Diplomarbeit

Early symptoms in idiopathic Parkinson's disease
A retrospective study

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List of Abbreviations

αSYN	αSynuclein
Aβ	amyloid β protein
AAN	American Association of Neurology
ABPI	ankle brachial pressure index
AD	Alzheimer's disease or autosomal dominant
ADL	activities of daily living
AGE	advanced glycation endproducts
AHI	apnea-hypopnea index
ALP	alkaline phosphatase
ALS	Amyotrophic lateral sclerosis
ALT	alanine aminotransferase
Aon	anterior olfactory nucleus
ApoE	apolipoprotein E
AR	autosomal recessive or androgen receptor
AST	aspartate aminotransferase
ATP13A2	P-type ATPase
BG	basal ganglia
BMI	body mass index
BSIT	brief smell identification test
CBC	complete blood count
CBD	corticobasal degeneration
CCSIT	cross cultural smell identification test
CJD	Creutzfeldt-Jakob disease
CO	carbon monoxide
COMT	catechol-o-methyl transferase
CS2	carbon disulfide
CSF	cerebrospinal fluid
CT	computed tomography
CVD	cerebrovascular disease
DA	dopamine agonist
DAT	dopamine transporter
DCC	deleted in colorectal cancer
DDPAC	disinhibition dementia parkinsonism amyotrophy complex
DIP	drug induced parkinsonism
DLB	dementia with Lewy bodies
DMV	dorsal motor nucleus of the vagal nerve
DRBA	dopamine receptor blocking agent
DTI	diffusion tensor imaging
EDS	excessive daytime sleepiness
EEG	electroencephalography
ELLDOPA	Earlier vs Later L-DOPA study
EMG	electromyography
ENS	enteric nervous system
EOG	electrooculography
EPHB1	ephrin receptor B1
ER	endoplasmatic reticulum
ET	essential tremor
FA	fractional anisotropy
fPD	familiar Parkinson's disease

FTDP-17	frontotemporal dementia with parkinsonism linked to chromosome 17
FXTAS	fragile X associated tremor/ataxia syndrome
GA	Golgi apparatus
GABA	gamma amino butyric acid
GHS-R1a	functional ghrelin receptor
GIGYF2	GRB10 interacting GYF protein 2
GIRK	G-protein activated inwardly rectifying potassium channel
glu	glutamate
GPe	external globus pallidus
GPi	internal globus pallidus
GR	glucocorticoid receptor
GSS	Gerstmann-Sträussler-Scheinker disease
GTPCH1	GTP-cyclohydrolase 1
GWAS	genome wide association study
Hcrt	Hypocretin
HD	Huntington's disease
HDAC	histone deacetylase
Hg	mercury
HIV	human immunodeficiency virus
H/M ratio	heart / mediastinum ratio, used in MIBG-scinitgraphy
HY	modified Hoehn and Yahr scale
IBZM	iodobenzamide, SPECT-tracer of postsynaptic striatal neurons, reduced uptake in atypical parkinson syndromes
123-I-FP-CIT	(123)I-N-omega-flouropropyl-2-beta-carboxymethoxy-3-beta-(4-iodophenyl)-nortropane, SPECT-tracer of striatal presynaptic dopamine transporters, reduced uptake in Parkinson's disease
iLBD	incidential Lewy body disease
INR	intranuclear rodlets or international normalized ratio
K-ATP	ATP sensitive potassium channel
KF rings	Kayser-Fleischer rings
LB	Lewy body
LBVET	Lewy body variant of essential tremor
LC	locus ceruleus
LD	levodopa
LLR	long latency reflexes
LN	Lewy neurite
LPS	lipopolysacharide
LRRK2	leucine rich repeat kinase 2
MAO-B	monoamine oxidase B
MARS	molecular adsorbent recirculating system
MB	Marinesco body
MDS	Movement Disorder Society
MIBG	metaiodobenzylguanidine, scintigraphy-tracer
MM	mirror movements
MMSE	Mini Mental State Examination
Mn	manganese
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSA	multisystem atrophy
NA	norepinephrine

NFT	neurofibrillary tangles
NIP	neuroleptic induced parkinsonism
NM	neuromelanin
NMDA	N-methyl-D-aspartic acid
NMS	non-motor symptoms
NO	nitrogen monoxide
N/OFQ	Nociceptin/Orphanin FQ
NPH	normal pressure hydrocepahlus
NPTX II	Neuropentraxin II
NTL	lateral tuberal nucleus
NTNG1	Netrin G1
OD	olfactory dysfunction
OERP	olfactory event-related potentials
OH	orthostatic hypotension
Olb	olfactory bulb
Omi/HtrA2	a serine protease, nuclear protein with mitochondrial targeting sequence
P75NTR	p75 neurotrophin receptor
PB	pale bodies
PCD	programmed cell death
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PDH	pyruvate dehydrogenase
PET	positron emission tomography
PiD	Pick's disease
PINK1	PTEN induced kinase 1
PKAN	pantothenat kinase associated neurodegeneration
PLMS	periodic limb movements in sleep
PML	promyelocytic leukaemia protein or progressive multifocal leuko-encephalopathy
PPN	pedunculopontine nucleus
PPE-A	precursor protein of enkephalin A
PS	Parkinsonian syndrome
PSG	polysomnography
PSP	progressive supranuclear palsy
QoL	quality of life
RAGE	receptor for advanced glycation endproducts
RBD	rapid eye movement sleep behaviour disorder
RET	rearranged during transfection
RLS	restless legs syndrome
RSWA	REM sleep without atonia
SAS	sleep apnea syndrome
SD	standard deviation
SDH	subdural hematoma
SE	Schwab and England activities of daily living scale
SEMA5A	Semaphorin 5A
Shh	Sonic hedgehog
SK channel	small conductance calcium-activated K (potassium) channel
SLE	systemic lupus erytematosus
SNc	substantia nigra, pars compacta
SNr	substantia nigra, pars reticulata
SNP	single nucleotide polymorphism

SPECT	single photon emission tomography
SPEM	smooth pursuit eye movements
SPR	sepiapterin reductase
SSPE	subacute sclerosing panenecepahlitis
SSR	sympathetic skin response
SSRI	selective serotonine reuptake inhibitor
STN	subthalamic nucleus
SUMO-1	small ubiquitin like modifier 1
SVD	small vessel disesae
TCS	transcranial brain parenchyma sonography
TM	tuberomamillary nucleus
TNFα	tumor necrosis factor α
UCH-L1	ubiquitin C-terminal hydrolase L1
UKPDSBB	United Kingdom Parkinson's disease Brain Bank
UPDRS	Unified Parkinson's disease Rating Score
UPS	ubiquitine proteasome system
UPSIT	University of Pennsylvania smell identification test
VEP	visual evoked potential
VP	vascular parkinsonism
WD	Wilson's disease
XDP	X-linked dystonia-parkinsonism

Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by a broad spectrum of motor and non-motor features. Early PD is characterized by several non-motor features; among the most prominent are olfactory dysfunction, sleep and mood disturbences, pain, paraesthesias and autonomous dysfunction. The aim of this diploma thesis was to shed light on the early phase of PD. The core question was: What are the characteristic features of patients with PD before they visit an outpatients' department for movement disorders. Therefore, a retrospective study was carried out, using data of 242 patients with parkinsonism which were derived from medical records of patients who visited the outpatients' department for Parkinson's disease and movement disorders at the Department of Neurology, Medical University Graz, for the first time. Statistical analysis was perfomed using SPSS 14.0.

Conclusion: The majority of patients was found in an intermediate disease stage and was not naive to dopaminergic drugs when seen by a specialist for the first time. Frequently retrospective derived early non-motor symptoms in sporadic PD were depression, sleep disturbences and shoulder/neck pain. Around one third of patients were taking an antidepressant drug and around every tenth patient was taking a benzodiazepine in the early phase of PD. Besides the cardinal motor features of PD, highly prevalent early motor symptoms were clumsiness, micrographia, limping gait and decreased armswing. The most frequently availabe diagnostc tests at the patients' first visit at the outpatients' department were conventional brain imaging data (MRI, CT). Besides the core issue of this study, a high prevalence of PD with concomitant diagnosis of essential tremor was demonstrated, accounting for around every tenth patient with PD. Furthermore, it was demonstrated that PD patients with motor fluctuations were younger at disease onset than those without fluctuations. Actually, the early phase of PD is usually rather a domain for genereal practitioners and settled neurologists, whereas, unfortunately, only the intermediate disease stage is confined to the neurologist skilled in movement disorders. Nevertheless, watchful waiting and permitting motor features to develop is not an option in early PD, as this is the time when putative disease-modifying agents should take action.

Zusammenfassung

Das idiopathische Parkinson-Syndrom (IPS) ist eine progressive, neurodegenerative Erkrankung und ist durch ein breites Spektrum von motorischen und nicht-motorischen Symptomen charakterisiert. Die Frühphase des IPS ist klinisch gekennzeichnet durch das Auftreten vieler nicht-motorischer Symptome. Unter den wichtigsten sind olfaktorische Dysfunktion, Schlaf- und Gemütsstörungen, Schmerzen, Parästhesien und autonome Symptome. Das Ziel dieser Diplomarbeit war es, Aspekte der Frühphase des IPS zu beleuchten. Die Kernfrage war: Welche charakteristischen Merkmale haben PatientenInnen mit IPS bevor sie eine Ambulanz für Bewegungsstörungen aufsuchen. Aus diesem Grund wurde eine retrospektive Studie durchgeführt, in der Daten von 242 PatientenInnen mit Parkinsonsismus verwendet wurden. Die Daten wurden aus den Krankenakten vom Erstbesuch der PatientenInnen in der Ambulanz für Morbus Parkinson und Bewegungsstörungen, Institut für Neurologie, Medizinische Universität Graz, entnommen. Die statistische Analyse wurde mit SPSS 14.0 durchgeführt.

Schlussfolgerung: Die Mehrheit der PatientenInnen befand sich schon in einem intermediären Erkrankungsstadium und erhielt bereits dopaminerge Medikamente wenn ein(e) in Bewegungsstörungen erfahrene(r) NeurologeIn sie zum ersten Mal sah. Häufig beobachtete Frühsymptome bei IPS waren Depression, Schlafstörungen und Schulter/Nackenschmerzen. Ungefähr ein Drittel der PatientenInnen nahm ein Antidepressivum und ungefähr jeder/jede Zehnte ein Benzodiazepin in der Frühphase von IPS. Neben den motorischen Kardinal-symptomen von IPS waren Ungeschicklichkeit, Mikrographie, Nachziehen eines Beines und reduziertes Armmitschwingen beim Gehen häufige motorische Frühsymptome. Die am häufigsten bereits durchgeführten diagnostischen Tests bei Erstbesuch in der Ambulanz waren Ergebnisse konventioneller Bildgebung (MRT, CT). Neben der Kernfrage dieser Studie wurde außerdem eine hohe Prävalenz von IPS mit begleitendem essentiellem Tremor nachgewiesen werden, ein Zustand der ungefähr bei jedem/jeder zehnten PatientenIn mit IPS vorlag. Weiters wurde ein früherer Erkrankungsbeginn bei PatientenInnen mit motorischen Fluktuationen nachgewiesen. Tatsächlich ist die Frühphase von IPS im Allgemeinen eher eine Domäne von HausärztenInnen und niedergelassenen NeurologenInnen, wohingegen unglücklicherweise erst das intermediäre Erkrankunsstadium den in Bewegungsstörungen erfahrenen NeurologenInnen vorbehalten ist. Trotzdem sind abwartendes Offenlassen und das Gestatten motorischer Symptome sich zu entwickeln keine Option in der Frühphase von IPS, da gerade dies der Zeitpunkt ist, zu dem eine möglicherweise krankheitsmodifizierende Substanz eingreifen sollte.

1. Introduction

1.1. Synopsis

Why dost thou quiver, man?
It is the palsy, and not fear,
Provokes me.

William Shakespeare
King Henry VI, part 2, act IV, scene VII
From Stien R [1]

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by a broad spectrum of motor and non-motor features [2]. The variable clinical phenotype implies that PD is a heterogeneous disease with distinct subgroups [3]. PD is an αSynucleinopathy [4, 5] and the second most common cause for neurodegeneration after Alzheimer disease (AD) with an age dependent prevalence, afflicting approximately 1.6 % of the population older than 65 years and 3.6 % for those aged 85 – 89 years [6]. It has a major impact on activities of daily life (ADL) and perceived quality of life (QoL) [7, 8].

1.1.1. Molecular pathology of Parkinson's disease

The neuropathological hallmarks are first a progressive loss of neuromelanin (NM) containing dopaminergic neurons in the substantia nigra, pars compacta (SNc) with a predilection of the ventral lateral tier, which projects to the dorsal putamen [9] and second, the presence of proteinacious, intracytoplasmic inclusions termed as lewy bodies (LB) and lewy neuritis (LN) in surviving neurons. The major component of these structures is aggregated α-Synuclein (αSYN) [10, 11], the key player in PD which is highly phosphorylated [12], ubiquitinated [13], nitrated [14] and furthermore contains dopamine adducts [15].

The brainstem type LB displays a central core with a surrounding halo and maturates from the peripheral portion of pale bodies (PB) which arise via compaction from diffuse cytoplasmatic staining [16]. Severeal proteins interact with αSYN and contribute to its fibrillization, among the most important are the synphilin-1 complex [17, 18], agrin [19], tau [20] and 14-3-3 [21].

Likewise, advanced glycation endproducts (AGE) are involved in αSYN crosslinking [22, 23] and possibly influence signal transduction cascades via its receptor RAGE [24, 25]. Moreover, neuronal pentraxin II (NPTX II), the most highly upregulated gene in the affected SNc, is found in close association to αSYN aggregates [26, 27] and is expressed in hypocretin (Hcrt) cells of the hypothalamus, which are strikingly diminished in PD [28].

There is an intriguing interface between αSYN and tau [29, 30], which is the major component of neurofibrillary tangles (NFT) in AD [31], given that both proteins can promote the fibrillization of each other [32]. Furthermore, tubulin, which is co-localized with αSYN in LBs, can seed αSYN-fibrillization [33]. Another molecular link between PD and AD is implicated by αSYN – amyloid β protein (Aβ) interaction [34, 35, 36].

Additionally, αSYN [37], tau [38] and Aβ [39] are natively unfolded proteins, devoid of secondary and tertiary structure, which need a structural transformation into a partially folded conformation to initiate fibrlillization. The resulting intermediates (αSYN-oligomers) are aggregation prone and may represent the toxic element in αSYN pathology [40].
αSYN exists as two confomers: a membrane-bound form with a helical structure and a more abundant, natively unfolded free cytosolic form. The membrane-bound form has a higher tendency to form aggregates than the cytosolic form. Moreover, the aggregation of cytosolic αSYN can be seeded by preformed membrane-bound αSYN -aggregates [41].

A small percentage of newly synthesized αSYN is secreted from cells via unconventional vesicular exocytosis in normal neurons and further αSYN is found in the CSF and blood plasma at nanomolecular levels. Intravesicular αSYN is aggregation prone and under abnormal conditions, aggregated αSYN is secreted [42]. Moreover, there is evidence for host to graft disease propagation in patients with PD, given that some of the transplanted dopaminergic neurons display LBs and LNs [88]. These observations are in favour of the suggested hypothesis of ‘permissive templating’ and a ‘prion-like’ spreading mechanism [89].

1.1.2. Intranuclear pathology - MBs and INRs in PD

In normal neurons, αSYN localizes to presynaptic axon terminals and to the nucleus. In PD, αSYN mediates neurotxicity in the nucleus by forming abnormal αSYN-histone complexes. This toxicity can be rescued by administering histone deacetylase (HDAC)-inhibitors. Marinesco bodies (MB) are intranuclear inclusions in pigmented neurons of the SN and LC and immunoreactive to ubiquitin, ataxin-3, PML, SUMO-1 and contain HDAC-4, vacuole creating protein and glucose-3-phosphate-dehydrogenase. Their frequency increases with advancing age in normal individuals, thus for a long time they were considered as a benign phenomenon. However, recent studies demonstrate that they are associated with significant decline in striatal dopamine markers and further LB-containing neurons are more likely to contain MBs. Moreover, MBs are more frequent in dementia with Lewy bodies (DLB) and myotonic dystrophy than in age matched controls. MBs may represent the aggregation of ubiquitinated proteins induced by dysfunction of the ubiquitine-proteasome system (UPS). It is still a matter of debate if there is a causal link between MB- and LB-formation, if MBs are transitory or stable entities and what's the origin of MBs.

Intranuclear rodlets (INR) are frequently associated with MBs. They are immunoreactive for βtubulin, GR and PML and further are increased after MPTP exposure. They are believed to represent a protective intanuclear sequestration of monomeric βtubulin, which explains the marked decrease of INRs in AD. Tubulin can seed the fibrillization of αSYN, thus INRs which influence tublun turnover may be implicated into the pathogenesis of PD [43, 44, 45].

1.1.3. Pathological staging

Staging:

Braak et al. suggested six successive neuropathological stages (Table 1) in PD, indicating that αSYN pathology advances with an upward progression in a topographically predictable sequence and mirrors the selective vulnerability of neuronal populations, which share a long, thin, unmyelinated or poorly myelinated axon as their common predisposing feature [46]. This system, as shown in table 1, is currently used for neuropathological staging in PD.

Table 1 Stages in the evolution of PD-related pathology, modified from [46]

Stage 1
medulla oblongata Lesions in the dorsal IX/X motor nucleus and/or intermediate reticular zone
Stage 2
medulla oblongata and pontine tegmentum Pathology of stage 1 plus lesions in caudal raphe nuclei, gigantocellular reticular nucleus, and coeruleus–subcoeruleus complex
Stage 3
midbrain pathology of stage 2 plus midbrain lesions, in particular in the SNc
Stage 4
basal prosencephalon and mesocortex Pathology of stage 3 plus prosencephalic lesions. Cortical involvement is confined to the temporal mesocortex (transentorhinal region) and allocortex (CA2-plexus). The neocortex is unaffected.
Stage 5
neocortex Pathology of stage 4 plus lesions in high order sensory association areas of the neocortex and prefrontal neocortex
Stage 6
neocortex Pathology of stage 5 plus lesions in first order sensory association areas of the neocortex and premotor areas, occasionally mild changes in primary sensory areas and the primary motor field

Criticism:

However, there is emerging criticism on the Braak PD stgaging system, based on the following facts [47, 48, 49]:

1) Deviation from the stereotype caudo-rostral propagation can be observed in a subset of patients.

2) Around half of the subjects with abundant αSYN-pathology are neurologically intact.

3) There is no relation between Braak stage and Hoehn and Yahr score.

4) The induction site of PD could propably be in the ENS, which is not part of the current staging system.

5) In 7 % the dorsal motor nucleus of the vagal nerver (DMV) is not affected even though αSYN inclusions are found in the SN and cortical regions and in some cases the spinal cord is affected without involvement of DMV, demonstrating that DMV is not an obligatory trigger site [107].

6) LBs could actually rather represent a marker of cytoprotection than of forthcoming cell death [50, 51].

These findings call for a reevaluation of the current staging system. The question arises if the correlation of clinical time course with post mortem pathological staging based on the presence of LBs, is reasonable.

1.1.4. Ten points defining early events in the pathology of Parkinson's disease

Early events in the pathology of PD compromise of:

1) Incidental Lewy body disease (iLBD) is based on the presence of LBs in normal individuals and exhibits a prevalence approximately 10-fold more common than PD. ILBD is preclinical PD with subthreshold αSYN-pathology and not a regular aging phenomenon. However, if this condition evolves to PD or is a slowed or halted disease process remains unknown. [52, 53]

2) Microglial activation, revealed by a double tracer PET study in drug-naive patients with early PD, targeting both neuroinflammation and neuronal loss in the nigrostriatal system [54].
   There is evidence for cross-talk between αSYN and microglia, given that first, nitrated αSYN induces a switch from quiescent to neurotoxic phenotype in microglia and second, microglial activation causes modification and aggregation of αSYN through releasing free radicals [55, 56].

3) Early intracellular changes in SNc neurons with normal morphological appearance consist of increased pigment density associated with a concentration of αSYN to the lipid component of the pigment and a loss of associated cholesterol [57].

4) The earliest αSYN-oligomers appear in the membranous compartments, not in the cytosol [41].

5) There is inhibition of ER to Golgi trafficking by αSYN in a dose-dependent manner and consequently an accumulation of undocked vesicles, which form vesicle clusters in the cytosol. Moreover, fragmentation of the Golgi apparatus (GA) is present in PD. Both processes may represent early steps in PD [58, 59].

6) Presymptomatic compensatory mechanisms counter dopaminergic cell loss and striatal dopamine depletion during the premotor phase of PD. This process can be described as the sequential activation of three stages, compromising of [60]:
   A) dopamine homeostatic compensatory mechanisms with an upregulation of striatal dopamine turnover, D2-receptors and enkephalin precursor protein (PPE-A) and further hypertrophy of SNc neurons [61, 62]
   B) changes in the activity of the basal ganglia output structures
   C) compensatory mechanisms outside the BG

7) Diffuse cytoplasmatic staining and formation of PBs are implicated in the morphogenesis of LBs [16].

8) The occurrence of LNs is prior to that of LBs [16]. Striatal terminals are lost before dopaminergic cell bodies, suggesting a 'dying back' mechanism [85].

9) The presence of extranigral LBs is prior to affection of the SNc (table 2).

10) Magnetic resonance diffusion tensor imaging (DTI) is based on water diffusivity and allows visualisation of neuronal projections. A decrease of fractional anisotropy (FA) is an indicator of histological abnormality in even normal appearing white matter on conventional MRI. Patients with PD show low FA values in the nigrostriatal projection in early stages, corresponding to dopaminergic cell loss during the premotor

phase which lasts until 70-80 % of cells are lost and parkinsonism becomes overt. In later stages, loss of FA can also be observed in subcortical white matter, most likely due to damage of the corticostriatal and thalamocortical projections [106]. Furthermore, the miswiring hypothesis suggests early damage to the white matter [100].

1.1.5. Extranigral αSYN-pathology

The presence of extra-nigral αSYN-pathology (table 2) is an essential point, indicating that:

1) the SNc is not the induction site of PD, giving rise to a premotor period, during which several non-motor features develop.

2) PD is a 'multisystem disorder' with the involvement of multiple neurotransmitter types (table 7).

3) the affection of the enteric nervous system (ENS), the dorsal motor nucleus of the vagal nerve (DMV) and the olfactory bulb (olb)/anterior olfactory nucleus (aon) are early events in the course of PD [63], leading to the "dual hit hypothesis" [64, 65] which assumes that a neurotropic pathogen invades through the mucosal barrier at these predilection sites [106].

Accordingly, motor symptoms due to nigral pathology are just the tip of the iceberg [66] within the 'PD complex' [67].

Table 2 Extranigral Lewy bodies in sporadic Parkinson's disease

A) extra CNS and spinal cord level	
cutanous nerves	[68]
ENS: myenteric and submucosal plexus, VIPergic neurons	[69]
adrenal glands (medulla)	[70]
cardiac sympathetic nerve	[71]
spinal cord	[72]
sympathetic ganglia	[73]
sacral parasympathetic nuclei	[73]
pelvic plexus	[73]
submandibular ganglion	[74]
B) CNS-nuclear level	
astrocytes	[75]
olfactory system	[46]
dorsal motor nucleus of the vagal nerve	[46]
raphe complex	[46]
pedunculopontine nucleus (PPN)	[46]
gigantocellular reticular nucleus	[46]
locus ceruleus (LC)	[46]
amygdala	[76]
magnocellular nuclei of the basal forebrain:	[46]
N. basalis Meynert (substantia innominata)	
interstitial nucleus of the diagonal band of Broca	
hypothalamus	[77]
lateral tuberal nucleus (NTL)	
tuberomamillary nucleus (TM)	
thalamus	[78]
intralmainar nuclei	
neostriatum	[79]
C) cortical level [46]	
hippocampus, parahippocampus	
temporal, cingulated and insular cortices	
primary and secondary sensory fields, premotor areas	

1.1.6. Genetics of PD

Disease-related genes trigger familiar forms of PD, termed as fPD, and thirteen chromosome loci have been identified so far, displayed in Table 3. Approximately 5 to 10 % of patients with the clinical picture of a parkinsonian syndrome (PS) carry a mutation in one of the known genes that cause monogenic fPD. A positive family history is not always given, either because of recessive inheritance, or because of reduced penetrance of a dominant mutation. An early age at onset in many (but not all) patients helps to distinguish the hereditary from sporadic cases. The presence of LBs in fPD is not an obligatory sign, as e.g. PARK2 mutation demonstrates [80]. Several SNPs are responsible for susceptility to PD, as genome wide association studies (GWAS) reveal [81].

