Early Parkinson's Disease

Incidence, clinical features and quality of life in a population-based cohort study.

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Contents

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Scientific environment

The present study was based on the Norwegian ParkWest study, a multicentre study conducted as a joint initiative from and with participation of the Norwegian Center for Movement Disorders and all five departments of Neurology in the study area. The author was PhD student at the University of Bergen and the Centre for Clinical Research at the Haukeland University Hospital provided support for statistics.

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Abstract

Background: The prevalence of Parkinson's Disease (PD) in Norway is about 100/100 000 inhabitants. For planning of health care needs and for research purposes, incidence figures are considered the more valuable information, but have in Norway not been available for PD. Earlier incidence studies have shown variable results, likely due to methodological differences. To improve comparability, research criteria for high quality incidence studies of PD have been proposed in 2003.

PD is more frequent in men than women, but the underlying causes are not clear. As the difference does not persist throughout all studies and geographic areas, further evidence on the issue is needed, also concerning clinical disparities between genders.

Non-motor symptoms have in the last two decades been increasingly recognized as important contributors to the clinical picture of PD, the disease burden and the quality of life of patients. Knowledge on the presence, severity and consequences of non-motor symptoms, including autonomic and sensory disturbances, is best for mid-stage and advanced PD, but insufficient for the earliest disease stages. There are furthermore discussions as to whether motor or non-motor symptoms are the most important contributors to reduced quality of life in PD.

Patients and methods: We followed proposed research criteria and aimed to recruit all cases of incident PD from the Norwegian counties Sogn og Fjordane, Hordaland, Rogaland and Aust-Agder, comprising a base-population of about 1 million inhabitants. Cases with probable PD were invited to further examinations and longitudinal follow-up. Motor symptoms, non-motor symptoms and quality of life were assessed soon after diagnosis in drug-naïve state, and one year and 3 years later.

Results and conclusions: Based on 265 cases identified during 22 months and finally diagnosed as incident PD, the crude incidence of PD in Norway was estimated to 13.7/100 000, corresponding to 12.6/100 000 when adapted to a European standard population. This figure is in line with other modern incidence studies in Europe,

although there is a persisting, considerable range of the presented incidence numbers (8.4-15.8/100 000). Further homogenization of the methodology for incidence studies may therefore be needed, but could be difficult to achieve.

We confirmed an increased risk for PD in men with a male to female ratio of 1.58. Beside a slightly later onset in women clinical differences were lacking in our study. We could thus not provide supporting evidence for neuroprotective mechanisms in women that are effective after PD has become clinically overt.

Autonomic and sensory symptoms and signs were very frequent in early, untreated PD. Most frequent were reduced olfaction (59%), urinary problems (47%), increased saliva/drooling (42%), constipation (39%) and sensory complaints (34%), all of which occurred significantly less frequent in controls matched for age and gender. Most patients (58%) were not impaired in their daily activities by any of these symptoms. Although health-related quality of life (HRQoL) was overall reduced in patients compared to controls already at diagnosis, the contribution of autonomic symptoms was small. The main predictors of reduced HRQoL were fatigue and depression, and to a minor degree also sensory complaints. The most important motor symptoms to affect HRQoL were impairment of gait and of the ability to conduct personal needs as eating, dressing, hygiene and to turn in bed. These issues have not been highlighted earlier, and should guide the focus of treating physicians to the here mentioned symptoms in the meeting with patients with very early PD.

Our results further indicate that, overall, non-motor symptoms have more impact on HRQoL than motor symptoms, both at the time of diagnosis and three years later. As our patients were initially drug-naïve, this dominance seems to be independent of the often reported better recognition and treatment of motor vs. non-motor symptoms.

List of publications

Paper I:

Alves G., Müller B., Herlofson K., HogenEsch I., Telstad W., Aarsland D., Tysnes O-B., Larsen J.P., for the Norwegian ParkWest study group (2009): **"Incidence of Parkinson's disease in Norway: the Norwegian ParkWest study"**, *J Neurol Neurosurg Psychiatry, Vol. 80: 851-857.*

Paper II:

Müller B., Larsen J.P., Wentzel-Larsen T., Skeie G.O., Tysnes O-B.(2011): **"Autonomic and sensory symptoms and signs in incident, untreated Parkinson's Disease: Frequent but mild"**, *Mov Disord, Vol. 26: 65-72.*

Paper III:

Müller B., Assmus J., Larsen J.P., Haugarvoll K., Skeie G.O., Tysnes O-B. (2013): **"Autonomic symptoms and dopaminergic treatment in den novo Parkinson's disease"**, *Acta Neurol Scand, Vol. 127: 290-294.*

Paper IV:

Müller B., Assmus J., Herlofson K., Larsen J.P., Tysnes O-B. (2013): **"Importance of motor vs. non-motor symptoms for health-related quality of life in early Parkinson's disease"**, *Parkinsonism Relat Disord, Vol. 19: 1027-1032.*

Abbreviations

CBD	Corticobasal degeneration
COMPASS	Composite Autonomic Symptoms Scale
COMT	Catechol-O-methyltransferase
CT	Computed x-ray tomography
D1	Dopaminergic receptor type 1
D2	Dopaminergic receptor type 2
DBS	Deep brain stimulation
DLB	Dementia with Lewy bodies
ESS	Epworth Sleepiness Scale
FOG	Freezing of gait
FP-CIT-SPECT	Fluoropropyl-carbomethoxy-iodophenylnortropane single photon emission computed tomography
FSS	Fatigue Severity Scale
GPe	Globus pallidus externus
GPi	Globus pallidus internus
HRQoL	Health-related quality of life
HY	Hoehn & Yahr scale
ICD	Impulse control disorder
LED	Levodopa-equivalent daily dose
LRRK2	Leucine-rich repeat kinase 2
MADRS	Montgomery and Aasberg Depression Rating Scale
MAO-B	Monoamine oxidase type B
MCS	Mental compound score of the SF-36
MIBG	^{123}I-mataiodobenzylguanidine
MMSE	Mini mental state examination
MPP^+	1-Methyl-4-phenylpyridinium (metabolite of MPTP)
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI	Magnetic resonance imaging
MSA	Multiple system atrophy
MSA-C	Multiple system atrophy- cerebellar subtype
MSA-P	Multiple system atrophy- parkinsonian subtype
NMDA	N-methyl-D-aspartate
NMS-Quest	Non-Motor Symptoms Questionnaire
NMSS	Non-Motor Symptoms Scale
NSAID	Non-steroidal anti-inflammatory drug
PCS	Physical compound score of the SF-36
PD	Parkinson's disease
PDSS	Parkinson's disease sleep scale
PET	Positron emission tomography
PIGD	Postural instability and gait difficulty subtype of PD

pMDS-UPDRS	Preliminary version of the Movement Disorders Societies revision of the UPDRS
PSP	Progressive supranuclear palsy
QoL	Quality of life
RBD	Rapid eye movement sleep behaviour disorder
REM	Rapid eye movement
SAS	Starkstein Apathy Scale
SCOPA-AUT	Scales for Outcome in Parkinson's disease-Autonomic
SF-36	Short-form Health Survey
SNc	Substantia nigra, pars compacta
SNr	Substantia nigra, pars reticulata
SPECT	Single photon emission computed tomography
SPSS	Statistical Package for the Social Sciences
SSRI	Selective serotonine reuptake inhibitor
STN	Nucleus subthalamicus
UK	United Kingdom
UKPDBB	United Kingdom Parkinson's Disease Society Brain Bank
UPDRS	Unified Parkinson's Disease Rating Scale
UPSIT	University of Pennsylvania Smell Identification Test
Vim	Ventral intermediate nucleus of the thalamus

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder primarily defined by movement disturbances which usually are asymmetric and include involuntary shaking (tremor), stiffness (rigidity), slowness and reduced amplitude of movements (bradykinesia), and frequently also disturbances of balance (postural instability). Beside the motor disturbances, a large variety of non-motor symptoms are observed in PD which range from autonomic, sensory and mood disturbances to impaired cognition and sleep. PD occurs mainly in individuals aged 60 years or older, but can also affect much younger people. Beside a minority of clearly inherited cases, the cause of Parkinson's disease is not known.

1.1 Historical background

James Parkinson, an English surgeon, was in 1817 the first to describe the symptoms of the disease today named after him in his "Essay on the shaking palsy"[1], which was based on the observation of six patients. Although he characterized the condition by its motor symptoms, he also recognized non-motor symptoms affecting autonomic function and sleep. In 1877, Jean-Martin Charcot in Paris improved the clinical description of the condition and honoured Parkinson's work by introducing the term "maladie de Parkinson" (Parkinson's disease). Although James Parkinson hoped his work would stimulate research on the pathophysiological background of the disorder,[2] it took until 1953 to identify characteristic neuropathological changes and cell loss in the substantia nigra as key-factors in PD.[3]

At this time, there was no treatment available to reduce the symptoms of the disease and it led to death from the complications of immobility. In 1957, Arvid Carlsson demonstrated the reversibility of drug-induced parkinsonism in animals by administration of levodopa,[4] and some years later, dopamine-depletion in the striatum of patients with PD was found.[5] This led to the crucial trial of Birkmayer and

Hornykiewicz, who for the first time administered levodopa to patients with parkinsonism by injection, what induced dramatic, although transient improvement of motor function.[6] In 1967, George Cotzias had optimized the treatment by stepwise and slow increase to higher doses, thus achieving pronounced symptom reduction and less side effects.[7] Since then, treatment options have improved substantially, and many patients can achieve close to normal motoric functioning at least up to some years after the diagnosis of Parkinson's disease is established. Side effects of levodopa, especially motor fluctuations, have stimulated the development of dopamine agonists with longer half-life, and beneficial effects of Bromocriptine were reported in 1974.[8] Thermoelectric lesions of thalamic neurons were before and after the introduction of levodopa applied for effective tremor reduction. From the1990s, this was increasingly replaced by deep brain stimulation, which offers better control of effect and side effects in selected patients and includes further targets in the basal ganglia.[9,10]

The large variety of non-motor symptoms associated with PD was widely neglected until the early 1990s, but has since achieved increasing attention. Cognitive, autonomic, sensory and sleep-related symptoms are now accepted as core features of the disease and recognized as major contributors to reduced quality of life in PD.[11,12] Symptoms like olfactory dysfunction, constipation and REM sleep behaviour disorder (RBD) frequently antedate the manifestation of motor symptoms considerably, thus defining a period of pre-motor PD.[13] In the first decade of the 21st century, PD-specific rating scales have been developed or modified to cover also non-motor symptoms extensively.[14-16]

In 1912, the German-American neurologist F.H. Lewy discovered protein-rich inclusions in brainstem neurons of patients with PD.[17] These structures, today known as Lewy bodies, are still the histopathological hallmark of PD. When in 1997 the first mutation causing familial PD was discovered in the α-synuclein gene, the content of Lewy bodies was short after identified as accumulations of the protein α-synuclein.[18] This initiated a fundamental improvement of the knowledge and understanding of the

pathophysiological mechanisms in PD. Based on the now possible immunostaining of α-synuclein in Lewy bodies, Heiko Braak could develop a histopathological model of gradual spreading neuropathological changes from the brainstem to midbrain and cerebral structures.[19] His model integrates the frequently observed initial appearance of selected non-motor symptoms, followed by the classical motor symptoms and in later stages by cognitive impairment due to cortical involvement. It does, however, not explain the whole variety of observed clinical courses and pathological findings.

Today, more than 20 mutations are known that are associated with monogenic familiar PD or an increased risk to develop the disease,[20] and knowledge about the neuropathology and pathophysiology of PD and its symptoms has improved considerably.[21,22] However, while about 10-20% of cases of PD may possibly be explained by monogenetic mechanisms, the essential disease-causing mechanisms for the remaining 80-90% of cases remain unknown even today.

1.2 Etiology and pathophysiology

1.2.1 Basal ganglia

Movements are finally initiated by signals from the motor cortex, which projects via the pyramidal tract to lower motor-neurons in the brainstem and medulla, and further via cranial or peripheral nerves directly to the executing muscles. Movements are frequently complex themselves, but do also interact with external and internal circumstances mediated by sensory-motor, sensory, emotional and cognitive signals. The role of the basal ganglia is to facilitate complex and automated movements and adapt them to current and memorized multifactorial circumstances.

The basal ganglia are subcortical nuclei or neuron-groups composing a functional network. They include the striatum (caudate nucleus and putamen), globus pallidus externus (GPe) and internus (GPi), substantia nigra (with pars compacta, SNc, and pars reticulata, SNr) and nucleus subthalamicus (STN). Cortical input to the striatum

is processed in this network and the output from GPi and SNr is facilitating or inhibitory for cortical activity. The superior objective is to facilitate wanted and inhibit unwanted movements.[23,24] Beside a circuit for modification of motor activity, the basal ganglia comprise also circuits to process oculo-motor, associative/cognitive and limbic signals.[25]

The hypokinetic movement disturbances in PD may be explained by a model of the functional connectivity within the basal ganglia, proposed in 1990.[24] Dopaminergic nigro-striatal projections from the SNc are excitatory for a direct pathway via type 1 dopaminergic (D1)-receptors, and inhibitory for an indirect pathway, via D2 receptors.[26] Reduced activity of nigro-striatal neurons to both pathways leads to increased GPi/SNr activity, which inhibits thalamo-cortical excitatory feedback, meaning movement is rather inhibited than facilitated.

In early PD, overactivity of the basal ganglia can compensate for the beginning loss of nigro-striatal dopaminergic activity. With further progression, the balance is deranged and the inhibitory output increases.[27] It is estimated that motor symptoms emerge when about 60% of dopaminergic neurons in the SNc and 80% of striatal dopaminergic activity are lost.[28]

However, basal ganglia function is today regarded as much more complex, including feedback mechanisms, multiple interconnections between several ganglia, and modulation of firing patterns in response to reduced dopaminergic activity – as opposed to changed net activity.[29]

1.2.2 Neuropathology

Degeneration of dopaminergic neurons in the substantia nigra pars compacta is the central pathological mechanism in PD. This process is usually associated with the occurrence of eosinophilic, α-synuclein containing protein-aggregations called Lewy bodies and Lewy neurites, the histopathological hallmark of PD.[30,31] However, beyond the substantia nigra, neuropathological changes are also observed in other

brainstem nuclei (nucleus basalis of Meynert, dorsal motor nucleus of the vagal nerve, locus coeruleus, raphe nucleus), nucleus Edinger-Westphal in the midbrain, striatum, cerebral cortex and the olfactory bulb, as well as parts of the peripheral nervous system and several organs like skin, retina, submandibular glands and the heart.[22] This may explain the broad spectrum of non-motor symptoms associated with PD.

Based on the dominating presence of α-synuclein pathology, PD is classified as a synucleinopathy, together with Dementia with Lewy bodies (DLB), Multiple system atrophy (MSA) and Pure autonomic failure. Other neurodegenerative disorders with parkinsonian features like Alzheimer's disease, Corticobasal degeneration and Progressive supranuclear palsy (PSP) are characterized by abnormal accumulation of tau-protein, and therefore grouped as tauopathies. Interestingly, both groups show some clinical and histopathological overlap, indicating shared pathophysiological mechanisms at least in a proportion of cases.[32] Another typical pathological feature of Alzheimers-disease, β-amyloid plaques, is also overlapping and frequently found in PD with dementia and Dementia with Lewy bodies.[33]

In PD, the pathognomonic Lewy bodies and Lewy neurites are localized in the cytoplasma of neuron bodies and neurites, respectively. More than eighty years after their initial description by Friedrich H. Lewy,[17] the protein α-synuclein, normally involved in synaptic membrane processes, was discovered as their main component.[18,21] Abnormal accumulations of α-synuclein occur as oligomers, protofibrils and fibrils, the latter accumulating further to Lewy neurites or Lewy bodies.[34] Although associated with neuronal degeneration, Lewy bodies are not necessarily the cause of cell death. It has been suggested that α-synuclein oligomers and protofibrils are cytotoxic, while the fibrillar aggregates may represent a protective cellular storage form which prevents from cell death until the load of abnormal proteins exceeds the storage capacity.[34,35]

The primary structure responsible for the degeneration of unwanted proteins is the ubiquitin-proteasome system, which depends on mitochondrial energy-supply. Its failure and the resulting insufficient removal of pathologic proteins like α-synuclein

are associated with neurodegeneration.[36] Mitochondrial dysfunction has been linked to PD initially due to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridin), an impurity in synthetic heroin which in the 1980s led to parkinsonian symptoms in drug-addicts by destruction of dopaminergic neurons in the substantia nigra.[37,38] After oxidation to MPP^+, it accumulates in mitochondria and inhibits complex I, an essential part of the respiratory chain, and leads finally to toxic insult of the cell.[39] Animal models of MPTP-induced parkinsonism have contributed enormously to the understanding of basal ganglia function, the pathogenesis of PD and to the development of treatment for PD. Mitochondrial dysfunction has further been linked to PD based on findings involving other complex I inhibitors like pesticides or certain herbs,[40,41] reduced complex I activity found in substantia nigra and frontal cortex,[42-44] several gene-mutations linked to mitochondrial function[35,39] and increased oxidative stress.[35,45]

Also lysosomal dysfunction facilitates the PD-specific, pathological protein aggregations[46] and mutations in the glucocerebrosidase gene, which encodes for a lysosomal enzyme, increase the risk for PD.[47] Other factors that seem to be involved in the pathophysiology of PD are iron-accumulation, dopamine itself and neuromelanin, all of them being associated with increased oxidative stress and neurodegeneration.[48,49]

The observation that more severe symptoms in PD are associated with more widespread occurrence of Lewy bodies, while motor symptoms only become manifest when severe damage of the substantia nigra is already reached, motivated the German pathologist Heiko Braak to study a large series of cases with variable degree of Lewy body pathology, including cases without clinical symptoms of parkinsonism. In 2003, he published a hypothesis based on findings in 110 cases, suggesting a sequential development of Lewy pathology and corresponding degeneration:[19]

- In stage 1 and 2, the olfactory nucleus and bulb, medulla oblongata and pontine tegmentum are affected, including the nuclei of vagus, glossopharyngeus, raphe and coeruleus.
- Only in stage 3, the midbrain is reached with pathology in the substantia nigra pars compacta.
- In stage 4, lesions occur also in the basal prosencephalon and mesocortex.
- In stage 5 and 6, increasing pathology of the neocortex is observed.

