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Fatigue, mood disorders and sleep problems in patients with Parkinson's disease

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Introduction

The focus of this study is on fatigue, sleep disturbances and depression in patients with Parkinson's disease and their impact on quality of life and how they are related to each other. In this introductory chapter a description of Parkinson's disease is given, followed by information on its consequences for patients' quality of life in a theoretical model. The research questions are then formulated, and the chapter ends with an outline of the thesis.

1.1 Parkinson's disease: a general picture

1.1.1 Historical background

Parkinson's disease (PD) was first described by James Parkinson (1755-1824) in 1817, a surgeon, working in London (1). In his words, the disease is characterized by "involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace, the senses and intellect being uninjured" (2). He described the slow progression of the disease, with prominent trembling in some body parts, the strange posture (this being most observable whilst walking, but sometimes whilst sitting or standing) or the slowness of movement, which unduly stresses the reduction in muscular power. Strangely, his essay contains no reference to rigidity, a symptom which was added by Charcot some sixty years later (3). Parkinson described in the hands of the six cases analyzed in the *Shaking Palsy* the start hesitation – the problems of initiating movements and subsequent falls. He managed to describe the impact on the reduction of daily living activities like writing, reading and eating. "As the disease proceeds, employments are accomplished with considerable difficulty, the hand failing to answer with exactness to the dictates of the will ... writing now can be hardly at all accomplished; and reading, form the tremulous motion, is accomplished with some difficulty ... whilst at meals the fork not being duly directed frequently fails to raise the morsel from the plate: which, when seized, is with much difficulty conveyed to the mouth."

Currently recognized nonmotor features were reported anecdotally by him, but even he managed to recognize sleep disturbances ("the tremulous motions of the limbs occur during sleep, and augment until they awaken the patients, and frequently with much agitation and alarm"),

bowel constipation (“the bowels ... demand stimulating medicines of very considerable power”), swallowing problems, salivation problems, delirium or extreme exhaustion. In his cases he also described the fatigue of the extremities – weakness was more pronounced and also started earlier in the upper extremities when compared with the lower ones.

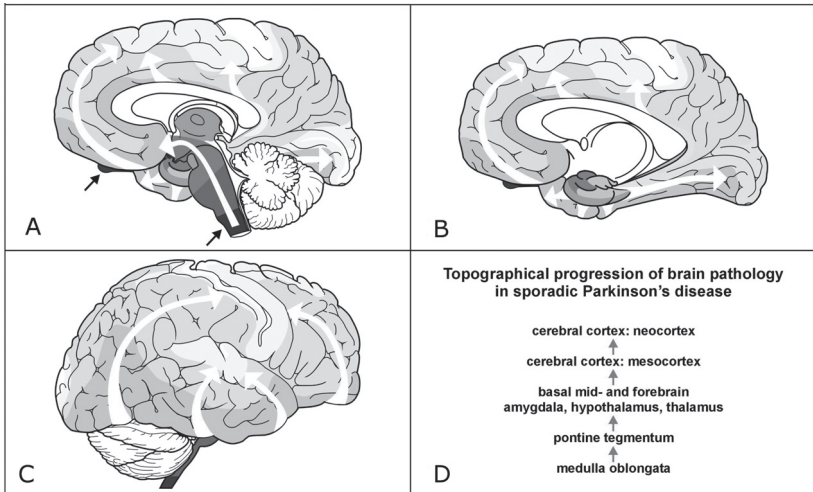
1.1.2 Pathology

Parkinson’s disease (PD) is defined as a slowly progressive neurodegenerative disorder with no identifiable cause. PD is characterized by loss of pigmented neurons and gliosis, most prominently in the substantia nigra and locus coeruleus, and by the presence of Lewy bodies in degenerating neurons (4). The underlying neuronal degeneration in PD is believed to occur slowly in the decades preceding the onset of the symptoms. (5). Recent research in PD pathology has brought a new concept of PD – the neuronal changes are distributed not only in the structures of basal ganglia but throughout the entire nervous system – not only the central but also the peripheral and the enteric nervous systems (CNS, PNS, ENS). As a result, PD has come to be acknowledged as more than a monosystemic disorder with preferential obliteration of nigral dopaminergic neurons (6). The primary pathological changes in PD include inclusions of α -synuclein (Lewy bodies), and the presence of these aggregations (Lewy body pathology) is mandatory for the neuropathologic confirmation of the clinical diagnosis.

As in nearly every illness, individuals cross from a subclinical phase to a symptomatic manifestation. Up to 80% of dopaminergic neurons are already lost before the first clinical symptoms of PD appear. Neuropathologically spoken – clinical and preclinical manifestation could be differentiated from each other by virtue of changes in the topographic distribution pattern. Each stage displays newly affected regions in addition to those involved in previous stages (Figure 1.1 and 1.2). Physical contacts between susceptible regions may play a key role in the pathogenesis of PD, since all of the vulnerable nerve cells are closely interconnected projection neurons with a long and sparingly myelinated axon. In fact, routes do exist that would permit the propagation of the pathologic process in sporadic PD via retrograde axonal transport and transsynaptic transmission of a still indeterminate pathogen (7).

Since diagnosis in living subjects is based entirely on neurological examination and no antemortem biological marker exists, it is common for patients with PD to receive their diagnosis quite late in the disease process, or for some patients to be misdiagnosed. Due to all of these factors, it is difficult to perform epidemiological studies in PD.

