Non-motor symptoms in Parkinson's disease

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Summary and conclusions

Recent insights in the clinical spectrum of PD emphasize the important role of non-motor symptoms such as olfactory impairment, autonomic dysfunction, sleep problems, cognitive problems, and psychiatric manifestations in the disease process.[1] This thesis characterizes these non-motor domains in patients of the PROfiling PARKinson's disease (PROPARK) cohort and describes their relations with other domains of the disease as well as their impact on disability and quality of life. Furthermore, the phenotypic characteristics of mutation carriers in this patient cohort were evaluated.

Chapter 1 is the introduction to this thesis. It shortly outlines the recent insights in pathophysiology and symptomatology of PD. For decades, the focus of PD management and research has been on the dopaminergic system and the motor symptoms of the disease. More recently, it has become clear that in addition to the substantia nigra, PD may also affect other regions of the brain. Furthermore, in PD cell loss is not restricted to dopaminergic neurons, which may explain the occurrence of non-motor symptoms. However, in contrast with the motor symptoms of PD, our insights in the non-motor domains of PD are still limited. Concerning the potential causes of PD, there is compelling evidence for a role of genetic factors in the disease. Therefore, the aims of this thesis were to characterize the non-motor domains and their relations with other domains of the disease on a cross-sectional level, to establish the influence of non-motor domains on disability and health-related quality of life, and to evaluate the phenotypic characteristics of mutation carriers in the PROPARK cohort.

The purpose of the study in **chapter 2** was to evaluate the relation between olfactory impairment (OI) and other impairment domains in PD, as well as to evaluate the characteristics of OI in patients with certain genotypic characteristics. Olfactory function was evaluated with the odor identification (ID) and discrimination (DIS) tests of the Sniffin' Sticks in 295 non-demented PD patients and 150 controls with a similar overall age and sex distribution. Furthermore, demographic and clinical characteristics were evaluated and genetic analyses were carried out in patients. Sixty-one percent of the patients had an impaired ID and 43% had an impaired DIS. No significant correlations

> 0.4 were found between ID and DIS scores and other demographic or clinical variables. Age and sex accounted for the 22% explained variance of the ID score regression model, whereas age, sex, and disease duration accounted for the 15% explained variance of the DIS score regression model. Normal ID scores were found in *Parkin* and *DJ-1* mutation carriers (homozygous or heterozygous compound, n=6). Carriers of apolipoprotein E (*APOE*) ε2- or *APOE*ε4 allele(s) had no significantly different olfactory scores compared to non-carriers. The allele distribution of the alpha-synuclein (*SNCA*)-REP1 polymorphism in groups with a normal or impaired ID or DIS was comparable. Our conclusion is that in PD, OI may not be related to other impairment domains, which may indicate that olfaction is an independent feature of the disease. *Parkin* and *DJ-1* mutation carriers had normal ID scores but the number of patients with mutations is too small to draw conclusions. The *APOE* genotype (*APOE*ε2 or *APOE*ε4 alleles) and *SNCA*-REP1 polymorphism do not seem to influence olfaction in PD.

Chapter 3 describes the evaluation of the full spectrum of autonomic symptoms (AS) in patients with PD and the assessment of relations between AS and demographic, disease-related, and clinical variables. A reliable and valid instrument, the SCOPA-AUT, was used to evaluate the occurrence of AS in 420 patients with PD and 150 controls. In patients, demographic, disease-related, and motor and non-motor symptoms were also evaluated. For all autonomic domains, patients with PD reported more symptoms compared to controls, with the greatest differences in the gastrointestinal and urinary domain. Higher age, greater disease severity, and higher doses of dopaminergic medication were related to more autonomic problems. Autonomic symptom severity was associated with significantly more motor dysfunction, depressive symptoms, cognitive dysfunction, psychiatric complications, nighttime sleep disturbances, and excessive daytime sleepiness. It can be concluded that AS are important features of PD and that these symptoms increase with increasing age, disease severity, and medication use. The prominent presence of AS warrants increased clinical awareness and highlights the need for efficacious therapies for the wide spectrum of problems related to this domain of PD.

In **chapter 4** the occurrence of nighttime sleep problems (NSP) and daytime sleepiness (DS) in patients with PD was evaluated, and their relations with demographic, disease-related, and clinical characteristics were assessed. The SCOPA-SLEEP questionnaire was administered to 420 PD patients and 150 controls to evaluate NSP and DS. In patients, other disease-related and clinical characteristics were also evaluated. Excessive DS (EDS) (43 versus 10%), excessive NSP (ENSP) (27 versus 9%), and the use of sleep medication (17 versus 12%) occurred in significantly more patients than controls. Difficulties with falling asleep were similar in both groups. In both patients and controls, women experienced more NSP compared to men. In patients, depressive symptoms accounted for 21% of the NSP variance and was the major contributor to the total explained variance (30%). Furthermore, NSP were related to dopamine-agonist and levodopa dose, whereas DS was related to age, dopamine-agonist dose, and disease severity. NSP and DS occur frequently in PD, with EDS being reported more commonly than ENSP. No strong relations were found between DS and demographic or clinical variables. The strong relation between NSP and depressive symptoms in PD calls for future studies to explore the nature of this relation.