With each stage, the severity of pathology in the affected structures increases.

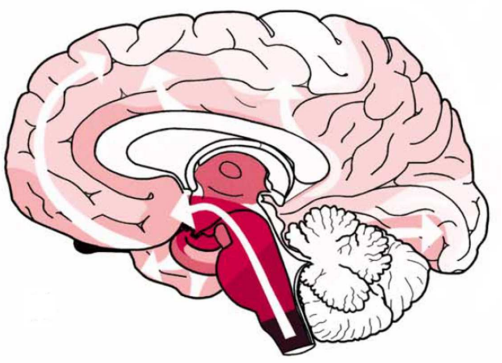

Figure 1: Progression of PD-related neuropathology as supposed by H. Braak et al. (2003).[19] More intense color indicates earlier and more severe affection. (Copy from original publication)

There has been substantial critic of this hypothesis, mainly based on a lack of a clinico-pathological correlation with respect to severity of parkinsonism, and the fact that cases with the two initial stages of α-synucleinopathy did not show affection of the substantia nigra, which means it remains hypothetic to propose that these individuals would – if not died – have proceeded further according to the staging scheme or developed clinical PD.[50] However, Braak's hypothesis has shed a new light on the earliest stages of PD including the time when the disease is pathophysiologically established, but motor symptoms have not yet emerged, the premotor phase. It has long been recognized that some autonomic symptoms and

hyposmia are associated with PD already in the early stages[51-53] or increase the risk to develop PD,[54] and Braaks model may explain these phenomena in part by initial involvement of brainstem structures and the olfactory bulb. However, the model has limitations as the spinal cord and peripheral nervous system were not examined.[19]

The molecular mechanisms for the hypothesized spreading pathology as well as its initiation are not yet resolved. Braak and coworkers have suggested that the initial changes occur in the olfactory bulb and/or the gastrointestinal mucosa, induced by an exogenous, neurotropic, unknown biological agent. Centripetal axonal transmission to brainstem nuclei then would allow further spreading within the central nervous system – the dual-hit hypothesis.[55-57] Based on a number of pathophysiological similarities it has hereupon been suggested that PD and other neurodegenerative disorders may be prion-like diseases. Essential in this context are protein-misfolding and intercellular transmission of the abnormal proteins,[58] a mechanism suspected after Lewy-patholgy was identified in graft cells transplanted into the striatum of PD patients.[59,60] There is, however, no evidence for infectious attitude in PD, and no clue of what could be the initiating pathogenic external agent.

1.2.3 Etiology and risk factors

Despite a small group of monogenic familial cases with PD or a parkinsonism at least in part resembling PD, there is no known single cause of PD. However, a number of factors have been identified that may interact with the risk to develop PD, but with considerable variability concerning degree and direction of the modification, as well as the quality and quantity of the available evidence. An interaction between genetic risk factors and environmental or other individual factors is suspected and has been shown in single studies. Overall, available evidence on risk-factors for PD explains only a minor proportion of cases and underlines the presumably heterogeneous etiology of this disorder.

Genetic factors

Mitochondrial dysfunction, α-synuclein accumulation and protein-mishandling in the ubiquitin-proteasome-system are pathways of a number of gene-mutations identified in PD.[35,39] Some mutations cause classic Mendelian, familial parkinsonism with autosomal dominant or autosomal recessive heredity. Recent advances in genetic research have allowed genome-wide association studies and promoted the identification of a number of risk-loci. They are associated with modified risks to develop PD ranging from a 1,1 to 1,4-fold increased risk to 0,95 to 0,7-fold decreased risk to develop PD, which is accumulated when several risk-loci are present in the same individuals.[20]

The first gene mutation identified in PD was in the α-synuclein gene (SNCA, PARK1), a rare cause of autosomal dominant PD.[61] A number of mutations in the gene lead to synthesis of abnormal α-synuclein protein, which can impair mitochondrial function and accelerate formation of pathologic α-synuclein aggregates.[62,63] The clinical picture resembles classic PD in a proportion of cases, but for the rest, the clinical spectrum is broad with several atypical findings. Interestingly, cases with triplication of the gene present more severe phenotypes than duplication, indicating a relation between gene defect-dosage and severity.[20,64]

Mutations in the LRRK2-gene (leucin-rich repeat kinase 2, PARK8) are the most common known cause of autosomal dominant PD and several mutations associated with increased risk of PD have been identified. Clinical and histopathological changes resemble to a large extent sporadic PD with widespread typical Lewy-patholgy, but atypical cases and tau-pathology do also occur.[20] Of special interest is the age-dependent penetrance of the most common G2019S mutation in the LRRK2-gene, ranging from 28% at 59 years to 74% at 79 years, which leads to a pattern of sporadic occurrence.[65]

The most common mutations in autosomal recessive PD occur in the Parkin gene (PARK2) and may account for about 10% of young-onset PD cases. Lewy-bodies lack

usually, but were found in some cases.[20,66] Mutations in PINK1 (PARK6) and DJ-1 (PARK7) are less frequent, but clinics and pathology are in many aspects similar to Parkin-mutations.[67]

Age

Increasing age is a known risk factor for both PD and other neurodegenerative diseases as e.g. Alzheimer's disease. A systematic review of available incidence studies from 2003 documents an extremely rare occurrence of PD before the age of 40. The incidence is reported to 3-10/100 000 at age 40-49 and increases in some studies to over 100/100 000 for over 70 years old individuals. The peak-incidence is often found for the decade 70-79 years, others report further increase for age above 80.[68] The underlying mechanism is not resolved. Continuous increase of the incidence throughout all ages could indicate that neurodegeneration in PD simply is an exaggeration of normal aging, ultimately indicating that we all would develop PD if we lived long enough. Increased oxidative stress, mitochondrial dysfunction and abnormal protein deposition (including α-synuclein) are joint features of both aging and PD, but the pattern of cell loss is different in PD and aging.[69,70] Age-related changes may, however, increase the susceptibility for induction of Parkinson-specific neurodegeneration. The cause of this selective vulnerability is not clear, but dopaminergic neurons, especially their synapses, may be more prone to degeneration as production of dopamine increases oxidative stress.[70]

Gender

Parkinson's disease occurs in men about 1.5 times as frequent as in women, at least in western populations and with a considerable heterogeneity between studies.[71-75] The male-preponderance seems to increase with age and is often absent in the group under 60 years of age. In addition, there is no evidence for gender-related differences in the risk for PD in Asian populations, independent of age.[72]

The onset of PD symptoms seems to be slightly delayed in women compared to men.[76] Other reports on differences in the clinical appearance of PD in women vs.

men include more frequent initial presentation with tremor,[76,77] worse instability scores in early PD,[77,78] more problems related to sleep/fatigue and mood/cognition,[77,79,80] more frequent or more severe dyskinesia,[81-83] while REM sleep behaviour disorder (RBD) occurs more frequent in men.[84] However, none of these findings is consistent in all reports, the overall severity of motor-symptoms is usually reported similar in men and women,[76,78,79,81] and differences in the natural rate of progression have not been described.

The most consistent gender difference in PD remains therefore the increased risk for PD in western men vs. women older than 60 years.[72] Estrogens are thought to play a role here, as their neuroprotective effect on dopaminergic neurons has been demonstrated in animal models,[85,86] and oestrogen can reduce oxidative stress and protect dopaminergic neurons against apoptosis.[87] In accordance with that, Haaxma demonstrated better preserved dopaminergic activity in dopamine transporter imaging with single photon emission computed tomography (SPECT) in women vs. men with PD.[76] But clinical studies show conflicting results. Women who underwent oophorectomy prior to menopause had an increased risk to develop PD,[88,89] but no effect was found for early menopause or oestrogen-replacement therapy.[88,90] A small clinical trial of oestrogen-use in women with PD showed improvement of motor symptoms, but follow-up was short.[91] Inhibition of the dopamine-degrading enzyme Catechol-O-methyltransferase (COMT) by oestrogens may account for this symptomatic effect.[92]

Increased divergence of the risk curves after menopause-age and a similar risk for men and women at young age and in Asian populations indicate that oestrogens cannot be the only mediator of gender-related risk disparities. Alternative explanations include a gender-specific distribution of risk-genes, differential handling of α-synuclein, chromosome X-mediated susceptibility and male lifestyle risk factors.[93-96] However, also these mechanisms may finally be transmitted by oestrogen-effects.

Lifestyle, environment and health-related factors

A body of evidence suggests a slight reduction of the risk to develop PD for smoking or other use of tobacco or nicotine-containing fruits, as well as for caffeine consumption, also shown in our own study.[96-98] A similar effect has been suspected for moderate alcohol consumption, but evidence is weaker.[96,98] For humans exposed to pesticides in their environment, an increased risk to develop PD has been suggested,[99-101] as also for farming, rural living and well water use, but causation has not been established.[98] Gene-environment interaction may be of importance for these risk-factors and explain some of the heterogeneity in available evidence.

Week evidence suggests a possible risk-reduction for PD by increased levels of uric acid, possibly due to its antioxidant effect, and by use of NSAIDs, particularly ibuprofen, possibly due to its anti-inflammatory properties.[96,98]

1.3 Diagnosis and differential diagnosis

1.3.1 Diagnosis

The diagnosis of PD is based on anamnestic information about the symptoms and their development, clinical examination, response to dopaminergic treatment and observation over time. The cardinal symptoms include resting tremor, bradykinesia (slowness and poverty of movements with reduced amplitude), rigidity to passive joint movements and disturbances of gait and posture. Asymmetric distribution and symptom alleviation by levodopa are important supportive characteristics, and also the presence of olfactory dysfunction seems to be of confirmatory diagnostic value.[102,103] Distinct cognitive impairment and severe autonomic disturbances may emerge subsequently, but are not typical for early PD.

Other causes of parkinsonism need to be excluded. Although some radiological features can, in addition to specific clinical symptoms and signs, support the diagnosis

of PD or other parkinsonian disorders, there is no reliable biomarker available for the diagnosis of PD. The gold standard for the definite diagnosis of PD therefore still remains the post mortem histopathological demonstration of neuronal loss in the substantia nigra with Lewy bodies in the remaining neurons.[31]

The difficulty to set a correct clinical diagnosis of PD has been demonstrated in clinico-pathological studies with an accuracy of less than 80% even for neurologists or physicians associated with a specialized centre for movement disorders.[104,105] However, a later study showed improved clinical diagnostic accuracy to 90%, probably facilitated by application of clinical diagnostic criteria and increased awareness of the challenges in diagnosing PD.[106]

The most widely used clinical diagnostic criteria are those suggested by the United Kingdom Parkinson's Disease Society Brain Bank (UKPDBB) in 1988 and those published by Gelb in 1999.[30,31] Beyond their clinical significance, they are of special importance in the context of research, as a correct diagnosis of the included subjects is essential for adequate interpretation of the results. In both classifications, the diagnostic certainty increases when dopaminergic treatment improves symptoms and when observation over some years shows progression of the disease. The diagnosis of PD is therefore particularly challenging in patients with early and yet untreated parkinsonian symptoms.

The diagnostic criteria of the UKPDBB and Gelb are presented in appendix I and II.

1.3.2 Differential diagnosis

Disorders that lead to symptoms as tremor, bradykinesia and gait problems are referred to as parkinsonism. Parkinson's disease is the most frequent cause of parkinsonism, but there are several other distinct conditions that may lead to similar motor symptoms.

The most important and in early stages most challenging differential diagnoses are other progressive, neurodegenerative disorders which have their typical onset in the same age-groups as PD.

Multiple system atrophy (MSA) is characterized by parkinsonism of varying severity with initial or early occurrence of autonomic failure (orthostatic hypotension and urogenital dysfunction) and affection of the corticospinal tract. The parkinsonian (MSA-P) subtype shows most similarities to PD and may initially even be asymmetric and respond to levodopa. In the cerebellar subtype (MSA-C), rapid progressing parkinsonism is associated with progressive cerebellar symptoms as gait- and limb ataxia and postural instability and with severe dysphagia. Neuropathologically, MSA is characterized by striatonigral and olivopontocerebellar degeneration with glial cytoplasmatic inclusions containing fibrillized α-synuclein, and is therefore characterized as synucleinopathy in line with PD.[107]

Dementia with Lewy bodies (DLB) is defined by progressive cognitive decline early after or before parkinsonian symptoms emerge, with fluctuating cognition and recurrent visual hallucinations. REM sleep behaviour disorder and severe neuroleptic sensitivity occur frequently. Lewy body pathology is found in neurons in brainstem nuclei, especially the substantia nigra and nucleus ruber, and in various limbic and neocortical regions.[108] Clinically and histopathologically, there may be a continuum from DLB via PD with dementia to PD without dementia.

Progressive supranuclear palsy (PSP) is an akinetic-rigid parkinsonian syndrome with very early postural instability, vertical ocular gaze palsy (in early stages slow vertical saccades), early dysphagia and dysarthria, and frontal cognitive impairment.[109] Median survival is only 5.6 years from diagnosis.[110] In PSP, abnormal accumulations of tau-protein, so-called neurofibrillary tangles, are associated with neuronal loss in substantia nigra, subthalamic nucleus and globus pallidus, in addition to variable affection of other basal ganglia, diencephalon, cerebellar peduncles and the brainstem.[111] Consequently, PSP is classified as tauopathy.

Another tauopathy is corticobasal degeneration, which typically shows pronounced asymmetric limb rigidity or akinesia with dystonia or myoclonus. Limb apraxia, cortical sensory deficit or the alien limb phenomen (non-recognition of the own limb) are additional diagnostic criteria. Dementia is in many cases a presenting or dominating feature of corticobasal degeneration.[112] Neuronal loss with neuronal tau-positive inclusions is found in the cortex, substantia nigra and globus pallidus with additional changes in other structures.[113]

Localized or disseminated cerebral vascular lesions are the cause of parkinsonian symptoms in vascular parkinsonism. The clinical signs include bradykinesia, rigidity and falls, but tremor is usually absent. The onset is later than in PD[114] and often not, as widely suggested, acute, but insidious, with a relentless rather than stepwise further progression.[115] Treatment with levodopa may lead to at least temporary improvement. However, symptoms are in most cases symmetric with predominant affection of the lower body, pyramidal signs (a red flag for the diagnosis of PD) are frequent, and pathological findings in structural neuroimaging are much more frequent than in PD.[114,115]

A number of drugs can induce Parkinson-like symptoms. Most frequent are antipsychotics/neuroleptics, but also antiemetics, calcium-channel blockers, antidepressants and even some antiepileptics may cause extrapyramidal symptoms, primarily due to dopamine receptor type 1-antagonistic action. Drug induced parkinsonism is typically bilateral, symmetric, with more prominent bradykinesia and rigidity than in PD. However, 30-50% show asymmetric symptoms and tremor at rest, usually with postural tremor. Thus, clinical differentiation from PD can be difficult, especially as recovery after cessation of the actual drug can take weeks or months and is not always complete.[116]

Further causes of secondary parkinsonism include infections (though seldom), toxins (e.g. MPTP, manganese and cyanide), structural lesions involving the basal ganglia (tumor, vascular malformation, ischemia, demyelination), hydrocephalus, multiple subcortical vascular lesions, head trauma and metabolic and endocrine disturbances.

Other examples are Wilson's disease, the neurodegenerative Huntington disease – especially in young cases – and the enzyme deficiency-related Neuroacanthocytosis and Gauchers disease. Tremor in PD may sometimes be difficult to distinguish from essential tremor or other tremor forms.

1.3.3 Imaging

Routine computed x-ray tomography (CT) and magnetic resonance imaging (MRI) are usually normal in PD and primarily used to exclude a range of secondary causes of parkinsonism. In a proportion of cases with MSA and PSP, routine MRI shows degenerative changes, which then can facilitate the diagnosis. Atrophy of the putamen is seen in MSA and PSP, but not in PD. Putaminal hyperintensity, a putaminal lateral hyperintense rim and a hyperintense cross-structure in the pons ("hot cross bun" sign) are typical for MSA-P, while midbrain atrophy with the "humming bird" sign indicates PSP. MRI with planimetry can visualize reduction of midbrain diameter and midbrain/pons area ratio in PSP.[117] More advanced MRI techniques such as diffusion imaging, susceptibility weighted imaging and magnetic transfer imaging may increase the diagnostic value of MRI further, but it is unclear whether they can improve early diagnosis.[117,118]

SPECT (single photon emission computed tomography) and PET (positron emission tomography) use radioactive tracers to detect reduced presynaptic activity in dopamine-transporters or DOPA decarboxylase in the striatum. They are predominantly used to distinguish neurodegenerative parkinsonian disorders from non-degenerative conditions as essential tremor, but may have potential to differentiate between other neurodegenerative parkinsonisms as well.[119,120,121] Interestingly, cardiac sympathetic denervation with decreased myocardial uptake of ^{123}I-mataoidobenzylguanidine in MIBG-SPECT is typical for PD already at early disease stages, but not for MSA, and may therefore be helpful to distinguish those conditions.[122-124]

In the last decade, hyperechogenecity of the substantia nigra in transcranial sonography of the midtbrain in patients with PD has received increasing attention.[125] It can confirm clinically suspected PD and identify individuals with increased risk to develop the disease, at least in research settings.[124] Together with reduced olfaction and asymmetry of motor symptoms, high values for specificity and positive predictive value have been achieved.[126]

1.4 Epidemiology

Knowledge about the epidemiology of a disease provides information about its occurrence in the investigated population, differences compared to other geographic or ethnic populations, risk factors and trends over time. Thereby it contributes clues to understand factors related to the etiology of the condition and provides vital data for health care planning.