Fig 1.1 Schematic diagrams of the progression of the PD pathological process (7)

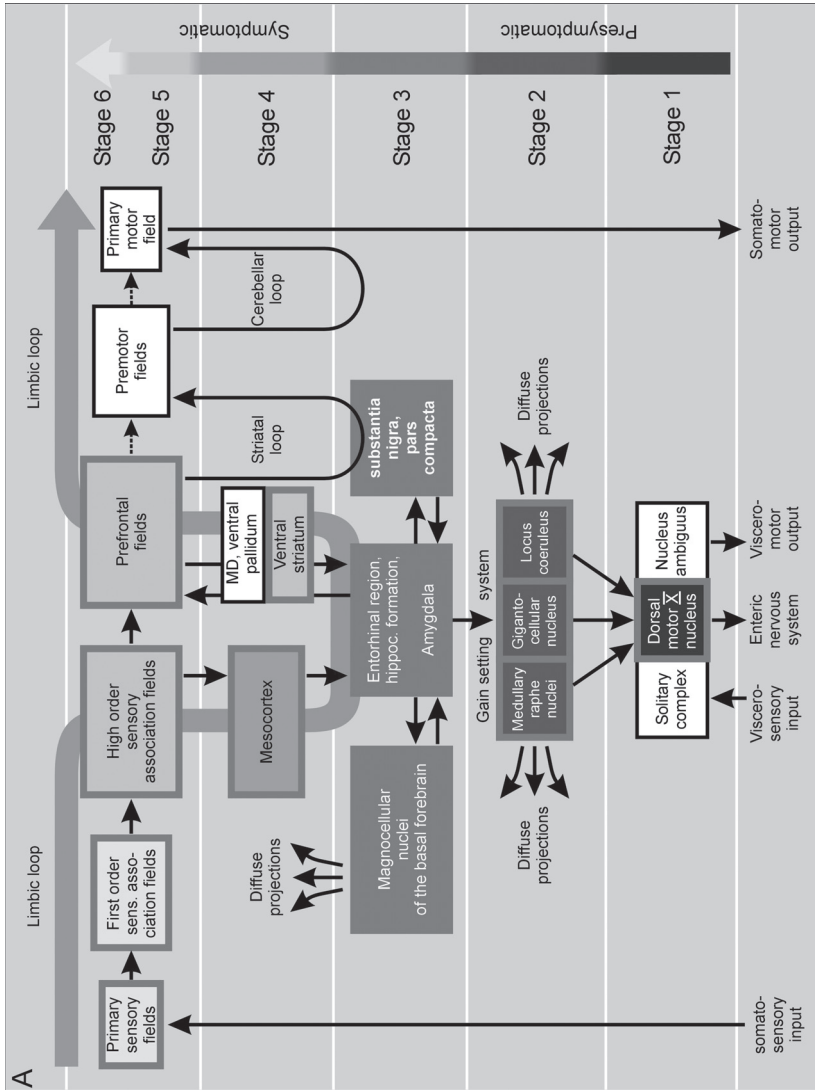


Braak en Del explained this figure as follows: “Schematic diagrams showing the caudo-rostral progression of the PD-related pathological process (white and red arrows). The earliest predilection sites in persons with stage 1 inclusions are the dorsal motor nucleus of the vagal nerve and anterior olfactory structures (black arrows)” (7). in text

1.1.3 Epidemiology

Idiopathic Parkinson’s disease is observed in all countries, all ethnic groups and all socioeconomic classes. The prevalence of PD in industrialized countries is generally estimated at 0.1-0.3% of the entire population, although the prevalence in Africans or Asians is less compared with whites (one-third to one-half) (8). In industrialized countries reported incidence rates of PD are 11-18 per 100,000 person-years (9). The incidence in all European countries where vital statistics are kept is similar. The incidence of PD is larger in men than in women in every decade of life (10). This gender difference is explained by a theory of estrogen protection from neurodegeneration (11), although its role is still controversial.

Fig. 1.2 Diagram of presymptomatic and symptomatic phases in PD (7)



Braak en Del explain this figure as follows: "Spatio Spatio-temporal diagram showing proposed presymptomatic and symptomatic phases in sporadic PD together with major subdivisions of the cerebral cortex and limbic loop (entorhinal region, hippocampal formation, amygdala), as well as involved lower brainstem nuclei. Uninvolved areas appear in white. The superordinate centers of the limbic (and striatal) loops undergo the most damage in sporadic PD. Note how the pathological process successively encroaches upon interconnected subcortical nuclei and cortical areas." (7)

PD is characterized by motor problems” the typical tetrad of hypo- and bradykinesia, resting tremor, postural instability and rigidity are the core features of Parkinson’s disease (12). The overall course of the disease is quite variable. In the majority of patients, the mean period of time from inception of the disease to a chairbound state is 7.5 years, but again, with a wide range (13,14). On the other hand, as many as one-third of cases are relatively mild and such patients may remain stable for 10 years or more.

1.1.4 Treatment

Currently there is no cure for PD, and no existing therapy has been shown clearly to slow down or reverse the progression of the disease. The most important goals of management are thus to preserve functional independence and health-related quality of life (HRQOL). Toward this end, treatment is directed at providing symptomatic relief for both motor and nonmotor symptoms while minimizing undue adverse effects.