The objective of the study described in **chapter 5** was to evaluate cognitive functioning in patients with PD and to assess relations between cognitive functioning and demographic, disease related and clinical variables. The SCOPA-COG, a reliable and valid instrument for measuring cognitive functioning in PD, was used to evaluate 400 patients with PD and 150 controls that were matched for overall age, sex, and education distribution. In patients, demographic and disease-related characteristics were evaluated, together with symptoms in the motor and non-motor domains. On all four cognitive subdomains, patients scored significantly lower than controls, with the largest differences for executive functioning and memory. After correction for age and years of education, cognition as measured by the total SCOPA-COG score was impaired in 22% of patients. Across all patients, more severe cognitive impairment was associated with significantly more impairment in the motor, autonomic, depressive, and psychotic domains. Patients with the postural instability gait difficulty (PIGD)

dominant phenotype showed more cognitive impairment compared with patients with the tremor dominant phenotype. However, PIGD scores were significantly worse with increasing disease severity, contrary to tremor scores. Therefore, the difference in cognitive scores between PIGD dominant patients and tremor dominant patients likely reflects more advanced disease. Cognition is an important domain of the clinical spectrum of PD and poorer cognitive performance is associated with greater impairment in motor and non-motor domains in PD.

In **chapter 6** the evaluation of psychotic symptoms (PS) and compulsive symptoms (CS) in patients with PD was described, as well as the relation of these symptoms with other aspects of the clinical profile of PD. There was no significant correlation between psychotic and compulsive scores in the 353 evaluated patients. PS occurred in 65% of patients, with item frequencies (score ≥ 1) ranging from 10% (paranoid ideation) to 55% (altered dream phenomena). Autonomic impairment accounted for 20% of the 32% explained variance of PS in the regression analysis, whereas cognitive problems, depression, daytime sleepiness, and dopamine agonist (DA) dose together explained the remaining 12%. CS occurred in 19% of patients, with item frequencies (score ≥ 1) of 10% for both sexual preoccupation and compulsive shopping/gambling. Patients with more severe CS (score ≥ 2 on one or both items) were significantly more often men, had a younger age at onset, a higher DA dose, and experienced more motor fluctuations compared to the other patients. It can be concluded that PS and CS are common but unrelated psychiatric symptoms in PD. The relations found between PS and cognitive problems, depression, daytime sleepiness, and autonomic impairment suggest a resemblance with Dementia with Lewy Bodies. The prominent association between PS and autonomic impairment may be explained by a shared underlying mechanism. Our results confirm previous reports on the profile of patients developing CS, and mechanisms underlying motor fluctuations may also play a role in the development of CS in PD.

Early-onset Parkinson's disease (EOPD) has been associated with mutations in the *Parkin, DJ-1, PINK1, LRRK2* and *SNCA* genes. In **chapter 7** the contribution of these genes in the EOPD patients (age at onset ≤ 50 years) in the PROPARK cohort was assessed, as well as the phenotypic characteristics of the mutation carriers.
The unrelated Dutch EOPD patients, 187 in total, were screened for mutations in all exons of *Parkin, DJ-1* and *PINK1* by direct sequencing and gene dosage analysis. Additionally, analysis of the A30P mutation and exon dosage of *SNCA* as well as sequencing of exons 19, 31, 35, 38, 41 and 48 of *LRRK2* was performed, and phenotypic characteristics were assessed. In 4% (7/187) of the patients, pathogenic variations could explain disease including six patients carrying homozygous or compound heterozygous mutations in *Parkin* (n=5) or *DJ-1* (n=1) and one patient carrying a heterozygous *LRRK2* mutation. Seven novel mutations were found in this study, and phenotypic characteristics of mutation carriers varied widely. The most frequently mutated gene in this EOPD cohort is *Parkin*, followed by *DJ-1, PINK1* and *LRRK2*. The conclusion of this study was that mutation carriers varied highly with regard to the phenotypic characteristics, comparable to the variability seen in sporadic EOPD. The low overall mutation frequency indicates that extrapolation of mutation frequencies from other populations should be applied with caution.

