Non-motor symptoms in Parkinson's disease

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1

Introduction: The spectrum of non-motor symptoms in Parkinson's disease

Parkinson's disease

In 1817 James Parkinson was the first to describe a disease that now bears his name.[1] In a manuscript entitled "An Essay on the Shaking Palsy", he characterized Parkinson's disease (PD) as "involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from walking to a running pace". Furthermore it was emphasized that the senses and intellects of patients suffering from the disease, remained uninjured.[1] Nowadays PD is known as the second most common neurodegenerative disorder after Alzheimer's disease[2], with prevalences increasing with age, up to 4% in the highest age groups.[2,3]

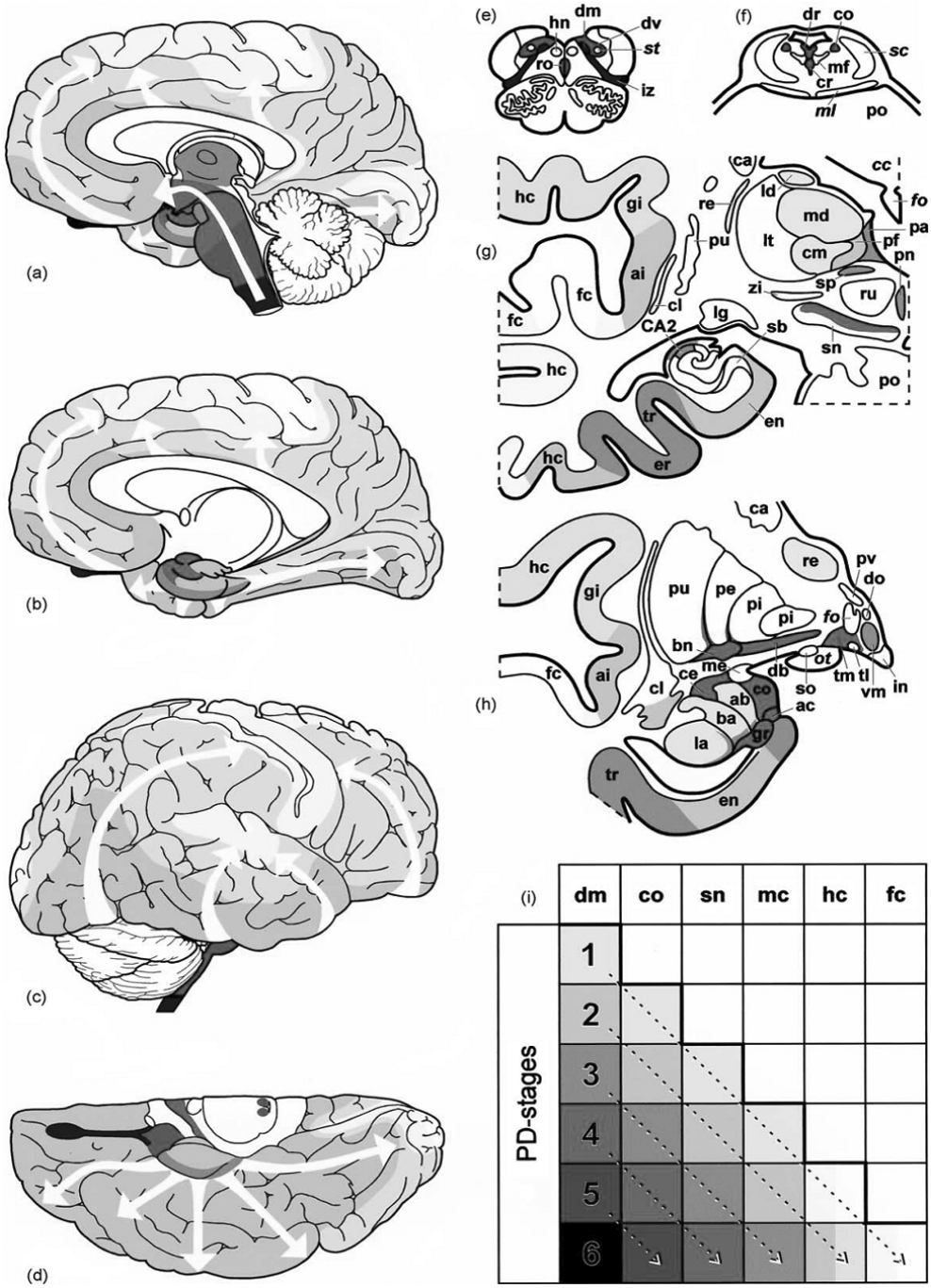
The diagnosis of probable PD based on the United Kingdom Parkinson's Disease Society Brain Bank's clinical criteria requires the presence of bradykinesia and at least one of the other motor symptoms resting tremor, rigidity, or postural instability. Exclusion criteria are other causes of parkinsonism such as a history of repeated stroke, head injury or treatment with neuroleptics at the onset of the symptoms. Furthermore, early severe autonomic involvement or dementia are considered as exclusion criteria.[4] For the definite diagnosis of PD post-mortem confirmation is required[2] and according to clinicopathological studies autopsy confirms the clinical diagnosis of PD in 80-90% of the cases.[5]

