The surviving, but dying catecholaminergic neurons may contain Lewy bodies, an important pathological feature. Lewy bodies are spherical, eosinophilic cytoplasmic inclusions with a dense core and peripheral halos, found in pigmented cells. In PD the most important anatomical sites where these bodies are located are the substantia nigra and locus ceruleus. They are not specific to PD. They appear as well in some other neurodegenerative...
disorders, like Alzheimer’s disease (AD). AD however is associated with cortical Lewy bodies, particularly in frontal, temporal, anterior cingulate and insular regions, whereas PD is associated with subcortical Lewy bodies, mainly in the substantia nigra. Lewy bodies are also seen as an incidental finding in about 10% of people older than 60 years. Gibb and Lees\textsuperscript{30} discovered that the age-specific prevalence of Lewy bodies in the brains of persons without clinical PD increased from 3.8 to 12.8% between the sixth and ninth decade of life. It has been suggested that the presence of incidental Lewy-bodies constitutes actually a presymptomatic stage of PD\textsuperscript{30}. McKeits however suggests a relationship between this “incidental” pathology and dementia with Lewy bodies\textsuperscript{62}.

The mechanisms of cell death in PD are still unknown. Several factors have been mentioned to play a role in neuronal degeneration in PD, like mitochondrial dysfunction, oxidative stress and excitotoxity and free radical production. It is believed that the neuronal death in the pars compacta of the substantia nigra is apoptotic\textsuperscript{6, 7}, but this has not been universally accepted yet and necrosis has been suggested as well.

### Other movement disorders in the elderly

Aging is a unequivocal risk factor for PD\textsuperscript{87}. It is also a major risk factor for several other movement disorders and neurodegenerative diseases.

There are many causes of movement or gait disorders in the elderly, of which some can easily be mistaken for PD. The many characteristics and patterns of gait disorders may look difficult and require special expertise, but simple observation of the patient and its gait may yield valuable information. The history from patients may reveal a stepwise progression, suggesting vascular disease. Pain with walking usually excludes a neurodegenerative cause of the gait disorder. Magnetic Resonance Imaging (MRI) may be used for screening for hydrocephalus or multiple infarcts. Positron emission tomography (PET) scans of the brain may for example help for diagnosing PD, MSA or PSP. Gait disorders in the elderly, irrespective their underlying pathology, contribute to the risk of falling and fractures\textsuperscript{89}. The higher risk of falling limits the elderly in their mobility and independence, also because of the fear of falling itself. Imms and Edholm surveyed in 1981 a group of older people (mean age, 78 years) and found that half of them limited their activity because of their concerns about mobility\textsuperscript{40}.

Many signs of gait disorders, slowing down and stiffening up, are accepted as being part of aging. However most of these signs may be signals of an underlying disease. Critchley already warned in 1931 that “an abnormal gait in the aged is frequently the result of disease outside the nervous system” (Critchley, 1931). In many cases gait disorders are of orthopedic (osteoarthrosis, osteomalacia, unsuspected fractures), endocrinological
(hypothyroidism), psychological (depressive state, fear of falling) or general (general muscle weakness) origin. Circulatory or respiratory systems may play a role as well in determining gait velocity because of the need to minimize energy expenditure. The incidence of subtle extrapyramidal signs on neurological examination of elderly persons with no known neurologic or psychiatric disorder is high. Bennett et al. showed that 35% of people over 65 years old had these subtle changes, while around 3% in similarly aged persons had PD. In a community study in North Carolina, 15% of adults over 60 years of age had some degree of difficulty with ambulation. In Western Europe 20-25% of people aged 80 or older, use mechanical aids for walking. A review of the variety of conditions, which can cause gait disorders or may be confused with PD, will be given here.