Table 3 summary of the genetics in familiar PD, modified from [80, 81, 82, 83, 84]

Locus	Map position	Gene product	Inheritance	Clinical characteristics
PARK1	4q21-q23	αSynuclein missense mutations	AD	Dementia
PARK2	6q25.2-q27	Parkin	AR	Early onset, LD-induced dyskinesia, foot dystonia, sleep benefit, susceptility to leprosy
PARK3	2p13	SPR?	AD	Dementia
PARK4	4q21	αSynuclein triplications and duplications	AD	Dementia, postural tremor
PARK5	4p14	UCH-L1	AD	Not described
PARK6	1p35-37	PINK1	AR	Early onset, tremor dominant
PARK7	1p38	DJ-1	AR	Early onset, dystonia, psychiatric alterations
PARK8	12cen	LRRK2	AD	Late onset, tremor
PARK9	1p36	ATP13A2	AR	Kufor-Rakeb syndrome, very early onset, spasticity, supranuclear upgaze paresis,dementia
PARK10	1p32	unknown	AD?	Late onset
PARK11	2q34	GIGYF2	AD?	Late onset
PARK12	Xq21-q25	unknown	X-linked	Late onset
PARK13	2p12	Omi/HtrA2	?	Late onset

1.1.7. Pathogenesis of Parkinson's disease

1.1.7.1. Pathogenetic concepts in PD at a molecular level

Pathogenetic pathways in PD exhibit reciprocal effects and thus they cannot be viewed separate from each other. Table 4 gives an overview of the involved pathways (modified from [85-87], taken from this chapter or listed beneath). These pathways represent multiple hits, ultimately converging to neuronal death. Nevertheless, the mechanism of final cell death in PD is still unsettled and evidence for the role of programmed cell death (PCD) is incomplete.

Table 4 Overview of pathogenetic concepts in PD at a molecular level

● altered protein degradation and quality control involving ubiquitine proteasome system (UPS) and autophagy/lysosomal pathway, resulting proteolytic stress	[92]
● toxic properties of αSYN-oligomers	
● mitochondrial dysfunction	[93]
● oxidative and nitrative stress	[94]
● neuroinflammation	[104]
● humoral immune-mediated injury with IgG binding to dopaminergic neurons	[105]
● dysregulated kinase signalling	
● excitotoxicity	
● disruption of calcium homeostasis	[95]
● calpain activation, resulting in p25 formation	
● iron dysbalance	
● increased free cytosolic dopamine	
● impaired ion channel function of GIRK, K-ATP, L-type Ca channel (Cav 1.3), Ca activated K-channels (SK channels) or pumping function of Na/K-ATPase	
● diminished neurotrophic support	
● membrane permaeabilization due to annular αSYN-oligomers with pore-like properties	[96]
● susceptility factors: e.g. SNPs	
● lack of resilient factors: e.g. antioxidant capacity	
● acceleration of fibrillization by molecular crowding	[97]
● polycation induced oligomerization and accelerated fibrllization of αSYN	[98]
● impaired ER to Golgi transport, ER stress and unfolded protein response	[99]
● αSYN interaction with tau, aβ, tubulin, NM and lipid membranes	
● incresead levels of ApoE	
● αSYN interaction with AGE, RAGE activation	
● intranuclear pathology: αSYN-histone complexes, MBs, INRs	
● abnormal axon-guidance-molecule signalling	[100]
● dependence receptors	
● disruption of axonal transport, 'dying back'	
● impaired vesicle trafficking	
● exocytosis of vesicles containing αSYN-oligomers	
● environmental triggers	

The etiology of PD remains to be enigmatic; however, it is assumed that exogenic factors combined with a genetic basis may be crucial. Actually, PD could also represent a developmental disorder, caused by disturbance of the immature BG at critical developmental stages in utero or perinatal [90]. Furthermore, LPS is increased in the chorioamniotic environment of women with bacterial vaginosis during pregnancy. Given that prenatal LPS exposure causes an increase of TNFα and dopaminergic cell loss, it is suggested that prenatal infections could be a risk factor for PD [91].

Axon guidance molecules control brain network formation during development and are responsible for synaptic maintenance, repair and plasticity in the adult. SNPs within the axon guidance pathway are predictive for PD (table 5). Possibly, these genes contribute very early to the pathogenesis of PD, during the premotor phase or during brain development. This point of view is termed as the miswiring hypothesis [100].

Table 5 SNPs in genes of the axon guidance pathway predisposing to PD, adapted from [100]

● Netrin G1 (NTNG1)
● SLIT3
● Deleted in colorectal cancer (DCC)
● Ephrin receptor B1 (EPHB1)
● SEMA5A

Dependence receptors induce PCD in the absence of ligand availability. Thus, their expression leads to a state of cellular dependence on their respective ligands which maintain cell survival. Several dependence receptors are implicated in tomorigenesis and neurodegeneration such as ALS and PD, as shown in table 6 [108].

Table 6 Dependence receptors in PD

● p75 neurotrophin recepror (P75NTR)	[109]
● Androgen receptor (AR)	[110]
● RET (receptor for GDNF)	[111]
● Sonic hedgehog (Shh)	[112]
● Laminin receptor	[113]

PD is a ‘multisytem disorder’ and involves abnormal patterns of various neurotransmitters:

Table 7 Neurotransmitters other than dopamine implicated in the pathogenesis of PD, modified from [28, 114, 115, 116, 117, 118, 182]

● Serotonin	● Nociceptin, Orphanin FQ (N/OFQ)
● Glautamat (glu)	● Norepinephrine (NA)
● GABA	● NO
● Acetylcholine	● Hypocretin (Hcrt)
● Endocanabinoids (anandamide, 2-AG)	● Neurosteroids
● Endogenous opiods	● Melatonin
● Adenosine	

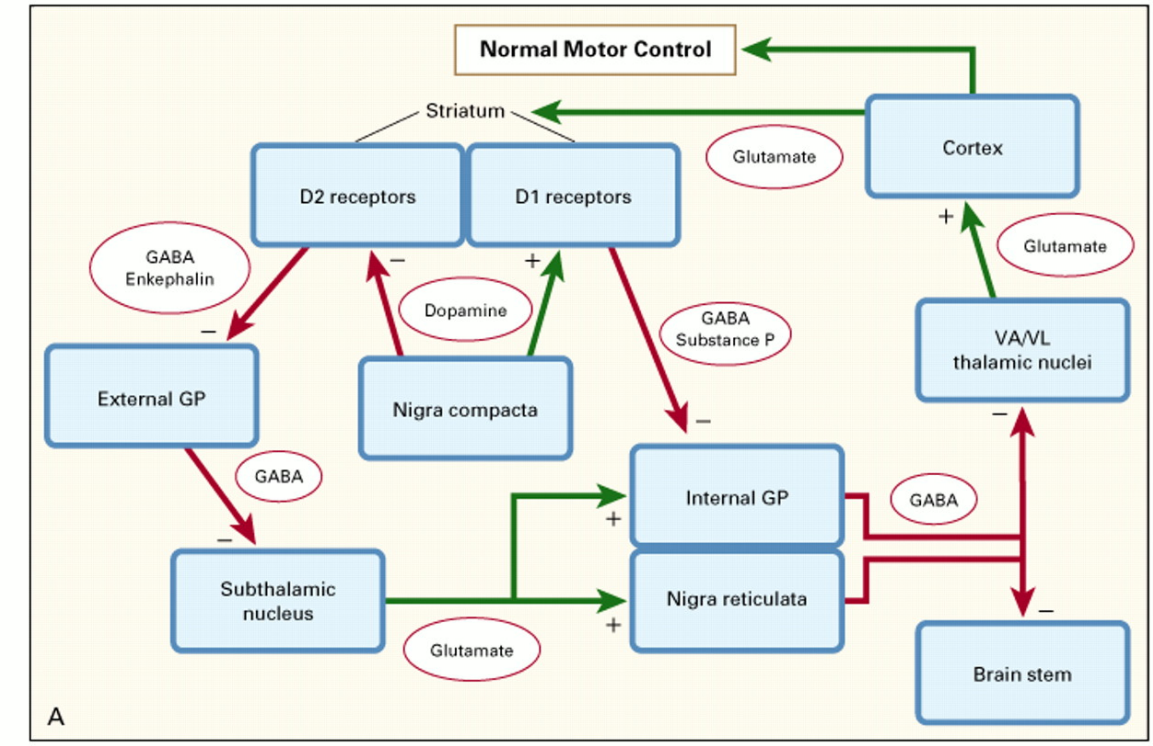
1.1.7.2 Basal ganglia circuitry in PD

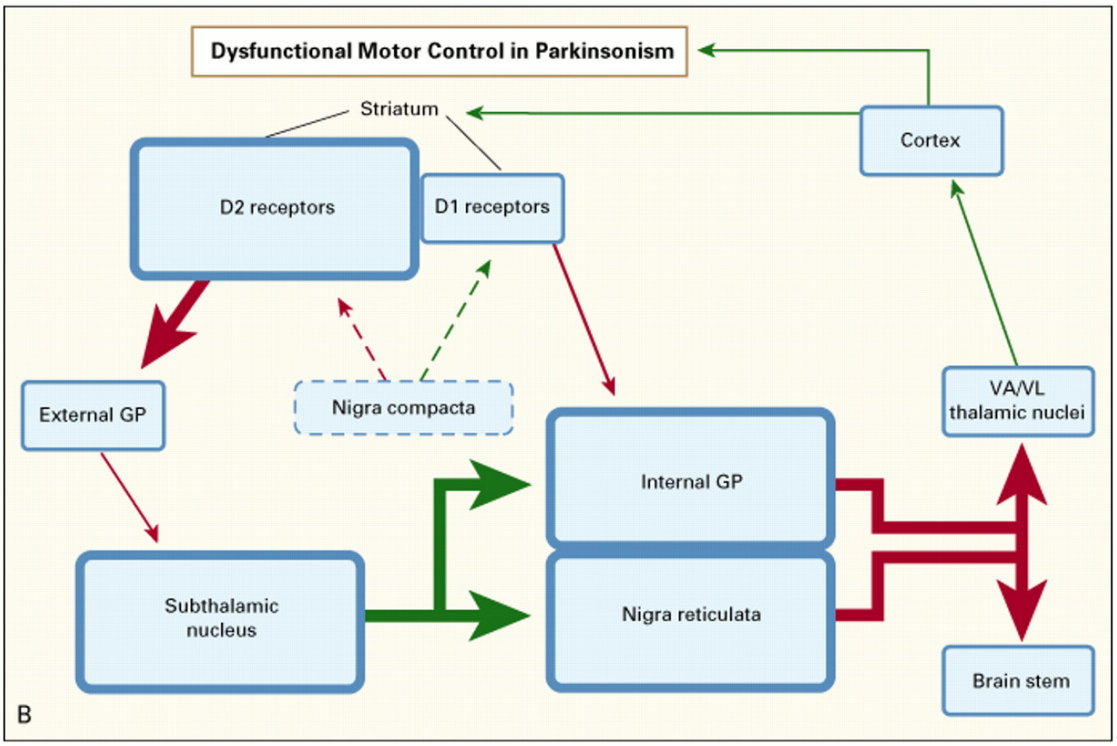
BG-circuitry compromises of anatomically and functionally segregated parallel loops that involve specific thalamic and cortical areas: motor, limbic, prefrontal and oculomotor loop. Considering the motor loop, two pathways link the striatum with the BG-output nuclei GPi and SNr:
The direct pathway arises from GABAergic striatal neurons containing substance P and dynorphin, and projects monosynaptically to the output nuclei.
The indirect pathway arises from GABAergic striatal neurons containing enkephalin and projects polysynaptically to the output nuclei via intercalated GPe and STN.
Additionally, a hyperdirect pathway from the cortex to the STN is postulated.

Dopamine from the SNc excites striatal neurons in the direct pathway through dopamine D1 receptors (D1Rs), while it inhibits striatal neurons in the indirect pathway through dopamine D2 receptors (D2Rs). Thus, these pathways have opposing actions.

According the classical “rate model” of basal ganglia (BG) circuitry, striatal dopamine depletion leads to imbalance in the direct/indirect pathways in favour of the indirect pathway. Thus, disinhibition of output nuclei and consequent reduction of thalamocortical activity takes place. Clinically, this abnormal condition is reflected by an impediment of movement, termed as bradykinesia. (Figure 1)
Furthermore, abnormal firing patterns, neuronal synchronization and the involvement of the pedunculopontine nucleus (PPN) shed new light on the BG-circuitry. [101, 102, 103]

Figure 1 Normal and dysfunctional motor control in parkinsonism, from [103]





Green arrows: excitatory pathways, red arrows: inhibitory pathways, dashed arrow: dysfunctional nigrostriatal dopamine system

1.2. Clinical features and diagnosis of Parkinson's disease

1.2.1. Diagnosis of PD

1.2.1.1. Clinical diagnostic criteria for Parkinson's disease

The diagnosis of sporadic PD is made on the basis of clinical criteria [2]. Conventional imaging (MRI, CT) is useful to exclude secondary causes of parkinsonism. Unfortunately, the definite diagnosis of PD can only be performed by neuropathology.
The UK Parkinson's disease society Brain Bank criteria (UKPDSBB, table 8) for PD are international standard and proposed by the Movement Disorder Society (MDS) and the American Association of Neurology (AAN). Accordingly, the diagnosis is a 3-step-procedure. First, parkinsonism is diagnosed for patietnts who display bradykinesia and one of the additional cardinal symptoms: rest tremor, rigidity and postural instability. In a second step, exclusion criteria that indicate other diseases, such as atypical parkinsonism, are ruled out. Finally, in a third step, supportive criteria for PD are assessed. [119]
The diagnosis of PD should be reviewed regularly and re-considered if atypical symptoms develop.

Table 8 UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria for Parkinson's disease, from [119]

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 crisis ● 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 tumor or communicating hydrocephalus on CT scan
● Negative response to large doses of levodopa (if malabsorption is 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 ten years or more

1.2.1.2 Routine diagnostic tests for patients with parkinsonism

There are abundant routine clinical tests for patients who present with parkinsonism (Table 9). It depends on the clinical picture and on patient history which of them have to be performed. Diagnostic tests are useful in differentiating PD from symptomatic PS, atypical PS and essential tremor, especially in early stages of the disease.
It is suggested that conventional imaging (MRI or CT), should be carried out to exclude secondary causes of parkinsonism. Especially in young patients, Wilson's disease should be ruled out by analysis of copper and ceruloplasmin status.

Table 9 Routine diagnostic tests for patients with parkinsonism

● Imaging:
  Conventional: CT, MRT
  F-Dopa-PET
  SPECT: 123I-FP-SPECT (presynaptic, DAT)
  IBZM-SPECT (postsynaptic, D2R)
  MIBG-Scintigraghy (cardiac sympathetic innervation)

● dopaminergic challenge tests (levodopa, apomorphine)
● tests to assess autonomic dysfunction:
tilt table test, Schellong test, urodynamic study, sympathetic skin response (SSR)

Additional non-routine tests:

● Basal ganglia-sonography
● sphincter EMG
● Electrooculography (EOG)
● olfactory tests
● serum ceruloplasmin, serum copper, 24-hr basal urinary copper,
slit lamp examination for K-F rings
● polysomnography
● blink reflex
● long latency reflexes (LLR)
● tremor analysis
● neuropsychologic tests
● EEG

1.2.1.3 Clinical staging and rating systems of Parkinson's disease

The Unified Parkinson's disease rating scale (UPDRS) and the modified Hoehn and Yahr scale (HY) are frequently used scales to assess the clinical course of PD are.

The semiquantitative UPDRS (Appendix A) provides a core assessment tool to focus on global impairment or specific elements in more detail. It presents a multidimensional approach with four different sections. The UPDRS is a standard scale for both clinical and research domains. UPDRS scores correlate with HY and Schwab and England scales and exhibit a high degree of reliability and validity. Limitation is that several NMS are not covered by the scale. Currently, the development of a new version of the UPDRS is on the horizon. [120]

The HY scale (Appendix B) provides an overall assessment of severity based on clinical features and functional disability. It focuses on the issues of unilateral versus bilateral disease and the presence or absence of postural reflex impairment and leaves other aspects of PD unassessed. Progression in HY stage correlates with motor decline and deterioration in quality of life. Time to the development of a given HY stage can be used to distinguish patients with PD from other atypical parkinsonian syndromes. The modified HY scale is widely used and contains 0.5 increments. [121]

1.2.2 The clinical spectrum of Parkinson's disease

Clinical features of PD can be divided in motor symptoms defining parkinsonism, and non-motor symptoms (NMS), which can partly predate parkinsonism and are due to widespread pathology (table 2). Some NMS can also represent adverse drug effects of antiparkinsonian agents. In sum NMS add significantly to the overall disability in PD. Table 10 gives an overview of common motor and non-motor symptoms. For detailed review of NMS during the premotor phase, please see chapter 1.3.

Table 10 Overview of motor and non-motor symptoms in Parkinson's disease, modified from [122, 123, 124, 125, 186]

A) motor symptoms
Bradykinesia, Akinesia, Hypokinesia
Tremor at rest (4-6 Hz, pill rolling tremor), rigidity (facultative with cogwheel phenomenon), postural instability
Hypomimia, dysarthria, sialorrhoea, dysphagia
Gait: Decreased arm swing, slow and shuffling gait with short steps
Flexed posture, freezing of gait, festination, turning en bloc
difficulty turning in bed or arising from chair
difficulty in activities of daily living, e.g. cutting food, buttoning
Micrographia
Striatal deformity (striatal foot, striatal hand)
camptocormia
dystonia
abnormal eye movement, pupil reactivity and blink reflex
B) non-motor symptoms
Neuropsychiatric symptoms
Depression, apathy, anxiety, anhedonia, fatigue
Illusion, hallucinations, delusions and psychosis (drug induced)
Panic attacks
Confusion, attention deficit
'Tip of the tongue' phenomenon
Frontal-executive dysfunction, visuospatial dysfunction
Bradyphrenia, Dementia
Obsessive-compulsive behaviour
pathological gambling, compulsive shopping, binge eating, hypersexuality
punding (complex repetitive stereotyped behaviour)
Sleep disorders
REM sleep behaviour disorder (RBD)
Excessive daytime sleepiness (EDS)

Vivid dreaming
Restless legs and periodic limb movements in sleep (RLS/PLMS)
Sleep fragmentation, reduced sleep efficiency, reduced slow wave sleep, reduced REM-sleep
Insomnia
Sleep attacks
Sleep disordered breathing, Sleep apnea syndrome

Autonomic symptoms

Bladder disturbances
    Urgency, Nocturia, Frequency
Sweating
Erectile dysfunction
Orthostatic hypotension
    Falls related to orthostatic hypotension
    Coat hanger pain

Gastrointestinal symptoms

Constipation
Nausea, gastro-esophageal reflux, vomiting
Reduction of gustatory function
Dysphagia

Sensory symptoms

Pain
Paraesthesia
Olfactory dysfuntion
Colourvision deficits, Diplopia, Blurred vision
Vestibular deficits

Other symptoms

Dry eyes (xerostomia)
Seborrhoea
Weight loss
Weight gain (possibly drug induced)

Non-motor symptoms related to motor fluctuations

Anxiety, Drenching sweats, Slowness of thinking, Fatigue, Akathisia, Irritability, Hallucinations

Drug Induced non-motor syndromes:

Dopamine dysregulation syndrome
Serotonin syndrome
Parkinson hyperpyrexia syndrome

1.2.3 Classification of Parkinsonian syndromes

Parkinsonism can be described as a motor syndrome according the UKPDSBB criteria. There is a bulge of diseases which can exhibit parkinsonism, table 10 gives an overview. For a detailed summary of familiar PS please see table 3. Rare inborn errors of metabolisation are also included in the classification below. In making the differential diagnosis of PD, each of them should be taken into account.

Table 11 Classification of Parkinsonian syndromes, modified from [182, 126]

I familiar PS
II sporadic PD
III symptomatic PS

- vascular parkinsonism (VP)
- metabolic
  - Hypoparathyroidism
  - Pseudohypoparathyroidism with basal ganglia calcification (Fahr syndrome)
- normal pressure hydrocephalus (NPH)
- noncommunicating hydrocephalus
- head trauma
  - recurrent trauma (dementia pugilistica)
  - midbrain trauma
  - chronical SDH
- intoxication
  - CO, Mn, Hg, CS2, MPTP, cyanide, methanol, pesticides
- posthypoxic
- drug induced parkinsonism (DIP)
  - typical/atypical neuroleptics
  - SSRI (fluoxetin)
  - antiemetics (metoclopramid)
  - reserpine
  - captopril
  - tetrabenazine
  - lithium
  - valproic acid
  - Ca-antagonists (cinnarizine, flunarizine)
  - amiodaron
  - phenothiazine
- infectious
  - postencephalitic (Economo epidemic 1916-1927, Encephalitis lethargica)
  - HIV, Coxsackie virus, Japanese encephalitis B virus, St. Louis encephalitis virus, West nile virus
  - Progressive multifocal leukoencephalopathy (PML)
  - Subacute sclerosing panenecepahlitis (SSPE)

Neurolues
Toxoplasmosis
Prion diseases: Creutzfeldt-Jakob disease (CJD)
Gerstmann-Sträussler-Scheinker disease (GSS)

- multiple sclerosis (MS)
- systemic lupus erytematosus (SLE)
- tumor (especially meningioma)
- paraneoplastic
- Westphal-variant of HD
- Hemiparkinson-Hemiatrophie syndrome
- Polycythemia vera
- Acanthocytosis
- Psychogenic movement disorder

IV Neurodegenerative disorders

- αSynucleinopathies
  Multsystem atrophy, parkinson type (MSA-P, striatonigral degeneration)
  Multisystem atrophy, cerebellar type (MSA-C, olivopontcerebellar atrophy)
  dementia with Lewy bodies (DLB)
- Tauopathies
  Progressive supranuclear palsy (PSP)
  Corticobasal degeneration (CBD)
  Alzheimer's disease (AD)
  Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17)
  Pick's disease (PiD)
- Trinucleotide repeat diseases:
  Machado-Joseph disease (SCA 3)
  Fragile X associated tremor/ataxia syndrome (FXTAS)
  Huntington's disease (HD)

V Rare metabolic disorders accompanied with a PS

- Wilson's disease (WD)
- Aceruleoplasminaemia
- Hereditary Hemochromatosis
- Neuroferritinopathy
- Pantothenat kinase associated neurodegeneration (PKAN)
- GTPCH1 deficiency
- Tyrosin-hydroxlase deficiency
- Respiratory chain disorders
- PDH deficiency
- Lysosomal storage diseases
  Kufs disease type B
  Nieman-Pick disease type C
  Gaucher disease
  GM1/2 gangliosidosis
  Ceroid Lipofuscinosis
  Chediak-Higashi syndrome
- Hyperphenyalaninaemia
- Phenylketonuria

- Homocystinuria
- 1-2-OH-glutaric aciduria
- Cerebrotentinous xanthomatosis
- Polyglucosan body disese

VI others

- ALS/PD complex of Guam (Lytico Bodig)
- ALS/PD complex of Kii (Muro disease)
- Guadeloupean atypical parkinsonism
- Down syndrome
- X-linked dystonia-parkinsonism XDP (DYT 3, Lubag, endemic in the Phillipine island of Panay)
- Dopa-responsive dystonia (Segawa Syndrome)
- Pure pallidal degeneration
- Disinhibition dementia parkinsonism amyotrophy complex (DDPAC)
- Familial parkinsonism with peripheral neuropathy

1.2.4. Differential diagnosis of Parkinson's disease and red flags

Differentiating PD from atypical Parkinson-Syndromes can be difficult, espacially in early stages. Thus, when making the diagnosis of PD one should consider the UKPDSBB criteria, use diagnostic tests (table 9) and be aware of red flags. These are warning signs that indicate other diagnosis than PD (table 12). Atypical Parkinson-Syndromes include Dementia with Lewy bodies (DLB), progressive supranuclear palsy (PSP), multi system atrophy (MSA) and corticobasal degeneration (CBD). Thus, these symptoms should not be missed in clinical examination. Moreover, when the clinical picture raises doubt on the diagnosis of sporadic PD and rather indicates atypical parkinsonism, an IBZM-SPECT, which is focusing on postsynaptic D2R, should be carried out.