Although PD is a disease with a great impact on the wellbeing of many subjects, its causes are still largely unknown. The occurrence of cell loss in the substantia nigra in patients with PD was first recognized by Tretiakoff in 1919.[6] In 1957 Carlsson demonstrated that dopamine was an important neurotransmitter, which particularly had high levels in the basal ganglia, a brain area important for movement.[7] By treating animals with the drug reserpine, the dopamine levels decreased and the animals showed changes in their movement pattern, similar to the symptoms of PD. After administration of L-Dopa, the precursor of dopamine, the symptoms of these animals greatly improved.[8,9] In 1960, Hornykiewicz discovered that the striatal concentrations of dopamine in patients with PD, were considerably decreased. Against the background of findings of Carlsson and his own, Hornykiewicz initiated a study

in which patients with PD were treated with L-dopa. In line with the findings of Carlsson, L-dopa alleviated the motor symptoms of patients with PD.[10] In the following four decades L-dopa was the mainstay in the treatment of PD.[11]

Based on recent new pathological findings, Braak and colleagues introduced a model in which the fixed caudo-rostral spread of α-synuclein pathology in PD was categorized in six stages (Figure 1).[12] In this model, the preclinical phase is characterized by degeneration of the olfactory bulb and the dorsal motor nucleus of the vagus nerve (stages 1 and 2). The clinical phase of PD is characterized by progression of the disease process to the substantia nigra and other deep nuclei of the midbrain and the forebrain (stages 3 and 4).[12] Further progression is characterized by damage in limbic structures and the neocortex (stages 5 and 6).[13] Together, the findings of Braak et al. showed that the disease process inflicts damage far beyond the substantia nigra and that it affects both dopaminergic and nondopaminergic neurons.[14] Inspite of its inspiring role for different levels of PD research, subsequent studies have failed to reproduce the predictable pattern of spread of α-synuclein pathology and support of the existence of a medullary induction site of α-synuclein pathology in all PD brains.[15-17] In a recent study, 47% of the cases did not show a typical caudo-rostral spread of α-synuclein through the PD brain, and in 7% the dorsal motor nucleus of the vagus was not affected even though α-synuclein inclusions were found in substantia nigra and cortical regions. The most affected regions in this study were the substantia nigra in 100% of cases followed by the nucleus basalis of Meynert in 98.5% while a high incidence of α-synuclein was also observed in the spinal cord.[15] Inspite of the latest developments on the pathology of PD, the mechanisms involved in the pathogenesis are not clearly understood.