**Essential tremor (ET)**

One of the commonest causes of misdiagnosis of PD is essential tremor (also known as senile tremor, which is a misnomer). It is inherited as an autosomal dominant disorder with incomplete penetrance. A familial incidence is common in about one-third to one-half of cases. In the elderly however it is often sporadic. The incidence of essential tremor increases with climbing age. Considering prevalence Rautakorpi's study reported a prevalence of 12.5% in his population. In a study of a population aged 65 and older, Louis et al. found a prevalence of 4%. A higher prevalence of 23% in a population of people older than 70 years has been observed by Elble. Essential tremor is an action tremor with a frequency of 8- to 12-Hz (the resttremor in PD is 4- to 6-Hz). It may sometimes be present at rest as well, but generally increases with activity. The amplitude increases with age. According to Marttila and Rinne essential tremor accounted for 26% of cases of presumed PD. This misdiagnosing can occur because of many reasons. Both conditions frequently occur in the elderly. Parkinsonian patients sometimes suffer from a postural action tremor of the hands, as seen in ET. Patients with ET may have some bradykinesia and rigidity, which could be normal in the elderly. Besides, some hallmarks of PD, like asymmetric manifestation and a resting component of the tremor, can also be found in cases of ET.

However, there are also some striking differences between these two disorders. Essential tremor frequently involves the head in contrast to tremor in PD. Conversely, a resttremor of the leg or slow vertical jaw tremor is often seen in PD, but rarely in essential tremor. Also, hypokinesia may be present in PD, but not in ET.

**Vascular parkinsonism**

This results from multiple small cerebral infarcts, especially in the basal ganglia secondary to hypertensive cerebrovascular disease. Some patients with vascular parkinsonism present with a progressive gait disorder without a medical history of strokes. Chronic
Hypertension leads to fibrinoid necrosis and occlusion of arterioles supplying the basal ganglia. An akinetic rigid syndrome with urinary incontinence, dysarthria, abulia and dementia may occur. The extrapyramidal signs may coexist with pyramidal dysfunction like weakness, hyperreflexia, spasticity, pseudobulbar palsy, emotional lability and Babinski signs. These pyramidal signs may be important in differentiating this disorder from PD. The patient is slow and walks wide-based (unlike in PD) with short, shuffling, somewhat irregular footsteps. Postural stability may be impaired. As in PD freezing and start hesitation may occur.

However the upper body may show little or no parkinsonian features, thus no facial hypomimia may occur. Another term used for this disorder is lower body parkinsonism. Another striking difference with PD is usually the absence of tremor and no fatigue or decrement of rapid alternating movements. In vascular parkinsonism symptoms are symmetric in contrast to PD. However, if signs and symptoms are not clear cut, the differential diagnosis may be difficult.

Computerised tomography shows multiple infarcts but sometimes misses small ones. Magnetic resonance imaging demonstrates infarctions in the deep gray matter structures and ischemic changes in periventricular white matter. According to Sudarsky, vascular parkinsonism accounts for 15 - 16% of the gait disorders among elderly patients.

Multiple system atrophy (MSA)
MSA refers to a sporadic, gradually progressive, idiopathic neurodegenerative process of adult onset characterized by varying proportions of cerebellar dysfunction, autonomic failure, pyramidal signs and parkinsonism, that is poorly responsive to L-dopa therapy. Cell loss and gliosis (without Lewy bodies) are not only present in substantia nigra, but also in multiple other structures, like striatum, olives, pons, cerebellum, intermediolateral cell columns and Onuf's nucleus in the spinal cord. Most commonly MSA begins in the early 50s, progresses more rapidly than PD and has a reduced life expectancy (median survival = 9.3 years), this in contrast to PD (see above).

Parkinsonism occurs in 90% of patients with multiple system atrophy and is the dominant motor disorder is 80% of patients. In contrast to PD, the parkinsonism in MSA is usually bilateral. Unlike PD, tremor is often not the classical rest tremor, but an action tremor. Cerebellar dysfunction and pyramidal signs both occur in about half of patients.

