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Importance of motor vs. non-motor symptoms for health-related quality of life in early Parkinson's disease

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ABSTRACT

Background: The relative impact of motor- and non-motor symptoms on health-related quality of life in early Parkinson's disease is poorly documented.
Methods: 188 patients with incident Parkinson's disease from a population-based study were examined at the time of diagnosis, before initiation of dopaminergic treatment, with follow-up of 166 patients three years later. Health-related quality of life was assessed by the 36-item Short-form Health Survey (SF-36). Motor and non-motor variables were derived from the Unified Parkinson's disease rating scale and other established scales.
Results: Multiple regression analyses showed that the non-motor symptoms strongest associated with reduced SF-36 scores at diagnosis and three years later were depression, fatigue and sensory complaints. The motor symptoms most related to impaired SF-36 scores were problems with gait and activities of daily living that cover personal needs. The variance of SF-36 mental summary scores was much better explained by non-motor vs. motor symptoms, both at baseline ($R^2 = 0.384$ vs. 0.095) and 3 years later ($R^2 = 0.441$ vs. 0.195). Also SF-36 physical summary scores were better explained by non-motor vs. motor symptoms with $R^2 = 0.372$ vs. 0.322 at baseline and $R^2 = 0.468$ vs. 0.315 after 3 years.
Conclusion: In early PD, including the phase before dopaminergic treatment is initiated, non-motor symptoms are more important for reduced health-related quality of life than motor symptoms. Fatigue, depression, sensory complaints and gait disturbances emerge as the most relevant symptoms and should be given corresponding attention in the management of patients with early PD.

1. Introduction

Both motor and non-motor symptoms contribute to disability and reduced quality of life (QoL) in Parkinson's disease (PD) [1,2]. The increasing focus on non-motor symptoms during the last decade has led to the impression that they are more important for PD patients than motor symptoms. This is supported by a number of studies on health-related quality of life (HRQoL) in PD [1,3–5], but is still seen as controversial. A recent review [2] found that the most frequently reported determinant of HRQoL in PD is the presence of depressive symptoms, followed by severity and disability of the disease.

Although both motor and non-motor symptoms are present from the earliest phase of the clinical disease [6,7], their presence and severity varies with disease progression. For example, a significant proportion of patients with tremor-dominant disease in the early phase convert to PIGD-subtype later [8]. Cognitive function is initially only slightly impaired and in a minority of the patients, but in late stages pronounced dementia is a frequent finding [9]. The impact of the different symptoms on HRQoL will consequently vary over time, but few reports focus on a specified stage or phase of PD [4,10], and only one report has focused on the very early phase of the disease [10].

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Patients suffering from PD are usually appropriately treated for their motor symptoms, while a significant proportion of non-motor symptoms still go unreported and are, consequently, not adequately treated [11]. This may lead to a relatively higher contribution of non-motor symptoms to reduced HRQoL compared to the better treated motor symptoms. It is therefore of interest to compare the impact of motor and non-motor symptoms on HRQoL in patients who have not yet received any treatment for their motor symptoms.

Although a large number of non-motor symptoms is recognized in PD, most studies dealing with HRQoL have focused on the impact of single symptoms or a small selection of non-motor variables [2]. On the other hand are motor symptoms frequently represented as sum-scores of UPDRS subscale ratings, not taking into account the unequal influence the different motor symptoms probably have on QoL-measurements.

Therefore we analyzed the impact of a spectrum of motor and non-motor symptoms on HRQoL measurements in a population-based cohort of patients with very early PD, covering the pre-treatment phase at time of diagnosis with follow-up three years later.

2. Material and methods

2.1. Patients

The current study is part of the Norwegian ParkWest study, a prospective multicenter population-based cohort study of patients with incident Parkinson's disease in western and southern Norway. Details on recruitment and diagnostic procedures have been published [12]. The 194 individuals who gave written informed consent to participation and fulfilled clinical diagnostic criteria for PD [13] at baseline as well as after a follow-up of at least 3 years, were enrolled in the current study. We excluded 5 patients who had taken antiparkinsonian medication within 14 days before baseline and one due to missing data on the HRQoL-questionnaire, leaving 188 patients eligible for baseline analyses.

Medical treatment was first initiated after the baseline visit and was based on individual clinical considerations. All patients were regularly followed-up with clinical examination every 6 months including therapy adjustment when required.

Seventeen patients dropped out of the study within three years after baseline due to death ($n = 11$), refused further participation ($n = 5$) and moved out of study area ($n = 1$), while five had not completed the HRQoL-questionnaire, leaving 166 patients for analyses after 3 years. The study was approved by the Regional Committee for Medical Research Ethics, University of Bergen.

2.2. Assessments

Patients were examined at baseline prior to initiation of anti-parkinsonian treatment and examinations after three years were performed in clinical "on". All collected data are based on either direct interview or examinations by trained study neurologists and nurses or self-report questionnaires from patients when appropriate.