However, this approach has proven to be problematic in practice. The most effective therapy for treating motor symptoms, levodopa, has been associated with an increased risk of motor complications (15). These motor fluctuations can impair HRQOL and cause significant functional and social disability, directly contrary to the management goals.

Before 1918, treatment was primarily supportive, but an epidemic of encephalitis, with its postencephalitic form of parkinsonism, led to the pursuit of effective therapies, first of all for vaccine development and later towards symptomatic therapy. A number of natural remedies had been tried – Charcot described the use of extracts of Bulgarian belladonna and atropine, which were initially received with great promise, but which fell short of expectations. By the early 1950, synthetic drugs became available to treat symptoms of PD, but with serious side effects.

The revolution in the treatment of PD started when levodopa was introduced into clinical practice in 1970s. Levodopa has become the cornerstone of symptomatic therapy. It is a precursor of the neurotransmitter dopamine. Its use emerged after various researchers in the late 1950s and 1960s demonstrated that dopamine depletion was characteristic for PD. Levodopa is still regarded as the most potent symptomatic therapy for PD, bringing in a ‘honeymoon’ period when started. But there is a catch in its use: Late complications such as motor fluctuations and dyskinesias are associated with chronic administration. To avoid these problems or at least to minimize them, other therapeutical possibilities have been studied.

Dopamine agonists have been used to treat symptoms of PD since the late 1970s, initially to supplement the beneficiary effect of levodopa. Recent research and methodological investigations have demonstrated therapeutical benefit in all stages of PD, both in combination with levodopa and as a form of monotherapy.

Monoamine oxidase inhibitors were discovered in 1950 and were first utilized in the treatment of depression. Monoamine oxidase (MAO) is an enzyme involved in the breakdown of catecholamines, including dopamine. Only after the discovery of the two types of MAO, A and B, did MAO-B inhibitors started to be widely used in PD. Currently their neuroprotective properties are being studied and being proved in vitro, but unfortunately not in vivo. In clinical practice they are used as a monotherapy or as adjunctive therapy to levodopa.

Catechol-O-methyltransferase (COMT) is another enzyme involved in the metabolic pathways of dopamine. Second-generation COMT inhibitors were introduced in the 1990s, and they were more potent, more selective and less toxic than their predecessors. They are currently available for use as adjunctive therapy in patients who have developed motor fluctuations.

Amantadine was initially marketed in the 1960s as an antiviral agent. It was used for several decades as therapy for PD, though current guidelines for PD treatment are inconsistent for how to use, or even whether to use this drug. Amantadine is used mostly as adjunctive therapy and occasionally in early monotherapy.

Anticholinergics are among the earliest class of pharmaceuticals used for the management of PD. In 1940 synthetic anticholinergics were introduced, replacing herbal preparations. With recent developments they have been moved to a less prominent role, because of their important side effects in susceptible individuals such as the elderly.

Agents with novel mechanisms of action are currently being developed with the aim of inhibiting programmed cell death, maintaining mitochondrial membrane potential with the reduction of oxidative damage or promoting the survival or regeneration of dopaminergic neurons. Adenosine receptors antagonist, activators of c-Jun N-terminal kinase (JNK), the aminomethyl chromane chemical group of drugs, or glial-derived neurotrophic factor (GDNF) all belong to this potential treatment.

The ideal drug for treating PD remains to be discovered, and significant advances are not envisaged in the near future. To have a major place among the already existing treatment methods, a new agent should have the following characteristics: (a) antiparkinsonian efficacy comparable to levodopa, (b) efficacy against dopa-resistant symptoms, (c) free of motor (dyskinesias) and psychiatric (i.e. hallucinations, delirium, psychosis) side effects, (d) quick start of action, (e) good initial tolerability and (f) easy and convenient to administer (16). Use of the most effective modalities for PD treatment and the optimization of this treatment, as well as effective treatment of nonmotor symptoms, can lead to improved functionality and HRQOL in a patient.

1.2 Parkinson's disease: Nonmotor dysfunction

James Parkinson accurately described the motor problems. Although he mentioned some nonmotor features of Parkinson's disease, for a long time Parkinson's disease was considered to be a disease with only motor features. Only in recent times have nonmotor features been noticed and become an inseparable element of PD.

Depression, anxiety, psychosis, apathy are among the most characteristic features of neuropsychiatric impairment of PD patients (17). Sleep problems, sexual dysfunction, falls, fatigue, autonomic dysfunction, olfactory problems, weight loss, sensory symptoms or cognitive impairment are other important nonmotor presentations of PD. These nonmotor symptoms contribute significantly to worse Health Related Quality of Life (HRQoL).

Some of nonmotor symptoms (NMS) are treatable if they are detected early (constipation, depression, sleep disturbances, anxiety, nausea) (18), though some may not be detected unless specifically tested for, like sexual problems, diplopia, olfactory dysfunction and weight change (18). These nonmotor problems are the result of dopamine dysregulation, but also may result from the non-dopaminergic-cell dysfunction (adrenergic, noradrenergic, serotonergic, cholinergic) of the pathways not involved in motor function (17). This could also explain why these symptoms respond poorly, if at all, to a standard antiparkinsonian treatment. Recognition and treatment of NMS is an important part of modern and comprehensive healthcare for PD patients (18).