Table 12 Red Flags in Parkinson's disease, from [127-130]

No response to high doses of LD	Marked antecollis
Rapid progression	Apraxia
Symmetrical signs at onset	Early severe autonomic dysfuntion
Supranuclear gaze palsy	Fluctuating cognition
Cerebellar signs	Neuroleptic sensitivity
Pyramidal tract signs	Sleep apnoe, excessive snoring
Oculogyric crisis	Inspiratory stridor
Early postural instability and recurrent falls	Alien limb
Hallucinations in the first 3 years (not related to medication)	Cortical sensory loss
	Early severe dysarthria/dysphagia
Myoclonus	Early dystonia
Jerky tremor	Vivid dreams
Early dementia	Pseudobulbar crying or laughing
PISA sign	Frontal release signs
Camptocormia	Raynaud syndrome
Cold hands/feet	Inspiratory sighs

1.2.4.1. Dementia with Lewy bodies (DLB), Parkinson's disease dementia (PDD) and Creutzfeldt-Jakob disease (CJD)

There you see about thirty outrageous giants, against whom I shall fight.

Cervantes, 1605

Don Quixote, Book I, chapter 8

From Garcia Ruiz PJ et al. [172]

DLB is the second most common cause for dementia after AD and accounts for up to 30 % of all demented patients [127]. The mean age at onset is 75 years, ranging between 50 to 80 years. Post mortem analysis of affected patients reveals abundant LBs in the neocortex and limbic areas in addition to nigral degeneration.
According the current clinical consensus criteria by McKeith et al. the diagnosis of DLB can only be made in patients with parkinsonism who develop dementia within 12 months of the onset of motor symptoms. [173]

The three main differential diagnoses for DLB are AD, PDD (Parkinson's disease dementia) and sporadic Creutzfeldt-Jakob disease.

PDD refers to dementia in the course of PD, after 12 months of the onset of motor symptoms. DLB and PDD show an overlapping clinical picture and similar underlying pathological processes. Thus, it is suggested that both entities represent different points at a spectrum of LB-disease. [173]

Symptoms most helpful in distinguishing DLB from PD are absence of rest tremor and visual hallucinations. Up to 70% of patients with DLB develop a symmetric akinetic-rigid syndrome, sometimes with action tremor or myoclonus. Gait abnormalities and postural instability can be prominent. [173]

MR-volumetry can be helpful in differentiating AD from DLB, where hippocampal and temporal lobe atrophy is less severe. [127]

Sporadic Creutzfeldt-Jakob disease is a prion disease with an incidence of 1 case per 1 million population per year. It affects typically patients in the seventh decade of life. Symptoms of the prodromal phase are a feeling of tiredness and abnormal exhaustion, behavioural change, depression and sleep disturbences. Further, visual hallucinations are a frequent finding at the beginning. The core clinical features are rapidly progressive dementia, cerebellar dysfunction, cortical visual impairment, stimulus responsive myoclonus and pyramidal / extrapyramidal symptoms. Patients can also exhibit pain, paresthesia and epileptic fits. The clinical diagnosis is supported by the detection of periodic sharp and slow wave complexes in the EEG, hyperintense signals in the basal ganglia on MRI and elevated levels of neuronal proteins, such as 14-3-3, in CSF. The disease duration in sCJD is shorter than in the BSE-related variant CJD (6 months and 14 months, respectively). [203]

The consensus guidelines for DLB by McKeith et al. (table 13) contain the core features and are helpful in making the differential diagnosis. Additionally, RBD and depression are frequently seen in DLB and their occurrence supports the diagnosis of DLB.

DLB patients show good responsiveness to cholinesterase-inhibitors and extreme sensitivity to side effects of neuroleptic drugs. [173]

Table 13 Consensus criteria for the clinical diagnosis of probable and possible dementia with lewy bodies, adapted from [128]

1. Progressive cognitive decline

● sufficient magnitude to interfere with normal social or occupational function
● Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression.
● Deficits on tests of attention or frontal subcortical skills and visuospatial ability may be especially prominent

2. Presence of one (possible DLB) or two (probable DLB) core features

● fluctuating cognition with pronounced variations in attention and alertness
● recurrent visual hallucinations
● spontaneous parkinsonism

3. Supportive features

● Repeated falls
● syncope
● transient loss of consciousness
● neuroleptic sensitivity
● systematized delusions
● hallucinations in other modalities
● Depression
● RBD

4. Exclusion criteria

● Stroke disease or evidence of any other brain disorder sufficient to account for the clinical picture

1.2.4.2. Multisystem atrophy (MSA)

MSA is a degenerative disorder of the central and autonomic nervous system characterized by abnormal αSYN aggregates in oligodendroglia (glial cytoplasmic inclusions, Papp-Lantos bodies) and neurons. It usually starts in the sixth decade and relentlessly progresses with death occurring after, on average, 9 years.

MSA presents with parkinsonism, autonomic, cerebellar and pyramidal dysfunction in various combinations. Characteristic features are shown in table 14. Two major motor presentations

can be distinguished: MSA-P (formerly striatonigral degeneration, 80 %) and MSA-C (formerly olivopontocerebellar atrophy, 20 %). A characteristic finding on MRI is the hot cross bun sign (cruciform hyperintensity in the pons). [127, 129] Consensus criteria are provided by Gilman et al. (table 14, 15).

Table 14 Clinical domains, features and criteria used in the diagnosis of MSA, adapted from [128]

I Autonomic and urinary dysfunction

A Autonomic and urinary features

1. Orthostatic hypotension (by 20 mmHg systolic or 10 mmHg diastolic)
2. Urinary incontinence or incomplete bladder emptying

B Criterion for autonomic failure or urinary dysfunction in MSA

Orthostatic falls in blood pressure (by 30 mmHg systolic or 15 mmHg diastolic) or urinary incontinence (persistent, involuntary partial or total bladder emptying, accompanied by erectile dysfunction in men) or both

II parkinsonism

A Parkinsonian features

B, R, T, I

B Criterion for parkinsonism in MSA

1 of 3 (R, T, I) and B

III Cerebellar dysfunction

A Cerebellar features

1. Gait ataxia (wide based stance with steps of irregular length and direction)
2. Ataxic dysarthria
3. Limb ataxia
4. Sustained gaze evoked nystagmus

B Criterion for cerebellar dysfunction in MSA

Gait ataxia plus one of items 2-4

IV Corticospinal tract dysfunction

A Corticospinal tract features

Extensor plantar responses with hyperreflexia

B No cortcospinaltract feature is used in defining the diagnosis of MSA

Table 15 Consensus diagnostic categories for MSA, adapted from [128]

● **Possible**

One criterion plus two features from separate other domains.
When the criterion is parkinsonism, a poor levodopa response qualifies as one feature (hence, only one additional feature is required)

● **Probable**

One criterion for autonomic failure/urinary dysfunction plus poorly levodopa responsive parkinsonism or cerebellar dysfunction

● **Definite**
Pathologically confirmed by the presence of a high density of glial cytoplasmic inclusions in association with a combination of degenerative changes in the nigrostriatal and olivopontocerebellar pathways

Exclusion criteria
For possible and probable:

● Symptomatic onset under 30 years of age
● Family history of a similar disorder
● Systemic diseases or other identifiable causes for displayed features
● Hallucinations unrelated to medication
● DSM criteria for dementia
● Prominent slowing of vertical saccades or vertical supranuclear gaze palsy
● Evidence of focal cortical dysfunction such as aphasia, alien limb syndrome, and parietal dysfunction
● Metabolic, molecular genetic, and imaging evidence of an alternative cause of features

---

1.2.4.3. Progressive supranuclear palsy (PSP)

PSP (Steele-Richardson-Olszewski-syndrome) is a tauopathy with prominent subcortical and cortical neurofibrillary degeneration. The mean age at disease onset is around 60 years and mean survival is 6 years. Altough a defining feature, supranuclear vertical gaze palsy is not specific to PSP, occurring also in vascular encephalopathy, DLB, CBD, Whipple's disease and HD. The speech of patients with PSP shows characteristic growling and groaning and marked difficulty in swallowing bears the danger of aspiration pneumonia. They exhibit an overactive frontalis muscle, resulting in folded skin on the forehead, raised eyebrows and surprised facial expression with the eyes wide opened. They have marked hypomimia and the blink rate is much reduced. The gait is characterised by erect axial position. Further, pseudobulbar palsy is a feature of PSP with dysarthria, dysphagia, palilalia or palilogia and pseudobulbar crying or loughing.

Characteristic findings on MRI are the mickymouse sign (marked mesencephalic atrophy) and the humming bird sign (atrophy of the dorsal tegmentum). [127, 129]
Clinical criteria for the diagnosis of PSP are provided by the NINDS-SPSP (table 16).

Table 16 NINDS-SPSP clinical criteria for the diagnosis of PSP, adapted from [128]

For possible and probable:
Gradually progressive disorder with age at onset at 40 or later

● **Possible**
Either vertical supranuclear palsy or both slowing of vertical saccades and postural instability with falls < 1 year disease onset

● **Probable**
Vertical supranuclear palsy and prominent postural instability with falls or the tendency to fall within first year of disease onset

● **Definite**
All criteria for possible or probable PSP are met and histopathologic confirmation at autopsy

Supportive criteria

● Symmetric akinesia or rigidity (proximal more than distal)
● abnormal neck posture, especially retrocollis
● poor or absent response of parkinsonism to levodopa
● early dysphagia and dysarthria
● early onset of cognitive impairment including ≥ 2 of:
  apathy
  impairment in abstract thought
  decreased verbal fluency
  utilization or imitation behaviour
  frontal release signs

1.2.4.4. Corticobasal degeneration (CBD)

CBD affects the motor nigrostriatal system plus a variety of subcortical structures with variable cell loss in the thalamus, STN, pallidum, red nucleus, dentate nucleus and scattered changes in other brainstem nuclei. Further, there is marked asymmetrical cortical degeneration in frontal-parietal areas. First symptoms appear usually between 60 and 65 years with a mean survival of 7.9 years.

Clinical hallmarks are strict asymmetric akinetic- rigid syndrome, upper limb jerky dystonia, alien limb behaviour, limb apraxia, irregular action and postural tremor, action myoclonus and exaggerated palmar grasp reflex. [127, 129]

Table 17 Proposed research criteria for CBD, adapted from [128]

● Chronic progressive course ● asymmetric onset ● presence of: 'higher' cortical dysfunction (apraxia, cortical sensory loss, or alien limb)
And ● Movement disorders - akinetic rigid syndrome ● Levodopa resistant ● limb dystonia ● focal myoclonus
Exclusion criteria
● Early dementia ● early vertical gaze palsy ● rest tremor ● severe autonomic disturbances ● sustained responsiveness to levodopa ● lesions on imaging studies indicating another pathologic condition

1.2.4.5. Vascular parkinsonism (VP)

Vascular parkinsonism (VP) is due to cerebrovascular disease (CVD) and accounts for approximately 3-6 % of all cases of parkinsonism.
Parhological hallmarks of VP are microscopic small vessel disease (SVD) pathology (perivascular pallor, gliosis, hyaline thickening, and enlargement of perivascular spaces) and the presence of strategically located macroscopically visible infarcts such as lacunae in the basal ganglia or thalamus and white matter lesions which disrupt thalamocortical projection. [131, 132]

Most patients present with bilateral bradykinesia, rigidity, postural instability and gait disorder predominantly characterised by shuffling gait. Further, VP is associated with cognitive disturbances.

According to the criteria by Zjilmans et al, the diagnosis of VP requires parkinsonism, CVD and a relationship between these two conditions (table 18). Further, two subtypes can be distinguished: acute and insidious onset of parkinsonism. Differential diagnosis for VP

include PD, gait disorder in subcortical arteriosclerotic encephalopathy (Binswanger's disease) and PD with concomitant Binswanger's disease.

Therapeutic intervention with LD should be tried in patients with VP. [131, 132]

Table 18 Possible Criteria for the Clinical Diagnosis of Vascular Parkinsonism, from [131]

A) Parkinsonism: bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions in either upper limb or lower limb, including the presence of reduced step length) and at least one of the following: rest tremor, muscular rigidity, or postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction.
B) Cerebrovascular disease, defined by evidence of relevant cerebrovascular disease by brain imaging (CT or MRI) or the presence of focal signs or symptoms that are consistent with stroke.
C) A relationship between the above two disorders.

In practice:
(1) An acute or delayed progressive onset with infarcts in or near areas that can increase the basal ganglia motor output (GPe or SNc) or decrease the thalamocortical drive directly (VL of the thalamus, large frontal lobe infarct). The parkinsonism at onset consists of a contralateral bradykinetic rigid syndrome or shuffling gait, within 1 year after a stroke.
(2) An insidious onset of parkinsonism with extensive subcortical white matter lesions, bilateral symptoms at onset, and the presence of early shuffling gait or early cognitive dysfunction.

Exclusion criteria for VP:
History of repeated head injury, definite encephalitis, neuroleptic treatment at onset of symptoms, presence of cerebral tumor or communicating hydrocephalus on CT or MRI scan, or other alternative explanation for parkinsonism.

1.2.4.6. Drug induced parkinsonism (DIP)

Extrapyramidal adverse events due to antpsychotic drugs consist of parkinsonism, tardive dystonia, acute dystonia, tardive dyskinesia and akathisia. Dopamine receptor blocking agents (DRBAs) such as neuroleptics can induce parkinsonism (NIP). Conventional neuroleptics are more likely to cause extrapyramidal symptoms than atypical neuroleptics. Nervertheless, atypical agents are far from safe and are also able to be a primary cause for parkinsonism and worsen symptoms in PD.

The clinical features develop within 1 to 3 months after introduction of DRBA or dose increment. After discontinuation, recovery occurs in 60–70% of the patients within 7 weeks, although complete recovery may take 6 months or more. Overall estimates indicate that 15% to 60% of patients treated with neuroleptics may develop DIP, depending on the potency and dose of the drug.

Features that would point to a diagnosis of DIP include subacute onset, bilateral symptoms from the outset, orofacial dyskinesias, and the prior or current treatment with DRBAs. Moreover, recovery after cessation of the inciting agent supports the diagnosis of DIP.

The second most common drugs causing parkinsonism after neuroleptics are metoclopramid and Ca-antagonists, other agents related to DIP are displayed in table 11. [133, 134]

1.2.4.7 Wlilson's disease (WD)

Wilson's disease (WD, hepatolenticular degeneration) is an autosomal recessive metabolic disorder. The abnormal gene in WD is ATP7B, sometimes also referred to as 'WND', located on chromosome 13. It encodes a metaltransporting P-type ATPase, which is expressed mainly in hepatocytes and functions in the transmembrane transport of copper. Absent or reduced function of the protein leads to decreased hepatocellular excretion of copper into bile. This results in hepatic copper accumulation and injury. Copper is released into the bloodstream and deposited in various other organs, notably the brain, kidneys, and cornea.

Failure to incorporate copper into ceruloplasmin is an additional consequence of the loss of functional ATP7B protein. The hepatic production and secretion of the ceruloplasmin protein without copper, apoceruloplasmin, results in the decreased blood level of ceruloplasmin. [135]

WD shows a prevalence of ca. 30 affected individuals per million population. The majority presents between 5 and 35 years. Clinically WD can present as liver disease, as progressive neurologic disorder (hepatic dysfunction being less apparent or occasionally absent), or as psychiatric illness. [135]

A combination of clinical findings and biochemical testing is necessary to establish the diagnosis of WD. Family screening using haplotype analysis or direct mutation analysis may be effective in identifying affected siblings of patients. [135]
The spectrum of clinical symptoms in WD is summarized in Table 19.

Table 19 Clinical Patterns of Hepatic, Neurologic, and Psychiatric Disease in Patients with Wilson's disease, adapted from [135]

Hepatic
- Asymptomatic hepatomegaly
- Isolated splenomegaly
- Persistently elevated serum aminotransferase activity (AST, ALT)
- Fatty liver
- Acute hepatitis
- Resembling autoimmune hepatitis
- Cirrhosis (compensated or decompensated)
- Fulminant hepatic failure

Neurological
- Movement disorders (tremor, involuntary movements)
- Drooling, dysarthria
- Rigid dystonia
- Pseudobulbar palsy
- Seizures
- Migraine headaches
- Insomnia

Psychiatric
- Depression
- Neuroses
- Personality changes
- Psychosis

Other systems
- Renal abnormalities: aminoaciduria and nephrolithiasis
- Skeletal abnormalities: premature osteoporosis and arthritis
- Cardiomyopathy, dysrhythmias
- Pancreatitis
- Hypoparathyroidism
- Menstrual irregularities; infertility, repeated miscarriages

---

Kayser-Fleischer rings represent deposition of copper in the Descemet's membrane of the cornea. In a patient in whom WD is suspected Kayser-Fleischer rings should be sought by slit-lamp examination by a skilled examiner. The absence of Kayser-Fleischer rings does not exclude the diagnosis of WD, even in patients with predominantly neurologic disease. KF-rings can also occur in patients with chronic choleastatic liver diseases. Sunflower cataracts, which are usually not obstructing vision, can also be found in slit lamp examination in patients with WD. [135]

Table 20 Clinical tests for the diagnosis of Wilson's disease, adapted from [135, 136]

- liver biochemistry
  AST, ALT, ALP, total and conjugated bilirubin, albumin, INR, CBC
- serum nonceruloplasmin-bound copper concentration
  elevated above 15 µg/dL
- total serum copper level
  less than 12 µmol/L
- serum ceruloplasmin level
  less than 20 mg/dL
- 24–hour urinary excretion of copper
  greater than 250 µg/24 hours
- Slit lamp: facultative KF-rings, sunflower cataract
- Liver biopsy
  Usually macronodular cirrhosis
  Hepatic copper content greater than 250 µg/g dry weight
- Neuroimaging:
  normal in ca. 50 %, increased density on CT and hyper- (gliosis) and hypointensity (Cu++) on T2 MRI in the putamen, hypointensity in pallidum, 'face of the giant panda', cerebral atrophy in 20 %
- transcranial brain parenchyma sonogaraphy (TCS):
  lenticular nucleus hyperechogenicity, correlates with disease severity

---

Serum ceruloplasmin concentration can also be elevated by acute inflammation, in states associated with hyperestrogenemia such as pregnancy, estrogen supplementation, and use of the oral contraceptive pill. [135]

The cornerstone of treatment consists of chelating agents. Other treatment modalities include the use of zinc salts and diets deficient of copper. In fulminant hepatic failure orthotopic liver transplantation is life saving. Bridging to transplant strategies include plasmapheresis and exchange transfusion, hemofiltration, dialysis and MARS. [135]

1.2.4.8 Essential tremor (ET)

Essential tremor (ET) shows a prevalence range between 0.4% to 3.9% and two types can be distinguished: young onset and old onset. ET might be a family of diseases unified by the presence of kinetic tremor, but also showing etiological, pathological and clinical heterogeneity. [137]

Family history is a risk factor for the disease. Susceptility loci have been found on chromosome 3q13 (ETM1) and 2p22 (ETM2). [137] Recently, Stefansson et al. [217] demonstrated that a sequence variant in the LINGO-1 gene, which is implicated in neuronal survival, axon regeneration and oligodendrocyte regeneration, confers the the risk for ET. Nevertheless, environmental factors may play a role, given that blood levels for harmane (aromatic beta-carboline) and lead are elevated in patients with ET compared with controls. [137]

Postmortem pathological findings are heterogeneous and suggest two subtypes [141]:

1) Cerebellar ET: degenerative changes in the cerebellum with reduction of Bergmann glia, Pukinje cell loss and increase of torpedoes: fusiform proximal axonal swelling in Pukinje cells which consist of accumulations of disoriented neurofilament.
2) Lewy body variant of ET (LBVET): brainstem LBs are found most abundant in the locus ceruleus. The pattern of LB distribution is different from PD, iLBD and age matched controls.

The clinical spectrum of ET includes several motor and non-motor symptoms [137-141]:

Motor features:

Kinetic arm tremor is usually bilateral with slight asymmetry and is often accompanied with an intentional component. The tremor frequency range from 4-12 Hz and is inversely correlated with age. Postural tremor is also present, shows wrist flexion and extension and exhibits lower amplitude than the kinetic tremor. The involvement of other body regions is possible and includes head, voice, jaw, tongue and legs. Tremor responds to ethanol in most patients. Although rare, rest tremor can also be found in patients with ET. Cogwheeling can be present but is not accompanied with rigidity. Further, patients show tandem gait abnormality, which is more severe in later stages.

Non-motor features:

Some recent studies claim that mild cognitive deficts and personality disturbances in the domain of harm avoidance such as increased levels of pessimism, fearfulness and shyness are seen in ET patients. Furthermore, some studies demonstrated sensory manifestations, including hearing impairment and olfactory dysfunction, which is milder than in PD patients.

Table 21 Clinical diagnostic criteria for definite and probable essential tremor, [138]

Definite essential tremor

- Postural tremor of moderate amplitude is present in at least one arm
- Tremor of moderate amplitude is present in at least one arm during at least four tasks, such as pouring water, using a spoon to drink water drinking water, finger-to nose manoeuvre, and drawing a spiral.
- Tremor must interfere with at least one activity of daily living.
- Medications, hypothyroidism, alcohol, and other neurological conditions are not the cause of tremor.

Probable essential tremor

- Tremor of moderate amplitude is present in at least one arm during at least four tasks, or head tremor is present.
- Medications, hyperthyroidism, alcohol, and other neurological conditions are not the cause of tremor.

Differential diagnosis for ET include PD, enhanced physiological tremor and drug induced tremor (table 22), dystonic tremor, hyperthyroidism, orthostatic tremor, Holmes (rubral) tremor, cerebellar tremor, task specific tremor, Wilson's disease, neuropathic tremor (especially in dysgammaglobuliaemic neuropathies) and psychogenic tremor.
Furthermore, ET-like tremor can be seen in X-linked recessive bulbar and spinal muscular atrophy (Kennedy disease) and fragile X associated tremor ataxia/syndrome (FXTAS) and hereditary motor sensory-neuropathy (Roussy-Levi syndrome). [137-141]
The mainstays for therapy are propranolol, primidone or both. Several other agents of second choice and deep brain stimulation are also available. [140]

Transcranial brain parenchyma sonography (TCS) was used in some studies to differentiate between ET and PD, if tremor occurs as a first clinical sign of the disease. TCS requires a sufficient transtemporal bone window. Patients with PD show hyperechogenicity of the SN. Disease severity of PD correlates with FP-CIT uptake but there is no correlation between FP-CIT uptake and SN hyperechogenicity. However, 8- 16 % of ET-patients show SN-hyperechogenicity and this population could be at risk to develop PD. [201]
The co-occurrence of ET and PD is an often recognized phenomenon. Moreover, PD related features like LBs and olfactory dysfunction are present in a subset of ET patients. Thus, these patients could be at risk to develop PD.
Clinical findings indicate that the combination of ET and PD is not just the result of chance.

Clinical features of patients with a combination of ET and PD (analysis of 53 patients) compromise of [202]:

1) identical gender distribution as PD (predominance of male gender, 67,9%) compared with equal gender distribution in ET (50% male)

2) initial cardinal sign of PD is rest tremor

3) side of greatest initial ET severity matches that with greatest PD severity

4) most patients develop PD either after a relatively short latency or afer a long latency of sveral decades.

Table 22 Drugs causing tremor, adaptd from [138, 140]

Centrally acting agents	**Steroids**
Neuroleptics	Progesterone (medroxyprogesterone)
Reserpine	Antioestrogens (tamoxifen)
Tetrabenazine	Adrenocorticosteroids
Metclopramide	
Antidepressants	**Miscellaneous**
SSRIs, tricyclics	Antihistamines
Lithium	Perhexiline
Valproic acid	Nifedipin
Lamotrigine	Antiarrythmics
MAO-inhibitors	Amiodarone, Mexilitine, procainamide
Cocaine	Calcitonin
Alcohol	Thyroid hormones
Nicotine	Cyclosporine
	Cytostatics
Sympathomimetics	Vincristine
Bronchodilators (beta-2-agonists)	Adriablastine
Theophylline	Cytosinarabinoside
Caffeine	Ifosfamide
Dopamine	

1.3. The premotor phase of Parkinson's disease

So slight and nearly imperceptible are the first inroads of this malady, and so extremely slow its progress, that it rarely happens, that the patient can form any recollection of the precise period of its commencement.

James Parkinson
An Essay on the Shaking Palsy, 1817 [142]

There is striking evidence for the existence of a premotor phase of variable length before the onset of classic motor symptoms in PD, derived from different strands. Clinical and imaging data on the premotor phase of PD will be subject of this section, for a summary of early pathologic and compensatory events that precede parkinsonism please see chapter 1.1.4.

Knowledge upon the premotor phase is important for several reasons [143, 144]:

1. The existence of a premotor phase has etiological implications as its time of onset would be the stage where a putative environmental or genetic agent strikes first.

