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The influence of age and approaching death on the course of nondopaminergic symptoms in Parkinson's disease

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ABSTRACT

Introduction: The influence of approaching death in addition to age and their interaction on the course of a broad spectrum of nondopaminergic features in Parkinson's disease (PD) has not been well studied. This study addresses this issue in a prospectively designed study.
Methods: During five years, the severity of axial symptoms, cognitive impairment, psychotic symptoms, autonomic dysfunction, depressive symptoms, and daytime sleepiness was annually evaluated in PD patients. For each domain a linear mixed-effect model was used to examine changes during follow-up and relations with age and death.
Results: Of 378 included patients, 43 died during follow-up. Higher age was associated with increased severity of all nondopaminergic features except depression, and with a higher rate of progression of axial symptoms and cognitive impairment. Patients who died during follow-up had a higher severity of all nondopaminergic features except autonomic dysfunction, and a higher rate of progression of axial symptoms, cognitive impairment, and psychotic symptoms, compared to patients who survived.
Conclusion: This study shows that the severity of most nondopaminergic features and the progression rate of axial and psychotic symptoms and cognitive impairment increase before PD patients die, independent of the influence of age. An interaction between age and approaching death did not have a significant effect on the course of the symptoms. Improving our understanding of the fundamental biology underlying these factors and the interaction with factors intrinsic to the disease, may have profound implications for the treatment of PD.

1. Introduction

Parkinson's disease (PD) is a multi-system disorder characterized by features that occur as a consequence of degeneration of dopaminergic and nondopaminergic neurons [1]. Aging is the single most important risk factor for PD. In addition, age and age at onset are important determinants of disease progression, with patients with higher age and age at onset showing faster clinical progression [2]. Previously, the results of two studies on the PROPARK cohort showed a relation between six predominantly nondopaminergic domains (PND; i.e. axial motor features, cognitive decline, depression, psychotic symptoms, excessive daytime sleepiness, and autonomic dysfunction) and that these domains were strongly related to age [3,4].

A retrospective study using information from case records reported an exponential increase in severity of various PND features (including frequent falling, visual hallucinations and cognitive disability) in the final stage of PD, irrespective of the age at which death occurred [5,6]. Based on these results, the authors hypothesized that age influences the rate of progression especially in the early and middle stages of the disease, whereas in the period before death clinical progression is ruled by factors intrinsic to the disease process with little influence of age.

The influence of age and approaching death on the course of a broad spectrum of PND domains has not been studied comprehensively. We addressed this issue by examining the influence of age, death and their interaction on the severity and progression of

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the aforementioned six PND domains using a prospectively designed study where data were annually collected in a standardized manner using valid and reliable instruments.

2. Methods

2.1. Study design

The study is part of the "PROfiling PARKinson's disease" (PROPARK) study, a longitudinal cohort study of patients with PD, who are profiled on phenotype, genotype, disability and global outcomes of health, using valid and reliable assessment instruments for PD. Findings obtained from five consecutive annual assessments (baseline and four years follow-up) of 414 patients who were assessed between May 2003 and December 2009 were used for analyses. From the sixth annual assessment, only recordings of survival or death were taken into account.

2.2. Patients

All patients fulfilled the United Kingdom Parkinson's Disease Society Brain Bank (UKPDBB) criteria for idiopathic PD at each assessment [7]. Patients were recruited from outpatient neurology clinics of both university and regional hospitals in the western part of The Netherlands. The majority of the patients were assessed at the Leiden University Medical Center (LUMC); patients who were unable to come to the hospital were assessed at home. Since age at onset and disease duration are related to various manifestations of the disease, the recruitment strategy was to obtain an adequate distribution of these determinants within the cohort. A total of 100 patients were recruited in each of the four strata based on age at onset (≤/> 50 years) and disease duration (≤/> 10 years). Patients who had undergone stereotactic surgery were excluded since this intervention may significantly alter the natural course of the condition.

2.3. Standard protocol approvals, registrations, and patient consents

The study was approved by the medical ethical committee of the LUMC and all patients gave written informed consent.

