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Clinical milestones in Parkinson's disease: A 7-year population-based incident cohort study

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ABSTRACT

Introduction: Clinical staging of Parkinson's disease (PD) is important for patient management and prognosis. The non-motor and functional features visual hallucinations, recurrent falls, dementia and nursing home placement are currently not included in clinical staging schemes, but have been suggested as clinical milestones with important prognostic implications in advanced PD. In this study, we sought to evaluate the potential of these four milestone events for clinical staging and prognosis during the early years of the disease.

Methods: We recruited 185 patients with incident PD and monitored prospectively every six months through seven years for emergence and consequences of four clinical milestones.

Results: One or more milestones were reached in 53.0%. Of the patients who reached the milestones, visual hallucinations appeared after a median of 3.3 (interquartile range 1.3–4.9) years from diagnosis, recurrent falls after 3.8 (2.8–5.2) years, dementia after 4.0 (2.1–4.8) years and nursing home placement after 5.4 (3.9–6.7) years. Presence of any milestone was associated with occurrence of other milestones (relative risks 1.9–6.3; all $p \leq 0.001$). Experiencing two or more milestones increased the risk of death during the study (relative risk 2.7, $p = 0.03$).

Conclusions: In early PD, visual hallucinations, recurrent falls, dementia and nursing home placement appear closely interrelated, possibly reflecting a shared neuropathological disease stage. All events convey important and sinister information on PD status and prognosis and are relatively easily accessible during routine clinical consultations. Therefore, they appear highly useful as clinical PD milestones and could possibly be incorporated into a novel disease rating scale.

1. Introduction

Clinical indicators of disease stage and prognosis remain essential in evaluation of Parkinson's disease (PD) progression, as no biomarkers are currently available for routine clinical use. The most widely accepted clinical staging system of PD, the Hoehn and Yahr scale, focuses exclusively on motor impairment. However, with progressive cerebral spread of Lewy body pathology [1], PD increasingly reveals itself as a multi-system brain disorder [2], and non-motor symptoms, including psychotic and cognitive problems frequently develop [3], adding substantially to the disease burden of patients and caregivers [4]. Consequently, it could be argued that clinical assessment of PD stage and prognosis should address these non-motor symptoms at least as extensively as motor disability. Furthermore, functional outcomes, such as falls and nursing home placement, could probably add usefulness to a clinical staging system.

A previous report [5] hypothesized that four clinical disease features, visual hallucinations, recurrent falls, dementia and nursing home placement, emerge as a cluster at similar latencies before death and, importantly, provide information on the Lewy body burden found post mortem. These clinical features may therefore offer valuable information on PD stage and prognosis. The study, however, was retrospective and performed in a selected sample of patients with long-standing disease who underwent

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autopsy. Thus, it is unclear if these findings are generalizable and whether they apply to patients with early disease. To clarify this important issue, we prospectively monitored a large, population-based, incident PD cohort for emergence of visual hallucinations, recurrent falls, dementia and nursing home placement during the first 7 years after diagnosis.

2. Methods

2.1. Participants

All participants in this study were derived from the Norwegian ParkWest project. In this prospective, population-based, multicenter longitudinal cohort study, we have followed patients with initially drug-naïve PD from diagnosis to investigate the incidence, neurobiology and prognosis of various aspects of the disease. We sought to include all inhabitants with newly-diagnosed PD in four counties in Western and Southern Norway between November 2004 and August 2006. To achieve this, primary care, nursing homes and private and hospital specialist clinics collaborated, as described previously [6]. Exclusion criteria included clinical or MRI signs indicating atypical or secondary parkinsonism, negative dopamine transporter imaging, or non-progressive parkinsonism or tremor. A total of 212 patients were initially included in the study. However, five were not drug-naïve at baseline, and 22 were excluded during follow-up due to possible or probable alternate diagnoses, leaving 185 patients eligible for this study. All patients met acknowledged research diagnostic criteria of PD [7,8].

2.2. Standard protocol approvals, registrations, and consents

The Regional Committee for Medical and Health Research Ethics, Western Norway, approved the study, and signed written consent was obtained from all participants.