2 Neuroprotective or disease-modifying strategies during this stage would provide most benefit to probably yet unaffected individuals, because of their ability to hamper or slow neurodegeneration. The advantage of this strategy would be longer neurological sanity, preservation of life quality and fewer burdens for caretakers and the health system. For now, no agent exhibits neuroprotective properties, but new promising drugs are on the horizon.

3. The identification of non-motor signs that develop during the premotor phase could also help to define a population at risk who consequently would undergo repeated and precise neurological examination to detect parkinsonism as soon as possible.

4. A better understanding of premotor symptoms could lead to the development of biomarkers for PD

It is assumed that the premotor phase of PD starts with the affection of the extranigral induction site and ends when parkinsonian motor signs become overt. It is highlighted first by subclinical, subthreshold αSYN-pathology and afterwards, when pathology is overwhelming and leads to cellular dysfunction, the emergence of several NMS. Therefore, the preclinical phase is longer than imaging data of the SN implies, which suggest that nigral cell loss antedates parkinsonism by 4-6 years [146].
Premotor and presenting symptoms in PD are summarized in table 23:

Table 23 Premotor and presenting symptoms in Parkinson's disease

- Olfactory dysfunction
  - odor discrimination, odor identification and odor detection treshhold, odor recognition memory
  - Phantosmia (olfactory hallucinations)
- Sleep disturbances
  - REM sleep beavior disorder (RBD)
  - Excessive daytime sleepiness (EDS)
  - Periodic leg movements during sleep (PLMS)
  - Sleep apnea syndrome (SAS)
- Autonomic dysfunction
  - Constipation
  - Sympathetic dysfuncion in the innervation of the heart
  - Erectile dysfunction
  - Urinary symptoms
- Neuropsychological deficits
  - Depression, anxiety
  - Cognitive impairment (without functional limitation or dementia)
- Pain, especially shoulder pain
- Foot dystonia
- Sensory disturbances
- Impaired colour discrimination and contrast sensitivity
- Abnormality in smooth pursuit eye movements (SPEM)
- Mirror movements (MM)

1.3.1. Olfactory dysfunction

Olfactory dysfunction in PD was first reported in 1975 by Ansari et al. With a prevalence of 70-90 % this NMS is as common as cardinal motor features. Deficits in all areas of olfaction can be defined: odor discrimination, odor identification, odor detection threshold and odor recognition memory. Profound deficits in all of these modalities have been found in the early stages of PD. However, true anosmia is rare in PD. Recent studies claim a progression of olfactory dysfunction over time. Olfactory dysfunction does not respond to dopaminergic medication. [144, 145]

Pathological findings:

No evidence of LBs is seen in the short lived olfactory neurons of the olfactory epithelium. Other structures of the olfactory pathway show αSYN-pathology, such as olfactory bulb, olfactory tract, anterior olfactory nucleus, primary olfactory cortex (olfactory tubercle, frontal piriform cortex, temporal piriform cortex) and secondary olfactory cortex (amygdala).

Interestingly, there is a doubling of tyrosine hydroxylase-positive periglomerular neurons in the olfactory bulb in PD cases compared to healthy controls, leading to dopamine overload in the olfactory bulb. As dopamine is known to inhibit transmission between axons of olfactory receptor neurons and dendrites of mitral cells in the olfactory bulb, it is possible that a tonic inhibition of olfactory neurotransmission occurs, related to a compensatory increase in dopamine receptors in extranigral sites. This explains why olfaction does not improve with LD therapy. In later stages, the number of dopaminergic neurons in the bulbus olfactorius decreases, which may relate to diminished dopaminergic inhibition and fluctuating function in olfaction. [144, 147]

Assessing smell loss in PD

Olfactory testing methods include [145]:

1. University of Pennsylvania smell identification test (UPSIT): In this 40- item test the patient is asked to scratch the surface of the testing card and to identify the odor released from four choices.

2. Cross cultural smell identification test or brief smell identification test (CCSIT, BSIT): This is a modified version of the UPSIT and contains only 12 items

3. Sniffin' Sticks: A pen like device is used to assess odor threshlod, identification and discrimination. The patient sniffs the pen, which delivers successive concentrations of n-butanol for threshold testing, 16 pairs of odorants for discrimination and 16 single odorants for identification from 4 stated choices.

4. Olfactory event-related potentials (OERPs): This test enables to quantify olfaction independent of sniff volume and memory, two points of weakness in the former testing methods. P1 reponse correlates with the olfactory bulb and P3 with the cortex. In PD the responses are slowed without reduction of amplitude. The stimulation of the trigeminal system revealed no pathologic findings.

Differential Diagnosis

Olfactory testing can be helpful in the differential diagnosis of parkinsonism: Olfaction is less impaired in MSA compared to PD and in PSP and CBD olfaction seems to be preserved. Severe impairment of olfaction is also seen in LBD and AD. Slight OD is seen in HD and ET. In non degenerative causes of parkinsonism olfaction remains intact, such as VP and MPTP-induced parkinsonism. [144, 145]

Olfactory dysfunction as a prodromal sign

Olfactory dysfunction (OD) probably serves as a biomarker and prodromal sign in early pre-symptomatic PD. Most convenient is its high prevalence and easy non-invasive assessment. The assessment of OD in asymptomatic individuals can help to identify a population at risk for PD.

This is a summary of eleven findings about the involvement of OD in the premotor phase of PD:

1. OD precedes motor deficts by 4-6 years. [144]

2. OD has been found in asymptomatic relatives of patients with sporadic and familiar PD. [146]

3. Subclinical degeneration of the nigrostriatal system is seen in some hyposmic relatives of PD patients. [146]

4. Idiopathic OD in relatives of PD patients is associated with an increased risk of developing PD of at least 10 %. This number may be even higher when a longer follow up period is considered. [144-146]

5. Impaired olfaction in neurologically intact individuals is a risk factor for developing PD within the following four years. [148]

6. OD is associated with iLBD. [149]

7. Patients with RBD can present with profound OD. The combination of these symptoms would fit to stage 2 of the Braak PD classification. [150]

8. Cardiac MIBG-scintigraphy correlates with OD independent of motor symptoms. [151]

9. When combining tests for olfaction, mood and motor impairment a specifity of 92% and sensitivity of 68% can be reached. [152]

10. TCS in individuals with idiopathic hyposmia can identify those who are at risk to develop PD. Combination of olfactory testing and TCS or SPECT might be a promising screening tool. [153]

11. Olfactory hallucinations, termed as phantosmia, occur in the absence of major smell deficits and might also present a premotor symptom. These early hallucinations are considered as pleasant or reminiscent by patients. They differ from olfactory hallucinations related to dopaminergic medication, which are unpleasant and accompanied by visual halluzinations. They were only described in case reports as far. [154]

1.3.2. Sleep disturbances

In this stage, the sleep becomes much disturbed. The tremulous motion of the limbs occurs during sleep, and augment until they awaken the patient, and frequently with much agitation and alarm.

James Parkinson
An Essay on the Shaking Palsy, 1817 [142]

1.3.2.1 Periodic limb movements in sleep (PLMS)

Periodic limb movements in sleep (PLMS) can cause sleep disruption in PD. They are more frequent in patients with PD than in controls. PLMS are present in untreated patients at early stages of the disease and may be due to a dopaminergic deficit and not related to dopaminergic therapy. [179]

Furthermore, the number of PLMS in PD correlates with a reduction of striatal b-CIT binding in SPECT. Thus, striatal dopaminergic nerve cell loss may be a causative factor for PLMS in PD. [180]

1.3.2.2. Sleep apnea syndrome (SAS)

Sleep apnea syndrome (SAS) is seen in patients with PD more frequently than in age matched controls. 20-50% of PD patients assessed with polysomnography show apnea, often despite a normal BMI. Usually recognized symptoms are snoring and daytime sleepiness. [158]
Sleep breathing disorders in PD are predominantly obstructive and they are also seen in early stages. [188]

If characteristic parameters of SAS, such as AHI-score and blood oxygen saturation are abnormal during the premotor phase remains to be elucidated.

1.3.2.3. REM sleep behaviour disorder (RBD)

And they found him with the sword in one hand, stabbing everything as if he were fighting, and it was of note that he had his eyes closed, for he was sleeping and dreaming that he was in a battle against the giants.

Cervantes
Don Quixote, Book I, chapter 35
From Garcia Ruiz PJ et al. [172]

REM sleep behaviour disorder (RBD) is a parasomnia, characterized by loss of normal skeletal muscle atonia during REM sleep with prominent motor activity and dreaming. In the absence of any associated neurological disorder, it is termed 'idiopathic' RBD.

'Secondary' or 'symptomatic' RBD refers to the combination of RBD plus another neurological disorder, such as narcolepsy or a neurodegenerative disease like PD.

REM sleep without atonia (RSWA) refers to the electrophysiologic finding of loss of EMG atonia during REM sleep and is assessed by polysomnography. Patiens with RSWA but without associated dream enactment behaviour are classified as 'preclinical' RBD. [155]

For diagnosis of RBD, both RSWA and dream enactment behaviour are required (Table 24).

Table 24 clinical diagnosis of RBD, 2nd edition of the International Classification of Sleep Disorders, (ICSD, 2005), from [155]:

I Presence of RSWA on PSG.
II At least one of the following:
  (1) sleep-related, injurious, potentially injurious or disruptive behaviours by history (i.e. dream enactment behaviour) and/or
  (2) abnormal REM sleep behaviour documented during polysomnographic monitoring.
III Absence of EEG epileptiform activity during REM sleep unless RBD can be clearly distinguished from any concurrent REM sleep-related seizure disorder.
IV The sleep disorder is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use or substance use disorder.

Interestingly, RBD in PD is associated with specific motor features: These patients show an increased frequency of falls and are less likely to be tremor dominant. Furthermore, these patients are more likely to have cognitive impairment and slowing in wake EEG than patients without RBD. [168] They also show an increased frequency of orthostatic hypotension and impaired colour vision. This data implies that in patients with RBD a distinct pattern of neurodegeneration is predominant. [169]

Clinical spectrum of RBD

The clinical spectrum of RBD compromises of vocalizations, swearing, screaming and motor activities that vary from simple limb jerks to complex behaviour with injuries to the patient or his bed partner. The dreams are characterised by violent content and often involve chases or attacks by animals. The exhibited behaviours mirror this dream content and can be described as 'acting out dreams'. [155]

Findings about the involvement of RBD in the premotor phase of PD:

1. RBD represents a prodromal sign in αSynucleinopathies including PD, DLB and MSA. RBD can precede PD by 3-17 years. [143]

2. The abnormal increase of muscle activity during REM-sleep correlates with decrease of striatal presynaptic dopamine transporters [156]

3. A marked reduction in cardiac MIBG-uptake is found in patients with idiopathic RBD compared to control subjects and patients with clinically diagnosis of PSP and MSA, but similar to those with clinically diagnosed PD and DLB. Thus, cardiac MIBG-scintigraphy could be an early diagnostic marker of RBD with Lewy body-related pathology. [157]

4. There is a strong correlation of OD and RBD, with increased risk of developing PD, as mentioned in the section above. [150]

1.3.2.4. Excessive daytime sleepiness (EDS)

Excessive daytime sleepiness (EDS) is a frequent complaint of PD patients. EDS is seen in 15.5% of PD patients compared with 4% of patients with diabetes mellitus and 1% of controls. In a longitudinal study over 4 years, EDS was found in 8% of PD subjects at baseline, and 21% at 4 years.

Any dopamine agonist and LD are able to cause EDS. Recent studies argue that it is the total load of dopaminergic drug, both agonist and LD, that give rise to daytime sleepiness, although it may be more frequently associated with the direct dopamine agonists and occurs more often in MSA than in PD.

EDS could also be a primary feature of PD, unrelated to dopaminergic agents or sleep disturbances. [158]

Hint for the involvement of EDS in the premotor phase of PD:

In the Honululu-Asia aging study, daytime sleepiness yielded a 3-fold increase in risk for future development of PD. [159]

1.3.3. Autonomic features

1.3.3.1. Constipation

The extanigral αSYN-pathology in the ENS is associated with prolonged intestinal transit time and constipation in PD. The prevalence of constipation in PD is increased and ranges between 28-61% as compared with controls (6-23%). [123]

Findings about the involvement of constipation in the premotor phase of PD:

1. Honolulu Heart Program: This study included 6790 males without extrapyramidal disease at enrolment who were followed up for 24 years. 96 developed subsequently

PD. The adjusted risk of PD in those with less than one bowel movement per day compared to those with one or more per day was increased about threefold. This finding implies that constipation is a harbinger of PD. [160]

2. There is a correlation between iLBD and bowel frequency: There is a fourfold excess of iLBD in those with <1 bowel movement per day compared to those with >1 bowel motion per day. [161]

1.3.3.2. Sympathetic dysfuncion in the innervation of the heart

Dysfunction of postganglionic sympathetic neurons can be measured by MIBG-scintigraphy and results in significant reduction of MIBG uptake. This condition is expressed by a decreased H/M ratio (heart/mediastinum). In PD the mean H/M ratio is 1.31 (SD 0.15), which is significant lower than in the control population: 2.24 (SD 0.14). No other organ with sympathetic innervation, such as lung, muscles or glands show reduction in MIBG-uptake. Patients with PD show abnormal heart rate variability and elongated QTc interval. [43, 162].

Furthermore, PD patients have a longer P wave duration and P wave dispersion than controls. These effects are not related to dopaminergic therapy. [187]
Moreover, extrasystoles occur more frequently in patients with PD than in controls. The abnormal decrease in systolic blood preasure after the extrasystole indicates baroreflex dysfunction in PD. Thus, orthostatic hypotension is part of the pathology of PD and not entirely related to dopaminergic medication.
Whether these features can be detected during the premotor phase remains to be elucidated. Another interesting question is if PD patient are susceptible to cardiac dysrhythmias.

Findings about the involvement of sympathetic dysfuncion in the innervation of the heart in the premotor phases of PD:

1. Correlation of MIBG abnormality and OD, as mentioned above [151]

2. LBs can be found in cervical sympathetic ganglia in the absence of DMV affection in cases with iLBD. [71]

1.3.3.3. Urogenital dysautonomia

Erectile dysfunction

Erectile dysfunction can be a prodromal sign of PD, as revealed by a retrospective questionnaire. This study was part of Health Professionals Follow up study and included 32616 men. The main conclusion of this study was that men with erectile dysfunction are 3.8 times more likely to develop PD. [164]

Urinary symptoms

Urinary symptoms, such as urgency and nocturia, are a presenting complaint in 3.9% of patients with PD as demonstrated by O'Sullivan et al. [170]

1.3.4. Psychiatric and neuropsychological impairment

1. Mood symptoms are often seen in PD patients, especially depression and anxiety. The average prevalence of depression is 40% with a range from 4-70%. The risk for depression is higher for patients with a younger onset. The cause of depression is a combination of organic, psychological and social factors.
   Depression can predate parkinsonism in PD by years or even decades. Approximately 20% of PD patients complain of mood disturbances before the onset of motor signs. [162]
   Interestingly, a recent study which included 1000 first degree relatives of 162 PD patients reveales that depression and anxiety disorders are more frequent in first degree relatives of patients with PD. [178]

2. Cognitive impairment in early stages of PD resembles that seen in frontal lobe damage and includes deficits in executive function such as planning and working memory. This impairment of the frontal lobe due to reduction in activity of the frontostriatal activity can be measured by fMRI. [165] Furthermore, a decay in visuospatial and visuoconstructive skills is seen in early stages and can be easily assessed via, e.g. the

clock drawing test or pentagram reproduction from MMSE. This abnormal condition may represent a predicting factor for later development of dementia. [166]

3. Deficits in non-verbal emotional information processing: The ability of decoding emotional facial expressions is reduced in early stages of PD. [167, 199] Furthermore, PD patients are frequently impaired in the recognition of emotion from specch prosody or the tone of a speaker's voice. [200]

1.3.5. Pain

Pain in PD can be centrally, caused by a neurodeganerative process that interferes with central pain processing pathways, or mechanically, related to motor symptoms such as rigidity. According to central pain, heat pain thresholds are decreased in PD patients and more marked in the initially affected side. In established PD, pain is a frequent complaint with a frequency of 40-50%, even when osteoarthritic and neuropathic causes are excluded. [123]

Neck pain, also known as coat hanger pain, is associated with orthostatic hypotension (OH) in PD patients. [122] When using tilt table testing, orthostatic hypotension is seen in 58% of PD patients (OH is defined as drop of systolic blood pressure by 20 mmHg). OH correlates with dopaminergic medication dose, severity and duration of the disease. Thus OH is usually confined to later stages of PD. [123]

Pain as an ealy symptom:

1. During the premotor phase, patients may report non-specific pain, which cannot be correlated with joint disease. This could relate to the pain gating mechanism at pontine level at Braak PD stage 2. [171]

2. A recent study by O'Sullivan et al. examined NMS in pathologically proven PD cases and pointed out that pain is the most frequent non-motor presenting complaint in patients with PD, seen in 15% of the cases. [170]

3. Shoulder pain can be a premotor symptom in PD and correlates with the side of initial rigidity or loss of dexterity. These patients are often first diagnosed as impingement or lesions to the rotator cuff. Occasionally they even get steroid injections or explorative arthroscopy. Frozen shoulder (paeriarthrits humeri, adhesive capsulitis) can be a presenting symptom in PD and occurs up to 2 years prior to parkinsonism. Frozen shoulder manifests as spontaneous pain and restriction of movement in the shoulder, in the absence of any demonstrable intrinsic joint abnormality. The initial symptom of parkinsonism in these patients is bradykinesia. [174]

4. Some patients present with cramp like calf pain, which are frequently worse at night. The symptoms may be confused with peripheral vascular disease. Exploring of the ankle brachial pressure index (ABPI) or duplex sonography of the lower limb arteries in these patients can prevent them from invasive testing (arteriogram). [175]

1.3.6. Dystonia

Dystonia, a sustained muscular contraction frequently accompanied by abnormal movements, postures or both, is sometimes found in PD patients. In atypical PS such as PSP, MSA or CBD, dystonia can be prominent in early stages. In advanced PD, dystonia usually represents a complication of dopaminergic treatment and manifests as early morning dystonia, off dystonia, diphasic dystonia or peak-dose dystonia. Kinsesigenic foot dystonia can be a presenting symptom in early onset PD. [176] In a prevalent PD population 0.9% of patients develop PD before the age of 40 and 5.4% before the age of 50. In this subset of patients with young onset Parkinson's disease (YOPD), foot dystonia can be a presenting symptom and occurs with a frequency of between 14% - 57%, whereas it is seldom a presenting feature in late onset Parkinson's disease (LOPD). Furthermore, patients with YOPD have slower disease progression, more frequent early dyskinesisa (72% vs 28% after 3 years) and fluctuations (64% vs 28% after 3 years) in response to LD treatment, less frequent gait disturbances and less frequent dementia when compared with LOPD patients. [177]

1.3.7 Sensory symptoms

Patients with PD often describe paraesthesia-like symptoms (tingling, numbness, formication). These abnormal sensory sensations are not associated with sensory loss and are not caused by somatic disease. These sensory symptoms can also precede the onset of parkinsonism. [181]

1.3.8 Colour discrimination

Impairment of colour discrimination is an early sign of PD. In the Farnswoth-Munsell 100 hue test the mean total error score for de novo PD patients was significantly higher than for age-matched controls. [183]
Furthermore, another study demonstrated that both colour discrimination and contrast discrimination are decreased in treated PD patients. [184].
Interestingly, a study with chromatic visual evoked potentials (VEPs) in LD-naive PD patients at early stages demonstrated a greater delay in blue-yellow VEPs than in controls. This finding suggests an early impairment of the blue-cone pathway in PD. [185]

1.3.9 Smooth pursuit eye movements (SPEM)

Significant differences in smooth pursuit eye movements (SPEM) are present in early LD-naive patients with PD in comparison to healthy age-matched controls. The symptom is responsive to subcutaneous apomorphin administration. [189]

Furthermore, abnormal saccades occur in a subset of unaffected first degree relatives of PD patients as well. This finding indicates that testing for saccadic movements could be useful to identify people who are at greater risk for PD. [190]

1.3.10. Mirror movements (MM)

Mirror movements (MM) are involuntary and unnecessary movements that accompany voluntary activity in homologous muscles on the opposite side of the body. They frequently involve the distal upper limbs during repetitive or alternating finger or hand movements.

MM occur in normal early childhood and in some disorders such as X linked Kallmann's syndrome, childhood hemiparesis, Klippel-Feil syndrome, Williams syndrome and stroke.

MM is a feature of asymmetric parkinsonism, particularly at an early stage when overall motor impairment is relatively minor. MMs occur in the relaxed, less affected or unaffected hand while voluntary movements are performed with the more affected hand. Moreover, it is the differential severity of motor impairment between sides that best predicts mirroring on the less affected side. [191]

When considering dopaminergic response, there is an inverse correlation between UPDRS change (UPDRS off - UPDRS on) and mirror movement change (mirror movements off - mirror movements on). From off to on, patients with large improvement in UPDRS scores show more MMs whereas those with small improvement in UPDRS scores show less MMs. Thus, mirroring is more prominent in patients whose motor response to dopaminergic treatment is greatest and less prominent in those whose response is less overt. [192]

1.3.11 Midlife obesity

Midlife obesity is a candidate prodromal feature for PD for several reasons:

1. Overweight people have decreased striatal D2 receptor availability and dopamine is involved in food intake. [143]

2. The locus coeruleus, which is affected in Braak stage 2, is important for the control of food intake and the sleep-wake cycle. [143]

3. Orexin peptides mediate these functions and one of their receptors, OX1, is expressed strongly in the locus coeruleus, hypothalamus and gut. [143]

4. Hypocretin (orexin) neurons are diminished in PD patients [28].

5. Ghrelin is a stomach-derived hormone and endogenous ligand for the growth hormone secretagogue receptor (GHS-R). It acts on the pituitary and the hypothalamus to stimulate the release of growth hormone and promote adiposity and appetite.
The fully functional receptor for ghrelin, GHS-R 1a, is also expressed abundantly in the SNpc. Interestingly, grehlin protects dopaminergic neurons against MPTP-neurotoxicity in the mouse model. [193]

Three large prospective studies have explored the possible association between midlife obesity and risk for PD [143]:

1) Midlife adiposity and PD risk was examined in the HHP study. The age-adjusted incidence of PD increased three times for individuals in the top quartile of biceps skinfold thickness and was independent of cigarette smoking, coffee consumption, physical activity, daily caloric and fat intake. The average time to diagnosis of PD was 19 years (range 2–30 years).

2) Greater waist circumference and waist to hip ratio were associated with increased risk of PD among never smokers with relative risks of about 2.0.

3) Individuals in a higher body mass index (BMI) category, defined as more than 23, are at increased risk of PD.

Midlife obesity is not a persistent condition. Actually, PD patients show a decline of BMI in advanced stages of the disease. It would be of interest if unique patterns of subcutaneous fat distribution can be identified for both the premotor and motor phase of PD and if grehlin blood levels are altered in these phases.