2.4. Measures

Measurement instruments for the different PND were derived from a prior project (Scales for Outcomes in PArkinson's disease: SCOPA) [8]. Outcomes of these measurement instruments are discrete sumscores referring to the severity of impairment in the domain. Axial symptoms (including the items rise, gait, and postural instability from the SPES/SCOPA-motor, range 0–9), cognitive impairment (SCOPA-COG, range 0–43), psychotic symptoms (SCOPA-PC, items 1–5, range 0–15), autonomic dysfunction (SCOPA-AUT, items 4–6, 8–16, range 0–36), depressive symptoms (Beck Depression Inventory (BDI), range 0–63) and daytime sleepiness (DS) (SCOPA-SLEEP section DS, range 0–18) were evaluated. Instruments were either self-completed (SCOPA-AUT, BDI, SCOPA-SLEEP) or administered by trained research associates (SCOPA-COG, SCOPA-PC, SPES/SCOPA). Scores of the SCOPA-COG were inversed to arrange that higher scores reflected more severe impairment in all domains. Age, age at onset (i.e. onset of first symptoms as perceived by the patient), disease duration, and disease severity (Hoehn and Yahr stage) [9] from the latest available assessment of the patient within the study period were used. Patients were recorded as deceased or survivor dependent on if they died or survived their period of study participation. Patients who deceased within 18 months after their last assessment were also recorded as deceased. Patients who were lost during follow-up and patients who were known to be deceased but whose exact date of death could not be retrieved were excluded from the analyses. For reasons of comparability, all patients who used anti-parkinsonian medication were assessed while they benefited from their medication (i.e., were 'on'). When exhaustion or off-periods were detected, patients were allowed to take a break or take medication. For each patient, a total levodopa equivalent (LDE) was calculated [10].

2.5. Statistics

For each nondopaminergic domain (axial, cognitive, psychotic, depressive and autonomic symptoms, and daytime sleepiness), linear mixed-effect models (LMM) were used to examine changes during the follow-up period and relations with covariates [11]. LMM take missing observations of the dependent variable into account under the assumption that the observations are missing at random. Since heterogeneity between patients was expected at baseline levels and for change of the clinical measurements over time, random intercepts and random slopes were used for the follow-up time in all models. Follow-up time in the LMM was modeled opposite to chronological time using years prior to the last observed assessment (last observed assessment in patients who survived or last assessment prior to death in patients who died). This timeline made it possible to evaluate the influence of age, death and their interaction on the severity of symptoms closest to death or end of study.

Covariates were age at last assessment (standardized value), death during follow-up (y/n) and time, expressed as years to last assessment. The following interactions were included: time*age and time*death (to assess whether the covariates influenced the rate of change in the domain), age*death (to evaluate whether the influence of age differed in patients who died or who survived), and the quadratic interactions age*age and time*time (to evaluate non-linear influences of age and time). The following double interactions were included: age*death*time (to evaluate whether the influence of age on the rate of change in a domain differed between patients who died or who survived), time*time*age and time*time*death (to assess if non-linear relations of time were influenced by age or death (i.e. accelerated increase in a domain score in time by higher/lower age or death/survival)), and age*age*time and age*age*death (to assess non-linear relations of age influenced by time or death (i.e. accelerated increase in severity by age influenced by time or by death/survival)).

For each domain, the saturated model included the domain score as dependent variable and included all covariates and all interactions, and a random intercept and random slope with an unstructured covariance matrix. The saturated model was simplified by stepwise excluding the non-significant double interactions, and the non-significant interactions. The final model consists of all significant (double) interactions and all covariates. A p-value < 0.05 was considered statistically significant. For the double interaction a more stringent threshold of $p < 0.01$ was considered because of multiple testing. Analyses were performed using SPSS 17.0 (SPSS Inc, Chicago, IL, USA).

3. Results

Of the 414 patients that participated in the PROPARK study, 36 patients in total were excluded: 31 patients had undergone stereotactic surgery, 3 were lost to follow-up, and from 2 patients the exact date of death was unknown. In total, data of 1654 visits of 378 patients with a mean (SD) follow-up time of 3.44 (1.31) years were analyzed. Patients who died during follow-up (N = 43) had 152