Health-related quality of life was measured with the 36-item Short-form Health Survey (SF-36) which consists of 36 questions covering physical, psychological and social aspects of quality of life and is recommended for use in PD [14,15]. A physical compound score (combined domains: Physical Functioning, Role-Physical, Bodily Pain, General Health) and a mental compound score (combined domains: Vitality, Social Functioning, Role-Emotional, Mental Health) were calculated. Higher scores indicate better quality of life and a score of 50 represents the mean value of a healthy reference population.

Motor symptoms and disease severity were assessed with the Unified Parkinson's Disease Rating Scale (UPDRS) part II–IV and the Hoehn and Yahr staging. Based on previous publications [16,17] and clinical considerations on relationship between UPDRS items we composed symptom scores as shown in Table 1. As sleep disturbances are in part motor manifestations, we included a variable "nocturnal motor symptoms" based on single items from the Parkinson's disease sleep scale [18]. The analysis at 3-year follow-up was supplemented by motor complications of dopaminergic therapy.

Non-motor symptoms were assessed with established assessment scales as shown in Table 1. For autonomic symptoms we used a preliminary version of the Movement Disorders Society version of the UPDRS, pMDS-UPDRS [7,19]. Although dysphagia and salivation usually are classified as non-motor symptoms, there is evidence for both autonomic and motor elements in the underlying mechanisms [20]. As this study aims to investigate the impact of motor vs. non-motor symptoms on HRQoL, we decided to exclude both symptoms in this study.

Table 1
Motor- and non-motor variables assessed.

Motor symptoms	
Communication	UPDRS II: Speech, handwriting (5,8) UPDRS III: Speech, facial expression (18,19)
Personal needs	UPDRS II: Cutting food, dressing, hygiene, turning in bed (9,10,11,12)
Tremor	UPDRS II: Tremor (16) UPDRS III: Rest tremor, action + postural tremor (20,21)
Rigidity	UPDRS III: Rigidity (22)
Bradykinesia	UPDRS III: Finger taps, hand movements, rapid alternating movements, leg agility, body bradykinesia (23–26,31)
Gait	UPDRS II: Freezing, walking (14,15) UPDRS III: Gait (29)
Axial symptoms	UPDRS II: Falling (13) UPDRS III: Arise from chair, posture, postural stability (27,28,30)
Nocturnal motor symptoms	Parkinson's Disease Sleep Scale (PDSS): Nocturia due to motor off, awakening due to dystonic extremities, tremor in morning (9 + 12+13, total 0–30, higher score = less symptoms)
Dyskinesia and fluctuations	UPDRS IV: Dyskinesia, fluctuations (32–39)
Non-motor symptoms	
Sensory complaints	UPDRS II: sensory complaints (17, score 0–4, higher score = increasing severity)
Autonomic dysfunction	pMDS-UPDRS I: Urinary dysfunction, constipation, lightheadedness when standing (10 + 11+12, each item range 0–4, total 0–12, higher score = increasing severity)
Cognitive function	Mini Mental State Examination (MMSE, 20 items, variable score 1–5, total 0–30, higher score = better cognitive function)
Depression	Montgomery and Aasberg Depression Rating Scale (MADRS, 10 items, each 0–6, total 0–60, higher score = increasing severity)
Fatigue	Fatigue Severity Scale (FSS, 9 items, each 1–7, total score is mean of 9 items range 1–7, higher score = increasing severity)
Apathy	Starkstein Apathy scale (SAS, 14 items, each 0–3, total 0–42, higher score = increasing severity)
Sleep disturbances	Parkinson's Disease Sleep Scale (PDSS, exclusive motor items (9,12,13) and daytime sleepiness (15), 11 items, each 0–10, total 0–110, higher score = less sleep disturbances)
Daytime sleepiness	Epworth Sleepiness scale (ESS, 8 items, each 0–3, total 0–24, higher score = increasing severity)

Numbers in parenthesis indicate item-number in UPDRS, pMDS-UPDRS and PDSS, respectively, if not other is indicated.
UPDRS II: unified Parkinson's disease rating scale, activities of daily living section.
UPDRS III: unified Parkinson's disease rating scale, motor section.
pMDS-UPDRS I: movement disorders society revised UPDRS, preliminary version.

Education was quantified as sum of years of school- and academic education. The Levodopa-equivalent daily dose (LED) was calculated according to a recent review [21].

2.3. Statistics

Statistics were performed using SPSS 20 (SPSS, Chicago, IL). For comparison between baseline and 3-year follow-up we used paired samples *t*-test and McNemar test, as appropriate. SF-36 physical component summary score and mental component summary score were calculated according to the published manual [22]. The association of motor and non-motor symptoms to SF-36 summary scores was investigated with regression models in different, independent sequences with increasing interaction of the variables. Each regression procedure was controlled for

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