Cerebellar dysfunction as the dominant symptom occurs in about 20% of patients. Autonomic failure appears in almost all patients with MSA. In PD patients it may occur as well, mostly in a late stage of disease, whereas in MSA it usually occurs earlier and more severe. Indeed, in MSA, autonomic failure may precede the motor symptoms by months or even years. Frequently, the first symptom is impotence in men and incontinence in both men and women (PD usually causes just frequency increase and urgency due to
hyperreflexia of the detrusor). Postural hypotension is another common feature in MSA, which may appear in PD as well, though less severe. Inspiratory stridor is present in about 30% of patients with MSA. When combined with parkinsonism it is highly suggestive of the diagnosis MSA\textsuperscript{72}. Other signs of autonomic failure are thermoregulation disturbances, gastro-intestinal problems and phenomena of Raynaud.

The response to levodopa of patients with MSA is usually absent or poor. However, in about 30% of patients an initial response has been reported, usually temporary. Levodopa induced dyskinesias are usually absent in MSA, so high doses of levodopa can be administered.

Differentiating MSA from PD may be very difficult, especially in an early stage of disease. There are some red flags suggesting non-idiopathic parkinsonism, like:

- Poor or no response to levodopa therapy
- Cerebellar, pyramidal or autonomic signs
- Symmetric start of symptoms
- Absence of classic rest tremor
- Early instability or falls
- Rapid clinical progression\textsuperscript{71, 74, 90}.

Some diagnostic tests may include external urethral (or anal) sphincter EMG, standard tests of cardiovascular autonomic function and imaging of the brain. Computed tomography or magnetic resonance imaging sometimes shows cerebellar or brainstem atrophy. Fluorodesoxyglucose positron emission tomography (PET) scanning may be useful as well\textsuperscript{20, 86}.

**Progressive supranuclear palsy (PSP)**

PSP, or Steele-Richardson-Olszewski syndrome, is an idiopathic degenerative disease, not uncommon in the elderly, which mimics PD. It occurs at a rate of 0.3 per 100,000 per year\textsuperscript{34} and its prevalence is 1.46 per 100,000. Pathologic investigation shows cell loss and neurofibrillary tangles, mainly in the brainstem, globus pallidus, nucleus subthalamicus and nucleus dentatus.

The clinical picture includes the tetrad of supranuclear gaze paralysis, axial rigidity, dementia and pseudobulbar palsy. It is associated with bradykinesia, severe postural disorder and frequent falls. Supranuclear gaze paralysis affects vertical gaze more than horizontal. Voluntary downgaze is slow and usually incomplete, but when the oculocephalic reflex is performed, full down gaze is obtained. Pseudobulbar palsy is characterised by dysphagia and dysarthria. Dementia is progressive and consists of slowing of cognition, memory deficits and personality changes suggestive of frontal lobe dysfunction\textsuperscript{52}. PSP may be distinguished from PD by the absence of rest tremor, the extended neck posture, rigidity more truncal than in limbs and abnormal eye movements. PSP patients have a stiff, broad-
based gait with ataxia. In contrast to PD patients they do not turn en bloc, but pivot. During pivoting they also tend to fall backwards.

**Cortico-basal degeneration (CBD)**

This disorder presents with a unique pattern of progressive impairment. It appears in mid-to late adult life, usually beginning after age 60. The duration of the illness until death is about 6 to 8 years. Pathologic and histologic evaluation reveal frontoparietal atrophy and neuronal loss, gliosis and swelling of the cell body with resistance to staining methods (achromasia). Prototypic findings are combined parkinsonian signs, other movement disorders and higher cortical dysfunction, with marked asymmetry of involvement. The most common extrapyramidal sign is rigidity, followed by bradykinesia. Sometimes tremor is present as well, but does not resemble the parkinsonian tremor. Tremor in CBD is more rapid (6-8Hz), is mainly during action, with varying amplitude. Other movement disorders include myoclonus and dystonia. Higher cortical dysfunction includes dyspraxia, involving the limbs, ocular and oro-facial muscles, cortical sensory loss, dementia (which usually occurs late in disease) and aphasia. A striking feature of CBD is the “alien hand/limb” phenomenon.