1.2.1 Sleep disturbances

Virtually all patients with Parkinson's disease experience sleep disruption (17).

a) Nocturnal symptoms

Previous studies have shown that nocturnal symptoms usually begin early in the disease course (19). Degeneration of central sleep regulation centers in the brainstem and the thalamocortical pathways is probably responsible (19). Parkinson's disease patients have been reported to have an abnormal sleep architecture, sleep disordered breathing due to obstructive sleep apnoea and a narcoleptic pattern of rapid onset of sleep (17). Nocturnal problems could be categorized subjectively as insomnia, motor, urinary and neuropsychiatric problems (19).

Restless Legs syndrome (RLS), Periodic Limb Movement disorder (PLMD) and REM Sleep Behavior Disorder (RBD) belong to the group of parasomnias that frequently occur in PD patients. RLS is marked by an urge to move accompanied by dysesthesias in the limbs that occurs at rest alleviated by movement. Symptoms occur in a circadian pattern, with onset usually in the evening hours when lying in bed to go to sleep. PLMD

may occur in association with RLS or independently. RLS and PLMD can both cause sleep disruption in PD patients and have been reported in some studies to show increased prevalence in PD (20).

REM behavior disorder (RBD) is a sleep disorder characterized by the occurrence of muscle activity during REM sleep with the occurrence of complex, vigorous, and sometimes violent behaviors (21). Patients and bedpartners have sustained lacerations and sometimes even fractures and dislocations as a result. RBD is present in 25 to 50% of PD patients. There have been no controlled studies of treatment interventions for RBD. In many patients, pharmacologic intervention for RBD may not be necessary if symptoms are mild and intermittent. In cases where behavior is more violent, putting either the patient or the caregiver at risk for injury, protective measures and treatment are indicated.

b) Excessive daytime sleepiness

Sleepiness is a ubiquitous phenomenon, experienced not only as a symptom in a number of medical, psychiatric and primary sleep disorders, but also as a normal physiological state by most individuals over any given 24 hour period. Sleepiness can be considered abnormal when it occurs at inappropriate times, or does not occur when desired (22). Excessive daytime sleepiness (EDS) affects up to 50% of patients with PD and could be also a preclinical marker (17).

EDS has been associated with more severe PD, greater PD-related disability, cognitive decline, more frequent hallucinations and a longer duration of levodopa therapy. Factors associated with development of EDS included dementia and a more rapid progression of parkinsonism (23). Other factors associated with EDS include the severity of PD and the duration of dopaminergic treatment (24). Several studies using polysomnography and the Multiple Sleep Latency Test (MSLT) suggest that daytime sleepiness may be a primary feature of PD and unrelated to PD treatments or nocturnal sleep disturbance (25,26). The current hypothesis is that sleepiness or a susceptibility to EDS may be an integral part of PD, reflecting the extent of the neurodegenerative process.

1.2.2 Fatigue

Fatigue is a common problem in virtually all chronic medical and many psychiatric disorders (27). Yet, research on the nature and treatment of fatigue has been challenging for several reasons. First, fatigue is experienced on a continuum that includes both a normal state and a pathological disturbance. What constitutes problematic fatigue for one person may not be for another, so that the notion of personal expectation may also play a role. Fatigue also occurs in several independent conditions that are often comorbid with the disorder being studied, such as sleep dysfunction, or it may be caused by medications. Finally, fatigue is one of the symptoms

included in the criteria for diagnoses of anxiety and depressive disorders (27).

Recognition of fatigue as a common problem in Parkinson's disease (PD) has occurred relatively recently. The first papers on fatigue in PD were published in 1993 (28,29). The lack of recognition of fatigue as an important symptom in PD is reflected in its absence from the Unified Parkinson's Disease Rating Scale (UPDRS) (30). So far, the understanding of fatigue in PD is in its early stages. Its impact in PD is generally underappreciated, and its treatment is empiric (31).

1.2.3 Depression

Depression is a common neuropsychiatric feature of PD and may be more common in PD than in other conditions with similar levels of disability (15). This type of depression is often associated with increased disability, a worse HRQOL, more rapid progression of motor impairment/disability and an increased mortality hazard ratio (2.66) (32,33). The prevalence of depression in PD ranges from 20% to 50% (32,33). Between 5% and 20% of these patients are diagnosed with major depression, with the remainder classified as nonmajor depression, including minor depression, subsyndromal depression and dysthymia (34).

Risk factors for depression in PD include an increased severity of cognitive impairment, female sex, possibly early-onset PD and a personal history of depression before diagnosis of PD (34). Depression is seen in all stages of PD and may be present prior to the onset of motor symptoms (35). Whether depression in PD is "reactive" or related solely to neuropathology is somewhat controversial. Most lines of evidence suggest a biological basis, stemming partly from studies that show a relationship between a history of depression and subsequent development of PD (17). Depression in PD is most likely related to a combination of neurobiologic and psychologic factors (34).

Of importance to managed care are recent studies that have underscored the lack of recognition and appropriate treatment of depression in PD (31,36). Most patients meeting the criteria for depression are not being treated or may be receiving suboptimal or ineffective treatment (36). This can lead to a rise in healthcare costs related to ongoing disability. A simple, reliable, routine screening method for depression in PD is needed, as well as the best treatment strategies.

