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Risk and course of motor complications in a population-based incident Parkinson's disease cohort

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ABSTRACT

Background: Motor complications may become major challenges in the management of patients with Parkinson's disease. In this study, we sought to determine the incidence, risk factors, evolution, and treatment of motor fluctuations and dyskinesias in a population-representative, incident Parkinson's disease cohort.

Methods: In this prospective population-based 5-year longitudinal study, we followed 189 incident and initially drug-naïve Parkinson's disease patients biannually for detailed examination of dyskinesias and motor fluctuations as defined by the Unified Parkinson's disease Rating Scale. We performed Kaplan–Meier survival and Cox regression analyses to assess cumulative incidence and risk factors of these motor complications.

Results: The 5-year cumulative incidence of motor complications was 52.4%. Motor fluctuations occurred in 42.9% and dyskinesias in 24.3%. Besides higher motor severity predicting both motor fluctuations ($p = 0.016$) and dyskinesias ($p < 0.001$), lower age at diagnosis predicted motor fluctuations ($p = 0.001$), whereas female gender predicted dyskinesias ($p = 0.001$). Actual levodopa dose at onset of motor fluctuations ($p = 0.037$) or dyskinesias ($p < 0.001$) rather than initial treatment with levodopa ($p > 0.1$) independently predicted development of motor complications. Motor fluctuations reversed in 37% and dyskinesias in 49% of patients on oral treatment and remained generally mild in those with persistent complications. No patients received device-aided therapies during the study.

Conclusions: More than 50% in the general Parkinson's disease population develop motor complications within 5 years of diagnosis. However, they remain mild in the vast majority and are reversible in a substantial proportion of patients.

1. Introduction

Parkinson disease (PD) is a relentlessly progressive movement disorder of unknown etiology [1]. With PD progression, the efficacy of pharmacotherapy deteriorates [2] and patients may develop motor complications, which can be broadly subdivided into motor fluctuations and dyskinesias. The risk for and time to emergence of these motor complications vary substantially among patients for reasons that are probably complex, including both disease- and drug-related factors, particularly treatment with levodopa [3,4].

Although motor fluctuations and dyskinesias may compromise quality of life [5], their evolution and prognosis are still incompletely investigated, as most previous studies assessed cross-sectional cohorts with established disease [6] or followed patients recruited from movement disorders centers or clinical trials [7]. This may result in both under- and overestimation of the risk of these motor complications. In addition, as treatment options have changed during the last decades, previous estimates might no longer be accurate. Finally, device-aided therapies have emerged as

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second-line treatments in patients with otherwise intractable motor complications [8,9]. Recent studies promote early initiation of these advanced therapies [9,10], which – however – are costly and may cause serious adverse events. Therefore, precise information on the evolution and potential reversal of motor fluctuations and dyskinesias using conventional pharmacotherapy is crucial for optimal patient selection to and timing of second-line treatment in PD.

To gain this important knowledge, we recruited a large, population-based, and initially drug-naive PD cohort that we monitored closely for emergence of motor complications for five years from diagnosis.

2. Methods

2.1. Subjects

All subjects participate in the Norwegian ParkWest project, a prospective, population-based, multicenter, longitudinal cohort study investigating the incidence, neurobiology and prognosis of PD. In order to establish a population-representative, incident PD cohort, we recruited patients with newly-diagnosed and untreated PD from the general population between November, 2004, and August, 2006, using multiple recruitment strategies, as previously described [11]. Briefly, all patients were screened, followed and treated by neurologists from the study group, who are experienced in movement disorders. Diagnostic procedures at baseline included a full medical history, comprehensive clinical, neuropsychological and neuropsychiatric assessments, laboratory tests, cerebral MRI, and, if indicated clinically, dopamine transporter imaging. Standardized follow-up visits were conducted every six months. Of 212 patients included in the original cohort, five were not drug-naïve at baseline and further 18 rediagnosed during follow-up, leaving 189 patients eligible for this study. All met widely acknowledged research criteria [12,13] for PD at latest follow-up. The study was approved by the Regional Committee for Medical Research Ethics, Western Norway. Signed written consent was obtained from all participants.