Figure 1. Progression of PD-related intraneuronal pathology



The pathological process targets specific subcortical and cortical induction sites (a-i). (a and e) Lesions initially occur in the dorsal IX/X motor nucleus and frequently (a and d) in the anterior olfactory nucleus as well. Thereafter, less susceptible brain structures gradually become involved (see white arrows). The pathology in the anterior olfactory nucleus expands less readily into related areas than that evolving in the brain stem. The brain stem pathology takes an upward course (see white arrows). (a-d, g-h) Cortical involvement follows, commencing with the anteromedial temporal mesocortex (tr and er in g and h). From there, the neocortex succumbs, beginning with high order sensory association and prefrontal areas. First order sensory association/premotor areas and, thereafter, primary sensory and motor fields follow suit. In (a-h), the gradual decrease in shading intensity is intended to represent the topographical expansion of the lesions during the course of the disease. Simplified diagram (i) showing the topographic expansion of the lesions (from left to right: dm to fc) and, simultaneously, the growing severity on the part of the overall pathology (from top to bottom: stages 1-6). With the addition of further predilection sites, the pathology in the previously involved regions increases. List of abbreviations: ab, accessory basal nucleus of the amygdala; ac, accessory cortical nucleus of the amygdala; ai, agranular and dysgranular insular cortex; ba, basal nucleus of the amygdala; bn, basal nucleus of Meynert; ca, caudate nucleus; CA1, first sector of the Ammon's horn; CA2, second sector of the Ammon's horn; *cc*, corpus callosum; ce, central nucleus of the amygdala; cl, claustrum; cm, centromedian nucleus of the thalamus; co, coeruleus–subcoeruleus complex; cr, nucleus raphes centralis; db, interstitial nucleus of the diagonal band; dm, dorsal motor nucleus of the glossopharyngeal and vagal nerves; do, dorsomedial nucleus of the hypothalamus; dr, nucleus raphes dorsalis; dv, dorsal nuclear complex of the glossopharyngeal and vagal nerves containing melanized projection neurons; en, entorhinal region; er, ectorhinal region (mesocortex); *fo*, fornix; fc, first order sensory association areas, premotor areas, as well as primary sensory and motor fields; gi, granular insular cortex; gr, granular nucleus of the amygdala; hc, high order sensory association areas and prefrontal fields; hn, motor nucleus of the hypoglossal nerve; in, infundibular nucleus of the hypothalamus; iz, intermediate reticular zone; la, lateral nucleus of the amygdala; ld, laterodorsal nucleus of the thalamus; lg, lateral geniculate body of the thalamus; lt, lateral nuclei of the thalamus; me, medial nucleus of the amygdala; *ml*, medial lemniscus; *mf*, medial longitudinal fascicle; mc, anteromedial temporal mesocortex; *ot*, optic tract; pa, paraventricular nucleus of the thalamus; pe, pallidum, external segment; pf, parafascicular nucleus of thalamus; pi, pallidum, internal segment; pn, parabrachial pigmented nucleus; po, pontine nuclei; pu, putamen; pv, paraventricular nucleus of the hypothala-

mus; re, reticular nucleus of the thalamus; ru, red nucleus; ro, nucleus raphes obscurus; sb, subiculum; sc, superior cerebellar peduncle; sn, substantia nigra; so, supraoptic nucleus; sp, subparafascicular nucleus; *st*, solitary tract; tl, lateral tuberal nucleus of the hypothalamus; tm, tuberomamillary nucleus of the hypothalamus; tr, transentorhinal region (mesocortex); vm, ventromedial nucleus of the hypothalamus; zi, zona incerta.

(Reproduced with permission from Braak et al. Neurobiol Aging 2003;24:197-211).

Pathogenesis

Environmental factors have long been suspected to participate in the pathogenesis of PD due to the existence of neurotoxins that preferentially damage the dopaminergic nigrostriatal pathway.[18] In the past few years, the discovery of genes responsible for rare monogenic parkinsonian syndromes (<5% of the patients) have shed light on genes that cause phenotypes resembling sporadic PD.[19,20] Genetic studies found mutations in autosomal dominant genes such as α-synuclein (*SNCA*) and leucine-rich repeat kinase 2 (*LRRK2*), as well as in autosomal recessive genes such as *Parkin*, *DJ-1*, and *PINK1*. These genes have been suggested to play a role in the proteasomal protein degradation pathway, in the oxidative stress response, and the mitochondrial functions. The presence of different causative genes indicates that PD is a highly heterogeneous disorder although on a functional level these causative genes may share common pathways for protein degradation and energy metabolism. Recent evidence indicates that genes involved in monogenic forms of PD may also act as susceptibility factors in the common sporadic form of PD.[21] The majority of PD cases are considered to be caused by a combination of genetic and environmental factors.[20]