1.2.4 Anxiety

Anxiety in PD has not been as well studied as depression. However, the majority of patients with depression will also meet criteria for an anxiety disorder and vice versa (34). Anxiety can be associated with greater physical and psychological distress than depression in PD.

Anxiety disorders in PD can be categorized as generalized anxiety disorder, panic disorder, social phobia and obsessive-compulsive disorder (OCD). Generalized anxiety disorder and panic attacks are the most common manifestations. While patients often try to avoid being seen in public places due to fear of embarrassment, this does not qualify for the diagnosis of social phobia.

There is some evidence that generalized anxiety or panic attacks in PD are a reaction to the distressing components of the disease (e.g., to the discomfort and fear of loss of motor control) (33). However, many specialists feel that both psychosocial and neuropathologic factors are contributory (37). Patients with PD should be screened for anxiety disorders.

1.3 The impact of Parkinson's disease on patients' life

Parkinson's disease has a severe impact on an individual's life, increasingly reducing the quality of life of PD patients (38-40). Patients with PD have worse QoL scores compared to the general population, whether measured using a generic or by a disease-specific instrument. Schrag et al. in a community-based cross sectional study of patients with PD showed worse health-related QoL in different domains – in mobility, activities of daily living, physical and social functioning, cognition, communication, bodily discomfort and emotional well-being (39).

Reduced QoL was associated with various clinical and psychosocial variables: disease severity (40), motor complications of levodopa therapy (38,41), sleep problems (42), pain (43), depression (40) and cognitive impairment (44). Karlsen et al. found a significant relationship between higher age and the physical mobility domain (45), while other studies did not report such a relationship (44). Longer disease duration was a significant predictor of worse QoL (41), and female gender was associated with worse QoL (46).

For chronic illnesses for which there is no cure, it is important to establish treatments that really makes people feel better. Thus, survival per se is no longer perceived to be the only end point; the goal is to improve, restore or preserve QoL. The QoL construct was introduced to more comprehensively evaluate the outcomes of a chronic disease or effects of treatment interventions (47,48).

The World Health Organization (WHO) defines QoL as an "individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns." It is a broad-ranging concept affected by an individual's physical health, psychological state, level of independence, social relationships and relationships towards the salient features of their environment (49).

Besides biological measures, other levels of clinical measurement

can be considered in clinical studies: impairments, disability and health-related quality of life (HRQoL). Impairments are the direct organic manifestations of the disease, such as consciousness and paresis (50). Disability can be defined as limitations in carrying out activities of daily living, such as self-care, mobility and activities inside or outside the home (50).

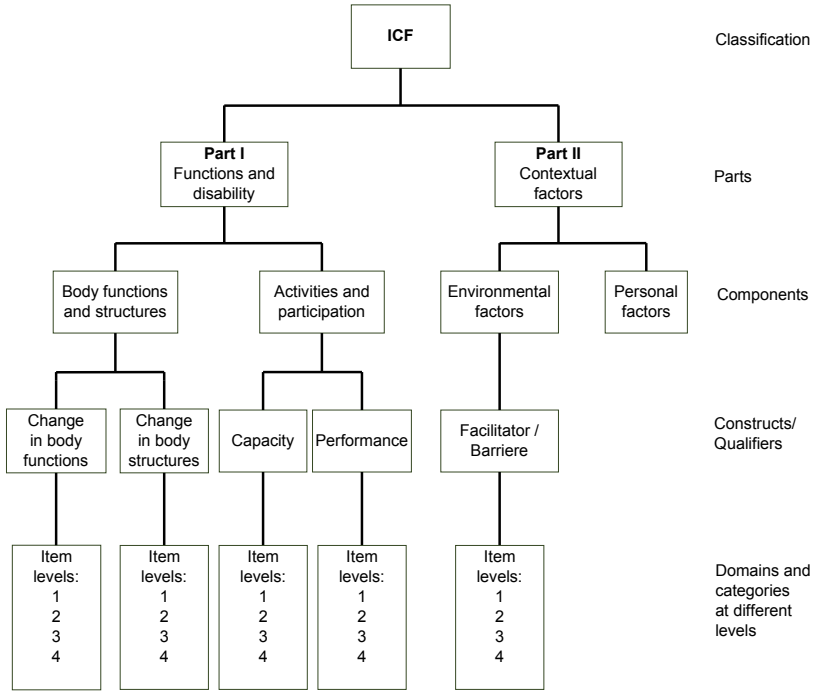
1.4 Conceptual framework

The conceptual framework of this study follows the model proposed by the WHO: the International Classification of Functioning, Disability and Health (ICF). The aim was to provide a framework for the description of health and health-related states of well-being. It is a biopsychosocial model integrating medical and social models reflecting disability as an interaction between the features of the person (the medical model) and the features of the overall context in which person lives (the social model). It has the potential to be used by various disciplines dealing with health and healthcare – scientific, as well as educational, political or sociological fields – as it is likely to become the generally accepted classification for describing functioning and health (50,51).

The ICF is formed by two parts. Part I represents Functioning and Disability. This part includes 2 components: Body functions and structures, and Activities and participation. Part II covers Contextual factors, and includes components of environmental and personal factors.