**Normal pressure hydrocephalus (NPH)**

This disorder is often idiopathic, but has also been associated with many neurological diseases. The classic triad of symptoms includes frontal dementia, urinary incontinence and gait disorder with unsteadiness. It is associated with enlargement of the cerebral ventricles on CT or MRI and a CSF pressure of 180 mm H₂O or less. A dynamic test is necessary to confirm the diagnosis of true (opposed to ex vacuo) hydrocephalus. The removal of 50 ml of cerebrospinal fluid may improve the symptoms of gait disorder. Mental dysfunction improves less than gait after a shunt. The patient walks wide-based with small steps, feet glued to the floor, marked imbalance and difficulty initiating walking. Postural instability with frequent falling may occur. Clinical signs may include hyperreflexia, extensor plantar responses and extrapyramidal signs, including hypokinesia and freezing during walking. Diagnosing NPH may be difficult since the three cardinal symptoms are common in the elderly. Besides gait disorder may precede other symptoms for several years and can be the only symptom for a long period. NPH is a common cause of gait disorders in the elderly, while in dementia it accounts for only 0 - 5% of persons with dementia. It should account for 4 - 6.7% of the gait disorders in the elderly.
Metabolic and endocrine disorders
Some of these disorders may produce akinetic-rigid syndromes. Hypothyroidism may cause parkinsonism with motor slowing. Hypoparathyroidism, resulting in calcifications of the basal ganglia, may produce a clinical syndrome consisting of parkinsonism, chorea, cerebellar dysfunction or a mixed extrapyramidal-pyramidal syndrome, resembling the lacunar state. Metabolic and toxic disorders causes gait disorders in 2.5% of the elderly.

Drug-induced parkinsonism
Many drugs commonly prescribed in the geriatric practice can affect gait. It can be caused by:
- drugs that deplete presynaptic dopamine stores, like reserpine or tetrabenazine
- neuroleptic drugs, like phenothiazines (chlorpromazine), butyrophenones (haloperidol), thioxanthines (flupenthixol) and substituted benzamides ( sulphiride)
- metoclopramide for gastrointestinal symptoms or migraine
- the atypical calcium blocking drug cinnarizine and flunarizine for vestibular disorders or hypertension
- others, like fluoxetine and rarely valproate

Drug-induced parkinsonism results in bradykinesia and rigidity with facial amimia, dysarthria and diminished or disappeared arm swing. Tremor is less common, but can be identical to the classic rest tremor of PD. Moreover symptoms of drug-induced parkinsonism usually are, just like in PD, asymmetrical. Drug-induced parkinsonism often resolves quickly within weeks after stopping those drugs. Sometimes this will take months, especially after depot neuroleptic medications.

Subclassification of PD
The variance in expression of the clinical syndrome of PD is large and suggests the existence of subtypes with distinct clinical patterns, especially concerning the age of symptom onset, rate of disease progression and clinical manifestations. Probably this clinical heterogeneity reflects a broad spectrum of manifestations of one pathological disorder: the loss of pigmented neurons in the substantia nigra pars compacta and the presence of Lewy bodies (intracytoplasmic inclusions). Several studies have tried to define clinical subgroups on the basis of distinguishing features, like family history of PD, variable progression and age of onset of symptoms of disease.
**Young-onset versus old-onset of PD**

Friedman has compared clinical expression of patients with onset age of symptoms above 70 years with patients with onset age below 45 years\(^{27}\). In this study there were some striking differences between these groups. The DATATOP (deprenyl and tocopherol antioxidative therapy of parkinsonism) study has investigated the variability in clinical expression by comparing several factors, like early versus late onset of disease, benign versus malign status, H/Y stage I versus H/Y stage II and tremor versus postural instability and gait disorder (PIGD) type\(^ {41}\). This study suggests that there are probably 2 different subtypes of PD: early-onset and late-onset of disease. Patients with early onset of PD progress at a slower rate, which has been confirmed by others\(^ {33}\). Patients with young-onset of disease are more sensitive to levodopa and to levodopa-induced dyskinesias, and dyskinesias seem to appear earlier in those patients. Not only will they develop focal dystonia early in the course of illness, but also end-of-dose phenomenon is more often observed in patients with young-onset of disease\(^ {29,73}\). Similarly, motor fluctuations, such as the wearing-off effect, tend to occur earlier in young-onset patients\(^ {47}\). Initial symptom in this group is usually tremor. This is in contrast to Friedman's results\(^ {27}\) who found that young-onset patients usually start with paraesthesia and have bradykinesia as dominant symptom. They tend to perform better on neuropsychological tests, but this may be explained by their younger age.