Non-motor symptoms

The new developments in the pathology of PD are in line with a growing body of clinical data underscoring that PD is not a pure motor disorder, but that patients may also suffer from many non-motor symptoms, such as olfactory impairment, autonomic dysfunction, sleep problems, cognitive problems, and psychiatric symptoms.[14]

Olfactory impairment

Olfactory impairment including deficits in olfactory detection, identification, and discrimination of odors in patients with PD is caused by degenerative changes in the olfactory bulb and anterior olfactory nucleus.[12,22,23] Because the olfactory disturbances may occur many years prior to the development of the motor features of the disease, evaluation of olfactory function has been mentioned as a potential early marker of the disease.[23-25]

Autonomic dysfunction

Autonomic symptoms include[14] gastrointestinal, urinary, cardiovascular, thermoregulatory, pupillomotor, and sexual functioning.[26,27] These symptoms most likely develop because of cell loss and Lewy body pathology in autonomic regulatory regions, including the hypothalamus, sympathetic and parasympathetic system, the adrenal medulla, and in the neural plexi innervating the gut, heart, and pelvis.[26,28,29] Autonomic symptoms occur almost in every PD patient at some stage of their disease.[26,29,30] Similar to olfactory impairment, obstipation has been suggested to antedate the occurrence of motor features in some patients with PD.[31]

Sleep problems

Disruption of nighttime sleep occurs in a major part of the patients with PD. Nighttime sleep problems are for instance problems with maintaining sleep and REM sleep behavioural disorder. Sleep in patients with PD is affected likely partly due to abnormalities in the pedunculopontine nucleus, serotonergic raphe nuclei, locus coeruleus, and the subcoeruleus nucleus. Other factors such as the existence of other non-motor and motor symptoms may play a role in the disturbance of nighttime sleep.[14] Nighttime sleep problems are usually present early in the disease course[32], and especially REM sleep behavioural disorder is mentioned as a premotor symptom in PD.[14] Excessive daytime sleepiness occurs in almost half of the patients and have been related to a combination of factors inherent to the disease as well as the use of antiparkinsonian drugs.[14]

Cognitive impairment

Dementia in PD is characterized by a dysexecutive syndrome with memory, attentional, and visuospatial problems and is a major risk factor for nursing home placement in PD.[33,34] Cognitive decline is linked to dopaminergic deficiency in the nucleus caudatus and mesocortical areas (due to degeneration of projections from the substantia nigra and ventral tegmental area) and cholinergic deficiency in the cortex (due to degeneration of ascending projections from the nucleus basalis of Meynert).[35]

Psychiatric symptoms

Psychiatric symptoms in PD include depressive, psychotic, and compulsive symptoms. Depressive symptoms in patients with PD have been related to pathological involvement of the serotonergic, noradrenergic, and dopaminergic systems[36] and are characterized by guilt feelings and lack of self-esteem.[14] Depressive symptoms can precede the motor symptoms in PD.[14]

Psychotic symptoms, such as hallucinations or illusions, are a predictor of nursing home placement and are related to mortality.[37] Pathologically, these symptoms are caused by degeneration of the pedunculopontine nucleus, locus coeruleus, dopaminergic raphe nuclei, basolateral nucleus of the amygdala, and the parahippocampus, as well as α-synuclein pathology in the frontal cortex and Lewy body pathology in the visuoperceptual systems.[38,39]

Compulsive symptoms, such as hypersexuality, pathological gambling, compulsive shopping, compulsive eating, hobbyism, and compulsive medication use are caused by a combination of personal, PD, and medication related factors. These symptoms occur in a minor percentage of the patients but the social consequences of these symptoms can be immense.[40]