1.4 Treatment of early Parkinson's disease

First treatment options for parkinsonism date back to traditional Ayurvedic Indian medicine, 1500 BC. Mucuna pruriens, a LD-containing plant, was used to treat a nervous malady resembling parkinsonism, termed as 'Kampavata'. A recent double blind, placebo controlled study revealed that administration of M. pruriens combines a rapid onset of action with a longer on time without increase of concomitant dyskinesias in camparison to conventional LD. [194]

Descriptions of parkinsonism can also be found in the ancient chinese literature as eary as 425 BC. The traditional Chinese medicine recommends an antitremor pill and Jinya wine as a treatment for tremor and rigidity. Both remedies contain the same herbs and gastrodia as a main element. These herbs show anticholinergic and antioxidant properties. Interestingly, recent studies claim that gastrodin increases dopamine levels and inhibits MAO-B activity in animal models. [195]

1.4.1 Dopamine agonists and L-Dopa

Treatment should start early in the course of PD to achieve better long-term motor results. The ELLDOPA study showed that untreated PD patients lose 8 points on the UPDRS motor scale during the first 10 months, whereas those patients who were treated with LD gained 6 points. [196]

LD has a short plasma half-life time of about 1–2 hours which results in a discontinuous or phasic dopamine receptor stimulation which causes dyskinesia. When LD is administered in a continuous way, i.e. application via a pump to the jejunum (DuoDopa® pump), dyskinesias occur less frequently, pre-existing dyskinesias decrease and off-time also decreases considerably in PD patients with motor fluctuations. [196]

Actually, early treatment with LD will cause dyskinesias in 50 % of late-onset patients after five years of treatment and in 80 % of early-onset patients. Thus, the plasma-half life time of dopaminergic agents seems to be the critical parameter and therapeutic strategies should aim

at most constant plasma levels. Even the shorter-acting dopamine agonists (DAs) have a lower incidence of dyskinesia than L-Dopa. [196]

Accordingly, treatment guidelines of the German Neurological Society suggest that de novo patients under the age of 70 without major concomitant disease should receive DAs as first line treatment. The initial use of LD is restricted to patients older than 70 or patients with multiple concomitant diseases. [196]

DAs can be divided in ergot and non-ergot agents. Ergoline DAs can cause pleuropulmonal and retroperitonal fibrosis and valvular heart stenosis. Therefore, these agents are not first-line. Common adverse effects of both ergoline and non-ergoline DAs are nausea, OH, edema, daytime sleepiness, impulse control disorders (pathologic gambling, compulsive shopping, binge eating) and hallucinations or psychosis. [197]

DAs have a relatively long plasma-half life time and the most long-acting non-ergoline drugs are rotigotine (Neupro®) and ropinirole slow-release (Requip ModuTab®), which can be applied once daily. Rotigotine is applied via a transdermal patch delivery system and is effective in both early and advanced stages. [196, 197]

Apomorphine (APO-go PEN®) has a rapid onset of action and a duration of benefit of approximately 90 minutes. Therefore it is used as a rescue medication in unpredictable off times, dosage failure and early morning off times. It can only be applied subcutaneously. In patients with motor fluctuations, apomorphine can also be administered via a pump in a continuous way. [197]

Table 25 Dopamine agonists, modified from [196]

Dopamine agonist *Trade name*		**Type**	**D1**	**D2**	**D3**	**D4**	**D5**	**λ**
	Dopamine (for comparison)		+	+	+	+	+	1,5
APO-go PEN®	Apomorphine	NE	+	+	+	+	+	0,3
Umprel®	Bromocriptine	E	-	+	+	+		3
Cabaseril®	Cabergoline	E	+	+	+	?	?	68
Dopergin®	Lisuride	E	+	+	+	+	?	2
Permax®	Pergolide	E	+	+	+		+	18
Sifrol®	Pramipexole	NE	+	+	+	+	-	8
Requip®	Ropinirole	NE	-	+	+	+	-	6
Neupro ®	Rotigotine	NE	+	+	+	+	+	6

Abbreviations: NE Non ergoline derivative, E ergoline derivative, D1-D5: dopamine receptors, λ plasma half life time in hours

1.4.2 MAO-B inhibitors

The class of MAO-B- (monoamine oxidase-B) inhibitors compromises of selegiline (Jumex®) and rasagiline (Azilect®). They are used as monotherapy in early PD or as adjunct therapy to LD. The multicenter, randomized, double blind, placebo controlled DATATOP trial investigated selegiline in early PD patients. After approximately 12 months of follow-up, significantly fewer subjects in the selegiline group (24%) required rescue LD therapy than in the placebo group (44%). At both 1 month and 3 months, the selegiline group had improved from baseline in UPDRS total, motor and ADL scores, while the placebo group had worsened. [198]

The randomized, double-blind, placebo-controlled TEMPO trial investigated rasagiline in early PD patients. At 26 weeks, those treated with 1 mg/day rasagiline experienced a 4.2-point improvement relative to placebo. [198]

Furthermore, rasagiline is also effective as an add-on therapy for controlling motor fluctuations. The PRESTO trial showed that rasagiline reduces daily off time in comparison to placebo. [197] Moreover, the currernt multicenter ADAGIO study, a randomized, double blind, placebo controlled delayed start study, investigates a putative disease modifying effect for rasagiline in early PD. Preliminary results are promising, thus, it is currently discussesd if rasagiline should be given in early PD. [205]

1.4.3 COMT-inhibitors

COMT- (catechol-o-methyl transferase) inhibitors are used as an adjunctive treatment to LD. They inhibit peripheral metabolization of LD and thus maximize LD bioavailability for the blood brain barrier transport. Further, they prolong plasma half life time of LD without increasing peak plasma levels.

The class of COMT-inhibitors compromises of entacapone (Comtan®) and tolcapone (Tasmar®). The use of tolcapone requires repeated liver function tests, especially during the initial 6 months, due to its' possible heapatotoxicity. There is also a combination of LD and entacapone availabe (Stalevo®). COMT-inhibitors are used in patients with motor fluctuations, especially in wearing off phenomenon. They prolong on-time, reduce off-time and improve motor function of LD-treated patients. They have a LD-saving effect of approximately 25%. Side effects are diarrhoea in the first month and harmless urine discoloration. [197]

1.4.4. Nondopaminergic therapy

Amantadine

Amantadine was formerlly known as a treatment for Influenza A. Amantadine (PK-Merz®, Hofcomant®) is effective for relieving tremor in early PD and improves LD-induced dyskinesias in advanced stages of PD. It acts as an NMDA-inhibitor, enhancer of dopamine release in presynaptic terminals and shows modest anticholinergic activity. In renal failure a dose reduction of amantadine is required. It should be used with caution in patients with cognitive impairment. [197]

Anticholinergic agents

Anticholinergics are typically reserved for the younger patient (<60 years of age) with predominant resting tremor and preserved cognitive function. These agents should be used with caution in older patients because of their potential side effects, including constipation, blurry vision, urinary retention, confusion, and hallucinations. [197]

2. Methods

2.1 Aim of the study and study design

The purpose of this diploma thesis was to shed light on the characteristic features of the early phase of PD. Especially it was intended to clarify the question: What are the characteristic features of patients with PD before they visit an outpatients' department for movement disorders?

Therefore, first, a retospective study was carried out, using data from 242 patients with parkinsonism and additionally 46 patients with ET. Clinical data were derived from medical records of patients who visited for the first time the outpatients' department for Parkinson's disease and movement disorders at the Department of Neurology, Medical University Graz. As an extension to the retrospective study, a questionnaire was designed with the intention to spot on features of the early phase of PD. 24 patients with parkinsonism were enrolled. The questionnaire is shown in Appendix D.

Second, a detailed review of the current literature on the topics of early pathological events, early clinical symptoms, early diagnosis and testing and initial treatment options in PD was performed, which is part of the introduction.

2.2 Retrospective study

The medical records of the patients' first visit at the outpatients' department for Parkinson's disease and movement disorders were screened for severeal items, as shown in table 26. Additionally, rating scales like the initial UPDRS (Appendix A), modified Hoehn and Yahr score (Appendix B), Schwab and England activities of daily living score (Appendix C) and the initial MMSE-score were noted for each patient at his/her first visit, if they were available.

Table 26 description of variables used in the retrospective study

- Age at onset of PD related symptoms

- Age at first visit of a specialized centre for movement disorders (outpatient's department for Parkinson's disease and movement disorders)

- Latency
  (Delay between the first PD-related symptoms the patient expirienced and their first visit of the outpatients' department for movement disorders)

- Gender

- Initial symptoms (relies on patient's report)
  - *Motor symptoms*
    (includes all motor manifestations related to parkinsonism)
  - *Non-motor symptoms*
    (includes sleep disturbences, mood disturbences, changes in cognition and behaviour)
  - *Sensible symptoms*
    (includes pain and paraesthesia)
  - *Autonomous symptoms*
    (includes all known autonomous disturbances related to PD)

- Olfactory dysfunction at first visit (relies on patient's report)

- Previous drug treatment (drug regime before first visit of a specialized centre for movement disorders)
  in the categories below all drugs available to date in Austria were considered
  - *Antiparkinsonian agents*
    - LD
    - DA
    - COMT-Inhibitors
    - MAO-B-Inhibitors
    - Amantadine
    - Anticholinergic drugs
  - *SSRI*
  - *Other Antidepressants than SSRIs*
  - *Neuroleptic drugs*
    - Typical neuroleptic drugs
    - Atypical neuroleptic drugs
  - *Benzodiazepines*
  - *Antidementia agents*

- Concomitant diseases
  all known concomatant diseases were considered and assigned to the following fields:
  - *Internal medicine*
  - *Neoplasia*
  - *Psychiatriy*
  - *Surgery*
  - *Neurology*

● Previously carried out diagnostic tests (before their first visit of outpatients' department for movement disorders)

Neurological tests

Test of internal medicine

Patients

242 patients presenting with parkinsonism at their first visit at the outpatients' department were enrolled. Patients with parkinsonism were assigned to clinical subgroups (sporadic PD, PS not further specified, PD with motor fluctuations, PD + ET, DIP, VP, PDD, PSP, MSA, DLB, atypical PS not further specified, early onset PD, Fahr's disease). The term sporadic PD, as used in this study, excludes patients with familiar PD and patients who presented with motor fluctuations at the first visit. The diagnosis was based on the UKPDSBB-criteria. Frequencies and gender distributions of these subgroups are shown in table 28 and figure 2.

3.3. Questionnaire

A questionnaire, as shown in Appendix D, was handed out to patients with parkinsonism who visited the outpatient's department. 24 patients with parkinsonism were enrolled. The variables used in this questionnaire are listed in table 27.

Table 27 Description of variables used in the questionnaire

● Initial symptoms (includes early motor and non-motor symptoms)

● Previously consulted doctors due to disease-related symptoms

● Number of previously consulted doctors due to disease-related symptoms

● Prevalence of selected diseases in family

● Prevalence of selected diseases in patient history

3.4. Statistics

A medical database was built up with MS Excel 2003, using data derived from medicial records of the outpatients' department and the questionnaire. All data were analysed using the statistical software program SPSS 14.0. Descriptive statistics are given in mean, standard deviation, absolte and relative frequencies. Results are displayed as frequency tables, bar charts, histograms and box and whisker blots.

3. Results

3.1. Retrospective study

3.1.1. Frequency distribution of clinical subtypes and gender distribution of patients with parkinsonism

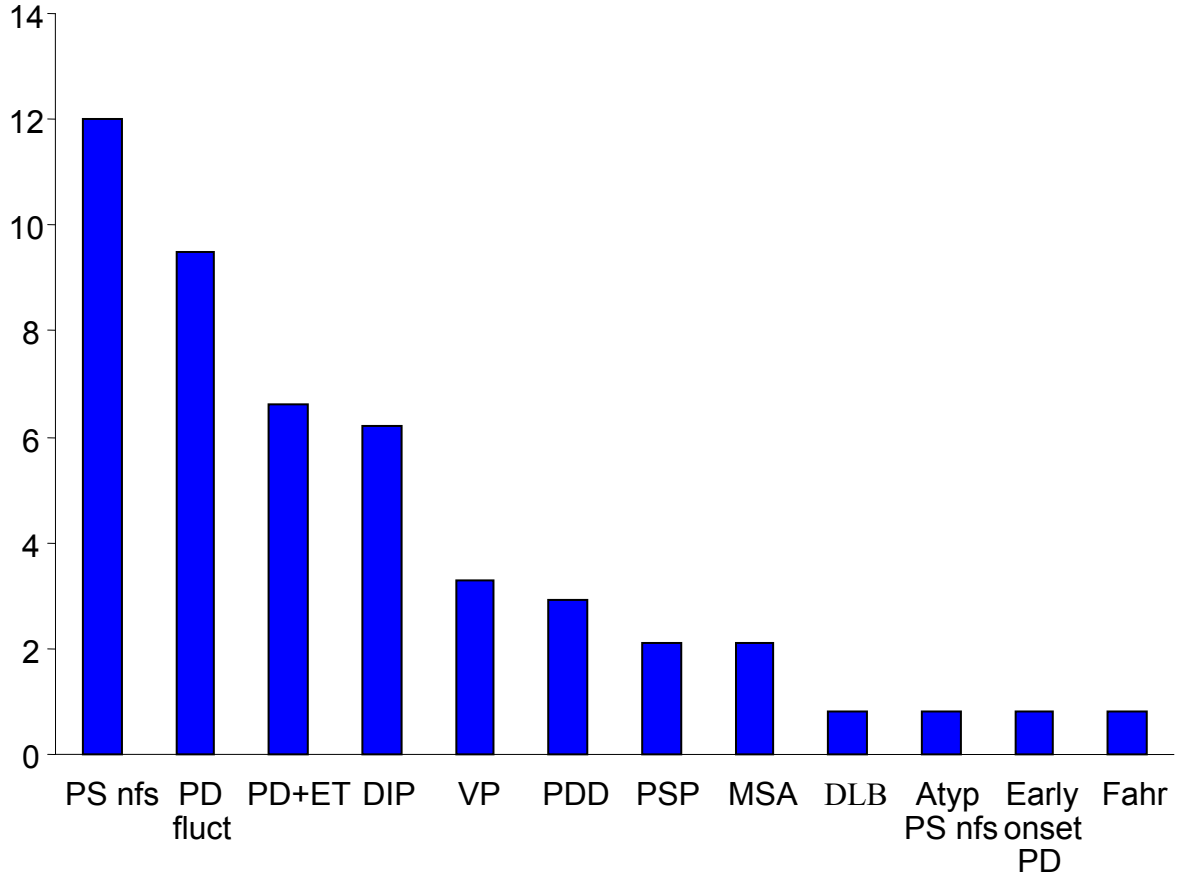
242 patients presenting with parkinsonism at their first visit at the outpatients' department were analysed. Table 28 gives an overview of disease and gender distribution of the study population. Furthermore, the distribution of relative frequencies of clinical subgroups in patients presenting with parkinsonism other than sporadic PD is displayed in Figure 2.
The group of patients with MSA consists of 3 cases with MSA-P and 2 cases with MSA-C. In the group of Parkinsonism not further specified (29 cases), patients got the later diagnosis of PD (7 cases), DIP (13 cases), VP (2 cases), PDD (1 case) or remained unclassified (6 cases, mainly because patients got lost to follow up). In the group of atypical PS not further specified (2 cases), one case was later classified as VP and the other case remained unclassified.

Table 28 Clinical subgroups with frequencies and gender distribution for patients presenting with parkinsonism

	n	%	m (%)	f (%)
Sporadic PD	126	52,1	77 (61,1%)	49 (38,9%)
Parkinsonism not further specified	29	12,0	20 (69%)	9 (31%)
PD with motor fluctuations	23	9,5	10 (43,5%	13 (56,5%)
PD + ET	16	6,6	7 (43,8%)	9 (56,3%)
DIP	15	6,2	8 (53,3%)	7 (46,7%)
VP	8	3,3	5 (62,5%)	3 (37,5%)
PDD	7	2,9	5 (71,4%)	2 (28,6)
PSP	5	2,1	3 (60%)	2 (40%)
MSA	5	2,1	4 (80%)	1 (20%)
DLB	2	0,8	1 (50%)	1 (50%)
Atypical PS not further specified	2	0,8	1 (50%)	1 (50%)
Early onset PD	2	0,8	2 (100%)	0 (0%)
Fahr's disease	2	0,8	0 (0%)	2 (100%)
total	242	100		

Figure 2

Relative frequency of parkinsonim other than sporadic PD



Abbreviations: PS nfs (parkinsonism not further specified), PD fluct (PD with motor fluctuations), PD + ET (Combination of PD and ET), DIP (drug induced parkinsonism), VP (Vascular parkinsonism), PDD (Parkinson's disease dementia), MSA (Multisystem atrophy), DLB (Dementia with Lewy bodies), Atyp PS nfs (atypical PS not further specified), Fahr (Fahr's disease)

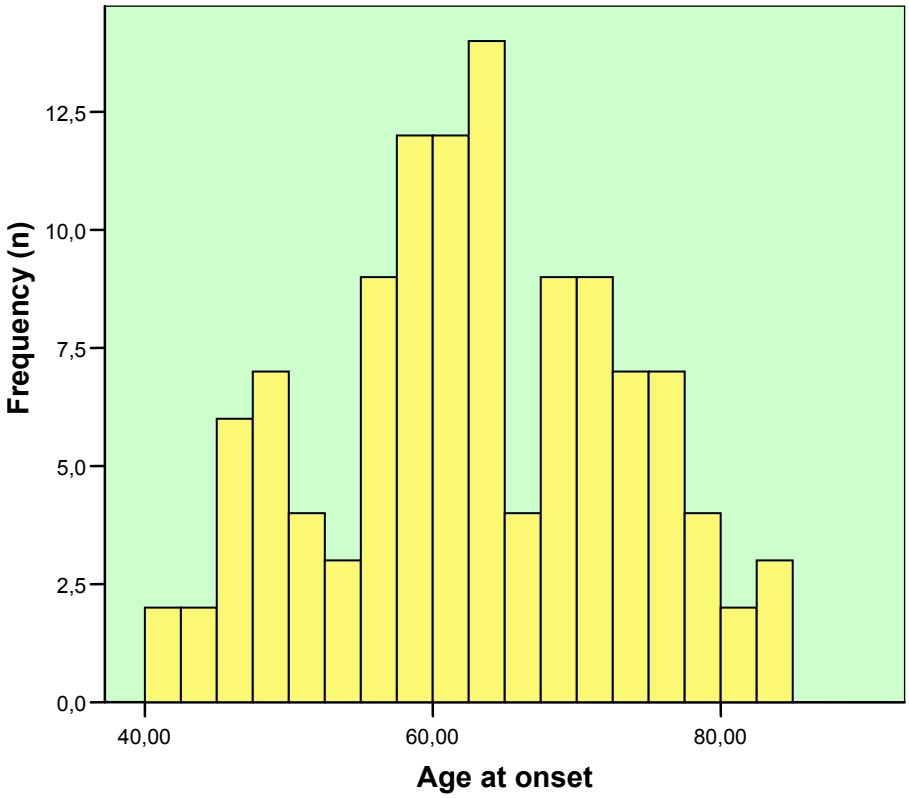
3.1.2 Age at onset, Age at first visit and Latency in parkinsonism

Table 29 gives an overview of age at onset, age at first visit and latency in patients presenting with parkinsonism. Data is given as mean ± SD in years. Furthermore, age at onset in sporadic PD is illustrated by a histogram (Figure 3).

Table 29 Overview of age at onset, age at first visit and latency

	Age at onset	Age at first visit	Latency
Sporadic PD	62,9 ± 10,2	68,4 ± 9,4	5,1 ± 5,0
Parkinsonism not further specified	68,2 ± 9,4	71,3 ± 9,7	2,2 ± 1,9
PD with motor fluctuations	55,9 ± 8,8	69,1 ± 8,6	12,7 ± 4,0
PD + ET	67,9 ± 8,1	74,1 ± 6,7	6,6 ± 6,9
DIP	64,5 ± 11,7	67,3 ± 11,5	1,9 ± 2,9
VP	73,5 ± 4,1	77,0 ± 4,0	3,3 ± 2,3
PDD	69,6 ± 11,6	75,2 ± 9,3	5,6 ± 4,6
PSP	68,1 ± 10,2	72,5 ± 9,3	4,4 ± 3,4
MSA-C	59,3 ±1,1	61,3 ± 0,3	2,0 ± 1,4
MSA-P	66,4 ± 8,0	70,7 ± 4,8	4,3 ± 3,2
LBD	70,7 ± 0,7	72,7 ± 0,7	2 ± 1,4
Atypical PS not further specified	52,8 ± 19,0	58,8 ± 24,7	6,0 ± 5,7
Early onset PD	24,9 ± 20,2	47,4 ± 9,6	22,5 ± 10,6
Fahr's disease	55,8	61,2 ± 6,3	1

Figure 3 Age at onset in sporadic PD



3.1.3 Initial symptoms in sporadic PD

At their first visit at the outpatients' department for movement disorders and Parkinson's disease, patients were asked if they could remember the initial motor and non motor symptoms related to their disease. Table 30 gives an overview of these symptoms, derived form 126 patients with sporadic PD. The number of cases and relatve frequencies are listed beside. In 14 patients with sporadic PD, patient's reprort of olfactory impairment was available from initial medical records, results are displayed in Table 31.

Table 30 Initial symptoms in 126 cases of sporadic PD

motor symptoms	**n**	**%**
Tremor upper limbs	80	63,5
Compromising of:		
tremor at rest	71	56,3
postural tremor	3	2,4
tremor not further specified	6	4,8
lower limb tremor	6	4,8
jaw tremor	2	1,6
rigidity/stiffness	17	13,5
clumsiness	29	23,0
genereal slowing down	26	20,6
gait disturbances	18	14,3
limping gait	9	7,1
decreased armswing	7	5,6
unsteady gait	7	5,6
flexed posture	6	4,8
shuffling gait	3	2,4
freezing	2	1,6
falls in history	2	1,6
micrographia	13	10,3
subjective feeling of weakness	6	4,8
dizziness	3	2,4
change in speech	3	2,4
sialorrhoea	3	2,4
hypomimia	1	0,8

sensory symptoms	**n**	**%**
shoulder/neck pain	8	6,3
pain at other location	5	4,0
paraesthesias	2	1,6

non-motor symptoms	n	%
Depression/anxiety/mood disturbences	6	4,8
Sleep disturbences	3	2,4
Vivid dreams/aggressive behaviour in sleep	2	1,6
Forgetfulness	1	0,8

autonomous symptoms	n	%
constipation	3	2,4
urinary incontinence	1	0,8
hyperhidrosis	1	0,8
orthostatic hypotension	1	0,8
urgency	1	0,8
frequency	1	0,8

Table 31 Patient's report of olfactory dysfunction in patients presenting with sporadic PD

Presence of ofactory dysfunction (Yes/No)	n	%
Yes	8	57,1
No	6	42,9

3.1.4. Baseline severity scores in patients with parkinsonism

The baseline severity scores were noted for all patients at their first visit at the outpatients' department for movement disorders and Parkinson's disease. Data from all scales available (UPDRS, modified Hoehn and Yahr scale, Schwab and England scale, MMSE) were taken into account. Results are displayed in table 32. Furthermore, for patients with sporadic PD, baseline UPDRS scores are given as box and whisker plots (Figure 4, 5), baseline modified Hoehn and Yahr scale and baseline Schwab and England scale as histograms (Figure 6, 7). Baseline MMSE for patients with PDD and DLB are displayed in Table 33.

