The Late Stage of Parkinson's –

Results of a large multinational study on motor and non-motor complications

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Abstract (250 words)

Introduction: There is little information on the late stages of parkinsonism.

Methods: We conducted a multicentre study in 692 patients with late stage parkinsonism in six European countries. Inclusion criteria were disease duration of ≥7 years and either Hoehn and Yahr stage ≥4 or Schwab and England score of 50 or less.

Results: Average disease duration was 15.4 (SD 7.7) years and mean total UPDRS score was 82.7 (SD 22.4). Dementia according to MDS-criteria was present in 37% of patients. Mean levodopa equivalence dose was 874.1 (SD 591.1) mg/d. Eighty two percent of patients reported falls, related to freezing (16%) or unrelated to freezing (21% of patients) or occurring both related and unrelated to freezing (45%), and were frequent in 26%. Moderate-severe difficulties were reported for turning in bed by 51%, speech by 43%, swallowing by 16% and tremor by 11%. Off-periods occurred in 68% and were present at least 50% of the day in 13%, with morning dystonia occurring in 35%. Dyskinesias were reported by 45% but were moderate or severe only in 7%. Moderate-severe fatigue, constipation, urinary symptoms and nocturia, concentration and memory problems were encountered by more than half of participants. Hallucinations (44%) or delusions (25%) were present in 63% and were moderate-severe in 15%. The association with overall disability was strongest for severity of falls/postural instability, bradykinesia, cognitive score and speech impairment.

Conclusion: These data suggest that current treatment of late stage parkinsonism in the community remains insufficiently effective to alleviate disabling symptoms in many patients.

Introduction

The clinical features of Parkinson's disease (PD), including motor and non-motor features, are well recognised. However, whilst many studies have concentrated on the earlier features of the disease and their treatment, there is surprisingly little information on the clinical problems encountered in the late stages of PD, even though this is the population with the greatest impairment requiring significant medical and non-medical management. Whilst many motor and non-motor can be present even in the early stages of PD, including mild slowness, anxiety, depression, sleep disturbances, constipation and orthostatic hypotension, they are typically less common and less severe than in advancing disease, and others, like motor complications, freezing and hallucinations are rare [1-4]. Most studies including patients in later disease stages addressed specific features such as hallucinations, are single-center or had small sample sizes [5-7]. In specialist practice, the proportion of patients in the late stages is also underrepresented as they are often too disabled to attend hospital or office-based appointments and do not receive adequate care [7]. Knowledge about the motor and non-motor features of late stage parkinsonism is required to inform appropriate management of and service provision for these patients. Therefore, we here describe the results of a cross-sectional investigation of the clinical features of late stage parkinsonism from a large, European cohort study.

Methods

Study design

The Care of Late Stage Parkinsonism (CLaSP) study is a longitudinal multicentre cohort study of patients with late stage Parkinsonism in the six European health care systems (UK, Germany, The Netherlands, France, Portugal and Sweden), identified

from primary care, care of the elderly, neurology and palliative care settings. Details of the protocol were published previously [8].

Inclusion Criteria

Patients were eligible for enrolment if they had been diagnosed for at least seven years with Parkinsonism and were classified as Hoehn and Yahr stage (HY) 4 or 5 in the "On"-state OR had developed significant disability (Schwab and England stage ≤50%) in the "On"-state [9]. Established clinical criteria (UK Parkinson's Disease Society Brain Bank Diagnostic Criteria [10]) were applied to distinguish subjects with PD from those with one of the different atypical parkinsonian syndromes.

Exclusion criteria

Patients with a diagnosis of "symptomatic PD" such as normal pressure hydrocephalus or drug-induced Parkinsonism, except if persisting following discontinuation of the causative drug, were excluded. Patients with Parkinsonism with a clear history of dementia occurring by history before the onset of Parkinsonism were also excluded.

Data collection

Assessments were undertaken during home visits or outpatient appointments. Due to concentration problems, fatigue or fluctuations of symptoms, we conducted assessments either on one or two separate home visits or two outpatient appointments within two weeks. All clinical data were entered in a central anonymised data management system.