Patients with late-onset of disease have a more aggressive form of PD with faster progression and greater motor disability. They have as initial symptoms bradykinesia, postural instability, rigidity and less often tremor, according to the DATATOP-study. This study also suggests that motor deterioration in PD does not necessarily parallel cognitive decline and it is postulated that cognitive impairment in PD results mainly from a nondopaminergic deficit. According to Friedman\(^ {27}\) old-onset patients with PD more often have tremor as both presenting and dominant symptom. Old-onset parkinsonian patients more frequently develop psychotic complications and less frequent dyskinesia as complication of levodopa treatment than young-onset ones. Friedman found a striking difference in symptomatology of psychotic complications. Whereas old-onset patients used to have simple, mostly visual hallucinations with preserved insight, young-onset ones tend to develop paranoid behaviour without preserved insight. The number of young-onset patients with psychotic complications however was very low in this study. There was no striking difference in overall functioning based on activities of daily living (ADL) between those two groups. According to Friedman\(^ {27}\), the lesion in young-onset PD concerns predominantly the dopaminergic system. This monosystemic lesion may explain the greater susceptibility to dyskinesia (and the fact that bradykinesia is the dominant symptom of this disease). Lower susceptibility to dyskinesia in old-onset parkinsonian patients could be the result of age-related decline in the number of dopaminergic receptors in striatum. In contrast old-onset patients are more susceptible to developing psychotic complications, probably due to more widespread lesions of the
central nervous system resulting from ageing. Older people are in general more likely to develop psychotic reactions to various external stimuli, e.g. infections, intoxications, etc. Age-related brain atrophy involving also other neurotransmitter systems is probably the reason for the different symptoms in PD between old-onset and young-onset patients.

Some studies have observed a higher frequency of a first-degree relative with PD in young-onset patients, although other studies found no difference in the number of affected relatives among young- and old-onset cases. Others have noted an increased exposure to farming and rural living in patients with young-onset of disease. Despite the differences in clinical manifestation, the cellular morphology and frequency of Lewy bodies in the substantia nigra are identical in young- and old-onset cases.

Other subtypes of PD
Several other studies have investigated the existence of possible subgroups of PD, including young onset, tremor dominant, postural instability/gait disorder predominant, benign and malignant forms. Comparing tremor-dominant versus postural instability/gait disorder-dominant PD (PIGD), greater motor disability has been found in the latter group. Patients with tremor as dominant symptom usually did not only have more severe tremor at rest, but also more severe action- and postural tremor. PIGD patients had, in addition to their greater postural and gait difficulties, more severe bradykinesia and rigidity.

Some authors have divided patients into benign or malignant groups based on duration of symptoms and stage of disease. Patients were arbitrarily considered to have a benign form of PD if they were Hoehn and Yahr stage 2 or less, combined with parkinsonian symptoms for 4 years or less. In contrast, patients with malignant PD were those with early postural imbalance, while disease duration is less than 1 year. Patients with a benign form of PD usually were younger at onset of disease and had tremor as dominant symptom. Indeed, benign tremulous parkinsonism is considered to be a well-recognized subgroup of patients with a relatively nonprogressive, long-term course of disease. The benign group had an earlier onset than the malignant one and the latter one performed slightly worse on the Mini Mental State Examination, although this difference was not statistically significant after adjusting for age. To distinguish the benign form from the malignant one, other factors may be important as well, like response to medication, genetic factors and cognitive impairment. Hely et al suggest that patients with a benign form of PD have mild dyskinesia, if present, and that none of these patients had dementia or hallucinations. All of them are responsive to drugs.