The prevalence (number of individuals affected at a certain point of time in a defined population) of Parkinson's disease in Norway was estimated to be 102/100 000 inhabitants in the county of Rogaland in 1995, which was in line with several other European studies.[127,128] As PD is a disease of later life, about 1% of the population 65 years or older are thought to have PD.[128,129] However, incidence rates (occurrence of new cases within a certain time period in a defined population) are considered a better measure for the frequency of a chronic disorder. Incidence numbers are better comparable between studies from different geographic, social, environmental or time areas, which are factors that affect the mortality of individuals with a disease and thereby the prevalence figures.

Until 2009, there were no incidence numbers available for Norway. In other European countries the incidence of PD ranged from 5/100 000 to 26/100 000. Rather than real distinctions in the investigated European populations, it is assumed that variations in the applied methodology and age-distribution in the investigated countries account for these differences.[68,128] Consistent throughout all studies are increasing incidence rates

with age. Some studies found the peak incidence between 70 and 80 years, while others report further increase after that. This has different consequences for etiological considerations (see "Etiology and risk factors"). However, diagnostic uncertainty increases in the oldest age-groups, and the smaller base population limits statistical power.[128] Despite methodological differences, an increased risk for men vs. women with a male-to-female ratio of 1,3-1,9 has been shown for a clear majority of incidence studies in Europe and Northern America, but not Asian countries.[72]

Challenges in PD-epidemiology

In a review on studies of the incidence of PD published until 2001, Twelves et al. found considerable methodological heterogeneity in the evaluated studies. This is problematic as the methodology has significant impact on the resulting incidence figures for PD:[68,128]

1. The method of case identification is important to achieve a collection of ideally all cases in the investigated area. Hospital data usually provide underestimates of the number of incident cases when patients also are diagnosed and treated in the primary health sector or by specialists outside the hospital. Door-to-door surveys are optimal in smaller base populations, but not feasible in large populations. It is of importance that the complete base-population is analysed.
2. A correct diagnosis is crucial. Retrospective screening of records not designed to provide a basis for a correct diagnosis in the setting of a study is a source of diagnostic error. A wrong diagnosis of PD is more likely to be given from primary physicians and neurologists outside a study. Incidence studies are particularly sensitive to misdiagnosis as they aim to identify cases in the early phase of PD, when the differentiation from other parkinsonian disorders is difficult. Thus, the optimal approach for a correct diagnosis of PD is considered to be a prospective examination of all potential cases by study neurologists with follow-up for several years.[68]
3. The time-point of incidence needs clear definition. This may be the time when the first symptoms occur, which usually has to be determined retrospectively

with the corresponding uncertainties. An alternative is the first time a disease comes to medical attention. This provides a purely prospective approach and states the initial diagnosis later in the course of the disease with increased diagnostic certainty, but cases that die with the disease before getting to medical attention will be missed.

4. The base population needs to be clearly defined and completely analysed with respect to incident cases. Moving to and from the study-area, as well as death, are challenging confounders that need to be handled according to defined criteria.

Several of these factors favour western and southern Norway for the conduction of an incidence study on Parkinson's disease. The health care system for neurological disorders is almost exclusively based on hospital-assigned specialists, and each hospital has defined geographic areas it is responsible to provide health care for. The guidelines of the Norwegian medical association assign the diagnosis of Parkinson's disease and the initiation of antiparkinsonian treatment to specialists in neurology. Furthermore, the population is relatively stable especially for the population above 40 years of age (Statistics Norway, www.ssb.no).

1.5 Clinical aspects

1.5.1 Motor symptoms

Parkinson's disease is primarily defined by its motor symptoms, which also represent the basis for the clinical diagnosis.

Tremor is an involuntary, rhythmical and oscillatory movement of a body part.[130] It is one of the most obvious symptoms in PD, potentially stigmatizing and may have impact on daily activities when pronounced, but is not an independent predictor of reduced quality of life in patients with PD.[131-133] PD-tremor is typically an

asymmetric, distal, 4-6Hz resting-tremor which disappears when the limb is moved, allowing the use of tools or to carry things.[130] It is more frequently seen in the upper limbs compared to the lower, occurs occasionally in in the jaw muscles or tongue, but neck, trunk and hips are not affected.[134] Some degree of tremor is reported in 70-80% of patients with PD during the course of the disease.[135-137] It may be the initial symptom or occur later in the course, and it may disappear after some years.[138] The severity of PD-tremor is not correlated to other motor symptoms, striatal dopamine depletion or histopathological nigrostriatal degeneration.[139,140] It has been suggested that resting-tremor in PD is generated by a neuronal network outside the basal ganglia, in the cerebello-thalamico-cortical circuit.[141]

Bradykinesia describes slowness, reduced amplitude and poverty of movements. It is a major characteristic of PD, but also of other parkinsonian disorders. Impairment of automated movements is seen as reduced eye-blinking rate, reduced mimics leading to a “masked face”-expression, and reduced arm-swing when walking. Voluntary movements are affected with difficulties in fine motor tasks as buttoning and handling tools,[142] all of that having consequences for daily life activities and social interaction. Bradykinesia is the clinical symptom that is strongest correlated to nigrostriatal dopaminergic deficit in Fluoro-dopa PET.[143]

Rigidity describes increased muscular resistance to passive displacement of joints as the elbow, wrist, knee or ankle, but occurs also in proximal joints and the neck. It is usually not recognized by the patients themselves, and as such not directly relevant to them. But it is associated with increased muscle tone at rest, which patients may perceive as unpleasant and exhausting. Worse, it is associated with pain, and especially shoulder pain is not infrequently an early symptom of PD, but misdiagnosed as frozen shoulder or another musculo-sceletal disorder.[142] Rigidity may appear smooth and continuous (“lead-pipe”-like) or staccato (“cogwheel”-like). Suspected pathophysiological mechanisms include increased activity of spinal cord motoneurons involved in the stretch reflex and increased primary motor cortex excitability, probably based on basal ganglia dysfunction.[134]

A number of *postural deformities* are associated with rigidity. Elbows and knees are often flexed also in earlier cases, but in later stages flexed neck with antecollis, kyphosis, scoliosis and tilting of the trunk (Pisa syndrome) get more frequent.

Gait problems include reduced speed, stride-length and elevation of the feet. One of the most disabling symptoms of PD is freezing of gait (FOG), a sudden, transient inability to move. It occurs when turning, starting to walk, walking through narrow spaces, when reaching a destination or – more "spontaneously" – in open spaces.[142] FOG may occur already early in PD, but is then less frequent and of shorter duration. With progression of the disease, it gets more frequent and disabling, leads often to falls,[144] and affects quality of life beyond its relation to mobility and gait.[145] FOG is typical, but not specific for PD as it is also observed in PSP and MSA-P. The pathogenesis of this phenomenon is not clear, but basal ganglia, frontal lobe and motor pattern generators in the spinal cord may be involved.[144,146]

Postural instability and gait disturbances with resulting falls are closely related features predominantly present in later stages of PD. When falls occur early, the diagnostic focus should be led to other parkinsonian disorders as PSP or MSA. However, falls are overall frequent in PD and were reported in at mean 39% and 46% of patients, respectively, in two meta-analyses.[147,148] Falling increases the risk for hip fractures,[149] but more than actually falling, the fear of falling impairs the patients' quality of life.[150] One cause of falls are impaired postural reflexes, and many falls result from sudden changes in posture as turning of the trunk, or during transfer, e.g. from sitting to standing. Typically, PD patients fall forward, possibly due to the frequently stooped posture.[144] Several mechanisms have been suggested as an underlying cause of the balance disturbances, including disturbed motor programing of postural corrections and central proprioceptive disturbances resulting in sway abnormalities, shift of the centre of gravity and overestimation of the limits of stability.[144,151]

Speech problems in PD are characterized as hypokinetic dysarthria and comprise hypophonia (low voice volume), slurred articulation, a monotonous voice and

dysphonia (hoarse or harsh voice).[152] Voice weakness may be present early, but problems increase with progression of the disease.[153] Dysarthria has traditionally been attributed to muscle rigidity and hypokinesia due to dopamine deficiency, but improvement by dopaminergic stimulation is inconsistent,[152] in line with the supposed involvement of cerebellar and cortical structures beyond the dopaminergic system.[154]

1.5.2 Motor subtypes

As Parkinson's disease is heterogeneous with respect to prognosis, rate of progression and complications of the disease and its treatment, attempts have been made to define subgroups that share common characteristics. Classification into a tremor-dominant vs. non-tremor dominant subtype has repeatedly demonstrated significant differences between the subgroups. The allocation to one of these motor-subtypes depends on the relative severity of tremor vs. akinesia and rigidity,[155] or tremor vs. postural symptoms and gait difficulties (PIGD),[156] usually based on standardized scoring-schemes as the Unified Parkinson's Disease Rating Scale (UPDRS).[157] It has been shown that the non-tremor dominant subtypes of PD are associated with higher mortality,[158,159] more impaired quality of life and daily life functions,[160,161] faster overall progression,[162,163] increased cognitive decline,[138,163,164] a higher number of non-motor symptoms,[161] more autonomic dysfunction,[165] drooling[161] and sleep disturbances[166] as compared to tremor-dominant patients. The pathophysiological background for these differences is not clear. Neuropathological studies have shown a higher cortical Lewy body load for the non-tremor subtype,[167,168] which may explain increased dementia. One imaging study found a different pattern of striatal dopaminergic activity in FP-CIT-SPECT in tremor vs. non-tremor subtypes,[169] and the same authors described later faster reduction of dopaminergic activity in akinetic-rigid patients after 2,5 years follow-up, in line with the clinical progression.[170]

1.5.3 Treatment-induced motor complications

Dopaminergic treatment over time induces fluctuations and dyskinesia in a considerable number of patients, what has been observed already short after the introduction of levodopa in treatment of PD.[171] Intermittent dosages of levodopa lead in the beginning to a continuous dopaminergic effect, but later in the course, parkinsonian symptoms re-emerge or increase before the next dose has become effective ("wearing-off"). Some patients develop fluctuations independent of medication intervals, with sudden, unpredictable shifts between "on" and "off" state. The unpredictable character of these "on-off" fluctuations can be the most difficult aspect of levodopa therapy for some patients.[172] However, an association of motor-fluctuations with impairment of quality of life parameters has only been documented in a minority of studies.[133]

Dyskinesia consist typically of involuntary, irregular, chorea-like or ballistic movements of the limbs, had and/or trunk, which occur as "peak dose" or "on period" dyskinesia, related to high plasma levels of levodopa. Less frequent are diphasic dyskinesia, emerging during the onset and offset of the levodopa-effect.[173] Within the first years of PD, dyskinesia are very seldom, but the frequency increases with longer disease duration.[174] Although dyskinesia can get distressing, disabling and even painful with increasing severity, their impact on quality of life is limited.[133,175]

Treatment with the short acting levodopa induces fluctuations and dyskinesia more frequently than treatment with the longer acting dopamine agonists, probably related to the more pulsatile stimulation of post synaptic dopamine receptors.[176-179] Changes in dopamine receptor affinity or in the N-methyl-D-aspartate (NMDA) receptors have been suggested as underlying causes of fluctuations.[180] Mechanisms thought to cause dyskinesia include presynaptic dysfunction of dopamine storage and -release, and an abnormal pattern of neuronal activity in the basal ganglia, finally leading to abnormal recruitment of cortical motor areas.[179,181]

1.5.4 Non-motor symptoms

James Parkinson mentioned already in his descriptions from 1817 constipation, urinary incontinence, drooling, sleep disturbances and daytime sleepiness as problems he had observed in the "shaking palsy". He was not aware of cognitive impairment and stated "the senses and intellects being uninjured".[1] However, by the end of the nineteenth century, reports on impaired memory, dementia and depression in PD appeared. Lewy found in 1923 that 54 of 70 PD patients were affected by pronounced mental disturbances, mostly dementia.[182] First from the 1990s, non-motor symptoms in PD gained considerable attention, and autonomic, sensory, neuropsychiatric and sleep-related symptoms are now widely accepted as important manifestations of PD.[183,184] It is documented that non-motor symptoms have significant impact on patients' quality of life,[11,131,185] on their caregivers,[186,187] and on health-economics,[188] and that hallucinations are a dominating predictor of nursing home placement.[189,190] Despite these facts, non-motor symptoms remain under-recognized by treating neurologists,[191] in part related to the non-declaration of symptoms by the patients.[192] One reason may be that patients do not associate non-motor symptoms with their Parkinson's disease, and therefore do not mention them in consultations. The early emergence of several non-motor symptoms requires sound knowledge on the prevalence and severity of these features to improve care for patients newly diagnosed with PD.

Neuropsychiatric symptoms

Cognitive impairment and dementia

Cognitive impairment is an overall frequent finding in PD, and in late stages the majority of patients will develop dementia.[193,194] Cognitive problems initially comprise executive dysfunction, impaired attention, working memory, verbal memory and visuospatial abilities.[195,196] These fronto-executive deficits lead to reduced organizational skills, impaired concentration, problems with retaining information while undertaking daily tasks and difficulties to focus attention, which interfere with

social and occupational functioning.[197,198] With progression of the disease, cognitive function deteriorates further. In addition to the aggravated impairment of executive function, patients with PD-dementia show impaired short-term memory, hallucinations and fluctuating attention. Despite some problems with verbal memory, severe language problems, a typical feature of Alzheimer's disease, are seldom.[199] The deficits in mild cognitive impairment seem to reflect the involvement of brainstem nuclei in early PD,[195] while the dominating finding in overt dementia is Lewy-body related degeneration in cortical and limbic structures.[200] Increasing evidence suggests a significant role of Alzheimer's disease like pathological changes and mechanisms in PD-dementia.[201,202]

Depression

Depression is one of the most frequent neuropsychiatric disturbances in PD, reported in 40-60% of patients, and may occur at any time throughout the course of the disease, also in the premotor phase.[203,204] Depressive symptoms include low mood, decreased interest in usual activities, reduced pleasure in otherwise enjoyable undertakings (anhedonia), feelings of guilt and worthlessness, with suicidality in severe cases. These are often accomplished by more somatic problems like impaired concentration and sleep, fatigue or loss of energy, weight loss or changes in appetite, and by physical complaints as muscle tension and gastrointestinal symptoms.[205] The latter features do overlap with symptoms also found in PD without depression, what may lead to non-recognition of depression as the underlying cause. Depressive symptoms interfere with most aspects of an individual's life including family, occupation, daily and social activities, and are the most frequent reported contributor to reduced quality of life in PD.[133] Depression may easily be interpreted as a reactive phenomenon to the patients' PD. However, more important seems to be the underlying neurodegenerative process, especially of the limbic system and basal ganglia.[206] Dopaminergic, noradrenergic and serotonergic neuronal systems are affected, all involved in regulation of mood and reward systems in both PD and the general populations.[204]

Fatigue

The overall prevalence of fatigue in PD ranges in most studies from 30 to 65%, with presence already in early stages.[207,208] It is one of the most disabling single symptoms that occur in PD, and has in 1/3 of patients in one study even outranged the PD-specific motor symptoms.[209] A major review on the issue quotes a patient: "I can live with the PD (not great, but livable), but the fatigue is unbearable."[210] Fatigue is a subjective perception and describes a sense of tiredness, lack of energy or inappropriate exhaustion with difficulties to initiate and sustain mental and physical tasks in the absence of motor or physical impairment.[210] The character of this perception overlaps with other non-motor symptoms, and fatigue is often associated with depression or sleep problems. However, the principally independent character of fatigue is reflected in the frequent occurrence also in patients without depression, sleep problems or dementia.[211,212] The pathophysiological mechanisms underlying fatigue in PD are poorly understood. A feedback loop in which pain, depression, fatigue, inactivity and deconditioning act synergistically to increase disability has been suggested by some authors,[210,213] while others suppose that failure in the integration of limbic input and motor functions within the basal ganglia reduces motivation of self-initiated tasks.[214,215]

Apathy

Another mood-related symptom frequently present in PD is apathy, characterized by reduced interest and participation in the main activities of daily living, a lack of initiative, a trend toward early withdrawal from initiated activities, indifference and flattening of affect.[216,217] Consequences include secondary increased functional decline, greater debility and familiar problems.[216] The features of apathy overlap with those of depression and cognitive impairment, and although those conditions frequently occur in combination, some patients with PD show apathy in the absence of depression or dementia.[218,219] Apathy may occur already as a presenting symptom at the time of diagnosis,[220] and the prevalence for later stages ranges up to 70%.[221] Thought underlying mechanisms include reduced limbic and ventral striatal

dopaminergic activity and involvement of the systems for reward, emotion and cognition.[222,223,224]

Psychosis

Psychotic symptoms are unusual in the first years of PD, but present in 60% or more of patients with late stages.[225-227] Most frequent are visual hallucinations, typically consisting of persons, less frequent of animals or objects. In less severe cases, patients have insight in the pathologic nature of the phenomenon, but this does not necessarily reduce the burden of experiencing hallucinations. Minor psychotic phenomena include visual illusions (misinterpretation of a real stimulus) and a sense of presence or passage, although nobody is there or passes by.[228,229] The risk for psychotic symptoms increases with older age, longer duration and greater severity of PD.[228] Also dopaminergic medication seems associated with psychotic symptoms, but findings are not consistent.[230] Complex interactions between disease and treatment-related effects are more likely to account for the development of psychosis, including impaired visual input and cognitive impairment leading to disinhibited release of stored visual memories.[228,230]

Anxiety

Anxiety disorders are reported in 30-40% of patients with PD, and most common are panic attacks, social phobia and generalized anxiety. Patients perceive excessive and often irrational anxiety or worry, nervousness, irritability, feelings of impending disaster, palpitations, hyperventilation and insomnia.[134,216,231] Anxiety is frequently, but not always related to fluctuations, especially the “off” state. Patients with anxiety have often coexisting depression and predominantly a non-tremor dominant motor subtype.[231,232] Anxiety may occur at any stage of PD, including the premotor phase, what probably represents the involvement of brainstem structures as raphe nuclei and locus coeruleus as well as the beginning dopaminergic deficit.[134,230,233]

Autonomic and gastrointestinal symptoms

The autonomic nervous system controls a large spectrum of visceral body functions, ultimately in order to maintain homeostasis and – thereby – ensure survival. Cardiovascular, genito-urinary, respiratory and elements of visual function as well as temperature are, largely involuntary, regulated by the parasympathetic and sympathetic nervous system. Gastrointestinal organs are in addition, and to a large extent, controlled by the enteric nervous system. The peripheral structures include neurons with ganglia localized paravertebral or closer to the endorgans, while the enteric nervous system is placed in the layers of the intestine walls. The immediate target structures are smooth muscles of organs as the intestine and urinary bladder to regulate peristaltic and release, blood vessels for control of blood pressure and perfusion, cardiac muscles to adjust frequency and contraction strength to the requirements, as well as glands for secretion. It is necessary to adapt these functions to the context of the current and superior circumstances of the individual. The core central structure for this is the hypothalamus, which integrates autonomic, endocrine, limbic and somatic information in order to achieve the optimal reactions, both autonomic and somatic. Other central autonomic structures as the reticular substance and autonomic nuclei in the brainstem are to some degree independent, but under superior control of the hypothalamus.[234,235] Affection of brainstem, enteric plexus and other peripheral autonomic structures by Lewy-body-related neurodegeneration is thought to represent the histopatholgical correlate of autonomic disturbances observed in PD patients also before the onset of motor symptoms,[201,236-238] as reflected in the Braak-hypothesis[19] and more recent suggestions of a peripheral induction of the neuropathological cascade.[55-57] The substantial presence of autonomic disturbances in the later stages of PD is well established.[194,239,240] However, by 2010, the frequency and severity of such symptoms in the earliest stages of PD was very insufficiently documented and predominantly derived from hospital-based, small cohorts not reflecting the large clinical variety of PD and mostly focused on few symptoms.[53,241,242] The considerable impact on quality of life as well as diagnostic and

therapeutic considerations require improved knowledge on autonomic symptoms in early stage PD.