Insight in how impairments and disabilities influence health-related quality of life (HRQoL) is important in determining and prioritizing care strategies for patients with PD. In **chapter 8** a model with factors that influence HRQoL in PD was described. The EuroQol-5D Visual Analogue Scale was used to assess HRQoL in 378 patients with PD. With multiple linear regression analysis and structural equation modelling a model with good fit was constructed, which identified various impairments and disabilities as important contributors to HRQoL in PD. Of the disabilities, psychosocial well-being had a larger impact on HRQoL than physical functioning. Of the impairments, depression had the largest contribution to HRQoL, followed by axial motor symptoms, gastrointestinal symptoms, and urinary symptoms. In addition, pain, psychiatric and motor complications, and daytime sleepiness had small but significant influences on HRQoL.

In conclusion, multiple factors such as disabilities, non-motor symptoms and axial motor symptoms, affect HRQoL in patients with PD. This study also shows that the impact of non-motor and non-dopaminergic symptoms on HRQoL in patients on symptomatic treatment aiming to alleviate mainly motor symptoms, is large. Research is warranted to develop and evaluate management strategies for those aspects that have an impact on HRQoL, such as psychosocial well-being, depressive symptoms, axial motor symptoms, gastrointestinal symptoms, and urinary symptoms. These findings call for a multidisciplinary approach with respect to the care of these features.

Concluding remarks

Domain interrelations

The extensive spectrum of motor and non-motor manifestations of PD, emphasizes not only the multisystem nature of the disease, but also the multifactorial etiology of these manifestations which may result from the disease, its drug treatment, or a combination of both.

In this thesis the first aim was to characterize non-motor domains important in PD and to evaluate their relations with other domains of the disease. Of the domains evaluated in this thesis, olfaction was the only domain that seemed unrelated to any of the other impairment domains of PD. Apparently, olfactory impairment in PD may behave as an independent feature of the disease. All other non-motor symptoms were related to symptoms of other domains, with the strongest relations found between nighttime sleep problems and depressive symptoms, and between psychotic and autonomic symptoms. Due to the cross-sectional design, the direction of the relations between these domains is not known, but in other studies for instance relations have been found in both directions for the relation between nighttime sleep problems and depressive symptoms.[2-5]

The relations found between the different impairment domains in PD may emerge through different causes. First, two domains may be related because of a shared underlying mechanism that is inherent to the disease, or may be induced by medication, or by a combination of both.

Second, a relation between impairment domains may emerge because different brain regions are simultaneously affected by the disease process. The pathological staging system of Braak, in which the upper brainstem, midbrain and limbic system become involved as the disease progresses, may explain the co-occurrence of features from these different domains.[6]

Quality of life

The second aim of this thesis was to establish the influence of non-motor domains on disability and HRQoL. Of the non-motor domains in PD, depressive symptoms and autonomic dysfunction were the most important contributors to HRQoL. The finding that cognition does not play a role in HRQoL in our study is surprising. A likely explanation for this finding is that the premorbid variance of normal cognition is large and, due to the fact that the cognitive tests evaluate current cognitive status, cognitive decline is not automatically reflected.

Mutation carriers

The third aim of this thesis was to evaluate the phenotypic characteristics of mutation carriers in the PROPARK cohort. We found a low overall mutation frequency in patients with early onset PD in our cohort, and the mutation carriers showed a wide phenotypic variability and seemed clinically similar to patients without these mutations. However, these findings have to be interpreted with caution due to the low number of mutation carriers in our cohort.

Future plans

This thesis is part of the PROPARK study, a longitudinal cohort study of patients with PD, who are profiled on genotype, phenotype, disability, and global outcomes of health, using valid and reliable assessment instruments for PD. To obtain more insight in the relations found in the cross-sectional analyses described in this thesis, longitudinal data analyses are required. This approach can be particularly helpful in understanding the temporal relations between different domains and the role of shared

factors like exposure to dopaminergic drugs on the occurrence of manifestations of different domains.

Finally, it is also evident that there is a wide phenotypic variability between patients, suggesting the existence of subgroups of patients with regard to clinical manifestations and progression of the disease. The next phase of the PROPARK-study involves the identification and characterization of subgroups of patients. If subgroups exist, this may have important consequences for domain interrelations, as these may vary per subgroup. The domain interrelations described in this thesis are therefore a first global indication of which and how domains may associate. Longitudinal research is needed to elucidate whether there are subgroups with different progression rates of the disease and whether the disease process is primarily spatially (simultaneous involvement of different brain areas) or temporally (sequential involvement of different brain areas) organized. Recognition of subtypes of PD may also contribute to a better understanding of how particular genotypes influence the phenotype expression. Collectively, this knowledge is of great importance for the understanding of the different mechanisms that may operate in PD and provide new directions for research and therapy, all of which could lead to a better quality of life and prognosis for patients with PD.

References

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