Outcome measures

The following instruments were used to comprehensively collect motor and non-motor features of late stage parkinsonism: the Unified Parkinson's disease Rating Scale (UPDRS) including its four parts: Mentation, Behavior and Mood (part I), Activities of Daily Living (part II), Motor Examination (part III), and Complications of Therapy (part IV) [11]. This scale was chosen instead of the MDS-UPDRS for the following reasons: At the design stage and start of the study, there were insufficient data available on the MDS-UPDRS to allow for sample size calculation using the experiences of daily living parts, particularly at the more severe end of the spectrum of disease. As the scale was specifically designed to be more sensitive at the mild stage of the disease [12], it was unclear whether this may have affected its sensitivity at the more severe stages. Subscores were derived for speech (item 18), facial expression (item 19), tremor (item 20 and 21), rigidity (item 22), bradykinesia (items 23-26), postural instability and gait impairment (PIGD; items 27-29) and body hypokinesia (item 30) [13]. Treatment complications were measured with the UPDRS – part 4 (UPDRS-IV), which were summarized for dyskinesia (items 32-34) and off-periods (items 36-39) [13]. In addition, the Hoehn and Yahr scale (HY) was used to describe disease stage [14]. To assess the occurrence and severity of non-motor symptoms, the Non-Motor Symptom Scale (NMSS) was used [15]. We recorded previous diagnoses of dementia. Assessment of cognitive function was performed using the Mini-Mental State Examination (MMSE) [16] and the Pill questionnaire to assess functional impact [17]. For diagnosis of dementia, the Movement Disorders Society criteria for dementia level I [17] were applied. As some patients were unable to perform all tasks on the MMSE due to motor impairment, we also calculated a percentage score out of the total completed items to account for physical limitations in completion e.g. due to speech impairment or dexterity and re-applied the criteria.

Disability was assessed with the Schwab & England Scale [9] with scores ranging from 0 (complete dependence/bedridden) to 100% (complete independence). The dopaminergic medication dose was calculated using the levodopa equivalent daily dose (LEDD) [18].

To determine the prevalence of motor and non-motor problems, we report the number and percentage of patients who had score of at least 1 on UPDRS items reflecting motor problems, and of at least 1 on the severity scores of the NMSS reflecting non-motor problems. For presence of impulse control disorders, we applied the question assessing this complication from the MDS-UPDRS. In addition, we report the prevalence of moderate to severe problems as defined by a score of 3 on the UPDRS items (moderately or severe impaired) and of at least 2 on the severity scores of the NMSS (some or severe distress to the patient).

Statistical analyses

Descriptive data are presented as either mean and standard deviation (SD) or median and interquartile range (IQR) and percentages. We performed an unpaired samples T-test to compare Schwab and England score between men and woman. Continuous variables were evaluated with Pearson or Spearman correlation coefficients, depending on the distribution of data. For multivariate analysis, multivariate logistic regression models were built using Schwab and England scores as outcome measure. If p-value was ≤ 0.1 in univariate analysis, variables were included in the multivariate analysis. To prevent collinearity between independent variables, bivariate correlations were calculated between all independent variables. If variables had a rho >0.5, they were considered to be collinear and the variable with the highest correlation with the outcome measure was included in the final model. A

backward stepping approach was used to select the final model using maximum likelihood estimates to discriminate between steps. Results were considered statistically significant if the Bonferroni-corrected p-value was <0.05.

Ethical approval

The study was approved by the ethical review board of each individual center. Written informed consent was obtained from all participants. In case the patients were unable to sign, consent was given by the legal representative, mostly a spouse or family member, in accordance with the country-specific legal requirements.

Results

Overall, 752 patients participated in the study. Twenty-three patients were excluded due to disease severity of milder degree (Hoehn and Yahr <3 and S&E >50%), and 37 participants due to a disease duration of less than <7 years. All remaining 692 participants were included in the further analysis. All scales had missing data <8%.