Orthostatic hypotension

Maintaining blood circulation to brain and heart is absolutely prioritized in cardiovascular regulation and ensured by a system including baroreceptors, direct cardiac and vascular innervation and hormonal systems. A change of posture from laying to standing requires contraction of peripheral blood vessels and increased cardiac output to counteract gravity-induced hypotension in upper body regions. Failure of this system can lead to suboptimal cerebral perfusion clinically recognizable as dizziness or lightheadedness, weakness, nausea, pain or unclear vision and can in severe cases cause loss of consciousness.[235] Symptoms of orthostatic hypotension become more frequent with increasing age and are present in 5-30% of the normal population above 65 years.[243] A review from 2011 found clearly higher numbers in PD, with a pooled prevalence of 30%, ranging from10 to 65%.[244] In only two of the 25 studies included, the disease-duration was <5 years, and these reported 14% and 18% prevalence, respectively. The basic pathophysiological mechanisms of orthostatic hypotension in PD include peripheral sympathetic denervation of resistance vessels and the heart,[245] as demonstrated for example by pathologic cardiac radionuclide scans.[246,247] In addition, insufficient intake of liquids and side effects of Parkinson-specific medication may be of importance.[235]

Sweating disturbances

Hyper- or hypohidrosis is reported to occur in overall 30-50% of patients with PD.[248,249] Hyperhidrosis is unpleasant, socially embarrassing and can affect quality of life.[250] Typical locations are head, face, neck and chest, and it is frequently related to "off" periods in patients with "wearing-off", or to dyskinesia.[250] Compensatory hyperhidrosis secondary to hypohidrosis of the palm has been suggested as an underlying mechanism.[251] But also heat intolerance and hypohidrosis are reported in

PD, what may indicate a more complex affection of the thermoregulatory system with both central and peripheral mechanisms.[248]

Genito-urinary dysfunction

Storage of urine in the bladder and its controlled release are functions of the lower urinary tract, and symptomatic disturbances have been reported in about 30-70% of patients with PD. Most frequent are storage-related symptoms like nocturia, urinary frequency, urgency and incontinence, which in this order represent increasing dysfunction.[252,253] Underlying these symptoms is an overactive bladder due to impaired control by a complex circuit including the pontine micturition centre, basal ganglia, cerebellum, hypothalamus and frontal cortex.[252] Parasympathetic denervation with impaired detrusor activity is thought to account for the less frequent voiding problems, which include hesitancy (delayed start of urination), weak stream and incomplete emptying.[254,255] The net effect of the basal ganglia on micturition is thought to be inhibitory,[252] and some authors suggest that storage problems in PD are mainly the result of dopamine deficiency-related hyperactivation of the micturation reflex.[255] However, the effect of dopaminergic treatment on urinary dysfunction is reported very controversial, indicating a more complex and variable interaction of central and peripheral mechanisms.[252,256]

PD patients are more dissatisfied with their sexual function and relationship than controls.[257] Sexual problems include decreased or increased libido, erectile dysfunction and decreased frequency of orgasm.[258] While hypersexuality is considered a side-effect of dopaminergic medication, hyposexual problems are thought to relate to the dopaminergic deficiency, affection of hypothalamus and sensory systems as well as sympathetic dysfunction.[255,258]

Constipation

Constipation is the most frequent gastrointestinal symptom typically reported in 50-70% of PD patients.[259-261] Reduced bowel movement frequency, increased stool consistency and incomplete emptying may cause discomfort or pain and interfere with

appetite and daily activities, but severe constipation is not very frequent.[262] Slow colonic transit, decreased phasic rectal contraction, weak abdominal strain and paradoxical sphincter contraction on defecation have been found in PD.[263] It is likely that these problems reflect impaired autonomic control by the vagal nerve, enteric nervous system and sacral parasympathetic structures, which are affected by α-synuclein-related pathology.[264,265] Constipation occurs often before the typical motor symptoms, and a reduced frequency of bowel movements is associated with an up to 4-times increased risk to develop PD later.[54] These findings have given raise to the hypothesis that the pathophysiological process of PD may actually start in the gastrointestinal system.[56,57]

Dysphagia

Subjective difficulties related to swallowing of food or liquids are reported by about 30-40% of PD patients, according to a recent meta-analysis.[266] Problems include reduced speed of oral preparation, slow oral transit, misdirected swallows with increased risk of aspiration and residual food in mouth or pharynx.[267] When objectively examined, over 80% of PD patients have abnormalities in the oral, pharyngeal or esophageal phase of swallowing,[266] most common being impaired mastication and oral preparatory lingual movements.[268] Dysphagia is usually not present before the onset of motor symptoms and more typical for later stages of PD.[260,269] The impact of dysphagia on the patients' and their caregivers' life is beyond chewing and swallowing, but affects also practical and social activities surrounding mealtimes.[270] Swallowing is a complex and stereotyped sequential process with interaction of voluntary and autonomic aspects, coordinated by a central pattern generator in the medulla. It is thought that affection of the pedunculopontine nucleus in PD causes impaired modulation of this medullary pattern generator, thereby leading to reduced control of swallowing.[271,272]

Drooling

Problems related to increased and decreased amounts of saliva both occur in PD, and dribbling can be present in more than half of the patients.[273] Severity and frequency of drooling increase with progression of the disease, and overt drooling is best known from patients in advanced stages.[273,274] While hyposalivation may lead to subjective discomfort and teeth-problems, increased saliva in mouth or drooling are embarrassing especially in social settings.[275] Sialometric studies have shown that saliva production is lower in PD patients, including early stages, compared to controls. Dopaminergic treatment stimulates saliva-production, but also treated patients produce still less saliva than controls.[276-278] Central mechanisms and Lewy-body pathology in the submandibular glands may explain this impairment of saliva-production.[278,279] Accumulation in, and loss of saliva from mouth are probably related to altered facial, oral and pharyngeal function, leading to reduced capacity to keep saliva in mouth, transport it backwards in the mouth and swallow it frequently enough.[274,280] Saliva-accumulation in the mouth or drooling only during night time have been reported in 43% of patients in one study, and the authors suggest that these symptoms may precede actual daytime drooling.[281]

Sensory symptoms

Hyposmia

Olfactory dysfunction is a well-established non-motor feature of PD which has been found in up to 90% of patients, depending on the tests applied.[282,283] This number is about 3-4 times that of healthy older adults[284] and exceeds even the 70-80% prevalence of the cardinal motor feature tremor.[136,137] The ability to detect, identify and discriminate odours is impaired unrelated to specific odorants, but total anosmia is rare.[52,283] Reduced olfaction precedes the clinical motor symptoms of PD by probably 2-7 years,[28] and otherwise unexplained hyposmia is a risk factor for later development of motor PD.[285-287] Although there is some evidence for a certain progression of the olfactory deficits during the early phase of PD,[52,288] it is generally

accepted as a very early established and rather stable deficit.[283,289] Based on its robust and high prevalence, hyposmia has been suggested and used as a supportive diagnostic feature for PD,[102,103] also well discriminating PD from other movement disorders like PSP, MSA, corticobasal degeneration and essential tremor.[290-292] The basis for impaired olfaction in PD is probably located in the olfactory bulb and olfactory cortex, where Lewy bodies and related pathology have been found.[19,293,294] Together with the enteric system, the olfactory system is hypothesized to be the locus where the initial PD-specific pathophysiological changes take place before further centripetal propagation according to the Braak hypothesis.[19,56,57]

Pain

Pain is frequent in the normal population, but even more frequent in patients with PD.[295,296] It is one of the 5 most frequent complaints already in early stages and the prevalence ranges from 40 to 85% according to a recent review, likely also depending on the assessment tools.[297,298] Most frequent is musculoskeletal pain, followed by dystonic and radicular-neuropathic pain, while central PD-related pain is relatively rare.[298,299] The characteristic of pain is often difficult to describe, and in addition to distinct pain, patients report abnormal sensations like cramping, numbness and tingling, which with increasing intensity become painful. Muscular stiffness, reduced mobility and pathologic posture can explain a large proportion of pain and sensory complaints. In addition are both peripheral and central parts of the nociceptive system affected in PD, with pathological findings in cutaneous nerve endings, the spinal cord and various brain stem nuclei involved in descending regulation of pain.[19,300,301] Also the basal ganglia are probably involved in pain processing, and hyperalgesia in response to pain stimuli has been reported in several studies.[302] An association of pain with female gender, fluctuations and depression has been shown, but longer disease duration seems not to increase the occurrence of pain. However, findings on risk factors are generally inconsistent.[303] Problematically, pain is not specifically treated in about half of PD patients.[298]

Sleep-related problems

Sleep-related disturbances are amongst the most important problems for patients with PD,[304] interfere with quality of life and often affect also the spouses considerably.[305,306] Most frequent is insomnia, with difficulties to maintain sleep, fall asleep or too early awakening in the morning.[307,308] Night time motor problems like difficulties turning in bed, tremor and early morning dystonia as well as a number of non-motor problems like nocturia, pain and depression interfere with sleep,[309] in addition to dopamingergic medication.[310] Restless legs syndrome occurs predominantly at the beginning of sleep with disagreeable restless feelings in the lower limbs which often only relieve by moving the legs,[311] but the condition overlaps with leg motor restlessness without diurnal fluctuations.[312] During REM-sleep, voluntary muscles are usually atonic. In REM-sleep behaviour disorder (RBD), this atonia is absent and patients act out their dreams, with increased risk for injuries of both the patient and bed partner.[311] Lower brainstem pathology is thought to account for RBD, what is, reminding Braaks hypothesis,[19] in line with its frequent emergence before PD-motor symptoms and the fact that apparently idiopathic RBD is associated with an increased risk for PD.[313]

Common in PD is also excessive daytime sleepiness, an increased tendency to fall asleep during the day. PD-pathology, disturbed night time sleep and sedative drugs are contributing mechanisms, in addition to dopaminergic drugs, which are also suspected to induce sleep attacks as a class effect.[311,314]

1.5.5 Treatment-related non-motor complications

A number of non-motor symptoms potentially deteriorate at least to some degree due to dopaminergic treatment, but there are considerable interindividual differences and evidence is conflicting. Generally, it is thought that constipation, orthostatic hypotension, daytime sleepiness and especially psychotic symptoms may worsen due to treatment with either levodopa or dopamine agonists. However, with progression of the disease and increasing duration of levodopa therapy, non-motor fluctuations have

been observed in autonomic, cognitive/psychiatric and sensory symptoms, resulting in significant disability mostly associated with the "off" state.[315]

Impulse control disorders

Distinct complications of dopaminergic therapy rather than PD-specific pathology are impulse control disorders (ICD), defined as the failure to resist an impulse or temptation to perform an act that is harmful to the individual or to others. They have been described in 6-17% of patients and include pathological gambling, hypersexual behaviour, compulsive shopping, compulsive eating and punding (intense fascination with repetitive handling, examining, sorting and arranging of objects).[316] Despite a clear association with use of dopamine agonists, more than levodopa, there is evidence that male gender (mostly for hypersexual behaviour and gambling), younger age and certain personality traits are predisposing factors for ICDs.[317] Dopaminergic pathways are involved in the brain's reward system and development of addiction, and are thought to play a key role in the generation of ICDs. Reduction or cessation of dopaminergic treatment, or switching to another dopamine-agonist, will usually improve ICDs.[316]

1.6 Quality of life

Quality of life is by the WHO defined as the "individuals' perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards and concerns". This includes the "individuals' health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment".[318] Essentially, quality of life is a subjective perception of the own well-being. It is multi-dimensional and includes physical, mental, social and spiritual aspects.

Quality of life in medicine

A role of medicine in quality of life (QoL), and vice-versa, has already in 1966 been highlighted in an editorial by Elkington, exemplified on patients undergoing renal transplant,[319] and the development of generic QoL measures began in the early 1970s. Subsequently, QoL assessments were highlighted as a factor in resource allocation in health care,[320] while others demanded to use quality of life measures in the evaluation of the care given, rather than the justification for giving care.[321,322] Independent of this, QoL became an increasing focus in clinical research, as it supplied a highly relevant aspect to the outcome-measures of clinical trials and for understanding different aspects of medical conditions. The term health-related quality of life (HRQoL) was introduced to include both personal health status and social well-being when assessing health.[323] Usually, assessments cover a range of different aspects of quality of life, including physical, mental, social and health-related aspects.

Quality of life in PD

A chronic, progressive disorder like Parkinson's disease, which is characterized by a wide range of motor and non-motor symptoms and leads to severe disability over time, will naturally interfere with quality of life. Consequently, quality of life has in the past decades been recognized as a relevant aspect of health, disease, treatment and research also in PD.[324] A number of generic (general) and disease-specific scales are now available to assess health-related quality of life.[325] Compared to the normal population, all aspects of quality of life are reduced in PD patients, and more so with increasing duration and more advanced disease.[326,327] It has also been demonstrated that both motor and non-motor symptoms have impact on HRQoL.[131,328] There is, however, controversy as to whether non-motor symptoms are more relevant than motor symptoms in tis respect.[329,330] A review from 2011 concluded that the most frequently reported determinant of reduced HRQoL in PD was the presence of depressive symptoms, followed by severity and disability of the disease.[133]

There are several challenges concerning the impact of motor and non-motor symptoms on HRQoL in PD: As patients frequently not report non-motor symptoms to their health-care personnel, these symptoms often remain not appropriately treated.[192] The resulting higher severity compared to the better treated motor symptoms has been suspected as the cause of a relatively stronger impact of non-motor symptoms on HRQoL measures.[330] Progression of PD goes along with changes in prevalence, severity and relative dominance of both motor and non-motor symptoms.[138,239,331] It can, consequently, be expected that the impact of different symptoms on HRQoL will vary during the course of the disease, but few reports have focused on a specific stage or phase of PD.[332,333] Until 2013, only one has investigated the impact of a variety of symptoms in the very early phase of PD.[333]

The multitude of motor and non-motor symptoms is another challenge for investigations, and most studies have focused on the impact of single symptoms or symptom-groups on HRQoL in PD, neglecting the impact of other symptoms.[133] There is also a variety of assessment tools for all symptoms with unequal detailedness and metric characteristics. All these factors hamper the judgment and comparability of studies that have assessed the importance of motor versus non-motor symptoms in PD.

Solid knowledge on the relative impact which the very different symptoms of PD have on quality of life will help to understand the patient's needs, and to focus efforts in clinical treatment as well as research.

1.7 Treatment

Treatment of PD, as of other disorders, includes the principal goals disease modification and symptom modification. The neurodegenerative process underlying idiopathic PD has up to date not been possible to prevent, reverse, arrest or even to retard substantially. Treatment in PD relies therefore today heavily on

pharmacological symptom control, while some non-pharmacological strategies may provide additional benefit.

1.7.1 Treatment for motor symptoms

MAO-B inhibitors

Monoamine oxidase type B (MAO-B) is an enzyme of the outer mitochondria membrane primarily found in glia cells around dopaminergic synapses in the brain. It metabolizes neurotransmitters including dopamine, and inhibition of MAO-B increases striatal extracellular dopamine levels.[334] This is reflected in a slight symptom-improving effect documented for the two currently available MAO-B inhibitors Selegiline and Rasagiline.[335,336] They are therefore recommended as an option for symptomatic treatment in early PD or as add-on to reduce fluctuations in patients on dopaminergic medication.[337] Nausea, headache and vertigo are usual side effects. Selegiline may induce insomnia due to its metabolite metamphetamine, which is not produced in the metabolization of Rasagiline.