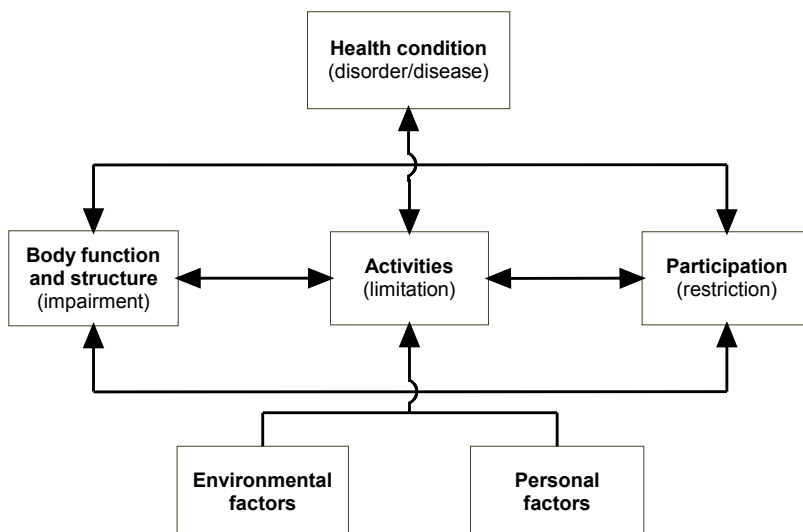
- *Body functions* are normal, physiological and psychological functions of body systems. *Body structures* represent the anatomical structure of the body – organs and systems of organs.
- *Activities and participation* covers the whole range of aspects for the fulfillment of the normal roles of an individual.
- *Environmental factors* comprise all the surroundings of an individual. They are external to individuals and can have positive or negative influence on an individual's performance as a member of a society, the capacity to execute tasks or on body functions or structure.
- *Personal factors* are the particular details of an individual's life and comprise also factors that are not part of the health condition or health status like age, gender, race, education and lifestyle.

Figure 1.3. Structure of the ICF (50)



In contrast with previous models, the ICF has moved away from the model of “consequences of the disease”, representing now “components of health”. While previous models were “disability-oriented”, the ICF terminology is now more neutral. Disability is in the context of ICF considered as an umbrella term for impairments in body functions and structures, limitations in activities and restrictions in participation. The term ‘Handicap’ was thus skipped and replaced by ‘Activities’ and ‘Participation’.

Figure 1.4 The ICF model of disability and the interaction of concepts (50)



1.5 Research questions

On an individual level, Parkinson's disease is a chronic progressive disease with a large impact on quality of life. Research on quality of life in PD has mostly focused on the typical motor aspects of PD and a variety of nonmedical, mostly sociodemographic, factors.

Newly recognized nonmotor features have given rise to a number of rather fundamental and conceptual questions – what is their origin – are they just a consequence of biochemical changes in the brain or do some other factors contribute to their development? What are the relationships between the separate nonmotor features - are they independent from each other, do they act simultaneously or do they influence one another? What kind of impact do they have on patients' lives? Despite the fact that a great deal of research has begun in this field, not enough is yet known to be able answer all of these questions.

Our research was conducted in order to evaluate medical and nonmedical variables, their interrelationships and their influence on QoL. Fatigue, depression, anxiety and sleep disorders became the focus of our research. As current knowledge lacks a comprehensive view on these nonmotor features, the main aim was to create a model of predictors of quality of life and to explore the relations between these nonmotor features of PD and to

discuss their clinical consequences. Therefore the following questions in the population of PD patients are discussed.

- 1 Which medical and sociodemographic variables influence quality of life in PD patients? Is QoL affected by nonmotor symptoms?
- 2 Does an interrelationship exist between some nonmotor PD features?

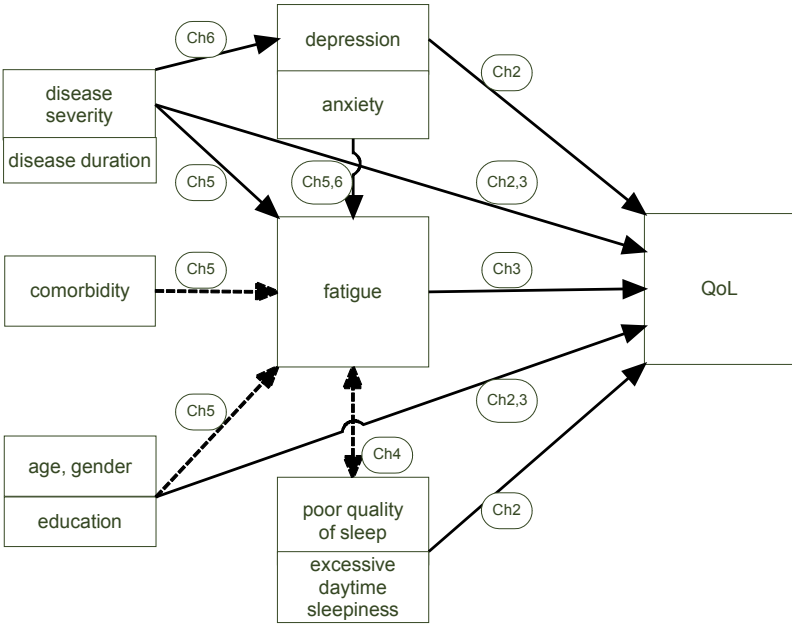
These general research questions are specified as follows:

- 1a Is there a relationship between daytime and nighttime sleep disturbances and different QoL domains?
- 1b How are different fatigue domains related to different QoL domains, and is there a difference between the physical and mental dimensions of QoL?
- 2 Is there a relationship between nighttime or daytime sleep problems and fatigue, or are they independent from each other?
- 3a Do mood disorders or comorbidities contribute to the development of fatigue?
- 3b Is there a causal relation between disease severity and depression and fatigue, and between depression and fatigue themselves?