Clinical features and complications

Disease duration was 15.4 (SD 7.7) years and most participants were in H&Y stage 4 and 5 (92.5%). The remaining 7.5% had Schwab and England scores ≤50 but Hoehn and Yahr stage <4. Mean age was 76.1 (SD 8.4) years and 54% were men. Mean total UPDRS score was 82.7 (SD 22.4). The prevalence of motor problems as assessed on the UPDRS is shown in figure 1, and of non-motor problems in figure 2. The mean UPDRS part I score was 5.3 (SD 3.2) out of a maximum score of 16, part II 26.8 (SD 7.6) out of 52, part III 45.6 (SD 15.0) out of 108 and part IV 5.1 (SD 3.5) out of 23. A previous diagnosis of dementia was present in 37%.

Dementia diagnosed according to the MDS-criteria for dementia was present in 40% of patients if all questions that were not completed were rated as errors, and in 37% if the MMSE was calculated as a percentage of questions that were completed. Eighty two percent of patients reported falls, either only related to freezing (16%) or unrelated to freezing (21% of patients) or occurring both related and unrelated to freezing (45%), and were frequent in 26%. Help was required for turning in bed by 51%, moderate-severe speech impairment was reported in 43% and moderate to severe swallowing problems and in 16%. Off periods occurred in 68% and were present at least 50% of the day in 13%, with morning dystonia occurring in 35%. Moderate-severe tremor was reported by 11%, and dyskinesias by 45% but were moderate or severe only in 7%. The average LEDD was 874.1 (SD 591.1) mg/d and correlations of LEDD with clinical features and complications were all negligible (rho<0.2).

The NMSS showed at least one moderate to severe non-motor symptom in 651 participants (98.6%) and the average participant had 15.7 non-motor symptoms and 11.4 moderate-severe non-motor symptoms. Hallucinations occurred in 44% and delusions in 25%. Impulse control disorders, were present in 16.5% and severe in 4.5%. For further individual symptom frequencies see figure 2 and supplementary materials.

Relationship of clinical features with Disability

Overall Schwab and England disability score was 33.9 (SD16.0) out of a maximum (most independent) score of 100. In the multivariate regression analysis with Schwab and England score as dependent variable, and using all clinical features that were significant in the univariate analysis with p<0.1 without collinearity, the clinical

features with predicting disability score in this late stage sample of parkinsonism were Hoehn and Yahr stage, MMSE score, bradykinesia, speech and ability to arise from a chair (see table 2).

Discussion

We delineate the clinical features and complications of the late stages of PD based on the largest study in this population to date. In this study, we purposefully included patients that were no longer seen in specialist clinics. The results from nearly 700 patients from six different countries are therefore likely to be representative of this underserved population. Unlike many earlier studies [19], gender distribution in our sample appeared representative of the PD population, with almost as many women as men, reflective of the greater longevity in women but higher prevalence of PD in men.

The severity of disease in this cohort was reflected in the high motor and non-motor scores on the UPDRS motor and ADL parts and the NMSS. Compared to results of other clinical studies, the UPDRS scores and frequencies on non-motor symptoms were higher than in patients with early disease[20, 21], but also than in patients who have advanced but not necessarily late disease[22]. However, motor complications including off-periods and dyskinesias, which are characteristic of PD leading to advanced therapies, were present only in 45% of this late stage population and moderate to severe in 7%[22-25]. Despite a large variety of symptomatic and supportive treatment options, most patients had moderate to severe motor and non-motor problems. The most common problems included falls, even in patients already bed-bound, off-periods for more of 50% of the day, speech and swallowing problems,

and autonomic and psychiatric complications such as constipation and bladder problems, fatigue and dementia.