There is some evidence that MAO-B inhibitors may delay progression of PD to a minor extent, presumably due to a neuroprotective effect.[338-340] As the findings are discussed, the drugs are not clearly recommended for neuroprotective treatment in PD.[341,342]

Levodopa

With its introduction in the 1960s, levodopa has revolutionized the treatment and prognosis of PD. In contrast to dopamine, it easily crosses the blood-brain barrier and is then metabolized to dopamine by the enzyme DOPA decarboxylase, thus substituting the reduced amount of endogenous dopamine, i.a. in the basal ganglia. As DOPA decarboxylase is also present outside the brain, levodopa is given together with the peripheral decarboxylase inhibitors carbidopa or benserazide. They increase central bioavailability and reduce dopamine-induced peripheral side-effects like nausea.[343] Levodopa is still regarded as the most effective drug to treat the motor

symptoms of PD,[344] best reducing hypokinesia and rigidity, and in a proportion of patients also tremor. However, axial symptoms and gait problems do usually respond less well to levodopa, and long term use leads in the majority of patients to fluctuations and dyskinesia.[344,345] Other side effects are, however, less frequent compared to dopamine agonists. To reduce the complications of levodopa it is usually not given as initial treatment in younger patients with longer life expectancy. Also a neurotoxic effect of levodopa has been suggested, but evidence for that has not been established.[346]

COMT-inhibitors

Levodopa is in the periphery and to a minor degree in the central nervous system also metabolized by the enzyme catechol-O-methyl transferase (COMT), mainly localized in the liver. Inhibition of COMT extends the half-life of levodopa and provides a more continuous availability of levodopa to the brain.[347] Entacapone is the by far most frequent used COMT-inhibitor today, as Tolcapone has in rare cases led to fatal liver toxicity. COMT-inhibitors are given as adjuncts to levodopa, and have shown to increase the levodopa effect and reduce "off" time and "off" severity in fluctuating patients.[348,349] Pronounced diarrhea limits unfortunately the use in some patients.

Dopamine agonists

Bromocriptine was the first oral dopamine agonists, introduced in the 1970s. It was an ergot-derivate, in line with the other first-generation agonists, in contrast to the non-ergot derivatives introduced later. Oral dopamine agonists have a differential affinity especially to D1 and D2 dopamine receptors, but their main advantage compared to levodopa is the longer half-life.[350] This is thought to be the primary cause of why dopamine agonists have less potential to induce fluctuations and dyskinesia, a widely documented benefit.[177,351,352] However, the dopaminergic effect is weaker compared to levodopa, while side effects as nausea, daytime somnolence and peripheral oedema are more prominent. They are consequently usually recommended as primary treatment for monotherapy in younger patients, but may also be effective as

supplement to levodopa to reduce fluctuations.[337,353] As dopamine agonists on ergot basis have shown a considerable risk to induce cardiac valve fibrosis, their use has become restricted and very limited.[354] Ropinirole, Pramipexole, Rotigotine and Piribedil are non-ergot agonists used today, Rotigotine as a transdermal patch. In recent years, the induction of impulse-control disorders has been recognized as a problematic side effect of all agonists, requiring specific attention and follow-up by the treating physician.[355]

Amantadine and Anticholinergics

The use of Amantadine and anticholinergic drugs (effective for tremor) is very frequent associated with side effects leading to discontinuation of treatment short after the initiation, and these drugs are no longer recommended in the Norwegian guidelines for treatment of PD.[356]

More advanced pharmacological treatment

Based on the disadvantages of pulsatile dopaminergic stimulation, methods for continuous application of dopaminergic drugs have been developed. They include today the subcutaneous infusion of the by itself very short acting dopamine agonist apomorphine and the intraduodenal application of a levodopa suspension via percutaneous endoscopic gastrostomy (PEG), both using an external pump. These treatment forms are primarily used in patients with advanced PD and more or less severe fluctuations.[357]

Surgery

For patients with advanced PD complicated by disability from motor fluctuations, dyskinesia or tremor despite optimal drug therapy, deep brain stimulation (DBS) of the nucleus subthalamicus (STN), globus pallidus internus (GPi) or ventral intermediate nucleus of the thalamus (Vim) has become a to some extent established treatment option. Fluctuations and dyskinesia are diminished by both STN- and GPi-DBS, but dopaminergic medication can be reduced more after STN-DBS, while

cognitive and psychiatric side effects are less prominent in GPi-DBS. Proper selection of patients with a reliable diagnosis of PD, distinct symptom improvement by levodopa, no or only mild cognitive impairment and no or well controlled psychiatric problems, is necessary to ensure satisfactory benefit from the surgical intervention.[10] Medication-resistant tremor is usually markedly improved by DBS of the Vim.[358]

Non-pharmacological treatment

Physical exercise is generally regarded to be of critical importance for PD patients.[359] Physical therapy in general is also in recent evidence-based recommendations rated as likely effective as symptomatic adjunct to levodopa and includes general exercise as well as movement strategy training with cuing and focussed attention. Speech therapy may improve dysarthria and dysphonia in some patients, but the evidence is insufficient for recommendations. The currently available studies do not enable to conclude on the use of occupational therapy and acupuncture in PD.[337,353]

1.7.2 Treatment for non-motor symptoms

Neuropsychiatric symptoms

Cognitive impairment in PD is associated with cortical cholinergic deficiency. The cholinesterase inhibitor Rivastigmin has shown well documented improvement of memory, attention and concentration.[360] The evidence for other cholinesterase inhibitors and the antiglutaminergic drug Memantine is weaker.[337,361] Adverse effects include nausea, tremor and urinary dysfunction.

Depression may be associated with suboptimal symptom control and fluctuations in PD, thus optimizing the dopaminergic therapy should be attempted. Pramipexole has shown an antidepressive effect independent of its impact on motor symptoms.[362] Use of the antidepressive selective serotonin reuptake inhibitors (SSRIs) is often necessary, but their effectiveness in PD is not optimally documented.[363]

As *anxiety* frequently is linked to depression, treatment with SSRIs can be effective. Optimized dopaminergic therapy is recommended, especially when anxiety occurs as part of the "off" state in fluctuating patients.[361] There is some evidence supporting cognitive behavioural therapy at least in the acute management of anxiety and depression.[364] Patients may have worries related to their future, the disease itself or their social situation, and corresponding measures will usually be at least of some help.

There is currently no established treatment for *apathy* in PD. Dopaminergic therapy should be optimized and comorbid depression treated first. In patients with cognitive impairment, also apathy may improve on treatment with cholinesterase inhibitors.[230,361]

In patients with *fatigue*, contributing factors like lack of sleep, depression, anxiety and orthostatic hypotension should be excluded or managed first, and patients may benefit from physical exercise. Methylphenidate, a dopamine transporter blocker, and Modafinil, primarily used to treat narkolepsy, improved fatigue in single studies.[365,366]

When *psychosis and hallucinations* occur, anticholinergic drugs, MAOB-inhibitors and Amantadine need to be withdrawn, dopamine agonists reduced or withdrawn. When improvement lacks, also levodopa should be lowered as far as possible.[361] Consistent evidence exists for effectiveness of the atypic antipsychotic Clozapine, but the risk of serious side-effects requires caution and monitoring. In clinical praxis, Quetiapin is frequently used, although the evidence is conflicting.[365]

Autonomic and gastrointestinal symptoms

For *orthostatic hypotension* it is recommended to try non-pharmacological measures first, such as sleeping in a head-up position to reduce night time hypertension, fragmentation of meals, avoidance of carbohydrate-rich meals, increased intake of water and salt, elastic stockings and increased physical activity.[235,365] Pharmacological treatment options include Fludrocortison to increase plasma volume, or the

sympathomimetic acting Midrodrine and Dihydroxyphenylserine, which have shown some efficacy in orthostatic hypotension, although not consistently.[367,368]

Literature concerning treatment of *sweating* disturbances in PD is extremely limited. As drenching sweats may occur as an "off" symptom, optimized dopaminergic therapy may lead to alleviation in those cases,[369] what is supported by a case report on improved off-related sweating after STN-DBS.[370]

Patients with significant *urinary dysfunction* should usually be examined by an urologist. Night-time polyuria can improve when fluid intake in the evening is reduced, but treatment with intranasal Desmopressin may be needed to reduce nocturnal urine production.[371] Urgency and incontinence related to detrusor hyperreflexia have shown improvement on anticholinergics, but cognitive function may worsen.[337,361] Bladder capacity and voiding volumes have shown improvement after DBS, but do not by themselves represent an indication for operative treatment.[372] For *erectile dysfunction*, improved dopaminergic treatment or subcutaneous injection of apomorphine have been suggested by some authors.[258,373] Phosphodiesterase-5 inhibitors have shown effect in one small, randomized trial.[374]

In cases of mild *constipation* the focus should be on increased intake of fluid and fibre, psyllium preparations and adequate physical activity, while anticholinergic drugs are to be avoided. For more severe cases, regular intake of stool softeners and intermittent use of laxatives is needed.[267] Macrogol is formally tested in PD patients and improved stool frequency and consistency.[375] Sufficient dopaminergic treatment should be ensured especially when defecation problems are "off" state-related.[361]

Patients with *dysphagia* will often profit from practical adaptions like taking more time to eat, a correct sitting position, smaller bites and careful fluid supplementation. Adaptations of the food itself may be needed, and in more severe cases thickeners for fluids are required. Levodopa and apomorphine have led to improvement at least in patients with early PD, indicating that optimized dopaminergic treatment and timing of meals to the "on" period may be reasonable efforts.[337,376]

As *drooling* is linked to oral, facial and pharyngeal function, improvement of these motor aspects by dopaminergic therapy sometimes reduces drooling. Xerostomia is a side effect of antidepressants and anticholinergics, which may be appreciated in drooling patients, although other side effects can limit the use.[377] Botulinum toxin injected in the salivatory glands is considered effective in a recent review.[365] As saliva production in PD patients generally is lowered despite excess from the mouth, utterly reduction of saliva increases the risk for problems with eating and dental health.

Pain and sleep-related problems

The management of *pain* in PD depends on the type of pain, requires often a multidisciplinary approach, and underlying causes should be eliminated.[361] Modification of dopaminergic treatment can reduce "off"-related pain and pain secondary to impaired mobility and posture, and is the first choice for central PD-related pain. Physiotherapy and general exercise are indicated in musculoskeletal pain. Direct analgesic treatment may be necessary in all pain types, including NSAIDs, tricyclic antidepressants, SSRIs, antiepileptic agents and opioid analgesics.[366]

Insomnia requires an initial analysis of sleep-related activities at both day and night-time. Restoring proper routines for timing of meals and bedtime can reduce problems falling asleep. For patients with difficulties to maintain sleep, some authors recommend increased dopaminergic treatment dosages short before bedtime to reduce off-related disturbances during the night.[378] However, this strategy may at least in early PD lead to poorer sleep quality and less REM sleep.[310] Hypnotics and other sedating medication are often required, but when their half-life is long, they may cause or increase *daytime somnolence*. The latter can also be a side effect of dopaminergic treatment, especially dopamine agonists.[378] For *REM sleep behaviour disorder*, Clonazepam is currently the standard treatment, but careful dose titration due to possible resulting daytime somnolence is also here required.[311]

2. Aims of the study

The overall aim of this study was to present improved evidence of the incidence and clinical characteristics of early PD with focus on non-motor features. To achieve this, we conducted four studies with the following aims:

Paper I

- To determine the incidence of Parkinson's disease in Norway and establish a representative cohort of patients with early PD for longitudinal investigations.
- To explore gender differences in the risk of PD and in clinical characteristics of early, untreated PD.

Paper II

- To describe the prevalence and severity of autonomic and sensory symptoms in a representative cohort of patients with early, drug-naïve PD.
- To identify clinical and demographic factors which interfere with autonomic and sensory symptoms in early, untreated PD.

Paper III

- To determine the influence of dopaminergic treatment on autonomic symptoms in early and previously untreated PD.

Paper IV

- To identify the factors contributing most to impaired quality of life in early PD.
- To determine if quality of life in patients with early PD is most affected by motor or non-motor symptoms.

3. Patients and methods

The here presented work was part of the Norwegian ParkWest study which was established to study the clinical course and neurobiology of Parkinson's disease in a representative cohort of patients. The study was approved by the Regional Committee for Medical Research Ethics, University of Bergen.

All investigations were performed by study physicians and/or study nurses in an unblinded setting, using either direct interview or scoring based on examination.

3.1 Base population and case identification

We aimed to recruit all cases of incident Parkinson's disease between 1st November 2004 and 31st August 2006 from a base population of about 1 052 000 inhabitants. The study area comprised four counties, and all five neurological departments from those counties participated. All these study centres are responsible to provide second-line neurologic health care for geographically determined regions which together cover the study area. Cooperation with the only neurologist exclusively practicing outside the participating hospitals was established.

According to the Norwegian Medicines Agency's regulations and guidelines, patients with suspected Parkinson's disease or other parkinsonism are to be referred to a specialist in neurology for diagnosis and initiation of treatment. This is incorporated in practice, as also indicated by a nationwide survey from 2006.[379]

To ensure a case identification as complete as possible, we applied the following:

1. All hospital departments, general practitioners, consulting physicians of nursing homes, geriatric care centres and other institutions for persons of older age were informed about the study by mail or email before and during the study period.

2. All referral letters to the participating study centres were hand searched for symptoms possibly representing formerly not diagnosed parkinsonism.
3. Hospital databases were screened electronically for patients diagnosed with PD for the first time during the screening period and for 3 months after (to capture delays in coding).
4. Six months after the end of the screening period, a random sample of the study population from Hordaland county, comprising 43 716 individuals, was performed by linkage to their general practitioners' electronic medical record system. Records dating back to one year before study start were searched for:
    a. Written terms including "Parkinson", "Parkinsonism", "ParkWest" and the cardinal motor features of PD,
    b. disease codes used by practitioners and hospitals for PD, parkinsonism and other movement disorders,
    c. anti-Parkinson drugs including their trade names.

    Patient files with hit on at least one search item were completely screened by the author to determine whether the current case was correctly referred or not referred to the study.

3.2 Diagnosis of Parkinson's disease

As the diagnosis of PD is challenging in the early phase, especially when dopaminergic treatment has not yet been applied, the diagnostic procedure comprised several stages:

1. Initial screening visit

    All individuals identified with possible incident parkinsonian symptoms were examined by study neurologists. Based on broad provisional diagnostic criteria, an initial study diagnosis was given:
    a. Incident PD (study-inclusion when consent given)
    b. Uncertain PD (later re-assessment)
    c. No PD (routine follow-up)

2. Baseline assessment

   Individuals with incident PD that consented to participation were investigated according to the study protocol. Those without consent were invited to routine follow-up for clinical re-assessment. Patients with initially uncertain PD that were later diagnosed with PD were then offered study-inclusion.

3. Follow-up

   Patients who participated in the study underwent follow-up twice per year with evaluation of clinical development and therapy response.

4. Final determination of the diagnosis

   After at mean 28 months from the initial screening visit, all available information from clinical notes, study protocols and radiological examinations were evaluated by two study neurologists (GA and JPL). The clinical diagnostic criteria provided by Gelb in 1999 were applied to determine a diagnosis of possible or probable PD.[31] The diagnosis of other parkinsonian conditions was based on the respective diagnostic criteria.[108,109,130,205,380]

A flowchart demonstrating the diagnostic evaluation process is shown in Figure 1, page 853 of paper I.

3.3 Definition of incidence

Cases were defined as incident PD if

- they had for the first time been referred to a specialist in neurology for possibly Parkinson-related motor-symptoms within the study period,
  OR
- parkinsonism had explicitly been suspected by a physician for the first time within the study period,
  AND
- they were finally provided with a diagnosis of Parkinson's disease by a study neurologist.

3.4 Control group

A control group was primarily recruited from among the patients' spouses or friends, excluding sib family members. A lower number of controls were recruited from clubs for elderly and similar organizations. Of the 205 recruited controls, subgroups matched for age and gender to the investigated patient group were included in the studies for paper II and IV.

3.5 Assessment of motor symptoms and disease severity

Motor symptoms of PD were assessed with the UPDRS,[157] which has become one of the most widely used scales to investigate the presence, severity and development of symptoms related to Parkinson's disease. It consists of 42 single items which cover information on neuropsychiatric disturbances in part I, activities of daily life in addition to sensory disturbances in part II, examination-based motor function in part III, and complications from therapy as fluctuation and dyskinesia in part IV. Ratings range from 0 to 4 with higher scores indicating higher severity.

To assess the pattern of parkinsonism in paper I, mean scores for the motor domains tremor, rigidity, bradykinesia and axial impairment were calculated based on the UPDRS part III according to Levy.[381]

For paper II, patients were classified into the motor subtypes PIGD, indeterminate, or tremor-dominant, using the UPDRS parts II and III as suggested by Jankovic.[156]

Based on clinical considerations and previous publications, we composed symptom variables for 8 motor symptoms for analyses in paper IV, using items from UPDRS II, III and IV.[382,383] A variable for nocturnal motor symptoms was calculated from three items from the Parkinson's Disease Sleep Scale (PDSS).[384] Details of the composition of motor variables are listed in table 1, page 1028 in paper IV.

Disease severity was measured with the Hoehn & Yahr scale (HY),[385] which is based on the uni- or bilateral presence of symptoms, the grade of postural instability and mobility. Scores range from 0 to 5, the highest score indicating that the individual is wheelchair bound or bedridden unless aided.

To access activities of daily living, the Schwab and England scale was used.[386] It rates the degree of independence from other persons to perform tasks of daily life. Total independence is indicated by score 100%, while 0% indicates a total dependent and bedridden individual.