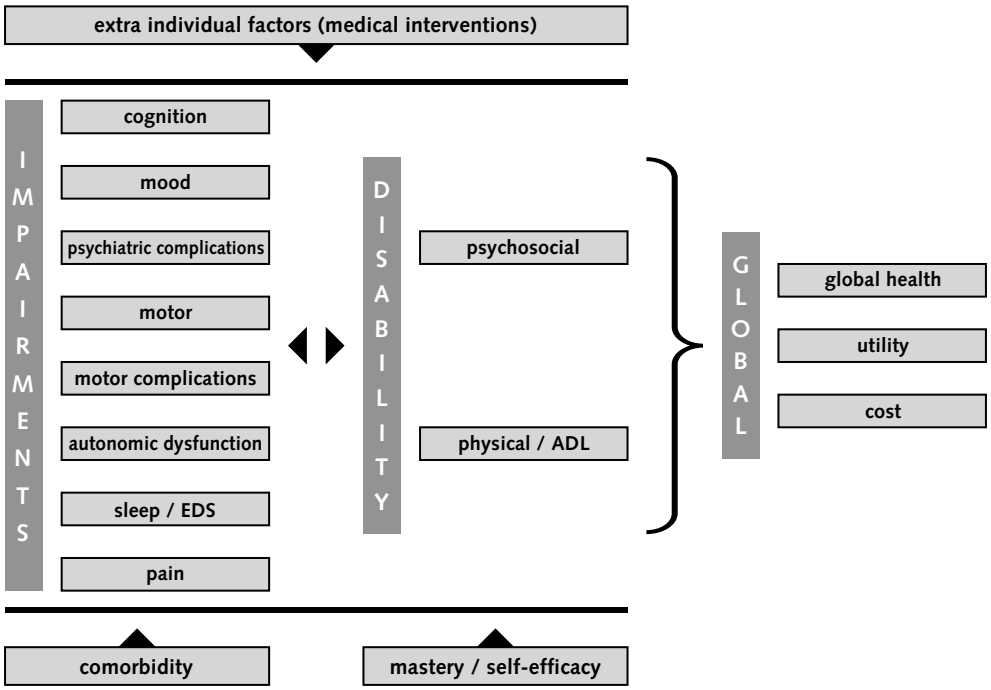
In contrast with the dopaminergic motor symptoms of PD, treatment options for non-motor symptoms are still very limited.[14] However, it has become increasingly clear that especially in the more advanced stages of the disease, non-motor symptoms dominate the clinical presentation of PD and greatly impact on quality of life.[14]

Till now, the prevalence of the different non-motor symptoms is not adequately documented due to the lack of sufficient adequately powered, community-based studies[14], as well as the lack of valid assessment instruments.

PROfiling PARKinson's disease

The PROfiling PARKinson's disease (PROPARK) study is a follow-up study of the SCales for Outcomes in PArkinson's Disease (SCOPA) study, which was carried out between 1999 and 2003. Based on the disablement process[41], within the SCOPA study a model of PD was developed, which summarizes the various motor and non-motor impairment domains, the disabilities, and more global outcomes of health important within the disease (Figure 2). The model also acknowledges the influence of personal and environmental factors. For every clinically relevant PD domain an assessment scale was included in the model. If a scale was available but clinimetric

Figure 2. The disablement process in Parkinson's disease



properties of the scale in a PD population had not been established before, this scale was evaluated. If there were no scales available for a particular domain, scales were developed and evaluated.[42] Assessment scales had to meet the criteria of a good reliability, validity, and responsiveness. Furthermore, scales had to be short and practical. For each domain, available scales meeting all abovementioned criteria were incorporated into the assessment battery.

The PROPARK study started in 2003 and is a longitudinal cohort study of over 400 PD patients, who are assessed annually and are profiled on phenotype, genotype, disability, and global outcomes of health, with the instruments from the SCOPA study. All patients receive a standardized assessment, including evaluation of demographic, and clinical characteristics, family history of PD, and medication use.[42] One of the aims of the PROPARK study is to characterize the important motor and non-motor domains of PD, as well as their relations with other impairment domains and disabilities as well as their impact on quality of life. This knowledge is important for improving patient management, but may also play a role in establishing a better framework for the assessment of clinical features in therapeutic and translational research studies.

Aims of this thesis

Using the baseline data of the PROPARK study, the aims of this thesis are to:

1. Characterize non-motor domains and their relations with other domains of the disease.
2. Establish the influence of non-motor domains on disability and health-related quality of life.
3. Evaluate the phenotypic characteristics of mutation carriers in the PROPARK cohort.

The accurate description of the occurrence of non-motor symptoms in PD patients, as well as insight in their relations with other disease-specific aspects, disabilities and quality of life may contribute to our understanding of the disease process and to development of disease management strategies.

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