2.2. Evaluation program and treatment

At baseline, a study neurologist performed general medical and neurological examinations and semi-structured interviews to obtain medical and drug history. Motor severity and disease stage in the drug-naïve state were rated using the Unified PD Rating Scale (UPDRS) [14] motor section (part III) and Hoehn and Yahr staging. Assessment of non-motor features included the Mini-Mental State Examination (MMSE), Montgomery Aasberg Depression Rating Scale (MADRS), Fatigue Severity Scale (FSS), PD Sleep Scale (PDSS), Epworth Sleepiness Scale (ESS), and Starkstein Apathy Scale (SAS).

Following baseline examinations, antiparkinsonian treatment was initiated and adjusted throughout follow-up by a study neurologist according to best clinical judgement. Drug changes in between study visits were allowed when deemed clinically necessary. Motor complications were assessed at 6-month intervals by clinical observation and the UPDRS complication of therapy section (part IV) with a score of $\geq$1 on items 36, 37, 38 or 39 defining presence of motor fluctuations and a score of $\geq$1 on items 32, 33 or 34 defining presence of dyskinesias. Type and dose of medications were recorded at each study visit, and levodopa-equivalent doses (LED) were calculated according to published recommendations [15]. Use of advanced therapies was also recorded, defined as subcutaneous apomorphine administration, continuous intestinal levodopa infusion, or subthalamic nucleus deep brain stimulation (STN-DBS), which all are provided at no personal or private insurance company costs in Norway.

2.3. Statistical analysis

SPSS 21.0 was used for statistical analysis. Incidence rates with 95% confidence intervals were calculated and expressed in relation to 1000 person-years of observation. Between-group differences were compared using t-tests, Mann–Whitney U-tests and χ^2-tests as appropriate. We performed Kaplan–Meier survival analysis to evaluate cumulative incidence rates of motor fluctuations and dyskinesias, and Cox regression analysis to assess baseline factors associated with evolution of these motor complications. Separate analysis of wearing-off was performed without significant changes in results, thus all motor fluctuations are presented as one group in the following. We considered age, gender, time since motor onset, and motor severity at baseline as primary risk factors of interest. In subsequent models adjusting for these variables, we also included a panel of non-motor symptoms (as these have been associated with motor complications in cross-sectional studies) assessed at baseline using MMSE, MADRS, FSS, PDSS, ESS, and SAS. Finally, we investigated the associations of initial treatment (levodopa vs. dopamine agonists) as well as actual LED at onset of motor complications with the development of motor fluctuations and dyskinesias. Two-tailed p-values <0.05 were considered significant.

3. Results

3.1. Baseline characteristics and subject flow

Baseline characteristics are given in Table 1 and the flow of subjects in Fig. 1. Of the 189 patients included at baseline, 183 (97%) completed 1 year, 173 (92%) 3 years and 158 (84%) 5 years of biannual follow-up, generating 1911 observations in total. Few subjects (7/189, 4%) withdrew from the study, whereas remaining loss to follow-up (24/189, 13%) was due to death. Median follow-up time was 5.0 (interquartile range 4.9–5.1) years.

3.2. Frequency of motor complications

Point prevalence rates increased progressively, reaching 38.0% for any motor complications, 31.0% for motor fluctuations, and 12.7% for dyskinesias at 5 years of follow-up (Table 2). The 5-year cumulative incidence of any motor complications was 52.4%, with a corresponding incidence rate of 158 (95% CI 132–189) per 1000 person-years of observation. For motor fluctuations, the cumulative

Table 1
Baseline characteristics of 189 patients with incident, drug-naïve PD.

Characteristics	Values
Number	189
Male, n (%)	114 (60.3)
Age, years	67.7 (9.3)
Time since diagnosis, months	1.6 (1.7)
Symptom duration, years	2.3 (1.8)
UPDRS motor score	23.4 (11.3)
Hoehn and Yahr stage	1.9 (0.6)
MMSE score	27.8 (2.5)
MADRS score	4.7 (5.2)
FSS score	4.4 (1.6)
PDSS score	118.9 (19.6)
ESS score	6.0 (3.6)
SAS score	15.6 (4.8)
Body weight, kilograms	76.5 (14.4)

Values are mean (SD) if not otherwise indicated. UPDRS = Unified Parkinson's Disease Rating Scale; MMSE = Mini-Mental State Examination; MADRS = Montgomery Aasberg Depression Rating Scale; FSS = Fatigue Severity Scale; PDSS = Parkinson's Disease Sleep Scale; ESS = Epworth Sleepiness Scale; SAS = Starkstein Apathy Scale.