Amongst the individual features of late stage parkinsonism, whilst a high rate of falls, hallucinations and dementia was expected, it is noteworthy that despite moderate doses of levodopa only a small proportion had moderate to severe dyskinesia. It is likely that, as in other phases of the disease, considerable heterogeneity exists and many no longer develop dyskinesias. This is also in keeping with previous reports that only approximately 50% of patients in the late stage of PD have a significant response to levodopa. Alternatively, some patients may not have received high enough doses of dopaminergic medications to develop dyskinesia, in agreement with previous findings in a study of Dutch nursing homes where many patients appeared to be relatively undertreated (3). Similarly, only 11% had moderate to severe tremor despite high overall motor scores, in keeping with the observations that many patients with the tremor subtype lose their tremor and develop the akinetic rigid subtype with longer follow-up [26, 27]. It is also noteworthy that a proportion of 16.5% of patients had moderate to severe impulse control disorders, even in the advanced stages of the disease, indicating that these should be proactively screened for in this population, and not just in the higher risk group of younger men [28].

Disability, as assessed by the Schwab and England scale, was strongly influenced by the presence of motor severity as assessed by the Hoehn and Yahr stage, overall bradykinesia and axial features but also speech impairment. This highlights the importance of communication problems in mediating patients' dependence on others. The other main predictor of disability was cognitive status whilst other clinical features such as nocturia, hypersalivation or pain had little or relationship to disability scores, and neuropsychiatric symptoms or autonomic dysfunction were no longer strongly

related to disability once these factors were accounted for. This is likely to be a reflection of the instrument used which assesses level of physical dependence on others, for which these features may be less relevant than for quality of life or broader or instrumental disability measures or quality of life measures. In this severely affected disease population it is important to stress, however, that individual symptoms, which may not be a frequent problem or a predictor of disability in the overall group once other factors are accounted for, may it still be a major burden for the individual patient.

Knowledge of the frequency of specific motor and particularly non-motor complications at this disease stage should inform both clinical management and future research studies in this vulnerable population. Whilst treatment for many of these complications exist, potential side effects on other parkinsonian features such as orthostatic hypotension or comorbidities such as ischaemic heart disease often limit their use [29]. This highlights the importance of finding new pharmacological or non-pharmacological options suitable for patients in this disease phase and providing care and support using other strategies. Many patients in the late stages no longer receive specialist input, which may be due to difficulties attending or the assumption that this will not provide useful benefit. However, adjustment of antiparkinsonian medication may improve some levodopa-responsive motor as well as non-motor features, discontinuation of medications that are no longer needed and may cause side effects may improve non-motor problems, and treatment of specific non-motor features, e.g. depression, constipation or hallucinations, may lead to overall improvement of quality of life[30]. Different models of care that allow patients to receive specialist input in non-specialist settings, may be beneficial to these patients [7, 31, 32]. In particularly, palliative care approaches that incorporate PD-expertise

may be well suited to address some of the non-levodopa responsive treatments with MDT input, non-pharmacological options and non-PD medications.

The high frequency of motor and non-motor symptoms also emphasized the need for the development of a pragmatic tool to improve recognition of these symptoms. The great variety in treatment strategies across patients observed in our study furthermore highlights the need to develop dedicated protocols and guidelines for management in this late stage population, to further harmonize treatment, and to ascertain that patients in advanced stages of PD – with their complex phenotype – receive the best possible care.

With the increasing population age and rising prevalence of PD expected over the next decades there is a growing challenge to deliver the appropriate care to patients who reach the late stages of this disorder [33]. This study is the first study that specifically characterises the clinical features of patients with late stage parkinsonism across several European countries. Combining the detailed assessments of patients in six different countries and across neurology, geriatric and palliative care settings, provides comprehensive knowledge on this hitherto little studied population. This information can then inform how best to provide effective care for this severely affected patient group and contribute to improved practices for clinical care.

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Authors' Roles

AS and RD conceived the program, designed the study and wrote the study protocol. All contributing authors contributed to the organization and execution of the study. The statistical analysis was designed by AS, performed by AH, with AS providing critical review. AS wrote the first draft of the manuscript with AH, and all authors providing critical review and critique.

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Appendix

Members of the CLaSP Consortium: Joaquim Ferreira, Margherita Fabbri, François Tison, Alexandra Foubert-Samier, Joy Read, Marjan Meinders, Raymond Koopmans, Carmen Richinger, Kristina Rosqvist, Michael Wittenberg, Petra Neuser