2.3. Assessment and follow-up

2.3.1. Examination program

Movement disorders neurologists from the study group diagnosed and managed all patients. We obtained demographic data, full medical history, extensive clinical and neuropsychiatric examinations, laboratory tests and cerebral MRI at diagnosis, and performed dopamine transporter imaging when deemed helpful in differential diagnosis. Patients were reassessed by movement disorders neurologists every 6 months and treated in line with best clinical judgement. We offered home visits to those unable or not willing to meet at the clinic in order to minimize attrition bias.

Clinical examinations every six months included the Unified PD Rating Scale [9] (UPDRS) part I (mentation, behavior and mood), II (activity and daily living), III (motor examination), V (modified Hoehn and Yahr staging [10]) and VI (Schwab and England activities of daily living scale [11]). In addition, we performed standardized neuropsychiatric and cognitive assessments at baseline and at 1, 3, 5 and 7 years of follow-up, including the Neuropsychiatric Inventory [12] (NPI) to obtain data on neuropsychiatric problems from close informants, the Mini-Mental State Examination [13] (MMSE) to assess global cognitive function, and neuropsychological assessments of verbal memory, attention, executive functioning, and visuospatial skills. Presence of mild cognitive impairment in PD (PD-MCI) and dementia associated with PD were determined based on all available information from patients and caregivers, and diagnosed according to published guidelines [14,15], as described previously [16,17]. The Montgomery and Aasberg Depression Rating Scale [18] (MADRS) was used for assessment of depressive symptoms. We also collected information on living situation and health care status using standardized interviews, as outlined in previous reports [19,20].

2.3.2. Milestones

We assessed clinical milestones as follows: visual hallucinations were defined as scoring 2 or more on UPDRS item 2 ("benign" hallucinations with insight retained), or having an NPI item 2 score of 1 or more (presence of hallucinations). Recurrent falls were defined as scoring 2 or more on the UPDRS item 13 (occasional falls, less than once daily) or 3 or more on item 14 (occasionally falls because of freezing). Dementia associated with PD was defined as fulfilling Movement Disorders Society diagnostic criteria [15], and nursing home placement as being admitted to a high-level, 24-hourly nurse staffed long-term care facility.

2.4. Statistical analysis

We used the IBM statistical package for social sciences 23.0 for all statistical analysis. Where the exact time of a milestone event was not known, we used the time point midway between the last study visit without the event and the visit where the event was first recorded. Evaluations of cumulative incidence rates of the different milestone conditions were performed, and we used Cox regression analysis to identify baseline risk factors for development of milestone conditions during the study. In these models, we analyzed the baseline factors age, gender, UPDRS motor score, MADRS score and presence or absence of PD-MCI using Enter method. Continuous predictor variables were dichotomized in order to meet the proportional hazards assumption in the following way: Age: over/under 70 years of age; UPDRS motor score: over/under the median baseline score of 20 points; MADRS score: over/under 7 (a cut-off previously used for normal versus mild depressive symptoms [21]). The proportional hazards assumption was tested and confirmed for all potential predictors using log minus log plots. Patients with a milestone condition at baseline (3 with recurrent falls and 1 living in a nursing home) were excluded from the Cox regression analysis. We calculated relative risks (RRs) and associated confidence intervals (CIs) and p values for associations between milestone events and death according to Altman [22]. Two-tailed p values < 0.05 were considered significant.

3. Results

3.1. Baseline characteristics and subject flow

Baseline characteristics are provided in Table 1 and the subject flowchart in Fig. 1. Of the 185 patients included, 182 (98.4%)

Table 1
Baseline characteristics.

Characteristics	Values
Number	185
Male, n (%)	111 (60.0)
Age, years	67.7 (9.2)
Time since diagnosis, months	1.6 (1.6)
Symptom duration, years	2.3 (1.9)
UPDRS motor score	23.4 (11.4)
Hoehn and Yahr stage	1.9 (0.6)
Schwab and England ADL- scale	88.2 (9.4)
MADRS score	4.6 (5.0)
MMSE score	27.8 (2.4)
PD-MCI, n (%)	39 (21.1)

All values are mean (SD) if not indicated otherwise.
ADL = Activities of Daily Living; MADRS = Montgomery Aasberg depression rating scale; MMSE = Mini-mental status examination; PD-MCI = Parkinson's disease with mild cognitive impairment; UPDRS = Unified Parkinson's Disease Rating Scale.

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