3.6 Assessment of non-motor symptoms

Cognitive function (paper I and IV)

Overall cognitive function was assessed with the Mini Mental State Examination (MMSE),[387] which consists of 20 items on different cognitive domains. Scores range from 0 to 30, the highest indicating normal cognitive function, while a score of 25 or lower is recommended for the diagnosis of dementia in PD.[388]

Depression (paper IV)

The Montgomery and Aasberg Depression Rating Scale (MADRS, 0-60) was used to explore depressive symptoms.[389] It is an observer-based rating scale recommended for use in PD.[390] The MADRS consists of 10 items, each ranging from 0 to 6 with higher scores for more severe symptoms. A score ≥20 was taken to indicate moderate or more severe depression.[391]

Apathy (paper IV)

We assessed apathy with the Starkstein Apathy Scale (SAS), which consists of 14 items, each rated on a four-point Likert scale, with a total range from 0 to 42 and higher scores indicating more severe apathy.[392] It is recommended for use in PD with a cut-off of 13/14 to detect clinically significant apathetic symptoms.[221]

Fatigue (paper IV)

Fatigue ratings were obtained with the Fatigue Severity Scale (FSS). The 9 items range from 0-7 and a score of 4 or higher marks clinically relevant fatigue.[393,394] The scale is recommended to assess the severity of fatigue in PD.[394]

Autonomic and gastrointestinal symptoms (paper II, III, IV)

Autonomic symptoms were assessed with three different questionnaires, all with a range of 0-4 or 0-3, where "0" indicates the absence and the highest score indicates the most severe characteristic of a symptom:

1. The UPDRS, range 0-4, for dysphagia and increased saliva/drooling.
2. A preliminary version of the Movement Disorders Societies revision of the UPDRS (pMDS-UPDRS), range 0-4, for constipation, urinary urgency, lightheadedness standing, increased saliva/drooling, dysphagia.[16] A score of "2" or more indicates that the severity of the respective symptom interferes with daily activities.
3. A questionnaire created for the study, range 0-3, for constipation, urinary dysfunction, increased sweating ("ParkWest questionnaire").

The pMDS-UPDRS and "ParkWest questionnaire" are shown in appendix III.

These questionnaires were applied on patients on all major study-visits. For controls, only the UPDRS and ParkWest questionnaire were applied at baseline.

In paper II, frequency calculations of autonomic and gastrointestinal symptoms at baseline were based on the UPDRS and the ParkWest questionnaire as they were available from both patients and controls. Severity scores were based on the pMDS-UPDRS as it provides reliable severity ratings based on a symptom's impact on daily activities. Paper III and IV are based on information from the pMDS-UPDRS only.

Blood pressure was measured manually after 10 min supine and again after 2min standing (paper II and III). Orthostatic hypotension was defined as systolic blood pressure drop of at least 20mm Hg according to published guidelines.[395]

Sensory symptoms (paper II and IV)

Sensory complaints as pain, cramping or other discomfort were in paper II assessed with one question from the UPDRS in patients and controls for its frequency, and with one question from the pMDS-UPDRS to access the severity in patients (paper II and IV).

Olfactory function was tested with two odours (vanilla and coffee), presented for patients and controls in open, dark glasses, eyes had to be closed (paper II only). Failure to identify or precisely describe the characteristics of both odours was taken to indicate hyposmia.

Sleep disturbances (paper IV)

A diversity of sleep related problems were assessed with the Parkinson's Disease Sleep Scale (PDSS), recommended for use in PD.[384,396] Fifteen questions cover sleep quality, motor and non-motor nocturnal disturbances as well as daytime sleepiness. Each item ranges from 0 (not present) to 10 (severe and always present). As one of the aims in paper IV was to specifically compare the impact of motor vs. non-motor symptoms on quality of life scores, we calculated a separate sum score for nocturnal motor symptoms (PDSS items 9: urinary incontinence due to motor "off"; 12: awakening in the morning due to dystonia; 13: tremor when awakening). Item 14 (unexpectedly falling asleep during the day) was removed as daytime sleepiness was assessed separately (see below). The remaining 10 PDSS items composed a score for non-motor sleep disturbances. There is no consensus on a cut-off value for the PDSS, but a sum score of 100 or lower for the total PDSS has been used to indicate more severe sleep problems.[397]

Daytime sleepiness was assessed with the Epworth Sleepiness Scale (ESS).[398] The likelihood to doze off in eight daily situations is rated with a range from 0 (would never doze) to 3 (high chance of dozing), leading to a maximum score of 24. A cut-off of 10/11 has been proposed to detect pathological daytime sleepiness.[396]

Details on the composition of non-motor variables for paper IV are shown in table 1, page 1028 in paper IV.

3.7 Assessment of quality of life

The Short-form Health Survey (SF-36) is a generic questionnaire, meaning it was not specifically developed for use in patients with PD and is thus applicable for healthy controls.[399] It assesses the health status with 36 questions in eight domains with summary scores for physical and mental health aspects. The physical compound score, PCS (combined domains: physical functioning, role-physical, bodily pain, general health) and mental compound score (combined domains: vitality, social functioning, role-emotional, mental health) were calculated according to the published manual.[400] Higher values indicate better quality of life and a score of 50 represents the age-specific mean for a normative control population. The SF-36 has frequently been used in patients with PD, has shown good reliability and discriminative validity and is recommended for use in patients with PD.[325]

3.8 Medication

Levodopa-equivalent daily dose

For the symptomatic treatment of Parkinson's disease, a number of pharmacological agents are used with different dopaminergic efficacy. To assess the impact of primarily dopaminergic medication on different symptoms, we calculated the levodopa-equivalent daily dose (LED) for each patient at the time of interest. For paper III, this calculation was based on a formula used in earlier publications:[401,402]

LED = milligram (mg) standard Levodopa + mg sustained release Levodopa x 0,75 + mg Levodopa taken together with Entacapone x 0,25 + mg Ropinirole x 16.67 + mg Pramipexole (salt) x 67 [mg Pramipexole (salt) equate mg Pramipexole (base) x 1.4].

In 2010, a systematic review on calculation of the LED in PD was published,[403] and the recommended formula from this review was used in paper IV. For three drugs, this formula used higher factors compared to the calculations for paper III, leading to slightly higher LED for some patients: Entacapone x 0.33 vs. 0.25, Pramipexole x 100 vs. 67 (salt), Ropinirole x 20 vs. 16.67.

Non-PD medication

Autonomic symptoms may be influenced by medication given for other conditions than PD. This was taken into account in paper III by registering non-PD medications and grouping the drugs with respect to the autonomic symptoms they may influence: Laxatives (constipation), cardiovascular acting agents (orthostatic hypotension and orthostatic dizziness), anticholinergics (sialorrhea and urinary dysfunction) and antidepressants (sialorrhea). Changes during the observation period were classified as potentially "increasing", "decreasing" or "neutral" in relation to the respective autonomic symptom and implemented in one of the regression analyses as a covariate.

3.9 Statistical analyses

Data on the population size and distribution of age and gender in the study area by 1st January 2005 were obtained from Statistics Norway, which provides official statistics about the Norwegian society (www.ssb.no). Crude incidence, age- and gender specific incidence rates and incidence rates corresponding to the 1991 European standard population were calculated.

For comparison between independent groups, χ^2-test was used for proportions (paper I, II, III), Student's t-test for means of approximately normally distributed data (paper I, II, III) and Mann-Whitney test for markedly skewed data (paper I, II). When

longitudinal results were compared, we performed McNemar test to assess changes in proportions (paper III, IV), paired samples t-test for changes of the mean in approximately normally distributed data (paper IV) and Wilcoxon signed ranks test for changes of the mean in markedly skewed data (paper III).

In paper II, a linear regression model was used to assess the relationship between the number of autonomic and sensory symptoms and different covariates. A logistic regression model identified risk factors for the occurrence of different autonomic or sensory symptoms.

In paper III, the association between changes in severity scores of autonomic symptoms and the daily levodopa-equivalent dose (LED) was tested with an ordinal regression model.

In paper IV, linear regression models were created to investigate the association of motor and non-motor variables with the physical and mental compound scores of the SF-36. Data from baseline and three years later were analysed separately in three main steps with increasing interaction of the included variables:

- In step 1, one regression model was run for each motor and non-motor variable with the SF-36 compound scores as dependent variable, corrected for age, gender and education.

- In step 2, the regression procedures were performed with either all motor variables or all non-motor variables included in the same model, to reduce the impact of covariance.

- In step 3, all motor and non-motor variables were included in the same regression models.

For the regression models in step 2 and 3, a stepwise backward procedure eliminated those variables not contributing relevant proportions to the current regression model (criterion: probability of F-to-remove ≥ 0.1). The proportion of variance of the SF-36

compound scores explained by the variables finally included in the models was calculated (R^2).

Statistical analyses were performed using SPSS versions 14.0-17.0 and 20 (SPSS, Chicago, IL) in addition to R 2.6.1 (paper I only).

4. Summary of results

Paper I

Paper I revealed an annual crude incidence of Parkinson's disease in western and southern Norway of 13.7 cases per 100 000 inhabitants per year, with a maximum for the decade 70-79 years of age. Adapted to the European standard population, the incidence rate was 12.6/100 000, with a clear male preponderance (male to female ratio 1.58 (CI 1.22-2.06)), which was present in all age groups. Electronic screening of general practitioners' medical records of a subpopulation identified no cases missed to referral. The clinical onset of PD was slightly later in woman compared to men (68.6 vs. 66.3 years, $p=0.062$), but measures of motor dysfunction, disease severity, disability and cognitive impairment were similar in men and women at the time of diagnosis.

Paper II

In paper II we found that autonomic and sensory symptoms were more frequent in patients with PD already at diagnosis when compared to controls matched for age and gender (2.9 vs. 1.1 out of 8 assessed symptoms, $p<0.001$). Most frequent in patients were reduced olfaction (59%), urinary problems (47%), increased saliva/ drooling (42%), constipation (39%) and sensory complaints (34%). The majority of patients (58%) were not impaired in their daily activities by any of these symptoms, and less than 10% reported a moderate or severe affection of their daily activities. More severe disease at diagnosis (Hoehn & Yahr stage) and the PIGD motor subtype were associated with a higher number of autonomic and sensory symptoms. Gastrointestinal symptoms and abnormal sweating were more frequent in more severe PD.

Paper III

In paper III we found that dopaminergic treatment of patients with early PD affects the presence and severity of autonomic symptoms only slightly. In the group of patients that used dopaminergic treatment one year after baseline (82%), constipation and orthostatic blood pressure drop increased. We observed also a tendency towards increased orthostatic dizziness and urinary dysfunction. Mean dysphagia scores were reduced after the initiation of dopaminergic treatment, and this was associated with higher levodopa-equivalent daily doses. No significant changes in autonomic symptoms were found in patients not treated with dopaminergic agents.

Paper IV

In paper IV we showed that health-related quality of life is reduced already from the time of diagnosis in patients with early PD. The non-motor symptoms with most impact on HRQoL-measures were depression, fatigue and sensory complaints, while the most important motor symptoms were gait disturbances and problems to perform daily activities for personal needs (cutting food, dressing, hygiene, turning in bed). Overall, the variance of both physical and mental quality of life sum-scores from the SF-36 was to a higher proportion explained by non-motor symptoms than motor symptoms, both at diagnosis and three years later. This was true both when motor and non-motor symptoms were analysed in separate regression models and when they were included in the same model.

5. Methodological considerations

5.1 Epidemiological issues

Investigation of incidence

The estimation of incidence figures relies heavily on the methodology applied, and our study followed to a large extent proposed scientific criteria:[68]

1. The base population and observation time are recommended to cover about one million patient years, which was exceeded in our study observing a population of about 1 million for 20 months. Due to the multi-centre approach, this population size was feasible to access.
2. The prospective approach ensured higher case ascertainment and data accuracy compared to retrospective methods.
3. We applied multiple sources of case identification to achieve as complete case ascertainment as possible. To verify this, an electronic search of the medical databases of urban and rural located general practitioners was performed in a subarea, but identified no cases of possible PD that had not been referred to the study. It is likely that the structure of the health-care system in Norway has contributed to this effective case ascertainment. Alternatively, a population screening for cases might have revealed additional cases, but was not feasible. It would also have detected cases in much earlier stages of PD, before the individuals seek health care, what could have led to an overestimation of the incidence-rates.
4. All patients referred for symptoms possibly representing parkinsonism were examined by study neurologists, ensuring proper diagnosis.
5. We defined the time of incidence by the date of diagnosis, which is considered the most practical approach. However, the risk of underestimation due to cases

that die before they have received the diagnosis may represent a minor confounder of incidence figures.

6. We used clear and consistent inclusion and exclusion criteria.
7. Follow-up improved diagnostic accuracy and the final diagnosis was set only after at mean 28 months of observation. That implies that some individuals had a shorter follow-up time, and single cases had not yet started with dopaminergic medication, meaning a risk for an incorrect diagnosis of PD was still present.
8. We reported incidence rates by standard age strata and the overall incidence adjusted to the 1991 European standard population, to enable comparison between studies.

Establishment of a representative cohort

To study clinical and biological aspects of a heterogeneous disease like PD, it is preferable to establish a cohort of patients as unselected as possible. Population-based studies are in this respect superior to clinic-based studies as the latter are likely to accumulate more severe, complicated and younger cases. Out of the 265 individuals we identified as having PD, a high proportion (80%) consented to further participation in the study and follow-up. The mean age of 68 years (range 42 to 88 years) reflects the typical older population affected by the disorder.[68] The anamnestic duration from the first PD-associated symptoms of 2.3 years corresponds to the usually observed and reasonable delay between the first occurrence of abnormalities and the diagnosis of PD. Thus, we are confident of having based our findings on a best possible unselected and therefore representative cohort of patients with early PD.

5.2 Assessment tools

The results of clinical studies depend on the tools used for assessment, and the studies in this thesis are to a large extent based on recommended scales and scores for the respective conditions. Due to lacking availability or practical issues, single symptoms were assessed with not or not fully established methodology.

Autonomic and sensory symptoms

The use of three different scales to assess autonomic and sensory symptoms was suboptimal. However, the now established and validated SCOPA-AUT, NMSS and NMS-Quest[14,15,404] were not available when this study was planned, and the COMPASS[405] was considered much too time consuming. We considered therefore the pMDS-UPDRS suitable to assess the severity of autonomic and sensory symptoms, what was supported by the later validation of the final MDS-UPDRS part I for assessment of non-motor symptoms in PD.[406] As it was not applied in the controls, the UPDRS and "ParkWest" questionnaire were used in combination to assess the frequency of autonomic and sensory symptoms in patients and controls. These scales have not been validated for the assessment of autonomic symptoms in PD. They provide, however, a meaningful and similar grading of symptom-severity, in the pMDS-UPDRS related to a symptoms impact on daily activities. An advantage was the application by interview, which likely has limited misinterpretation.

Olfactory dysfunction

Testing of olfactory dysfunction was limited to the identification of two odours, which is a more simple method compared to more sophisticated assessments of olfaction with odour-batteries as "Sniffin' sticks"[407] or University of Pennsylvania Smell Identification Test (UPSIT).[408] However, our results are in range of earlier prevalence figures of olfactory dysfunction in both patients (59% in our study vs. 45-90% earlier)[102] and controls (21% vs. 25%).[284] A recent study found about 45% of PD patients being anosmic and 51% hyposmic.[282] Using a more complex odour-

identification test may have revealed more hyposmic individuals also in our cohort, while we are confident to have identified the anosmic also with the test method we applied.

Quality of life

Quality of life was assessed with the SF-36, and statistical analyses were performed on the basis of compound scores for physical and mental HRQoL (PCS, MCS). As it has been shown that these two scores not necessarily reflect distinct measures of physical and mental health,[409] we were cautious in our interpretations and took the summary scores as a whole to reflect the overall health-related quality of life. It has also been recommended to use the eight domains of the SF-36 as more specific quality of life measures,[410] but this was not in accordance with the aim of paper IV and would have hampered the interpretation significantly due to a large number of results.

5.3 Statistical procedures

Statistical procedures are central and challenging elements of research which have to be chosen carefully for the specific data and questions assessed. The bivariate analyses and regression procedures performed in paper I-III represent standard practice for the respective problems investigated. The methodology used to determine the impact of motor vs. non-motor symptoms on quality of life measurements in paper IV is not established, but shows similarities to earlier publications.[383,411,412] Two problems dominate this type of analysis. First, the relatively large number of explanatory variables in addition to confounding factors may reduce statistic power when all are included simultaneously. Second, a varying degree of interaction between clinical variables exists often and can affect the effect-size and power of results for covariant variables and overall results. We have taken this into account by increasing the interaction of variables in three steps, thereby also documenting the association of the single candidate variables with quality of life measures, only

corrected for demographic factors (regression step I). This was followed by increasing the amount of involved motor- and non-motor variables in each regression procedure through step II and III. The backward regression led to a limited number of variables that explain the variance of SF-36 scores best and present a stronger and more simple, final model. Despite the advantages of this approach, stepwise regression procedures have drawbacks. One is that the final model with its limited number of variables neglects the higher number of variables originally involved, why the fit appears to be better than it actually is. Another problem is that the final results depend on which variables are excluded early in the procedure. The significance of a variable may differ depending on which other, possibly covariant variables are part of the model at each step, what means that a variable excluded early in the procedure could have had more significant impact in a later step. However, although we have not published this in the papers, we performed also forward regressions to control the reliability of the backward regression results, and ended up with similar results, supporting the presented data.