Table 32 Overview of baseline UPDRS, modified Hoehn and Yahr and Schwab and England activities of daily living score

	UPDRS I	UPDRS II	UPDRS III	UPDRS IV	UPDRS total	HY	SE
Sporadic PD *(n = 98/92/87)*	2,1±2,1	11,3±7,0	30,4±15,2	0,6±1,2	44,3±22,1	2,4±0,8	78,1±19,3
PS nfs *(n = 17/11/11)*	3,1±2,4	12,6±5,9	36,1±15,3	0,4±0,5	51,4±17,5	2,6±0,8	74,6±21,6
PD mot fluct (n = 17/17/17)	3,5±2,5	18,1±5,6	40,4±12,1	6,8±4,1	68,1±17,1	3,5±1,1	64,7±17,7
PD + ET *(n = 11/10/9)*	1,9±1,6	8,8±6,1	28,7±13,6	0,2±0,4	38,6±19,6	2,2±0,3	84,4±7,3
DIP *(n = 5/2/2)*	3,8±3,5	7,2±9,7	24,4±13,3	0,2±0,4	34,8±20,9	3,0±1,4	60,0±42,4
VP *(n = 3/1/1)*	1,7±0,6	12,0±10,4	32,5±22,6	0,0	42,0±35,5	4 (1c)	50 (1c)
PDD *(n = 4/5/4)*	5,0±4,9	22,8±8,5	62,3±11,0	0,5±0,6	90,5±22,7	3,5±1,2	42,5±25,0
PSP *(n =5/5/5)*	5,6±4,7	25,0±15,7	55,4±14,9	0,6±0,9	86,6±26,4	4,3±1,1	32,0±16,4
MSA-P *(n = 2/1/1)*	4,5±3,5	22,0±14,1	53,0±31,1	2,0±1,4	81,5±50,2	5 (1c)	10 (1c)
LBD *(n = 1/1/1)*	7 (1c)	12 (1c)	29 (1c)	2 (1c)	50 (1c)	3 (1c)	50 (1c)
Atyp PS nfs *(n = 1/1/1)*	1 (1c)	3 (1c)	37 (1c)	1 (1c)	42 (1c)	2 (1c)	80 (1c)
Early onset PD *(n = 2/2/1)*	3,0±2,8	11,0±4,2	30,0±7,1	5,0±7,1	49,0±7,1	2,5±0,7	90 (1c)
Fahr's disease *(n = 1/0/0)*	4 (1c)	7 (1c)	17 (1c)	1 (1c)	29 (1c)	na	na

Figure 4 Baseline UPDRS score of patients with sporadic PD

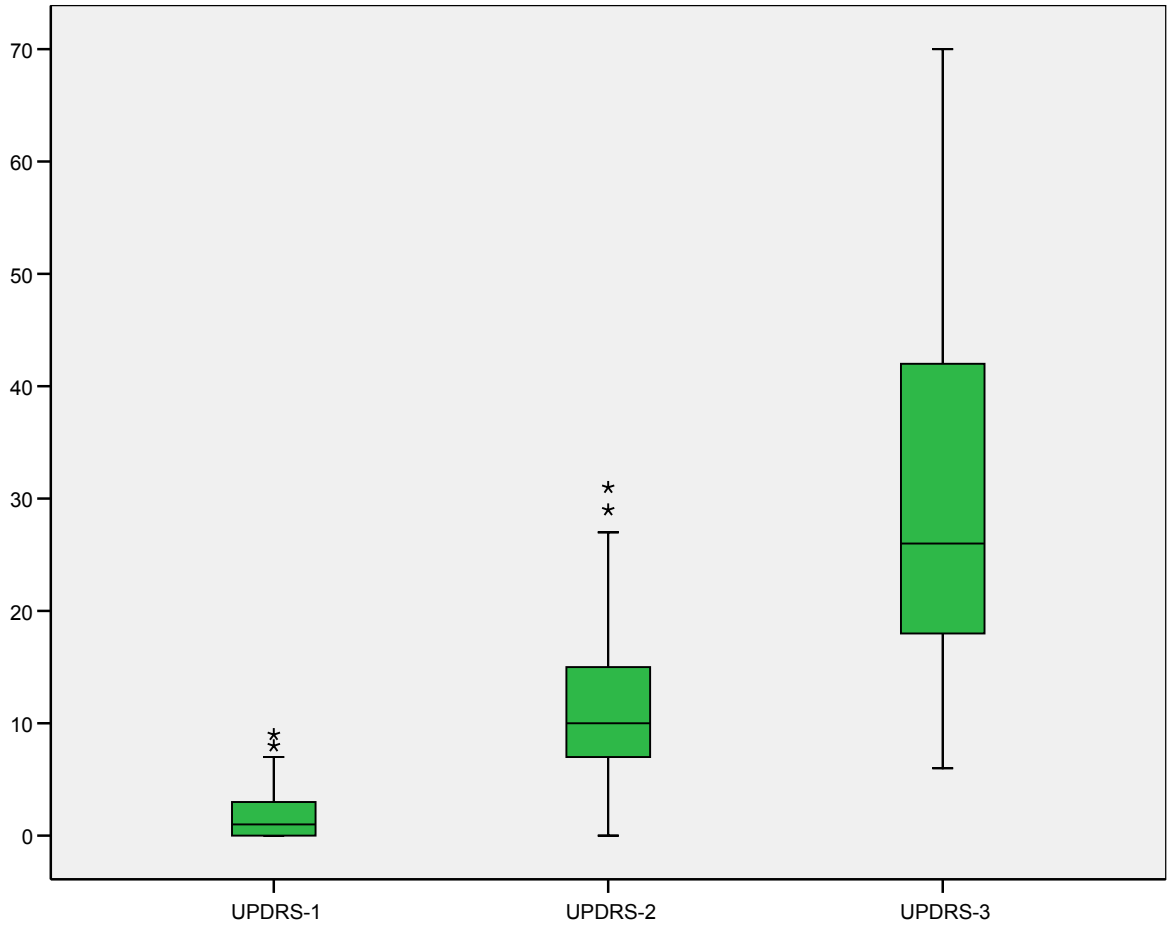


Figure 5 Baseline total UPDRS score in patients with sporadic PD

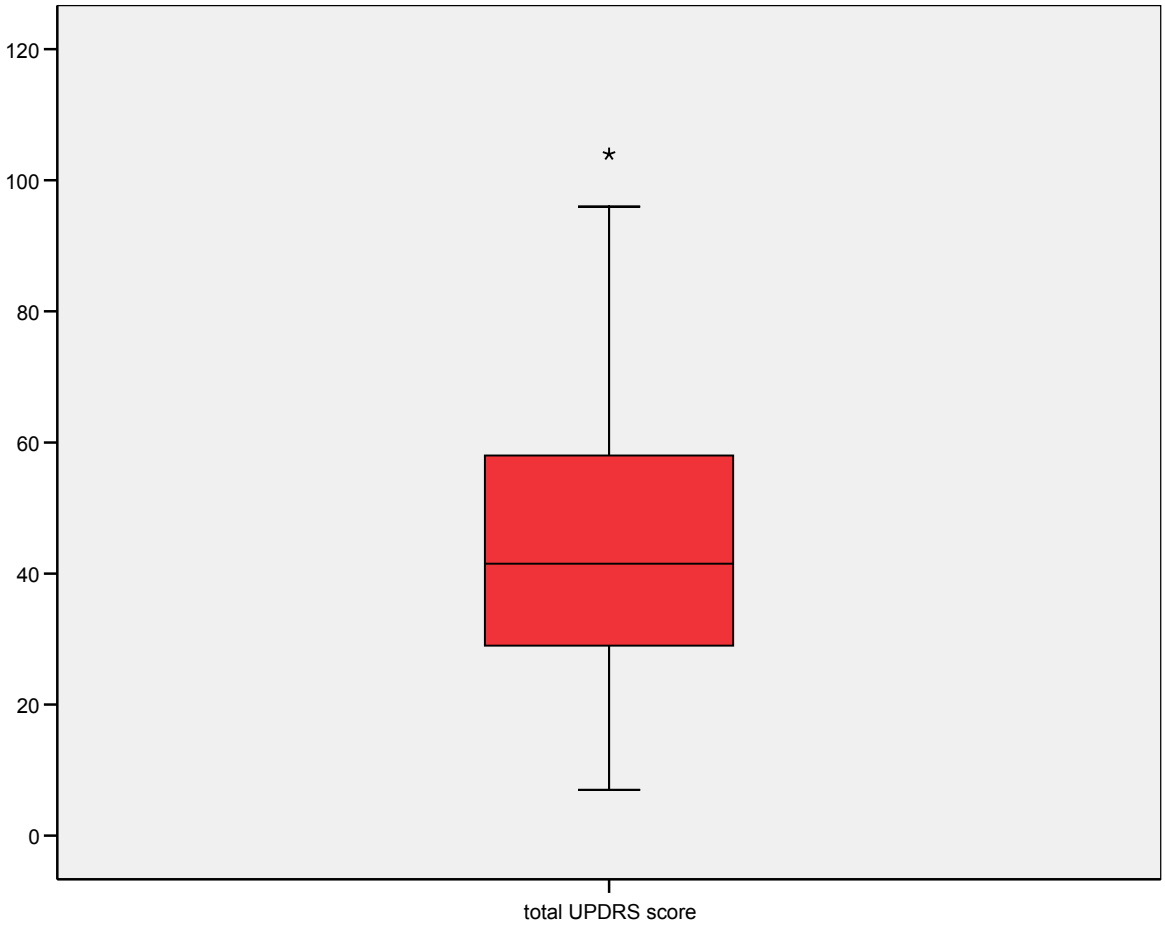


Table 33 Baseline MMSE score in patients wih PDD and DLB

	MMSE
PDD (n = 4)	21,8±2,1
DLB (n = 2)	23,5±2,1

Figure 6 Baseline Hoehn and Yahr score in sporadic PD

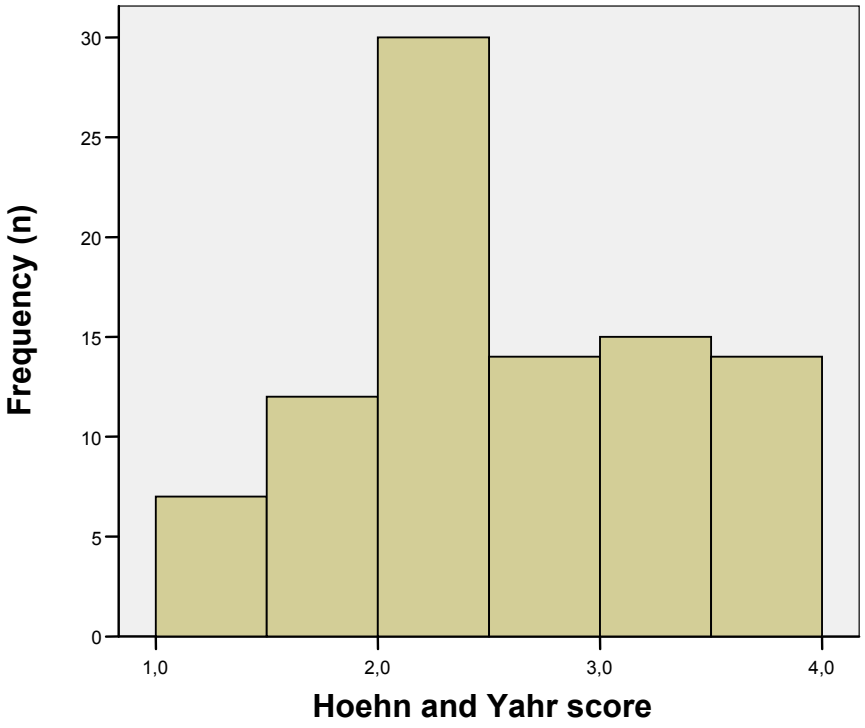
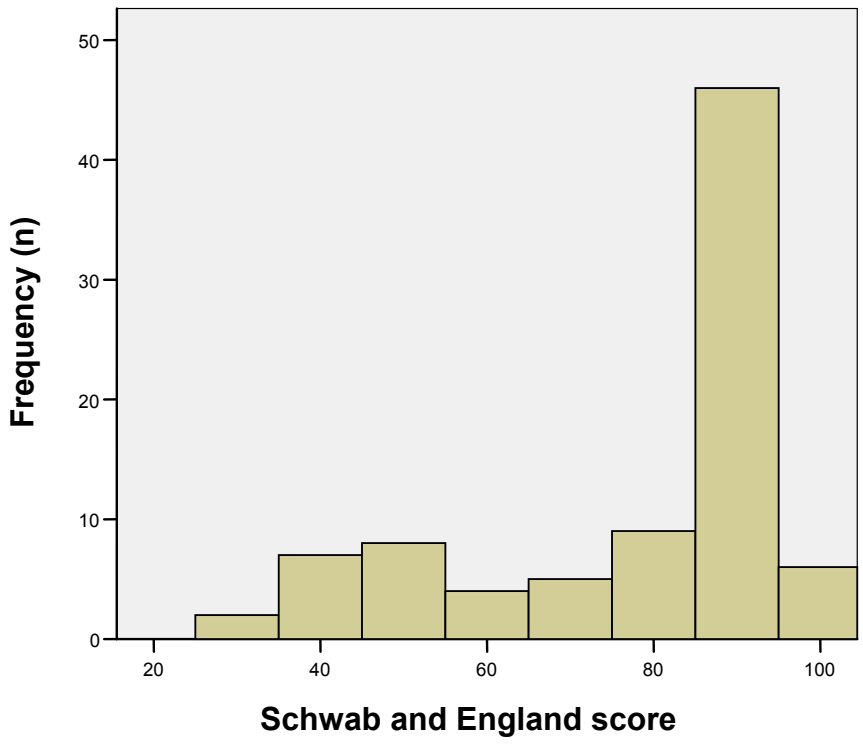


Figure 7 Baseline Schwab and England score in sporadic PD



3.1.5. Previous drug treatment in sporadic PD

Table 34

Overall antparkinsonian drug use		**n**	**%**
Patients naive to antiparkinsonian drugs		22	17,5
previously introduced antiparkinsonian drug		104	100,0
L-Dopa		**n**	**%**
LD + B	Madopar®	45	35,7
LD + CD + Entacapone	Stalevo®	13	10,3
LD + B	Madopar® CR	11	8,7
LD + CD	Sinemt retard®	5	4,0
LD + CD	Sinemet®	4	3,2
LD (L-Dopa), B (Benserazide), C (Carbidopa)			
Dopamine agonists		**n**	**%**
Pramipexole	Sifrol®	30	23,8
Cabergoline	Cabaseril®	15	11,9
Pergolid	Permax®	11	8,7
Ropinirole	Requip®	7	5,6
Rotigotine	Neupro®	2	1,6
total			51,6
COMT Inhibitors		**n**	**%**
Entacapone	Comtan®	3	2,4
Tolcapone	Tasmar®	1	0,8
total			3,2
MAO-B Inhibitors		**n**	**%**
Selegiline	Jumex®	16	12,7
Rasagiline	Azilect®	3	2,4
Selegiline	Selegilin Genericon®	1	0,8
Selegiline	Cognitiv®	2	1,6
Selegiline	Amboneural®	1	0,8
total			18,3
Amantadine		**n**	**%**
	PK-Merz®	16	12,7
	Hofcomant®	5	4,0
total			16,7
Anticholinergic drugs		**n**	**%**
Bornaprine	Sormodren®	5	4,0
Typical neuroleptic drugs		**n**	**%**
Melperone	Buronil®	1	0,8

Atypical neuroleptic drugs		**n**	**%**
Risperidone	Risperdal®	1	0,8
Quetiapine	Seroquel®	2	1,6
total			2,4

Selective serotonine reuptake inhibitors		**n**	**%**
Sertraline	Adjuvin®	1	0,8
Citalopram	Citalopram®	1	0,8
Escitalopram	Cipralex®	5	4,0
Fluoxetine	Fluctine®	1	0,8
Fluoxetine	Fluoxetin®	1	0,8
Sertraline	Gladem®	2	1,6
Paroxetine	Paroxetin®	2	1,6
Citalopram	Pram®	1	0,8
Citalopram	Seropram®	2	1,6
Paroxetine	Seroxat®	4	3,2
Sertraline	Sertralin®	1	0,8
total			16,7

Antidepressive drugs		**n**	**%**
Duloxetine	Cymbalta®	1	0,8
Reboxetine	Edronax®	1	0,8
Maprotiline	Ludiomil®	5	4,0
Mirtazapine	Mirtabene®	3	2,4
Mirtazapine	Remeron®	2	1,6
Amitriptyline	Saroten®	5	4,0
Mianserin	Tolvon®	1	0,8
Trazodone	Trittico®	3	2,4
Trazodone	Trittico retard®	3	2,4
total			19,0

Bezodiazepines		**n**	**%**
Oxazepam	Anxiolit®	1	0,8
Hydroxyzine	Atarax®	1	0,8
Triazolam	Halcion®	3	2,4
Zolpidem	Ivadal®	3	2,4
Bromazepam	Lexotanil®	2	1,6
Oxazepam	Praxiten®	2	1,6
Lorazepam	Temesta®	2	1,6
Alprazolam	Xanor®	2	1,6
Zolpidem	Zoldem®	1	0,8
Flupentixol + Melitracen	Deanxit®	1	0,8
Flunitrazepam	Bromazepam®	1	0,8
total			15,1

	n	%
Number of patients taking at least one Antidepressant drugs	38	30,2
Number of patients taking at least one Benzodiazepine	15	11,9

3.1.6. Concomitant diseases in sporadic PD

Table 35 Concomitant diseases in 126 cases of sporadic Parkinson's disease

Internal medicine	**n**	**%**
Hypertension	25	19,8
Hyperlipidemia	11	8,7
Osteoporosis	10	7,9
Arteriosclerosis	7	5,6
Diabetes mellitus type 2	7	5,6
COPD	7	5,6
Hyperuricaemia	5	4,0
Dysrhythmia	4	3,2
Coronary heart disease	4	3,2
Myocardial infarction	3	2,4

Neoplasia	**n**	**%**
Benign prostate hyperplasia	7	5,6
Prostate cancer	6	4,8
Meningioma	4	3,2
Colon carcinoma	3	2,4
Plasmocytome	1	0,8
Adrenal cortex adenoma	1	0,8
Bladder tumor	1	0,8
Cancer not further specified	1	0,8
Total		19,2

Surgery	**n**	**%**
Degenerative diseases of spine	15	11,9
Arthrosis	6	4,8
Cholecystectomy	4	3,2
Traumatic brain injury	3	2,4
Hysterectomy	3	2,4

Neurology	**n**	**%**
Stroke	10	7,9
Binswanger's disease	7	5,6
Polyneuropathy	6	4,8
Transient ischemic attack	3	2,4

Psychiatry	n	%
Depression	19	15,1
Panic attacks	2	1,6

3.1.7. Previous diagnostic tests in sporadic PD

Table 36 Previous diagnostic tests in 126 cases of sporadic PD

Neurological	n	%
MRI of the head	28	22,2
CT of the head	13	10,3
b-CIT-SPECT	12	9,5
EEG	11	8,7
ENG	10	7,9
Sonography of extracranial brain vessels	10	7,9
Apomorphine-test	7	5,6
Sonography of intracranial brain vessels	6	4,8
EMG	5	4,0
IBZM-SPECT	5	4,0
FDOPA PET	5	4,0
MRI of cervical vertebrae	3	2,4
CT of whole spine	3	2,4
MRI of whole spine	2	1,6
X-ray of spine	1	0,8
Lumbar puncture	2	1,6
EOG	2	1,6
neuropsychological testing	2	1,6
FDG-PET	1	0,8
Tremor-analysis	1	0,8

Internal medicine	n	%
Routine blood count, clinical biochemistry	12	9,5
ECG	9	7,1
X-ray of thorax	9	7,1
Transthoracic echocardiography	7	5,6
Thyroid hormone status	3	2,4
Sonography of abdomen	2	1,6
24h-ECG	2	1,6

3.1.8. Gender issues in early PD

Gender issues were exmined in patients with early sporadic PD. Considered variables were age at onset, age at first visit, latency and baseline severity scores (UPDRS, modified Hoehn ans Yahrs score and Schwab and England score). Results are displayed in Table 37 and 38, given as mean in years ± SD.

Table 37 Gender issues on Age at onset, Age at first visit and Latency in sporadic PD

	male	female
Age at onset	62,8 ± 10,3	63,2 ± 10,0
Age at first visit	68,6 ± 9,3	68,1 ± 9,7
Latency	5,8 ± 5,5	4,1 ± 3,9

Table 38 Gender issues on baseline UPDRS, Hoehn and Yahr and Schwab and England score in sporadic PD

	male	female
UPDRS 1	2,1±0,3	2,0±0,4
UPDRS 2	12,1±1,2	10,3±1,1
UPDRS 3	31,6±2,3	32,2±2,8
UPDRS 4	0,3±0,8	1,0±0,4
total UPDRS	46,1±3,5	45,4±3,9
HY	2,5±0,1	2,4±0,2
SE	76,9±2,9	78,9±3,4

3.1.9. Clinical features of 46 cases with ET and comparison to 16 cases with PD and ET

Table 39 Clinical features of 46 cases with essential tremor

Age at onset (n=39)	43,7±22,7	
Age at first visit (n=46)	61,2±15,2	
Latency (n=39)	16,4±17,7	
Gender	**n**	**%**
male	30	65,2%
female	16	34,8%
Hereditary	**n**	**%**
positive	27	61,4
negative	17	38,6

Figure 8 Age at onset in ET

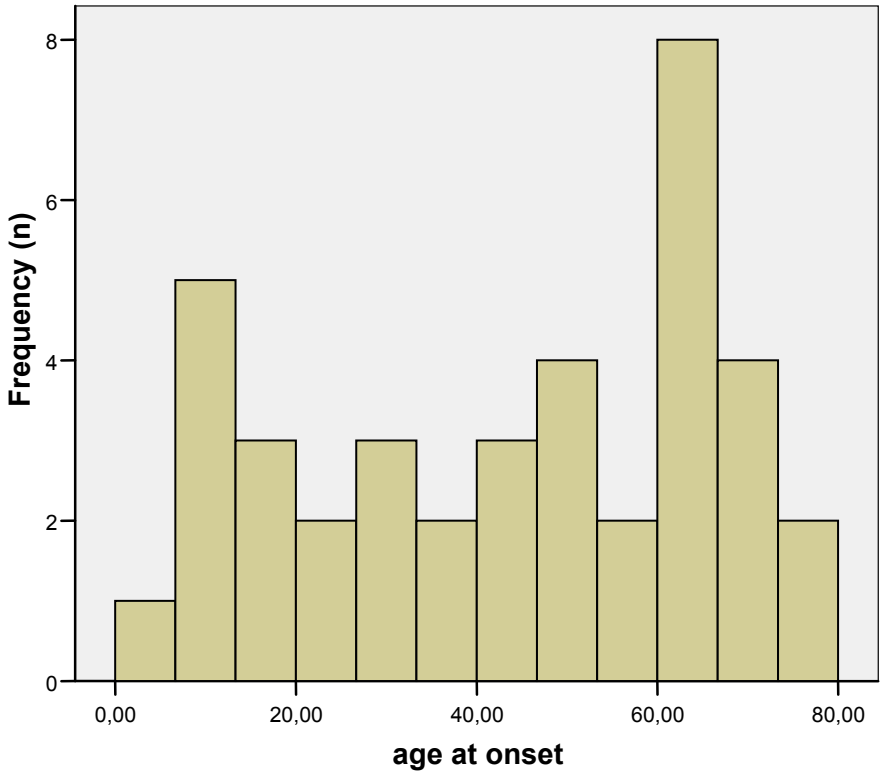
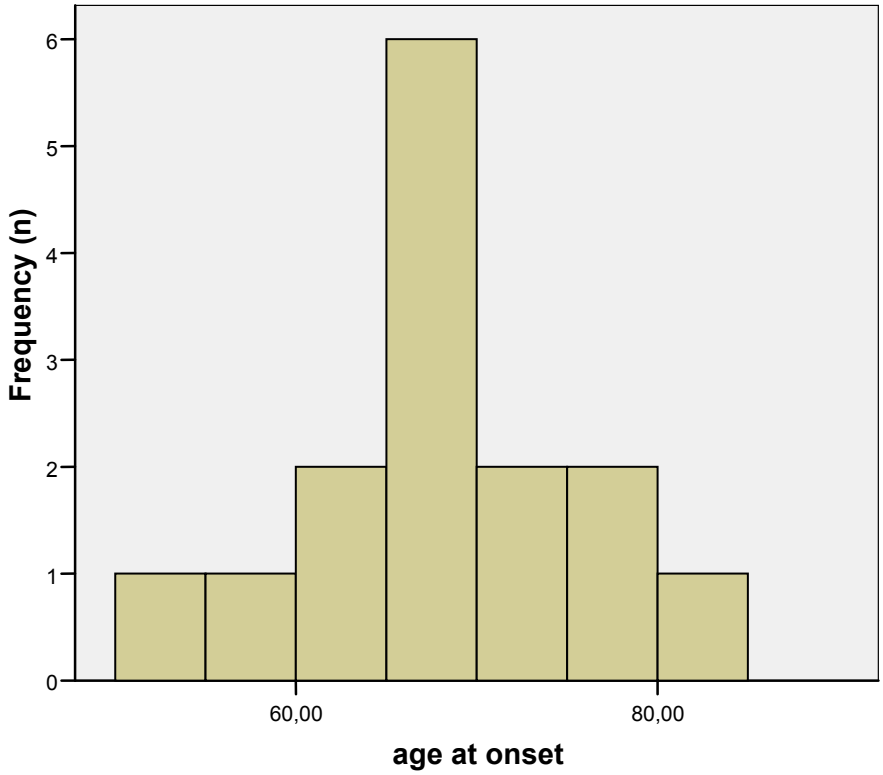


Figure 9 Age at onset in PD + ET



3.2. Questionnaire

Data derived from the questionnaires of 24 patients with pakinsonism were analysed. The observed variables are given as frequency tables below.