1.6 Study design

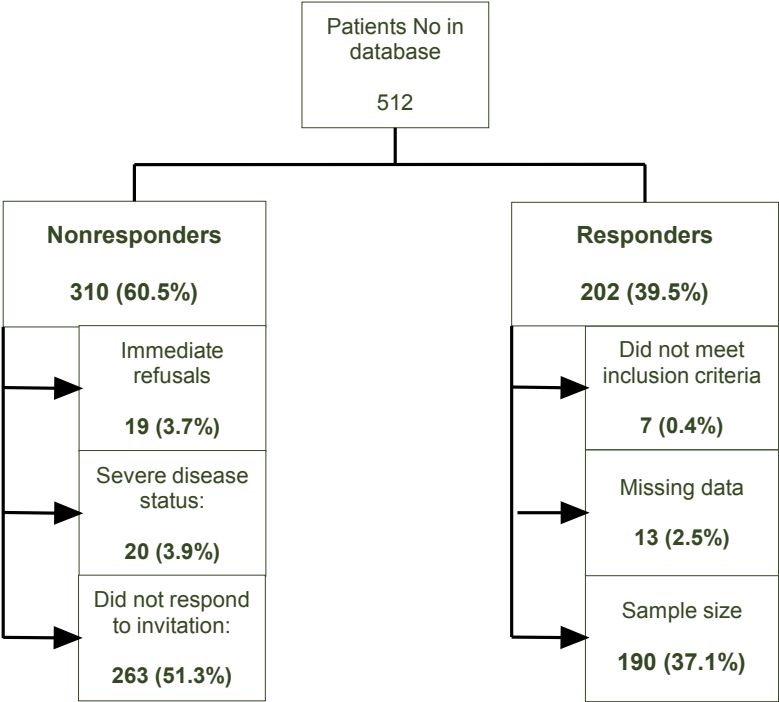
The study was designed as cross-sectional in order to evaluate quality of life and biomedical and psychosocial variables linked to QoL in patients with Parkinson's disease. The patients were recruited from the hospitals and outpatients departments in the East Slovakian region. Data collection started in February 2004 and ended in November 2005. All patients were diagnosed according to the United Kingdom Parkinson's Disease Society Brain Clinical Criteria (52; 52). Exclusion criteria were defined as follows: 1. presence of dementia; 2. disease duration longer than 15 years; 3. presence of comorbidity associated with the fatigue variable.

Figure 1.5 Conceptual model



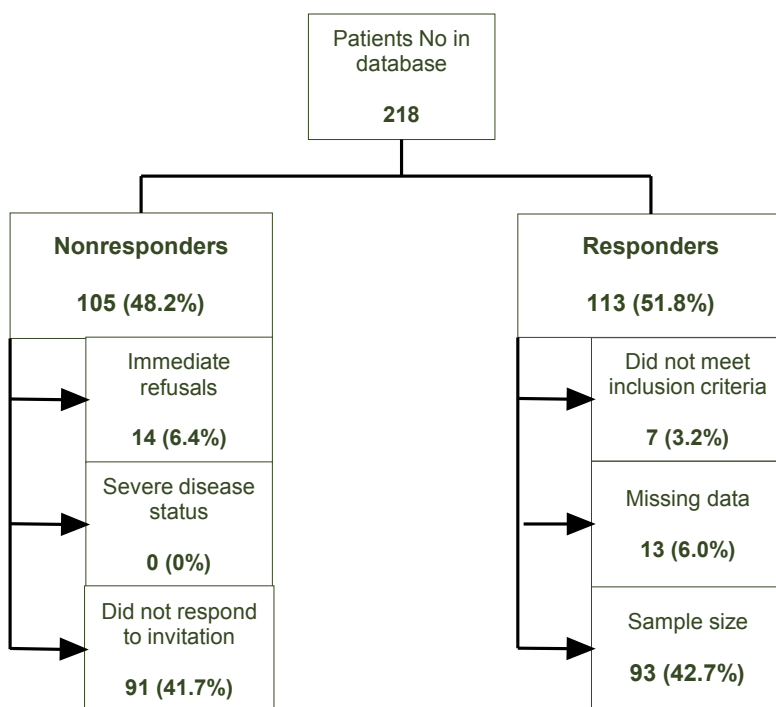
Based on the database records of outpatient neurologists, 512 PD patients were invited to participate in our study. A total of 19 patients refused immediately, 20 did not wish to participate because of the severity of disease status and 263 did not respond to the invitation. Out of responders, 7 patients did not meet inclusion criteria and 13 were excluded because of the missing data (these patients agreed to participate in the study, filled in the questionnaire, but refused to come for the oral interview); 190 remained for analysis (See Figure 1.6.). Most of the patients were recruited from several outpatient departments over the eastern part of Slovakia.