6. General Discussion

6.1 Incidence of PD in Norway

While prevalence-numbers for Parkinson's disease in Norway have been available since 1995,[127] the Norwegian ParkWest study was the first to provide incidence figures for the country. In paper I, we found a crude incidence of 13.7/100 000 with a corresponding number of 12.6/100 000 when adapted to the European standard population from 1991. These data are the result of a methodology based on recommendations for high quality incidence studies from 2003.[68] By January 2014, we could identify five further incidence studies on PD, most published after our paper I, which followed a similar methodology.[73-75,413,414]

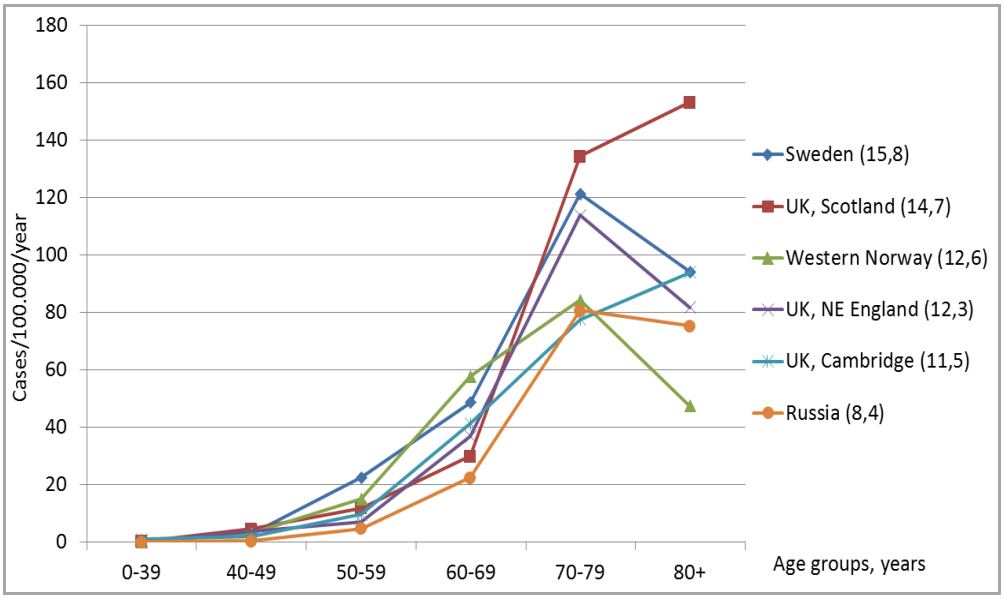

Figure 2: Incidence of PD in 5 European studies. Data matched for age and gender to 1991 standard European population. Respective overall incidence in parenthesis.

Figure (2) shows the standardized age-specific incidence figures of these studies and our own. The herein documented standardized incidence for the United Kingdom (UK), Sweden and Norway ranges from 11.5 to 15.8/100 000, while the Russian study found a much lower number of 8.4/100 000. Although biological causes for these differences cannot be excluded per se, methodological reasons seem more likely, including distinctions in health-attitude and health-care systems, which may have led to unequal accessibility of incident cases despite the efforts of the investigators.[415,416]

The incidence numbers of these latest studies are overall lower than those of the best studies published until 2001, which ranged from about 16 to 19/100 000.[68] It has been shown that the diagnosis given in early parkinsonism needs to be changed within the first year in about 30% of patients.[417] Increased focus on a correct diagnosis, including diagnostic re-evaluation after significant follow-up-time, may have contributed to exclusion of more cases in the later studies. However, these numbers document also that the improved methodological homogeneity not necessarily led to a closer range in the resulting incidence figures, even within a limited geographic area. An uncertainty of ±2-3 cases per 100 000 inhabitants may thus be as close as one can get to the "true" incidence numbers.

On the other hand, an underestimation of the incidence cannot be excluded for our study. Despite the multiple sources of case ascertainment, complete case identification is difficult to achieve in a large base population. The fact that no additional cases were identified by electronic screening of a subpopulation suggests, however, that we may indeed have recruited all incident cases. Yet, identification and diagnosis of PD represents a special challenge in the oldest age group. PD symptoms may be taken to represent features of normal aging, vascular or other neurodegenerative parkinsonism,[70] and cases in nursing homes may not come to primary care physicians for diagnosis.[418] Research criteria may be too narrow to include all variants of the broad spectrum of clinical PD, and even in a series of pathologically proven PD, 10% had been diagnosed with another parkinsonism during lifetime.[419] On the other hand, overestimation of the incidence of PD in the oldest age

groups is as well a risk. DLB, vascular parkinsonism and other tremor conditions are examples that led to changed diagnosis within one year of the initial diagnosis in another incidence study.[417] In our study, dementia with parkinsonism (13%) and vascular parkinsonism (7%) were among the most frequent conditions diagnosed instead of PD. These diagnostic challenges may also be the basis for the diverging incidence numbers for PD in the population ≥80 years also reported in the latest, methodologically improved studies shown in figure (2). While we found a decrease of the incidence in this age group along with two other studies, two reports describe a further increase of the incidence. Studies focused on screening of elderly populations for PD have revealed considerably higher incidence numbers with continuous increase for those aged 80+, but the results are weakened by a lack of follow-up.[420-422] Whether aging continuously increases the risk for PD throughout the whole lifetime remains therefore an open question.

6.2 Gender-differences in incident PD

We found a male preponderance for the incidence of PD throughout all age groups with an overall 58% increased risk for men vs. women after standardization. An earlier published meta-analysis reported a practically identical male to female ratio of 1.57,[72] and numbers in the above mentioned high quality incidence studies range from 1.30 to 1.83.[73-75,413,414] The anamnestic onset of PD symptoms was in our study slightly- albeit not significantly- later in women compared to men, in line with several earlier studies.[68,73-76] While the lower incidence and later onset of motor symptoms may suggest a neuroprotective mechanism in women, we could not find evidence for differences concerning the severity or pattern of motor features or overall cognition, also this consistent with other reports on incident or early PD.[73,74,78] One imaging study on previously untreated PD patients has also documented a similar progression rate of dopaminergic degeneration and deterioration of motor function for both genders.[76] Although a neuroprotective effect of oestrogens has been suggested from in vitro studies,[85,86] this has not been confirmed in clinical trials,[88,90] and the risk for

PD is furthermore similar in Asian women and men.[68] These and our findings seem therefore to indicate that at least European women have a lower susceptibility to get PD compared to men, but the underlying cause remains uncertain. We found no evidence for a presence of disease-modifying or neuroprotective mechanisms in women, at least within the first time after the disease has become clinically overt.

6.3 Non-motor symptoms in early PD

6.3.1 Frequency and severity of autonomic and sensory symptoms

Despite increasing recognition of non-motor symptoms as key-features in PD, their interference with quality of life and their development often before the onset of motor symptoms, autonomic and sensory symptoms are poorly investigated in the early stages of the disease. We have investigated the frequency and severity of these symptoms in a representative population-based cohort of 212 patients with incident PD. The often suggested influence of dopaminergic drugs on autonomic symptoms was avoided by examination prior to the initiation of PD-specific treatment. Furthermore, as autonomic problems also increase with higher age,[423] we compared the frequency figures to a control group matched for age and gender.

Paper II confirmed impaired olfaction as the most common non-motor symptom also in early PD, present in 59% of patients. Earlier reports have shown even higher frequencies (75 to 90%) but included more advanced disease stages and used more advanced tests.[51,102] It is not clear whether olfaction deteriorates with progression of PD.[52,288,289] If that was the case, it could explain higher frequencies for later stages. However, we could not find an association of olfactory dysfunction with age, disease severity or disease duration, in line with the general assumption that the olfactory deficit is rather stable in PD.[283,289] As explained in “methodological considerations”, we may have failed to identify a number of patients with milder hyposmia, what may also have influenced our results.[282]

After impaired olfaction, the most frequent autonomic and sensory disturbances were urinary dysfunction (47%), increased salivation/drooling (42%), constipation (39%), and sensory complaints (34%), while increased sweating (22%), dysphagia (19%) and orthostatic hypotension (18%) were not as frequent. All symptoms, with the exception of increased sweating, were much more frequent than in the control-group, what supports PD as the underlying cause.

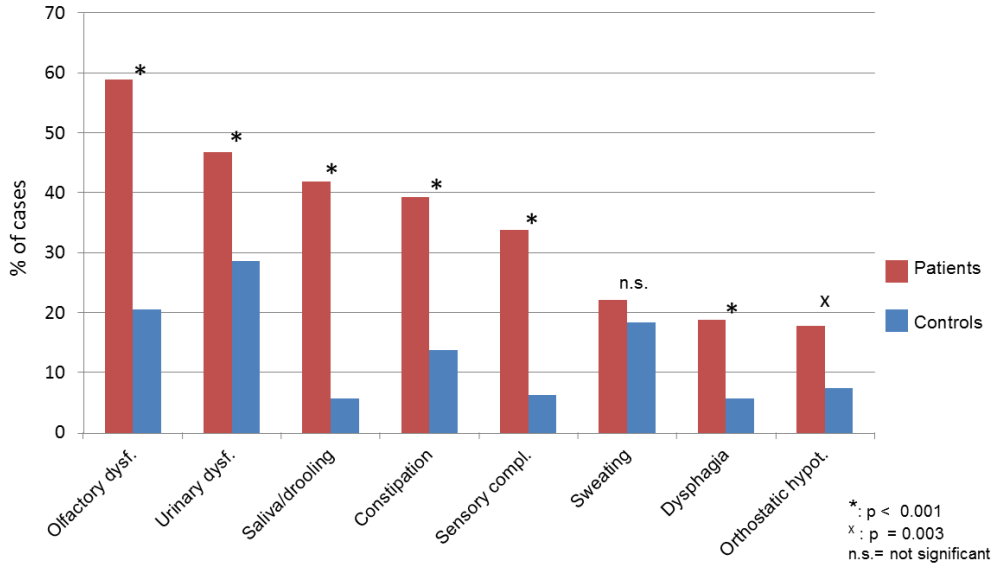

Figure 3: Frequency of autonomic and sensory symptoms and signs in patients at diagnosis vs. controls.

At the time of publication of paper II in 2010, comparable reports were lacking, but some further studies assessing multiple non-motor symptoms in early stages of PD have been published by now. The frequency numbers we reported have been largely confirmed by a population-based study from northern England[424] and a clinic-based study from China reporting on patients with a PD duration <2years.[425] However, two Italian, clinic-based studies on overlapping cohorts of early, drug-naïve PD patients found clearly lower numbers.[426,427] The mean age of patients was similar to our study in the English cohort, but lower (58-61 years) in the clinic-based studies, confirming

the known selection-bias connected to this recruitment-form. All these four studies used one of the validated, self-report non-motor screening questionnaires NMSQuest[424,426,427] and NMSS,[425] what seems to indicate that our assessment methods were sufficiently reliable.

Interestingly, our frequency figures also meet the range of earlier reports which included considerably later stages of PD,[404,428-430] what may indicate that autonomic and sensory symptoms mainly emerge during the very early stages of PD. This would, however, be in some contrast to the findings in the above mentioned, large Chinese study, which assessed non-motor symptoms in patients with a PD-duration of 2-5 years, 5-10 years and ≥10 years, respectively.[425] Constipation, urinary problems, dysphagia, drooling and increased sweating occurred all significantly more frequent with longer disease duration, while orthostatic dizziness and pain did not.

In the same study, Guo et al. have also documented increasing *severity* of non-motor symptom scores with longer duration of PD,[425] in line with the general perception. To our knowledge, the severity parameters of non-motor symptoms have not been formally assessed in other studies on early PD so far. In our study, the severity of autonomic and sensory symptoms was overall low at diagnosis, although for each symptom, 8-18% of patients reported a severity with at least a slight impact on daily function. This underlines the need to assess these symptoms already from the earliest stages of PD, especially as patients tend to underreport non-motor symptoms if not specifically asked about them under their medical consultation.[192]

The high frequency of increased salivation or drooling already at diagnosis was unexpected, as this has not been reported earlier. Our finding was, however, recently confirmed when even 56% of 159 patients with newly diagnosed PD reported sialorrhea in an English incidence-cohort.[424] Considering the high frequency in patients at diagnosis, especially in contrast to the very low frequency in age-matched controls, increased saliva or drooling could be considered a supportive feature for the diagnosis of PD, in line with reduced olfaction. However, drooling occurs also in MSA,[431] and analysis of the saliva composition could be a more specific marker for

PD.[279] Further studies on these issues will be needed to determine the diagnostic value of salivatory changes, possibly also for the identification of individuals at risk to develop motor-PD.

The PIGD-subtype of PD has, in addition to neuropsychiatric and sleep problems, in single studies also been associated with an increased risk for orthostatic hypotension[165] and drooling.[424] In our material, the PIGD subtype was associated with constipation, and patients with PIGD had, in line with a later published study on early PD,[424] overall a higher number of autonomic and sensory symptoms compared to those with tremor-dominant PD, already in this early stage of PD. Additionally, also a higher HY stage was associated with more autonomic symptoms, similar to findings in patient populations covering later stages of PD.[432]As axial symptoms are key-features for classification into higher HY-stages and the PIGD subtype, common elements in the underlying pathophysiology of early axial and autonomic symptoms in PD can be suggested. The PIGD subtype is associated with higher cortical load of Lewy bodies,[167,168] a different pattern of striatal dopaminergic activity[169] and pathology in extranigral midbrain structures.[433] This may indicate an overall more aggressive, or more widespread pathology in patients with early PD and axial symptoms, making them more likely also to develop more autonomic or other non-motor features.

6.3.2 Autonomic symptoms and dopaminergic treatment

Dopamine is involved in both central and peripheral mechanisms of autonomic regulation, but the influence of dopaminergic treatment on autonomic function is a matter of ongoing discussion and conflicting evidence. Colonic transit-time is increased in PD,[263,434] and this may be potentiated by dopaminergic treatment,[435] but findings differ.[436,437] Orthostatic hypotension in PD is caused by impaired cardio-vascular response to postural changes, and several studies suggest that dopaminergic treatment facilitates the problem.[438-440] The basal ganglia are involved in regulation of micturition, partly based on dopaminergic signaling.[441] However, both

improvement and worsening of urinary symptoms related to dopaminergic treatment have been reported.[252,442]

In paper III, we found only slight changes in autonomic symptoms after the initiation of dopaminergic treatment. Significant changes were observed for increased severity of constipation and orthostatic blood pressure, while slight worsening with borderline-significance was observed for urinary dysfunction and lightheadedness standing. Our results support in principle similar findings from two studies that investigated untreated patients with de novo PD 3 months and 2 years after baseline, respectively. In one of the studies,[242] light-headedness was the only autonomic symptoms that increased after dopaminergic treatment, in the other study, only constipation tended to increase, but non-significantly (p=0.092).[426] Although the observed changes were small, they seem to support the view that dopaminergic mechanisms may contribute to autonomic symptoms, and that this is to some degree also true in early PD.

Interestingly, we found a tendency to improved dysphagia in our patients, which was significantly correlated to higher LED. Although dysphagia is often labelled as non-responsive to dopaminergic treatment,[443,444] at least partial improvement has been reported following levodopa, apomorphine and stimulation of the subthalamic nucleus.[445-447] The conflicting evidence may reflect the unequal pathophysiological mechanisms contributing to dysphagia, with probable unequal responsiveness to dopaminergic stimulation. However, our data lend support to a recent publication suggesting that dysphagia at least in a proportion of patients can respond to increased dopaminergic treatment, and clinicians should be encouraged to try this in patients with dysphagia to reduce the risk for severe complications of aspiration.[376]

Despite these signs of some improvement in dysphagia, excess saliva or drooling was not reduced after the initiation dopaminergic treatment. A possible explanation may be that the clinical improvement in dysphagia did not include the mechanisms that actually account for the leakage of saliva from the mouth, as facial mimics, mouth opening and tongue motility.[274,280] Alternatively, the stimulatory effect of levodopa

may have increased the production of saliva in a number of patients,[278] and thus antagonized the positive effect of improved dysphagia. A closer analysis of the association between dysphagia, drooling and changes due to dopaminergic treatment also in the current cohort could shed some light on this interesting complex, but was not part of the present study.

In line with two studies on initially untreated patients,[242,426] findings for autonomic symptoms were similar in patients treated with levodopa and dopamine agonists, what is in some contrast to a Cochrane review from 2008 that concluded with a higher risk of constipation for treatment with dopamine-agonists compared to levodopa.[448] Furthermore, larger cross-sectional studies have described an association of higher LED with an increased number or severity-score of autonomic symptoms.[449,450] We could not reproduce this finding in our study, and it may reflect increased severity of the primary disorder in patients with higher levodopa-dosages rather than a dose-dependency of autonomic side-effects of dopaminergic drugs, as an association between the severity of dysautonomia-scores and HY-scores has also been shown, including in paper I.[449]

The relatively low dose of dopaminergic treatment used in our study (mean LED 251 ±140) may have contributed to the limited changes observed in our cohort. This hypothesis is, however, not supported by the two above mentioned studies on initially untreated patients, which reported similar findings despite higher LED in their patients (376±183 and 356±169, respectively).[242,426]

Although the overall changes in autonomic symptoms after dopaminergic treatment were very limited in our study, individual responses on dopaminergic treatment may spread largely from clear improvement to problematic deterioration, masked in the analysis of mean values. Winge has for example in 2004 concluded that urinary dysfunction can improve, deteriorate or remain unaffected by dopaminergic treatment, but the individual response is unpredictable.[256] Analysis of sub-groups of patients by type of response to dopaminergic treatment would be of relevance and interest in this respect, but was beyond the scope of the current studies.

6.4 The symptoms' impact on quality of life in early PD

Paper II has documented a frequent presence of several autonomic and sensory symptoms in early PD, but with overall low severity. It is widely accepted that non-motor symptoms have considerable impact on quality of life in mid- and later stages of PD, but their importance for the quality of life in early PD has been largely neglected. Reduced quality of life in PD has been variably associated with longer disease duration, increased disease severity (Hoehn & Yahr stage) and higher daily levodopa dosages.[326,327,451,133] This raises the question of when the disease actually starts to impair the quality of life of affected patients. Three reports on clinic-based patient groups with early PD are available.[161,332,333] Although they did not compare quality of life measures in patients to normative values or control-groups, their findings suggest reduced quality of life already early in PD. We have in paper IV investigated 188 patients from our representative, population-based cohort with newly diagnosed PD with the generic SF-36 questionnaire and found the sum scores for physical and mental health-related quality of life (42.5±10.0 and 45.9±11.2, respectively) significantly reduced compared to normative population samples (50 for both, $p<0.001$). The reduction was also true for comparison to a control-group matched for age and gender (SF-36 physical: 51.1; SF-36 mental: 54.9, data not shown in paper IV). Our results thus extend earlier findings of reduced quality of life in patients with PD to be true already from the time of diagnosis, despite overall only slight or mild symptoms.