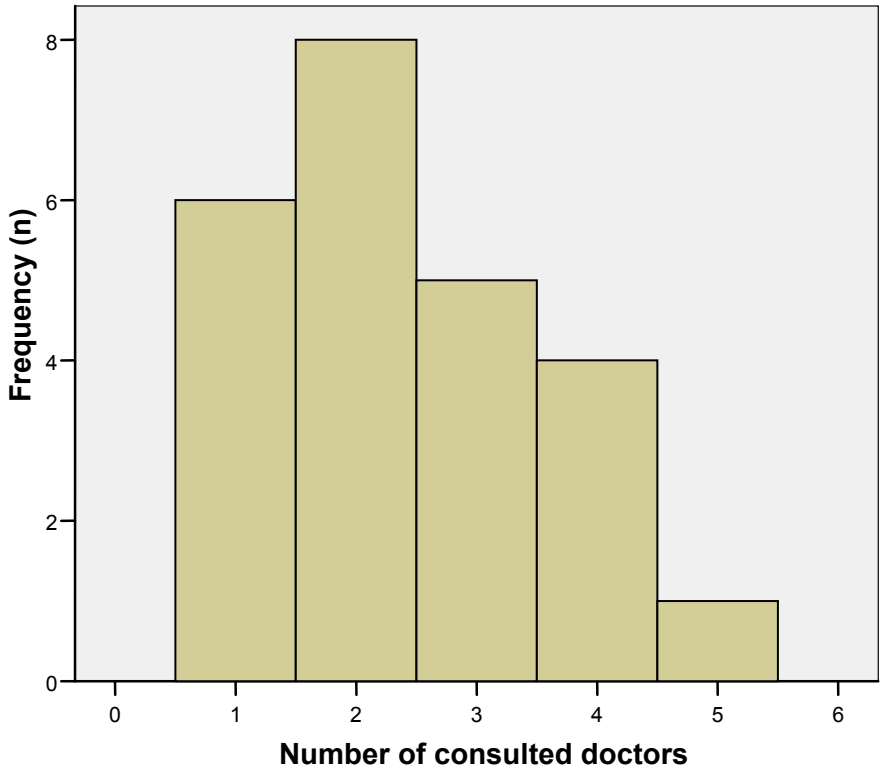
Table 40 Initial motor and non motor symptoms derived from the questionnaire

	n	%
tremble	16	66,7
slowing down of movements	16	66,7
change of gait	15	62,5
increased daytime sleepiness	13	54,2
handwriting slow or small	13	54,2
clumsiness of hands	13	54,2
shoulder pain or joint pain	11	45,8
dizziness	10	41,7
rising from chair is difficult	8	33,3
impairment of olfaction	8	33,3
constipation	7	29,2
changes of mood	7	29,2
change in sleep behaviour	6	25,0
dry eye	6	25,0
falls	6	25,0
muscular stiffness	6	25,0
change in speech	6	25,0
missing armswing when walking	5	20,8
increased fear	4	16,7
urinary incontinence	3	12,5
problems in swimming	2	8,3

Table 41 Previously consulted doctors due to disease-related symptoms

	n	%
Neurology	20	80
General practitioner	15	60
Orthopedics	7	28
Otolaryngology	6	24
Internal medicine	6	24
Psychiatry	4	16
Chiropractic	0	0

Figure 10 Number of previously consulted doctors due to disease-related symptoms



The mean number of previously consulted doctors due to disease-related symptoms in the 24 observed patients with parkinsonism was 2,4 ± 1,2.

Table 42 Prevalence of selected diseases in the family of patients with parkinsonism

	n	%
Stroke	5	20,8
Heart attack	5	20,8
RLS (Restless legs syndrome)	3	12,5
Impairment of olfaction	2	8,3
Parkinson	2	8,3
Sleep apnea syndrome	2	8,3
Alzheimer's disease	1	4,2
Not further defined movement disorder	1	4,2

Table 43 Prevalence of selected diseases in patient history

	n	%
High blood pressure	11	45,8
Elevated blood lipids	8	33,3
Hypothyroidism	7	29,2
RLS (Restless legs syndrome)	6	25,0
Cardiac arrhythmia	5	20,8
Diabetes	4	16,7
Stroke	3	12,5
Heart attack	2	8,3
Polyneuropathy	2	8,3
Gout /elevated uric acid	2	8,3

4. Discussion

The study demonstrates that the early phase of PD is characterized by several important peculiarities. In the past years many retrospective studies investigated the issue of early symptoms in PD. The search for a neuroprotective or disease-modifying agent became an emerging field of interest as well. Despite the growing knownledge upon the early phase of PD, there is at present no biomarker available that could definitely predict PD. However, in familiar forms of PD a genetic cause can be identified [80] and moreover, some SNPs are believed to cause susceptibility to PD [81, 100]. Furthermore, no agent is currently available that is able to slow or hamper neurodegeneration definitely in PD patients. Unfortuantely, patients with PD are still seen at the outpatients' department for movement disorders mainly at an intermediate stage and not at the beginning of their disease, when core motor symptoms are well established and a large number of dopaminergic neurons are already lost.

Latency, disease severity and gender issues

The mean latency in sporadic, non-fluctuating PD was 5,1 years and severity scales state that the majority of patients attend the outpatients' department for movement disorders during an intermediate disease stage, with a mean total UPDRS of 44,3, a mean modified Hoehn and Yahr score of 2,4 and a Schwab and England score of 78,1. The reason for this rather long latency could be the imperception of non-motor symptoms at disease onset, the slight motor impairments which could be misinterpreted as age-related symptoms and the prior consultation of settled physicians such as general practitioners, orthopedics and neurologists. However, putative neuroprotective or disease modifying drugs should be introduced as early as possible to provide most benefit for PD patients.

Gender issues were examined in patients with sporadic PD. In this study, a slight male predominance could be demonstrated (61,1% male, 38,9% female, M:F ratio 1,57). This finding supports the higher incidence rate of PD in males demonstrated by other studies: Among 14 studies conducted in Western populations, the M:F ratio was 1,58. Moreover, it is currently hypothesized that the higher incidence in males affects particularly the oldest age group. Possibly, one factor causing the gender difference could be the neuroprotective

property of female steroid hormones. [206] Accordingly, a recent study demonstrated an increased risk for parkinsonism in women who underwent oophorectomy before menopause [207]. Nevertheless, in contradiction to these findings, a female preponderance of PD was described by Kimura H et al. [208] among the Japanese population, arguing against the 'hormone hypotheses'. In conclusion, the issue of gender differences in PD incidence remains a matter of debate.
In this study no gender differences in baseline severity scores could be assessed. The sole observed difference was a slightly shorter mean latency in female than in male patients (4,1 yrs versus 5,8 yrs respectively) which could not be interpreted as significant. This finding argues against a major role of estrogen as a neuroprotective factor in PD because females are not more severe affected at baseline and there is no significant delay in age at onset for females compared to male patients.

Features of clinical subgroups of parkinsonism

Several findings can be drawn from the distribution of clinical subgroups in patients who present with parkinsonism. 242 patients were enrolled in the study and they constitute a representative sample of patients with parkinsonism.

Approximately half of the patients could be diagnosed as sporadic PD at their first visit. Taking together the relative frequencies of sporadic PD, PD with motor fluctuations, PD + ET, PDD and early onset PD one yields a relative frequency of 71,9%. Around every tenth patient had a secondary cause for parkinsonism (DIP 6,2%, VP 3,3%, Fahr's disease 0,8%). An atypical Parkinson-Syndrome (PSP 2,1%, MSA 2,1%, LBD 0,8%) was seen in 5% of patients presenting with parkinsonism. Thus, in this study population PD is the major cause for parkinsonism, whereas secondary and atypical PS are less common. Only 12,8% of patients could not be classified at their first visit. The later diagnosis in this group was mainly DIP. This finding indicates that making the diagnosis of DIP can be difficult, especially if the patient is not currently taking DRBAs and is not sure about previous treatment.

Around every tenth patient presenting with parkinsonism shows advanced PD with motor fluctuations. These patients show a mean latency of 12,7 yrs, which is more than double as high as in the group of sporadic, non-fluctuating PD (5,1 yrs). Moreover, the age at onset in

PD patients with motor fluctuations is earlier than in sporadic, non-fluctuating PD (55,9 yrs versus 62,9 yrs respectively). This finding is in line with the observation that an early onset of PD is associated with an increased risk of the development of motor fluctuations [177].

In this study population 6,6% of all patients presenting with parkinsonism show PD in combination with ET. Thus, PD + ET is the most prevalent clinical subtype after PD with motor fluctuations (9,5%) and twice as frequent as VP (3,3%). When taking together all patients with PD in the above described manner, one yields a relative frequency of 9,2% for patients with PD + ET. Thus, it could be demonstrated that around every tenth patient with PD has concomitant ET. Similarly, Tan EK et al. [215] found a prevalence of 5,9% of ET in 204 patients with PD in an Asian population.

This high prevalence indicates that there could be a relationship between ET and PD and a coexistance by chance seems unlikely. Recent studies argue that ET could be a risk factor for PD [201, 202]. Actually, a recently published population based cohort study of 3813 older people in central Spain revealed a 4-5 fold higher risk for the development of incident PD and a 3-4 fold increased risk for DIP in ET patients compared to age-matched controls without ET [209]. Moreover, Tan EK et al. [215] demonstrated in a cases control study of 204 patients with PD in an Asian population that patients with PD are 5-10 times more likely to have ET compared to controls.

Furthermore, evidence for a link between ET and PD can be shown at a pathological and radiological point of view: LBs are present in ET predominately in the locus ceruleus in around 25% of ET patients (LBVET) [141, 209]. Moreover, Isaias IU et al. [218] found that some ET patients present mild abnormalities of striatal dopamine transporters and a typical PD-like uptake loss.

Clinical features of PD with concomitant ET have been described previously in the literature. Minen et al. [202] found an identical gender distribution in 53 patients with PD + ET compared to PD, favouring male gender (67,9%), whereas gender distribution in ET was equally distributed. In contradiction, this study yielded a male predominance in ET (65,2 %) and sporadic PD (61,1%) as well. Similarly, Luis et al. found a male predominance of 57,2% in 128 patients with ET and Tan EK et al. [216] found a male predominance of 73,5% in 19 patients with childhood onset ET. These results indicate a male predominance in ET. Interestingly, in the 16 cases of PD + ET analysed in this study, a female predominance (56,3%) was found. This raises the question if the gender ratio given in these patients remains constant in larger study population.

Tan EK et al. [215] argue that patients with PD and ET have a lower dose of LD and a later age at disease onset compared to PD patients without ET. Accordingly, this study demonstrated that the mean age at onset in PD + ET was later than in spordic PD (67,9±8,1 versus 62,9±10,2 respectively). Further, the distribution of age at onset in PD + ET seems to be one-peaked (65-70 yrs), whereas ET seems to have three peaks (youth: 5-20 yrs, medium age: 40-55 yrs, advanced age: 60-67 yrs). It is known that the occurrence of ET is not restricted to an advanced age, as demonstrated by Tan EK et al [216] who showed a frequency of 15,5% and a mean age at onset of 10,8 ± 4,1 years for childhood onset ET among 120 patients with ET for an Asian population. In conclusion, it could be argued that ET starting at an advanced age is a risk factor for developing PD. Moreover, if PD + ET is a distinct disease with a clear-cut pathogenetic mechanism and not just an unlucky double-hit, one could actually use the term PD starting with isolated postural tremor.

Adverse drug reactions were responsible for parkinsonism in 6,2% of patients and were mainly caused by typical neuroleptic drugs. Patients with DIP show a very short latency (1,9 yrs) which could be due to, first, the acute, disturbing onset of symptoms and second, the expertise of the treating psychiatric.

VP is responsible for 3,3% of all cases with parkinsonism. These patients show the latest age at onset (73,5 yrs) of all patients who present with parkinsonism and a very short mean latency of 3,3 yrs, probably due to an acute onset of disabling symptoms that usually do not respond to L-Dopa. The findings are in line with the current literature that claims a prevalence for VP of 3-6% and a predominant affection of elderly patients [131, 132].

Even patients with advanced PD could be detected in the study population, mainly consisting of patients with motor fluctuations. Patients presenting with PDD made up a relative frequency of 2,9% of all patients presenting with parkinsonism. This low frequency could be due to a relative late onset of dementia in PD, thus, rather occuring in cases that were not enrolled in this study. Patients with PDD show a late age at onset (69,6 yrs) and a mean MMSE score of 23,8, comparable to that in LBD (23,5). The question if the disease onset in PDD is later than in PD without dementia can not be clarified due to the small number of PDD cases enrolled in this study.

Atypical PS (PSP, MSA, LBD, CBD) was diagnosed in 5% of all patients with parkinsonsim at their first visit. In the study population of 242 patients 5 cases with PSP, 5 cases with MSA and 2 cases with LBD were observed. Patients with an atypical PS show a shorter latency than patients with PD. This could be due to the rapid progression and relative non-responsiveness to L-Dopa. In general, these two features and additionally acute onset of symptoms seem to have a negative impact on latency, as demonstrated in cases of VP and DIP as well.

Drug treatment

Previous treatment with antiparkinsonian drugs was present in 82,5% of patients with sporadic PD, thus, the majority of patients is not drug-naive when seeing a skilled neurologist in movement disorders for the first time. Frequently used drugs were conventional LD and DAs. Interestingly, Stalevo®, which should be confined to patients with motor fluctuations, was used in 10,3% of patients, wheras MAO-B inhibitors, suited for early PD patients due to its putative disease-modifying properties, was prescribed in 18,3%, comparable to the use of amantadine (16,7%). Other antiparkinsonian treatment options were rarely used. Intriguingly, a large proportion of patients with sporadic PD were taking antidepressants: SSRIs were taken in 16,7% and antidepressant drugs other than SSRIs in 19,0%. In summary, 30,2% of all patients with sporadic PD were taking at least one antidepressant drug, and 11,9% were taking a benzodiazepine. These figures indicate that disturbances in mood and sleep are highly present in early PD.

Diagnostic tests

Diagnostic tests performed in patients with sporadic PD before their first visit at the outpatients' department mainly consist of conventional brain imaging. MRI was available in 22,2%, CT in 10,3% of cases. This data is useful to exclude some secondary cause of parkinsonism. Other frequently performed diagnostic tests prior to first visit were EEG, ENG and EMG. Imaging suited to confirm the clinical diagnosis of PD (b-CIT SPECT) or atypical PS (IBZM-SPECT) were previously performed in 9,5% and 4,0% respectively.

Previously consulted doctors due to disease-related symptoms

The vast majority of patients presenting with parkinsonism at the outpatients' department for movement disorders was previously treated by different physicians due to disease-related symptoms, as demonstrated by results of the questionnaire. The mean number of consulted doctors was 2,4 and the most frequently consulted were neurologists and general practioners. Patients also attended othopedics, most likely due to shoulder pain or gait disturbances.

Initial symptoms

Major initial motor symptoms, related to all 126 cases of sporadic PD, were tremor (63,5%), clumsiness (23%), general slowing down (20,6%), gait disturbences (14,3%), rigidity/stiffness (13,5%), and micrograghia (10,3%). These results confirm the long known fact that tremor is not a prerequisite for the diagnosis of PD, first described by Charcot in the 19th century [2]. The subjective feeling of general slowing down as an onset symptom refers to bradykinesia which is the cardinal symptom of PD and a prerequisite for the diagnosis. The reason why only around one of five patients describes bradykinesia as an onset symptom could be explained by its slight or imperceptable, subthreshold occurrence at baseline.
These findings are comparable to that of another recent study: O'Sullivan et al. examined retrospecively the prevalence of motor and non-motor symptoms as presenting complaints in 433 cases of pathologically-proven PD in the UK [170]. They obtained clinical data from general practitioners, who made an entry for all symptom complaints for every consultation. They found temor in 45,3%, bradykinesia in 31,4%, rigidity in 10,3% and unspecified gait disturbances in 11,8% as first symptoms of PD.
Furthermore, in this study of 126 patients with sporadic PD it could be demonstrated that limping gait (7,1%) and decreased armswing (5,6%) was an onset symptom and early recognized by the patients or their relatives. Moreover, lower limb tremor was an onset symptom in 4,8% of cases.
The subjective feeling of weakness, reported by 4,8% of patients, is possibly related to fatigue or depression and less likely to motor impairment. This symptom was already recognized by James Parkinson who used the term 'lessened muscular power' in his famous treatise 'An essay on the Shaking Palsy' in 1817 [142]. Fatigue in PD can be devided into physical and

mental fatigue. A recent study by Lou JS [213] demonstrated that subjective mental and physical fatigue is more frequent in PD patients than in controls.
Initial sensory symptoms in patients with sporadic PD were pain (6,3% shoulder/neck pain, 4% pain at other locations) and paraesthesias (1,6%). Shoulder pain could easily be misinterpreated as arthrosis and lead to the consultation of an orthopaedic. Neck pain could relate to coat hanger pain in orthostatic hypotension (OH), but this seems to be unlikely in the observed cases, as OH was not present and is rather confined to later stages of PD.
Among the most frequently reported initial non-motor symptoms besides pain was the category depression/anxiety/mood disorders (4,8%) and sleep disturbences (2,4%). Actually, the prevalence of these symptoms could be even higher when considering the widespread use of antidepressants and benzodiazepines as mentioned above. O'Sullivan et al. found pain in 15% as the most frequent presenting non-motor complaint. Unfortunately, pain was not further specified in this study, thus no figure for shoulder pain is given. Anxiety or depression was a presenting complaint in 2,5% in the study of O'Sullivan et al. [170] Other authors propose a prevalence of mood disturbances predating parkinsonism of approximately 20% [162]. This range in prevalence could be explained by the different ways the authors used to assess mood disturbances. It should also be considered that 'depression' in premotor PD might have its own peculiarities and could show some features that are not covered by conventional diagnostic criteria like the DSM-IV and the ICD-10. Actually, the concept of subthreshold depression has been developed which includes symptoms that overlap with PD: fatigue, sleep difficulties, appetite dysfunction and concentration difficulties [212]. However, the pathogenesis of depression in PD is still a matter of debate.
In conclusion, results from this study rather meet the figure of 20% for mood disturbances mentioned above, when considering how many patients are taking antidepressants or have the diagnosis of depression at baseline.

Initial autonomous symptoms were rare in sporadic PD. Nevertheless, the most frequent was constipation, which is believed to be a risk factor for PD and occurs with a frequency of 28-61% in manifest PD [123]. Actually, the relative absence of autonomous features at onset in PD confirms that the early occurrence of these symptoms is a Red Flag, indicating atypical parkinsonism. Therefore, on the one hand, the low frequency of autonomous features at onset could be a clinical hallmark of sporadic PD, on the other hand this state could be explained by a subtreshold, subclinical state in the early phase of PD, so that the patient is just not aware of the slight manifestation of the symptom.

Another explanation for missing early non-motor features could be that patients do not relate these symptoms to their movement disorder, thus, they do not complain about these features at their neurologist. Thus, some early non-motor symptoms that are imperceptible or difficult to perceive for patients could be examined by clinical testing, e.g. sympathetic dysfunction via measurement of heart rate variability or sleep disturbences via PSG. Nevertheless, this testing is yet not routine and is confined to clinical studies because they yield no biomarker that could predict incident PD definitely.

The questionnaire for patients with parkinsonism was developed as an extension to the retrospective study with the intention to assess properties of the early disease stage.
Most frequent initial symptoms of the motor category of the questionnaire were trembling, slowing down of movements and change of gait, each of them present in approximately two third of all patients with parkinsonism. Moreover, muscular stiffness, a core feature in a subset of patients with parkinsonism, was less frequently reported (25%). Interestingly, clumsiness and slow or small handwriting was present in around half of the patients.
Among the most frequent non-motor symptoms assessed by the questionnaire were increased daytime sleepinessness and pain, each of them present in approximately 50% of all patients. The frequencies of symptoms like impairment of olfaction, constipation, changes of mood, dry eye and changes of speech was intermediate, ranging between 25-35%.
The questionnaire allows easily checking for all premotor and motor symptoms of interest. Patients were able to recollect initial symptoms and their subjective judgement on impairment could serve as a clue for parkinsonism. Thus, questionnaires based on clinical symptoms could be used as a screening tool in a population at risk for developing PD. They could be handed out to relatives of PD patients, individuals with idiopathic hyposmia and patients with RBD.

Concomitant diseases

The analysis of concomtant diseases in sporadic PD patients yielded no increase in diseases concerning the field of internal medicine compared to individuals without PD. Interestingly, neoplasias were frequently present in patients with sporadic PD, affecting around every fith patient. The most frequent were benign prostate hyperplasia (5,6%) and prostate cancer (4,8%) which are most likely related to the advanced age of the analysed patients. Other

retrospectively assessed neoplasias were incidental, non-symptomatic meningioma (3,2%) and colon carcinoma (2,4%).
The association between meningioma and parkinsonism relies only on case reports [219-223]. In these rare cases the patients developed hemiparkinsonism at the contralateral side. The patients showed bradykinesia, resting tremor, rigor and gait disturbances with no or poor LD-responsiveness. Parkinsonism resolved completely after neurosurgical intervention. Symptoms resulting from increased intracranial pressure like focal motor and sensory deficits and seizures can support the diagnosis, although these symptoms are not obligate. In these cases, parkinsonism is believed to be due to direct compression of the BG or interference of BG-circuitry by the meningioma and the surrounding parenchyma edema. Another explanation could be a transtentorial herniation causing midbrain compression which could impair blood flow to the STN via the posterior cerebral artery.
A recent clinicoradiological study of 5033 individuals in Japan using MRI demonstrated a prevalence of incidental meningioma of 0,28% [210]. Vernooij et al. analyzed 2000 individuals in the Netherlands and found a prevalence for incidental meningioma of 0,9% [211]. Results from this study indicate a higher prevalence for incidental meningioma in sporadic PD than in individuals without PD when taking the two studies above as reference. Actually, this figure could be even higher because data from conventional imaging was available only in a subset of patients at baseline. Thus, it would be of interest to screen PD patients for incidental, asymptomatic meningioma to define the exact prevalence. However, an underlying pathogenetic mechanism that would link the occurrence of meningioma to PD is yet unknown.

There is a debate if LD therapy accelerates melanoma growth and if the incidence of melanoma is increased in patients with PD [204]. However, the analysed cases showed no increase of melanoma-incidence in PD patients, indicating that dopaminergic therapy and PD itself are not implicated in the genesis of melanoma.

It is noteworthy that certain genes are implicated in both oncogenesis and neuronal dysfunction. These include parkin as a possible tumor suppressor gene. The mutation of this gene is responsible for 50% of early onset PD and is contributing to tumorigenesis in mitotically active cells. Parkin is inactivated in breast, ovarian, lung and liver cancers and certain leukemias. [214]

Degenerative diseases of the spine and arthrosis were a common finding among the study population, which could propably partly relate to motor features of PD like flexed posture and gait disturbences. Neurological diseases were mainly due to vascular genesis and consisted of stroke, transient ischaemic attacks and vascular leucoencephalopathy. Intriguingly, 15,1% of patients had the diagnosis of depression and 30,2% were taking an antidepressive drug, indicating that this symptom plays an important role in the early phase of PD.

Results from the questionnaire yielded a high prevalence of RLS in patients with parkinsonism (25%) and their relatives (12,5%). This figure could be explained by several reasons: The early occurrence of PLMS in early PD was described previously [179, 180]. This state could be easily mixed up with RLS. Furthermore, calf pain could mimic true RLS in PD patients. Some PD patients could also have secondary RLS. The majority of PD patients got dopaminergic drugs prior to their visit at the outpatients' department, therefore symptoms of RLS should be masked by these agents. Thus, the true prevalence of primary RLS and its relationship to sporadic PD remains to be elucidated.

According the results from the questionnaire, approximately 10% reported that cardiac arrhythmias were present, whereas this symptom was a rare finding in the retrospective study. Probably, this could be explained by the fact that this state was not assessed by the examining neurologist. Nevertheless, the assumption that dysrhythmias due to cardial sympathetic dysfunction are more frequent in PD patients than in age and gender matched controls is tempting. Thus, further analysis of ECG data and heart rate variability in PD patients could be promising.

Conclusion

Conclusion: The majority of patients was found in an intermediate disease stage and was not naive to dopaminergic drugs when seen by a specialist for the first time. Frequently retrospective derived early non-motor symptoms in sporadic PD were depression, sleep disturbences and shoulder/neck pain. Around one third of patients were taking an antidepressant drug and around every tenth patient was taking a benzodiazepine in the early phase of PD. Besides the cardinal motor features of PD, highly prevalent early motor symptoms were clumsiness, micrographia, limping gait and decreased armswing. The most

frequently availabe diagnostc tests at the patients' first visit at the outpatients' department were conventional brain imaging data (magnetic resonance imaging, computed tomography). Besides the core issue of this study, a high prevalence of PD with concomitant diagnosis of essential tremor was demonstrated, accounting for around every tenth patient with PD. Furthermore, it was demonstrated that PD patients with motor fluctuations were younger at disease onset than those without fluctuations. Actually, the early phase of PD is usually rather a domain for genereal practitioners and settled neurologists, whereas, unfortunately, only the intermediate disease stage is confined to the neurologist skilled in movement disorders. Nevertheless, watchful waiting and permitting motor features to develop is not an option in early PD, as this is the time when putative disease-modifying agents should take action.

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Appendix A Unified Parkinson's disease rating scale (UPDRS)

I. Mentation, Behaviour and mood

1. Intellectual Impairment
0 = None.
1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.
2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.
3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.
4 = Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all.