Graham and Sagar have investigated the heterogeneity in PD, using a data-driven approach. They suggested the existence of three distinct subtypes:

- a motor only subtype, without intellectual impairment
- a motor and cognitive subtype
- a rapid progressive subtype
The latter group is characterized by an older age of disease onset than the other subtypes, rapidly progressive motor and cognitive disability and more orthostasis. Because of the rapid progression patients belonging to this subtype have a shorter life expectancy than the other groups. This is confirmed by Louis et al.\(^{54}\), who found that mortality increases with climbing of the years, the development of dementia and the severity of motor disability. Gender may be associated with a different progression of PD. According to the Sydney multicentre study of Parkinson’s Disease, dyskinesia develops earlier in women during the first 10 years of disease. After 10 years there is no significant difference in the prevalence of dyskinesia, but women tend to have a higher score in Hoehn and Yahr stage\(^{37}\).

**Brain metabolism in aging and Parkinson’s Disease**

During development and aging, the brain will change anatomically and physiologically to support the behaviour of normal adults. Chugani et al.\(^{8}\) have investigated the maturation of the brain during the first years of life by using positron emission tomography (PET) and 2-deoxy-\(^{18}\)F-fluoro-D-glucose (FDG). They discovered that in the first 4 weeks of life (the neonatal period), the most important region of metabolic activity is the primary sensorimotor area, while high activity was also found in the thalamus, brainstem and cerebellar vermis. The second postnatal month a small increase in metabolism in calcarine and temporal cortices can be seen. Approximately 3 months after birth, considerable rises in metabolic activity in the anterior parietal, temporal and calcarine cortices as well as in basal ganglia and cerebellar cortex were found. By 1 year, the metabolic pattern resembled that in adults, but absolute values were lower than adult ones. Adult rates were reached by 2 years of age. Metabolic rates continued to rise until 3 - 4 years, so values exceeded those of adults by a factor of approximately 2. These high values were maintained until age 8 - 9. At this age, they begin to decline and by the end of the second decade adult values are reached. The highest increases in metabolic activity were observed in the cerebral cortices\(^8\).

Aging is associated with the degeneration of specific neural systems. Normal aging is predominantly characterized by metabolic changes in the prefrontal cortex. By using FDG-PET scans metabolism of these systems can be investigated. Moeller and coworkers\(^{65}\) have tried to explore the metabolic topography of aging. They found various topographic profiles. One was characterized by relative frontal hypometabolism associated with covariate metabolic increases in the parietooccipital association areas, basal ganglia, mid-brain and cerebellum. Another one revealed relative basal ganglia hypermetabolism associated with covariate decreases in frontal premotor cortex\(^{65}\). Mielke et al also found a decline of regional cerebral glucose metabolism in frontal areas\(^{63}\).
Although the most important lesion in PD is located in the substantia nigra and its dopaminergic projections, lesions of the presynaptic nigrostriatal dopamine system result in widespread abnormalities in regional brain metabolism. To define the metabolic topography of parkinsonism the same strategy as above has been used. According to the results of Eidelberg and coworkers, the metabolic profile of PD is characterized by increased activity in the lentiform nucleus, thalamus, pons and cerebellum whereas activity was decreased in the lateral frontal, paracentral and parietal association areas. Increase in activity in the lentiform nucleus and thalamus in PD is consistent with experimental animal studies. Increased metabolism in the ventral thalamus has been confirmed by others. The subject scores for the metabolic profile in PD correlated with the individual Hoehn and Yahr score and with rigidity and bradykinesia ratings, but not with tremor. The reproducibility of this unique pattern of regional metabolic covariation in patients with PD has been assessed by Moeller et al. This topography appears to be highly reproducible across patient populations and tomographs.
Chapter 2

Reference List


Parkinson’s disease: symptoms and age dependency


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