We were interested to identify the factors that account for reduced quality of life in this early stage. For more advanced PD, a review from 2011 showed that the role of demographic parameters as age, gender and education is limited.[133] Depression was the factor most frequently reported with impact on quality of life, and in most reports depression impairs quality of life more than other variables.[131,132,333,451,452] Further frequent reported symptoms related to HRQoL[133] were anxiety,[132,453,454] fatigue,[132,455,456] gait impairment[132,457] and fluctuations[132,458]. Virtually all these earlier studies assessed only a limited selection of motor- and non-motor features, neglecting

possibly significant contributors to HRQoL, and produced therefore biased results. Patients with early, untreated PD have not been investigated in this respect, although the pre-medication state is of interest as a basis for longitudinal analyses and to indicate the consequences of the disease independent of treatment.

To fill this gap, we have collected information on a wide range of motor- and non-motor symptoms to study their independent impact on HRQoL in early PD, including the drug-naïve stage. Non-motor variables covered cognitive, autonomic, sensory and sleep-related problems, as well as mood-disturbances.

We found the highest regression coefficient in our baseline-analyses for MADRS-scores with mental SF-36 scores throughout all steps of the regression procedures ($\beta>0,5$ for regression steps 1,2 and 3, all $p<0.001$). This complements earlier findings on advanced[131,333,451,452] and late stages of PD[132,459] and confirms the importance of depressive symptoms for quality of life throughout the whole course of the disease, including the time of diagnosis. Our findings do, however, probably also reflect the naturally strong interrelatedness of depression and quality of life, interestingly demonstrated in a recent study on the general UK population. Of 11 comorbidities investigated, including cancer, breathing problems and stroke, quality of life was lowest in people with depression.[460]

In contrast to depression, fatigue showed a solid correlation to the *physical* SF-36 compound score at baseline. After 3 years, fatigue became the strongest contributor both to reduced SF-36 physical and mental compound scores. A clear impact of fatigue on quality of life in PD has been demonstrated in different studies[455,456] and it is by many patients perceived as one of, or even *the* most disabling symptom.[209] The question arises whether the predominant finding of depression as the most important contributor to reduced HRQoL is determined by the fact that most studies investigated depression, but not fatigue at the same time.[131,383,451,452,461] However, also studies that have investigated both symptoms simultaneously found that depression was strongest associated to HRQoL, including one study on early PD.[11,132,333,453] Methodological issues, including the applied assessment tools, may have contributed to the differing

findings in our study. Of importance may for example be that we report physical and mental SF-36 scores, as fatigue comprises both mental and physical fatigue, what is also reflected in the FSS-questions. In contrast, depression and the MADRS scale are heavily dominated by pure mental aspects. This inequality may have strengthened the impact of fatigue in the specific context of assessments in our study. Our results nevertheless underline the importance of fatigue for PD patients already in the earliest phase of the disease.

Sensory complaints as pain affect quality of life both in the general population and in more advanced PD.[11,296,460,462] We are only aware of one study that assessed the impact of pain on quality of life in early PD.[161] The authors found a pain-prevalence comparable to our study, but no correlation to quality of life. This study assessed the presence/absence of pain, in contrast to the five-point severity rating in our study. The latter may have been more sensitive to detect a correlation with HRQoL-scores in the context of the overall low severity of pain (paper II). As also an association between pain and depression has been reported,[463] covariance between those symptoms can be suspected. However, the significant contribution of pain to reduced physical SF-36 scores in multivariate models, in contrast to depression which impaired mental SF-36 scores, favours an independent role of pain for quality of life.

Autonomic symptoms contribute to reduced quality of life in more advanced PD, but usually less than cognitive/psychiatric symptoms.[11,12,132,464,465] Similar findings are reported from the only comparable study on early PD.[161] One study that specifically focussed on urinary dysfunction in early PD, showed also only a minor impact on HRQoL, which increased with more severe PD-symptoms.[466] In line with these reports, we found that the cumulative impact of constipation, urinary dysfunction and orthostatic dizziness on HRQoL was present, but mostly in bivariate analysis and negligible in multivariate analysis which included other non-motor symptoms, clearly ranging behind depression, fatigue and pain. Although we investigated only a selection of the autonomic symptoms associated with PD, especially constipation and urinary dysfunction are amongst those most frequently reported with impact on

HRQoL.[11,132,464] We therefore think that our findings confirm the general perception and conclusions from paper II and III, that autonomic symptoms are of overall limited severity in early PD.

Apathy, sleep problems, daytime sleepiness and cognitive impairment may have some impact on quality of life according to single reports on early PD,[161,333,467] but these are infrequent findings. Our results confirm thus that these symptoms are of generally limited relevance for the quality of life in patients with early PD, although this may differ in single patients with severe problems.

Postural instability, gait impairment and complications from therapy have been considered the most important motor symptoms for quality of life,[131-133,468] but also axial symptoms, bradykinesia, rigidity and speech problems contribute in some studies.[12,131-133,411] The best predictors of reduced HRQoL among the motor symptoms in our patients with early PD were impairment of gait and of the ability to conduct personal needs like dressing, eating, hygiene and turning in bed. This may at first appear surprising, as gait- and functional impairment are not pronounced in this early stage. However, a reduced ability to walk and perform personal needs threatens an individual's independence, what may explain the strong impact on perceived quality of life. Axial symptoms also showed a high correlation in the first, simple regression, but not in the more complex multivariate models. This could be related to the known covariance of axial symptoms and gait problems,[469,470] which may have erased the effect of axial symptoms when gait problems have been included in the same model.

To our knowledge, only one study has earlier investigated the impact of specific motor symptoms on HRQoL in early PD.[332] The authors reported axial impairment as the most important motor symptoms, but gait assessment was included in the sum score for axial impairment. Thus, our results specify and extend these findings and highlight the importance of gait impairment and impaired ability to perform personal needs for HRQoL in patients with early PD. The clinical impairment may appear mild, and patients may seem able to cope with these symptoms, but treating

physicians should take these two factors specific into account also for patients with very early disease.

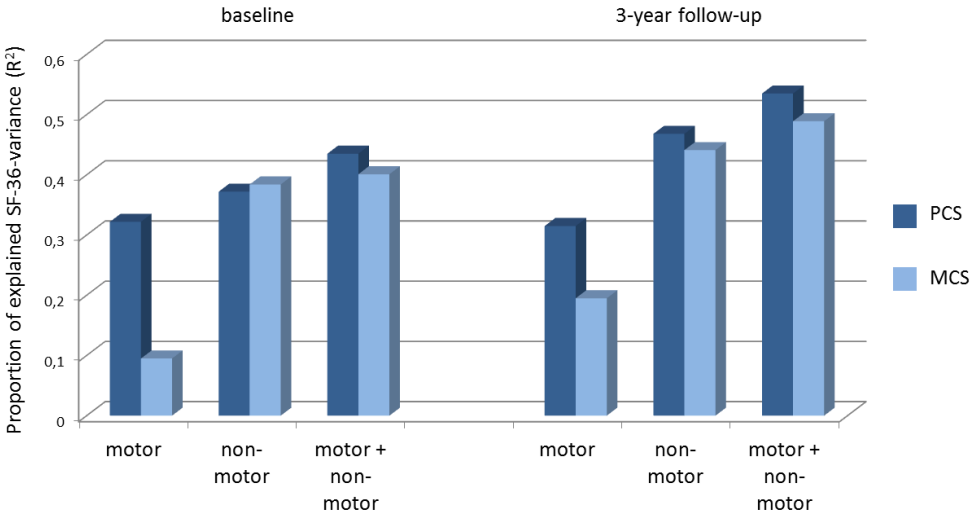

Figure 4: Proportions of the variance of SF-36 physical (PCS) and mental (MCS) compound scores explained by motor symptoms, non-motor symptoms, and both together.

There are ongoing discussions as to whether motor or non-motor symptoms are more important for quality of life in PD.[329,330] In available studies, mostly performed on patients with moderate or advanced disease, depression or a total non-motor symptom score have usually outranged the impact of motor scores.[12,131,132,333,464] To our knowledge, only one former study has compared the impact of a wider range of specific motor and non-motor features of PD with respect to quality of life. The authors found depression slightly superior to ADL functioning as the best predictors of quality of life scores in patients with a mean PD-duration of 9 years.[132]

We found that the variance of mental, but also physical SF-36 summary scores was to a larger extent explained by non-motor symptoms than motor symptoms. The results are consistent throughout the different steps of increasingly complex regression models and for analyses of both early, untreated patients and after 3 years follow-up. Our study is thus the first to document that non-motor symptoms predict quality of life in early PD better than motor symptoms when a wide range of both symptom-

categories is included in multivariate analyses. Furthermore, our results do not lend support to earlier suggestions that non-motor symptoms dominate in this kind of analyses only because they are less optimally treated compared to motor symptoms, and therefore relatively more severe.[330] However, with longer duration of the disease, the complications of dopaminergic treatment and pronounced gait disturbances may increase the impact of motor symptoms, albeit also the load of non-motor symptoms is expected to increase.

7. Final conclusions

The occurrence of PD in Norway is similar to other European countries, with a crude incidence of 13.7/100 000/year, corresponding to 12.6/100 000/year for the European standard population. The known male-preponderance of PD is also present in Norway, but significant clinical differences between genders lack at diagnosis. New evidence with respect to the underlying causes of the gender-related risk-disparities in PD was not found.

Autonomic and sensory symptoms are frequent in untreated PD already at diagnosis. Although mild and with overall limited impact on quality of life, problems may be more severe in single patients, what the treating clinicians should be aware of. The initiation of dopaminergic treatment is unlikely to cause problematic autonomic side-effects, at least when relatively low doses are used.

The main factors leading to reduced health-related quality of life in early PD are fatigue and depression, but also gait disturbances, impaired ability to conduct personal needs and pain contribute. Overall, non-motor symptoms are more important for impaired quality of life in early PD than motor symptoms.

Our findings underline the necessity to pay attention to non-motor symptoms already from the diagnosis of PD, although the consequences of motor-disturbances must not be neglected. In patients with dysphagia, dopaminergic treatment should be optimized as improvement may be achieved. Drooling should be further investigated with respect to its potential as a supportive diagnostic marker for PD or parkinsonism. Further incidence studies are needed to evaluate whether the currently available recommendations are sufficient to ensure homogeneous methodology, especially with respect to case-recruitment in the highest age-groups.

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9. Appendices

Appendix I

Criteria proposed by the UK Parkinson's Disease Society Brain Bank (*Hughes et al., JNNP 1992;55:181-184):*

UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria

Step 1 Diagnosis of Parkinsonian syndrome

- Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)
- And at least one of the following:
  - muscular rigidity
  - 4–6 Hz rest tremor
  - postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction.

Step 2 Exclusion criteria for Parkinson's disease

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- More than one affected relative
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- Presence of cerebral tumour or communicating hydrocephalus on CT scan
- Negative response to large doses of levodopa (if malabsorption excluded)
- MPTP exposure

Step 3 Supportive prospective positive criteria for Parkinson's disease

(Three or more required for diagnosis of definite Parkinson's disease)

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70–100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of 10 years or more

Appendix II

Criteria proposed by Gelb (*Gelb et al., Arch Neurol. 1999;56:33-39):*

Table 1. Grouping of Clinical Features According to Diagnostic Utility

Group A features: characteristic of Parkinson disease
- Resting tremor
- Bradykinesia
- Rigidity
- Asymmetric onset

Group B features: suggestive of alternative diagnoses
- Features unusual early in the clinical course
  - Prominent postural instability in the first 3 years after symptom onset
  - Freezing phenomena in the first 3 years
  - Hallucinations unrelated to medications in the first 3 years
  - Dementia preceding motor symptoms or in the first year
- Supranuclear gaze palsy (other than restriction of upward gaze) or slowing of vertical saccades
- Severe, symptomatic dysautonomia unrelated to medications
- Documentation of a condition known to produce parkinsonism and plausibly connected to the patient's symptoms (such as suitably located focal brain lesions or neuroleptic use within the past 6 months)

Table 2. Proposed Diagnostic Criteria for Parkinson Disease

Criteria for POSSIBLE diagnosis of Parkinson disease:

At least 2 of the 4 features in Group A* are present; at least 1 of these is tremor or bradykinesia

and

Either None of the features in Group B* is present

Or Symptoms have been present for less than 3 years, and none of the features in Group B* is present to date

and

Either Substantial and sustained response to levodopa or a dopamine agonist has been documented

Or Patient has not had an adequate trial of levodopa or dopamine agonist

Criteria for PROBABLE diagnosis of Parkinson disease:

At least 3 of the 4 features in Group A* are present

and

None of the features in Group B* is present (note: symptom duration of at least 3 years is necessary to meet this requirement)

and

Substantial and sustained response to levodopa or a dopamine agonist has been documented

Criteria for DEFINITE diagnosis of Parkinson disease:

All criteria for POSSIBLE Parkinson disease are met

and

Histopathologic confirmation of the diagnosis is obtained at autopsy (see Table 3)

**Group A and Group B are detailed in Table 1.*

Appendix III

Non-motor symptom questionnaires

ParkWest questionnaire (translated, original questions are in Norwegian):

1. Are you constipated?
2. Do you have problems passing water?
3. Do you sweat more than usual?

The answers were rated by the interviewer according to: 0=no symptom, 1=slight, 2=mild/moderate, 3=severe symptoms.

Preliminary version of the Movement Disorder Societies revision of the UPDRS (pMDS-UPDRS):

1.8 Pain and abnormal sensory sensations - On the average during the past week, have you experienced pain and abnormal sensory sensations as a result of your PD? By "pain and abnormal sensory sensations", I mean aching, cramping or other discomfort perceived by you to relate to PD and not to other medical conditions.

0: None. No pain or abnormal sensations.
1: Slight. Aching, cramping or discomfort, but without effect on daily activities.
2: Mild. Aching, cramping or discomfort occasionally interferes with daily activities.
3: Moderate. Aching, cramping or discomfort often interferes with daily activities.
4: Severe. Aching, cramping or discomfort interferes with daily activities to the point that it is a major contributor to overall disability.

1.9 URINARY PROBLEMS – On the average during the past week, have you experienced urinary problems as a result of your PD? By "urinary problems," I mean bothersome urinary frequency, urgency or incontinence.

0: Normal. No urinary problems.
1: Slight. Occasional urinary frequency or urgency but no major inconveniences to normal activities.
2: Mild. Urinary frequency or urgency sufficient to cause inconvenience and requiring some adaptations in daily function, although no incontinence.
3: Moderate. Urinary frequency, urgency with occasional incontinence; significantly interferes with daily activities such as social functions.
4: Severe. Frequent urinary incontinence, may need to use catheter.

1.10 CONSTIPATION IMPACT ON DAILY ACTIVITIES – On the average during the past week, have you experienced an impact from constipation on your daily activities as a result of your PD? By "an impact from constipation", I mean a bothersome change in bowel habits, discomforts, and preoccupation with bowel movements and their impact on independence in daily activities.

0: Normal. No constipation.
1: Slight. Constipation present, but without impact on daily activities.
2: Mild. Constipation has mild impact on daily activities.
3: Moderate. Constipation causes significant discomfort or inconvenience that makedly impacts on daily activities
4: Severe. Constipation dominates your concerns or you need physical disimpaction for handling constipation.

1.11 LIGHTHEADEDNESS ON STANDING – On the average during the past week, have you experienced lightheadedness on standing as a result of your PD? By "lightheadedness", I mean the impact of dizziness on your balance and safety when changing position from lying to sitting and sitting to standing.

0: Normal. No lightheadedness.
1: Slight. Lightheadedness occurs with changes in posture but has no impact on performance of daily activities.
2: Mild. Lightheadedness occurs with changes in posture so that you return to a sitting or lying position to manage symptoms. No falls and no loss of consciousness.
3: Moderate. Lightheadedness occurs with changes in position and has been associated with at least one fall in the past week, but without loss of consiousness.
4: Severe. Lightheadedness occurs with changes in posture and has been associated with at least one episode of loss of consiousness over the past week.

2.2 Handling saliva – On the average during the past week, have you experienced problems with handling saliva as a result of your PD? By 'problems with handling saliva' I mean the presence of excess saliva during the day and night and the dependence on handkerchiefs or tissues.

0: Normal. No problem.
1: Slight. Excess saliva with nighttime drooling.
2: Mild. Excess saliva with minimal drooling during the day.
3: Moderate. Excess saliva that causes daytime drooling, requiring frequent use of a tissue or handkerchief, specifically more than two times daily.
4: Severe. Drooling requires constant use of tissue or handkerchief.

2.3 Swallowing and chewing/manipulating food in mouth – On the average during the past week, have you experienced problems with swallowing and chewing or manipulating food in your mouth as a result of your PD? By 'problems with swallowing and chewing or manipulating food in your mouth', I mean ease of swallowing, presence of choking, time required to chew and swallow, and adaptations in food preparation in order to avoid choking.

0: Normal. No problems
1: Slight. Some difficulty with swallowing but no choking **or** extra time needed to chew food. However, food is not cut or prepared in a special way for you to chew or swallow.
2: Mild. Chokes but not daily, **or** expends considerable time and effort to chew food, but food is not cut or prepared in a special way for you to chew or swallow.
3: Moderate. Daily choking **or** food needs to be cut or prepared in a special manner because of difficulty chewing or swallowing.
4: Severe. Unable to obtain adequate nutrition without an alternative route for nutritional support (i.e. nasogastric tube or gastrostomy).