2. Thought Disorder (Due to dementia or drug intoxication)
0 = None.
1 = Vivid dreaming.
2 = "Benign" hallucinations with insight retained.
3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.
4 = Persistent hallucinations, delusions, or florid psychosis. Not able to care for self.

3. Depression
1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.
2 = Sustained depression (1 week or more).
3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).
4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. Motivation/Initiative
0 = Normal.
1 = Less assertive than usual; more passive.
2 = Loss of initiative or disinterest in elective (nonroutine) activities.
3 = Loss of initiative or disinterest in day to day (routine) activities.
4 = Withdrawn, complete loss of motivation.

II. Activities of daily living (for both "on" and "off")

5. Speech
0 = Normal.
1 = Mildly affected. No difficulty being understood.
2 = Moderately affected. Sometimes asked to repeat statements.
3 = Severely affected. Frequently asked to repeat statements.
4 = Unintelligible most of the time.

6. Salivation
0 = Normal.
1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.

2 = Moderately excessive saliva; may have minimal drooling.
3 = Marked excess of saliva with some drooling.
4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing
0 = Normal.
1 = Rare choking.
2 = Occasional choking.
3 = Requires soft food.
4 = Requires NG tube or gastrotomy feeding.

8. Handwriting
0 = Normal.
1 = Slightly slow or small.
2 = Moderately slow or small; all words are legible.
3 = Severely affected; not all words are legible.
4 = The majority of words are not legible.

9. Cutting food and handling utensils
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can cut most foods, although clumsy and slow; some help needed.
3 = Food must be cut by someone, but can still feed slowly.
4 = Needs to be fed.

10. Dressing
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Occasional assistance with buttoning, getting arms in sleeves.
3 = Considerable help required, but can do some things alone.
4 = Helpless.

11. Hygiene
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Needs help to shower or bathe; or very slow in hygienic care.
3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
4 = Foley catheter or other mechanical aids.

12. Turning in bed and adjusting bed clothes
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can turn alone or adjust sheets, but with great difficulty.
3 = Can initiate, but not turn or adjust sheets alone.
4 = Helpless.

13. Falling (unrelated to freezing)
0 = None.
1 = Rare falling.
2 = Occasionally falls, less than once per day.
3 = Falls an average of once daily.

4 = Falls more than once daily.

14. Freezing when walking
0 = None.
1 = Rare freezing when walking; may have starthesitation.
2 = Occasional freezing when walking.
3 = Frequent freezing. Occasionally falls from freezing.
4 = Frequent falls from freezing.

15. Walking
0 = Normal.
1 = Mild difficulty. May not swing arms or may tend to drag leg.
2 = Moderate difficulty, but requires little or no assistance.
3 = Severe disturbance of walking, requiring assistance.
4 = Cannot walk at all, even with assistance.

16. Tremor (Symptomatic complaint of tremor in any part of body.)
0 = Absent.
1 = Slight and infrequently present.
2 = Moderate; bothersome to patient.
3 = Severe; interferes with many activities.
4 = Marked; interferes with most activities.

17. Sensory complaints related to parkinsonism
0 = None.
1 = Occasionally has numbness, tingling, or mild aching.
2 = Frequently has numbness, tingling, or aching; not distressing.
3 = Frequent painful sensations.
4 = Excruciating pain.

III. Motor examination

18. Speech
0 = Normal.
1 = Slight loss of expression, diction and/or volume.
2 = Monotone, slurred but understandable; moderately impaired.
3 = Marked impairment, difficult to understand.
4 = Unintelligible.

19. Facial Expression
0 = Normal.
1 = Minimal hypomimia, could be normal "Poker Face".
2 = Slight but definitely abnormal diminution of facial expression
3 = Moderate hypomimia; lips parted some of the time.
4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at rest (head, upper and lower extremities)
0 = Absent.
1 = Slight and infrequently present.
2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently

present.
3 = Moderate in amplitude and present most of the time.
4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of hands
0 = Absent.
1 = Slight; present with action.
2 = Moderate in amplitude, present with action.
3 = Moderate in amplitude with posture holding as well as action.
4 = Marked in amplitude; interferes with feeding.

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)
0 = Absent.
1 = Slight or detectable only when activated by mirror or other movements.
2 = Mild to moderate.
3 = Marked, but full range of motion easily achieved.
4 = Severe, range of motion achieved with difficulty.

23. Finger Taps (Patient taps thumb with index finger in rapid succession.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

24. Hand Movements (Patient opens and closes hands in rapid succesion.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches.)
0 = Normal.

1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

27. Arising from Chair (Patient attempts to rise from a straightbacked chair, with arms folded across chest.)
0 = Normal.
1 = Slow; or may need more than one attempt.
2 = Pushes self up from arms of seat.
3 = Tends to fall back and may have to try more than one time, but can get up without help.
4 = Unable to arise without help.

28. Posture
0 = Normal erect.
1 = Not quite erect, slightly stooped posture; could be normal for older person.
2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
4 = Marked flexion with extreme abnormality of posture.

29. Gait
0 = Normal.
1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.
2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
3 = Severe disturbance of gait, requiring assistance.
4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)
0 = Normal.
1 = Retropulsion, but recovers unaided.
2 = Absence of postural response; would fall if not caught by examiner.
3 = Very unstable, tends to lose balance spontaneously.
4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased armswing, small amplitude, and poverty of movement in general.)
0 = None.
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.
3 = Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

IV. Complications of therapy (In the past week)

A. Dyskinesias

32. Duration: What proportion of the waking day are dyskinesias present? (Historical information.)
0 = None
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

33. Disability: How disabling are the dyskinesias? (Historical information; may be modified by office examination.)
0 = Not disabling.
1 = Mildly disabling.
2 = Moderately disabling.
3 = Severely disabling.
4 = Completely disabled.

34. Painful Dyskinesias: How painful are the dyskinesias?
0 = No painful dyskinesias.
1 = Slight.
2 = Moderate.
3 = Severe.
4 = Marked.

35. Presence of Early Morning Dystonia (Historical information.)
0 = No
1 = Yes

B. clinical fluctuations

36. Are "off" periods predictable?
0 = No
1 = Yes

37. Are "off" periods unpredictable?
0 = No
1 = Yes

38. Do "off" periods come on suddenly, within a few seconds?
0 = No
1 = Yes

39. What proportion of the waking day is the patient "off" on average?
0 = None
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

C. other complications

40. Does the patient have anorexia, nausea, or vomiting?
0 = No
1 = Yes

41. Any sleep disturbances, such as insomnia or hypersomnolence?
0 = No
1 = Yes

42. Does the patient have symptomatic orthostasis? (Record the patient's blood pressure, height and weight on the scoring form)
0 = No
1 = Yes

Appendix B Modified Hoehn and Yahr scale

1.0 Unilateral involvement only

1.5 Unilateral and axial involvement

2.0 Bilateral involvement without impairment of balance

2.5 Mild bilateral disease with recovery on pull test

3.0 Mild to moderate bilateral disease; some postural instability; physically independent

4.0 Severely disabling disease; still able to walk or stand unassisted 4.0: Severe disability; still able to walk or stand unassisted

5.0 Wheelchair bound or bedridden unless aided

Appendix C Schwab and England activities of daily living scale

100% = Completely independent. Able to do all chores without slowness, difficulty or impairment. Essentially normal.Unaware of any difficulty.

90% = Completely independent. Able to do all chores with some degree of slowness, difficulty and impairment. Might take twice as long. Beginning to be aware of difficulty.

80% = Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.

70% = Not completely independent. More difficulty with some chores. Three to four times as long in some. Must spend a large part of the day with chores.

60% = Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors; some impossible.

50% = More dependent. Help with half, slower, etc. Difficulty with everything.

40% = Very dependent. Can assist with all chores, but few alone.

30% = With effort, now and then does a few chores alone or begins alone. Much help needed.

20% = Nothing alone. Can be a slight help with some chores. Severe invalid.

10% = Totally dependent, helpless. Complete invalid.

0% = Vegetative functions such as swallowing, bladder and bowel functions are not functioning. Bedridden.

Appendix D

Anamneseblatt

Sehr geehrte Patientinnen und Patienten!
Sie wurden der Ambulanz für Bewegungsstörungen zugewiesen.
Bitte nehmen sie sich ein paar Minuten Zeit um diesen Fragebogen auszufüllen.
Kreuzen sie bitte alle zutreffenden Antworten an.

1. Name: **Geburtsdatum:**

2. Welche Symptome wurden von ihnen oder Angehörigen zuerst bemerkt?

- ☐ Veränderung im Schlafverhalten
- ☐ Vermehrte Müdigkeit am Tag
- ☐ Riechstörungen
- ☐ Schulterschmerzen oder Gelenkschmerz
- ☐ trockenes Auge
- ☐ Schwindel
- ☐ Stürze
- ☐ Zittern
- ☐ Ungeschicklichkeit der Hände
- ☐ Muskelsteifigkeit
- ☐ Verlangsamung von Bewegungen
- ☐ Veränderung des Gangbildes
- ☐ Fehlendes Mitschwingen eines Armes beim Gehen
- ☐ Veränderung des Sprechens
- ☐ Handschrift langsam oder klein
- ☐ Aufstehen aus Sessel erschwert
- ☐ Probleme beim Schwimmen
- ☐ Stimmungsschwankungen
- ☐ Vermehrte Angst
- ☐ Verstopfung
- ☐ Harninkontinenz
- ☐ andere: _____

3. Wie lange ist es her, dass sie die ersten Symptome bemerkten? ___Jahre, ___Monate

4. Welche Ärztinnen/Ärzte konsultierten sie bisher aufgrund dieser Symptome?

- ☐ Psychiatrie
- ☐ Neurologie
- ☐ Orthopädie
- ☐ HNO
- ☐ Allgemeinmedizin
- ☐ Innere Medizin
- ☐ Manualtherapie
- ☐ Keine Fachrichtung

5. Wurden bei ihnen bereits auf Grund der oben beschriebenen Symptome Untersuchungen durchgeführt?

- ☐ CT: Region:_____
- ☐ MRT: Region:_____
- ☐ Röntgen: Region:_____
- ☐ SPECT
- ☐ PET
- ☐ Szintigraphie
- ☐ Elektroneurographie (Karpaltunnel etc.)
- ☐ EEG
- ☐ Ultraschall (Hirngefäße, Hals, Herz, Bauch)
- ☐ Tremoranalyse

6. Hat oder hatte jemand in ihrer Verwandtschaft ähnliche Symptome?

☐ Ja, Verwandtschaftsverhältnis:_____ ☐ Nein

7. Gibt es in ihrer Familie:

- ☐ Parkinson
- ☐ Alzheimer
- ☐ essentieller Tremor
- ☐ Schlaganfall
- ☐ Geruchsstörung
- ☐ RLS (Restless legs Syndrom, Syndrom der unruhigen Beine)
- ☐ Herzinfarkt
- ☐ Schlafapnoesyndrom
- ☐ Nicht näher definierte Bewegungsstörung

8. Ist eine oder sind mehrere dieser Erkrankungen bei ihnen bekannt?

- ☐ Diabetes
- ☐ Bluthochdruck
- ☐ Schlaganfall
- ☐ Herzinfarkt
- ☐ erhöhte Blutfettwerte
- ☐ Herzrhythmusstörungen, Herzstolpern
- ☐ Polyneuropathie
- ☐ Schilddrüsenunter-funktion
- ☐ RLS (Restless legs Syndrom, Syndrom der unruhigen Beine)
- ☐ Gicht/erhöhte Harnsäure
- ☐ Schlafapnoesyndrom

9. Händigkeit: Sie sind: ☐ Rechtshänder/in ☐ Linkshänder/in

10. Die ersten Symptome zeigten sich:

- ☐ auf der rechten Seite
- ☐ auf der linken Seite
- ☐ auf beiden Seiten

11. Ihre Körpergröße: _____cm **Ihr Körpergewicht: _____kg**

12. Ist bei ihnen die Fähigkeit, Farben voneinander zu unterscheiden, eingeschränkt?

☐ Ja, seit ___Jahren, ___Monaten ☐ Nein

13. Welche Medikamente haben sie bisher gegen die oben beschriebenen Symptome eingenommen/verschrieben bekommen?

Parkinsonmedikamente	**Neuroleptika**	**Antidepressiva**	
☐ Madopar	☐ Solian	☐ Citalostad	☐ Ludiomil
☐ Madopar CR	☐ Abilify	☐ Citalopram	☐ Tolvon
☐ Sinemet	☐ Lanolept	☐ Cipralex	☐ Mianserin
☐ Sinemet retard	☐ Leponex	☐ Pram	
☐ Stalevo	☐ Zyprexa	☐ Seropram	☐ Edronax
	☐ Olanzapin Genericon	☐ Adjuvin	☐ Cymbalta
☐ Sifrol	☐ Seroquel	☐ Allenopar	☐ Jarsin
☐ Requip	☐ Quetialan	☐ Sertralin	☐ Psychotonin
☐ Permax	☐ Quetiapin Sandoz	☐ Seroxat	☐ Hypericum
☐ Cabaseril	☐ Risperdal	☐ Felicium	☐ Ixel
☐ Cabergolin Sandoz	☐ Risperidon	☐ Floccin	☐ Efectin
☐ Neupro – Pflaster	☐ Rispel	☐ Fluctine	
☐ Dopergin	☐ Aleptan	☐ Fluoxibene	☐ Trittico
☐ Umprel	☐ Invega	☐ Flux „Hexal“	☐ Trittico retard
☐ APO-go PEN	☐ Serdolect	☐ Fluxil	☐ Mirtabene
	☐ Dogmatil	☐ FluxoMed	☐ Mirtazapin
☐ Comtan	☐ Meresa	☐ Mutan	☐ Mirtaron
☐ Tasmar	☐ Zeldox	☐ Positivum	☐ Mirtel
	☐ Nipolept	☐ Floxyfral	☐ Remeron
☐ Jumex	☐ Orap	☐ Allenopar	
☐ Xilopar		☐ Fluoxetin	☐ Aurorix
☐ Azilect	☐ Truxal	☐ Parocetan	☐ Moclobemid
☐ Selegilin „Genericon“	☐ Fluanxol	☐ Paroxat	☐ Jatrosom
☐ Cognitiv	☐ Dapotum	☐ Seroxat	☐ Wellbutrin XR
☐ Amboneural	☐ Haldol	☐ Eostar	☐ Stablon
	☐ Nozinan	☐ Escitalopram	☐ Dalcipran
☐ PK-Merz	☐ Buronil	☐ Gladem	☐ Yentreve
☐ Hofcomant	☐ Decentan	☐ Tresleen	
	☐ Dominal forte	☐ Ennos	**Antidementiva**
☐ Akineton	☐ Delpral	☐ Paroxetin	☐ Aricept
☐ Sormodren	☐ Tiaprid	☐ Sertrapel	☐ Reminyl
☐ Parkopan	☐ Cisordinol		☐ Axura
	☐ Largactil	☐ Limbitrol	☐ Ebixa
		☐ Saroten	☐ Nootropil
	Ginkgoblatt-Extrakt	☐ Saroten retard	☐ Pirabene
	☐ Tebonin retard	☐ Tryptizol	☐ Cerebrolysin
	☐ Tebofortan	☐ Anafranil	☐ Cerebryl
	☐ Ginkgo Sanvita Lsg	☐ Noveril retard	☐ Exelon
	☐ Ceremin	☐ Harmomed	☐ Exelon - Pflaster
	☐ Cerebokan	☐ Deanxit	☐ Hydergin
	☐ Gingol	☐ Sinequan	

Datum: _____

Danke dass sie sich für diesen Fragebogen Zeit genommen haben!

Bitte geben sie ihn ihrer Ärztin/ihrem Arzt in der Ambulanz für Bewegungsstörungen!

Questionnaire

Dear patient!

You were assigned to the outpatients' clinic of movement disorders.
Please take a couple of minutes to answer this questionnaire.
Please put a cross next to all correct answers.

1. Name: **Date of birth:**

2. Which symptoms did you or your relatives recognize at first?

- ☐ Change in sleep behaviour
- ☐ increased daytime sleepiness
- ☐ impairment of olfaction
- ☐ shoulder pain or joint pain
- ☐ dry eye
- ☐ dizziness
- ☐ falls
- ☐ tremble
- ☐ clumsiness of hands
- ☐ muscular stiffness
- ☐ slowing down of movements
- ☐ change of gait
- ☐ missing armswing when walking
- ☐ change in speech
- ☐ handwriting slow or small
- ☐ rising from chair is difficult
- ☐ problems in swimming
- ☐ changes of mood
- ☐ increased fear
- ☐ constipation
- ☐ urinary incontinence
- ☐ others: _____

3. How much time has past since you have experienced the first symptoms?

___years, ___months

4. Doctors you have consulted due to these symptoms:

- ☐ Psychiatry
- ☐ Neurology
- ☐ Orthopedics
- ☐ Otolaryngology
- ☐ General practitioner
- ☐ internal medicine
- ☐ Chiropractic
- ☐ none of these

5. Which of the following tests have been carried out due to the symptoms described above?

- ☐ CT: region:_____
- ☐ MRI: region:_____
- ☐ X-ray: region:_____
- ☐ SPECT
- ☐ PET
- ☐ Scintigraphy
- ☐ Elektroneuronography (carpal tunnel, etc.)
- ☐ EEG
- ☐ sono (brain vessels, neck, heart, abdomen)
- ☐ tremor analysis

6. Have or had someone of your relatives similar smptoms?

☐ Yes, relationship:_____ ☐ No

7. Is there one or more of the following disease present in your family?

- ☐ Parkinson
- ☐ Alzheimer
- ☐ essential tremor
- ☐ stroke
- ☐ impairment of olfaction
- ☐ RLS (Restless legs syndrome)
- ☐ heart attack
- ☐ sleep apnea syndrome
- ☐ not further defined movement disorder

8. Do you have one or more of these diseases?

- ☐ diabetes
- ☐ high blood pressure
- ☐ stroke
- ☐ heart attack
- ☐ elevated blood lipids
- ☐ cardiac arrhythmia
- ☐ Polyneuropathy
- ☐ Hypothyroidism
- ☐ RLS (Restless legs syndrome)
- ☐ Gout / elevated uric acid
- ☐ sleep apnea syndrome

9. Handedness: You are: ☐ right-hander ☐ left-hander

10. The first symptoms appeared:

- ☐ on the right side
- ☐ on the left side
- ☐ on both sides

11. Your height: _____cm
Your bodyweight: _____kg

12. Is the ability of discriminating colours from each other impaired?

☐Yes, since ___years, ___months ☐No

13. Which of the following drugs have you taken/were prescribed up to now for the symptoms mentioned above?

Parkinson-drugs	**Neuroleptics**	**Antidepressants**	
☐Madopar	☐Solian	☐Citalostad	☐Ludiomil
☐Madopar CR	☐Abilify	☐Citalopram	☐Tolvon
☐Sinemet	☐Lanolept	☐Cipralex	☐Mianserin
☐Sinemet retard	☐Leponex	☐Pram	
☐Stalevo	☐Zyprexa	☐Seropram	☐Edronax
	☐Olanzapin Genericon	☐Adjuvin	☐Cymbalta
☐Sifrol	☐Seroquel	☐Allenopar	☐Jarsin
☐Requip	☐Quetialan	☐Sertralin	☐Psychotonin
☐Permax	☐Quetiapin Sandoz	☐Seroxat	☐Hypericum
☐Cabaseril	☐Risperdal	☐Felicium	☐Ixel
☐Cabergolin Sandoz	☐Risperidon	☐Floccin	☐Efectin
☐Neupro – Pflaster	☐Rispel	☐Fluctine	
☐Dopergin	☐Aleptan	☐Fluoxibene	☐Trittico
☐Umprel	☐Invega	☐Flux „Hexal“	☐Trittico retard
☐APO-go PEN	☐Serdolect	☐Fluxil	☐Mirtabene
	☐Dogmatil	☐FluxoMed	☐Mirtazapin
☐Comtan	☐Meresa	☐Mutan	☐Mirtaron
☐Tasmar	☐Zeldox	☐Positivum	☐Mirtel
	☐Nipolept	☐Floxyfral	☐Remeron
☐Jumex	☐Orap	☐Allenopar	
☐Xilopar		☐Fluoxetin	☐Aurorix
☐Azilect	☐Truxal	☐Parocetan	☐Moclobemid
☐Selegilin „Genericon“	☐Fluanxol	☐Paroxat	☐Jatrosom
☐Cognitiv	☐Dapotum	☐Seroxat	☐Wellbutrin XR
☐Amboneural	☐Haldol	☐Eostar	☐Stablon
	☐Nozinan	☐Escitalopram	☐Dalcipran
☐PK-Merz	☐Buronil	☐Gladem	☐Yentreve
☐Hofcomant	☐Decentan	☐Tresleen	
	☐Dominal forte	☐Ennos	**Antidementia**
☐Akineton	☐Delpral	☐Paroxetin	**agents**
☐Sormodren	☐Tiaprid	☐Sertrapel	☐Aricept
☐Parkopan	☐Cisordinol		☐Reminyl
	☐Largactil	☐Limbitrol	☐Axura
		☐Saroten	☐Ebixa
	Ginkgo-Extracts	☐Saroten retard	☐Nootropil
	☐Tebonin retard	☐Tryptizol	☐Pirabene
	☐Tebofortan	☐Anafranil	☐Cerebrolysin
	☐Ginkgo Sanvita Lsg	☐Noveril retard	☐Cerebryl
	☐Ceremin	☐Harmomed	☐Exelon
	☐Cerebokan	☐Deanxit	☐Exelon - Pflaster
	☐Gingol	☐Sinequan	☐Hydergin

Date: _____

Thank you for being so kind to answer this questionnaire!

Plaease give it to your doctor at the outpatients' clinic for movement disorders!

Appendix E

Curriculum vitae

Persönliche Daten

Name:	Johannes Viktor Golob
Adresse:	Am Stadlgrund 19, 8045 Graz
Mobil:	0676 6346024
Email:	johannes.golob@gmx.at
Geburtsdaten:	04.11.1982, Graz
Staatsbürgerschaft:	Österreich
Familienstand:	ledig
Zivildienst:	abgeleistet, 10/2001-09/2002 (Rotes Kreuz)

Aus- und Weiterbildung

Schulausbildung:

09/1989-07/1993	Volksschule Graz - Graben
09/1993-07/1994	Bundes(real)gymnasium Graz - Carnerigasse
09/1994– 06/2001	Bundesrealgymnasium Köflach

Hochschulstudium:

10/2002	Studium Humanmedizin an der Medizinischen Universität Graz
10/2002-07/2003	1. Studienabschnitt
10/2003-07/2007	2. Studienabschnitt
	Abschluss: objektiv strukturiertes klinisches Examen (OSKE)
10/2007	3. Studienabschnitt:
	6. Studienjahr / Praktisches Jahr am Universitätsklinikum Graz:
	10 Wo. Neurologie an der Abteilung für spezielle Neurologie
	5 Wo. HNO in der allgemeinen Ambulanz für HNO
	5 Wo. Allgemeinmedizin, Praxis von Dr. Walter Tutsch, Graz
	10 Wo. Chirurgie an der Abteilung für Neurochirurgie

Famulaturen:

07-08/2004	5 Wo. Innere Medizin am LKH Voitsberg, Abteilung für Innere Medizin
07-08/2007	3 Wo. Neurologie an der Medizinischen Universität Graz, Abteilung für spezielle Neurologie
09/2006	2 Wo. Dermatologie an der Medizinischen Universität Graz
08-09/2007	6 Wo. Neurologie an der Medizinischen Universität Graz, Abteilung für spezielle Neurologie

Vertiefte Ausbildung, Spezielle Studienmodule

- SSM Angewandte Physiologie (Prof. Schwaberger)
- SSM Klinische Endokrinologie – Eine multidisziplinäre Erfahrung (Prof. Dobnig)
- SSM Dermatoonkologie (Prof. Smolle)
- SSM Modernste Methoden zu Messung der Body Composition (Prof. Möller)
- SSM Neurophysiologie und Signaltransduktion (Prof. Schreibmayer)
- SSM Case based Learning in Klinik und Praxis (Prof. Smolle)
- Alpin- und Höhenmedizin (Prof. Schwaberger)
- Sportmedizin (Prof. Schwaberger)
- Elektrophysiologische Diagnostik neuromuskulärer Erkrankungen (Prof. Quasthoff)

Besondere Kenntnisse

Kenntnsse im Umgang mit Lipometer (Messung der subkutanen Fettverteilung)

Fremdsprachen:	Wissenschaftsenglisch in Wort und Schrift
	Französisch (Basis)
Führerschein:	B
Software/EDV:	MS Office-Applikationen, SPSS

Graz, Mai 2009 (Unterschrift)