Figure 1.6 Data collection – details on responders and nonresponders of the total sample



The first protocol did not include the sleep questionnaires, which were introduced into our study later. After both sleep questionnaires were added, 218 patients were asked to participate. Fourteen refused immediately and 91 did not respond to the invitation; 7 patients did not meet inclusion criteria, 13 were excluded because of missing data and consequently 93 remained for analysis (See Figure 1.7).

Figure 1.7 Data collection - details on responders and nonresponders of the sample after introduction of the sleep questionnaires



Data were collected by means of a mailed questionnaire comprising questions on sociodemographic background, medical history and current medication, as well as self-report questionnaires. After three weeks all patients were interviewed with a structured interview and were examined by the same neurologist, who assessed functional status and mental abilities. Patients who were not able to fill in the questionnaires by themselves because of motor impairment of their hands answered the questions during an oral interview.

Nonresponders did not differ significantly from the analyzed total group in age (mean difference, 1.9 yrs., SE=0.78; t=1.965; 95%CI 0.46 –

3.54). Nonresponders in the group with the sleep questionnaires also did not differ significantly from the analyzed group in age (mean difference 1.6 yrs., SE=1.22; t=1.315; 95%CI -0.798 – 4.003) or gender (difference between proportions 0.095, SE = 0.066, 95% CI -0.0343–0.224) (difference of proportions test) (28).

Table 1 Clinical and sociodemographic variables of the total study sample and the study sample with the sleep questionnaires

Variable	Total sample	Sleep sub-sample
	n, %, Mean±SD	n, %, Mean±SD
1. Gender		
Male	93 (48.9%)	46 (49.5%)
Female	97 (51.1%)	47 (50.5%)
2. Age	68.2 ± 9.3	68.0 ± 9.5
3. Disease duration	6.4 ± 4.7	6.1 ± 5.9
4. UPDRS* total	36.3 ± 20.5	35.3 ± 20.4
UPDRS III	16.1 ± 10.7	15.6 ± 10.7
UPDRS IV	3.3 ± 3.3	3.1 ± 3.0
5. H&Y*	2.2 ± 1.1	2.0 ± 1.2
≤ 2.0	115 (60.5%)	65 (69.9%)
> 2.0	75 (39.5%)	28 (30.1%)
6. S&E*	69.3 ± 22.3	69.6 ± 22.1
≤ 70%	88 (46.3%)	41 (44.0%)
> 70%	102 (53.7%)	52 (56.0%)
7. PSQI*		9.1 ± 4.9
≥ 5		68 (73.1%)
8. ESS*		7.76 ± 4.9
> 10		22 (23.7%)
9. Antiparkinsonian drugs used		
L-dopa	24 (12.6%)	10 (10.7%)
Dopamine agonists	43 (22.6%)	21 (22.6%)
L-dopa + COMT inhibitors	40 (21.1%)	12 (12.9%)
L-dopa + Dopamine agonists	27 (14.2%)	8 (8.6%)
L-dopa + COMT inhibitor + Dopamine agonists	23 (12.1%)	6 (6.5%)
Other	33 (17.4%)	36 (38.7%)

*UPDRS - Unified Parkinson's Disease Rating Scale. H&Y - Hoehn & Yahr Staging. S&E - Schwab & England Scale. PSQI - Pittsburgh Sleep Quality Index. ESS - Epworth Sleepiness Scale

The study was approved by the Ethics Committee of the University Hospital Kosice on the 17th of December 2002. Informed consent was obtained from each patient.

1.7 Outline of the thesis

Nonmotor symptoms are common in patients with Parkinson's disease. They are recognized as factors having a negative influence on quality of life, but the exact impact still remains unclear. Among all of the nonmotor symptoms, fatigue is one of the first three most disabling problems when rated by PD patients, thus fatigue, together with quality of life, is at the centre of our research.

Sleep problems, and especially sleepiness, started to attract attention after the reports of so called "sleep attacks" were connected with antiparkinsonian therapy (dopamine agonists) and it was determined that they could even lead to car accidents. The influence of excessive daytime sleepiness and poor night-time sleep on quality of life is described in Chapter 2.

In Chapter 3 the influence of fatigue on quality of life is presented. Five different fatigue dimensions are evaluated in order to explore their impact on eight quality of life domains. Linear regression analysis was performed in a stepwise manner in two blocks; the first block contained the variables that we controlled for (age, gender, disease duration, education level and disease severity) and the second block contained the five fatigue domains.

The aim of our research presented in Chapter 4 was to explore the relationship between sleep problems occurring either during daytime (excessive daytime sleepiness) or nighttime (quality of sleep) and fatigue. Series of linear regression were performed to evaluate separately sleepiness or sleep quality and their relationships with age, gender, disease duration, disease severity, depression and all separate fatigue domains.

The next chapters deal with fatigue and factors related to the development of fatigue in PD patients. In Chapter 5 the relative strength of disease duration, comorbidities, anxiety, depression and disease severity was explored in order to evaluate, using linear regression analysis, their influence on five domains of fatigue: general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue. The aim of Chapter 6 is to examine how disease severity explains the different fatigue domains, how disease severity explains depression, and how disease severity explains via depression the different fatigue domains using LISREL.

In the last chapter (7) the consequences of our research and their potential impact on clinical practice are discussed. In addition, the possible interventions which could lead to improvements of the quality of life of PD patients are presented in this final chapter.

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