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Short communication

Calculating clinical progression rates in Parkinson's disease: Methods matter

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ABSTRACT

Introduction: Disease progression in Parkinson's disease is often calculated in data from cross-sectional studies, where a severity score (e.g. UPDRS-motor score) is divided by disease duration. While this intuitively may seem a plausible approach, it is uncertain if these rates are similar to those calculated from longitudinal data. The aim of this study is to examine if progression rates calculated according to both methods yield the same results.

Methods: We calculated two progression rates in data from the PROPARK study: one where last follow-up SPES/SCOPA motor and activities-of-daily-living scores were divided by disease duration, and one in which baseline motor and activities-of-daily-living scores were subtracted from data collected at last follow-up, and where the difference was divided by the time that passed between both assessments. We subsequently calculated the rank order correlation between both approaches.

Results: We found that progression rates calculated from cross-sectional data are 1.5–2 times higher than those calculated from longitudinal data, and that the correlation between both methods is <0.50.

Conclusion: Progression rates calculated from cross-sectional data not only overestimate actual progression, but also yield a different rank order. We also discuss potential explanations for the discrepancy between both methods and argue that the method of calculating progression rates in data from cross-sectional studies in PD should not be used.

1. Introduction

Parkinson's disease (PD) is a progressive multi-system disorder, characterized by features that occur as a consequence of degeneration of dopaminergic and non-dopaminergic neurons [1]. This leads to a broad spectrum of impairments and disabilities that deteriorate over time, although medication, physiotherapy and surgery may improve some symptoms temporarily. The disease course is not similar across patients who may exhibit differences in phenotypic expression, which hints at the existence of subtypes of the disease [2]. Since growing evidence indicates that subtypes of the disease may also differ in rate of progression [2], the determination of progression rates is increasingly relevant. A method that is very commonly used in cross-sectional studies in PD is to calculate the progression rate by dividing the score of some severity measure (e.g. motor score of the Unified Parkinson's Disease Rating Scale [UPDRS] [2–5], the total score of the UPDRS [6], or Hoehn and Yahr [H&Y] scale [7]) by the length of the disease duration. The implicit assumption with this procedure is that this particular score is zero at disease onset. This, however, is not true because patients must have symptoms in order to be diagnosed, and hence their scores cannot be zero. The proper approach to calculate the average annual progression rate would be to take the actual score at disease onset into account – which, however, is typically not known in cross-sectional studies – or calculate the progression rate using information from multiple time points.

In the present paper we use data from the PROPARK study to demonstrate that values obtained from a cross-sectional approach yield different values than those obtained from a longitudinal model. In the latter approach the severity score at baseline is subtracted from the scores obtained at the last follow-up, and the resulting difference is divided by the amount of time that passed between both measurements. In an additional analysis we also calculated the average annual progression rates using data from all time points in a model without covariates and in a model with the covariates age, disease duration and dopaminergic medication

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dose. Although we are fully aware that these approaches imply a linear model – which is a too simplistic description of the course of the disease, especially in the light of the availability of effective treatment and the influence of age and disease duration [8,9]–, it was our intention to compare the average annual progression rates obtained by both approaches, and not to model the disease course as accurately as possible.

2. Methods

2.1. Patients

We used data from patients participating in the PROPARK cohort study who had a complete follow-up. The study is described in detail elsewhere [10]. In short, 414 patients with a diagnosis according to the United Kingdom PD Society Brain Bank criteria for idiopathic PD [11] were included and annually examined over a period of 5 years (i.e., 6 assessments) with a broad range of well-validated instruments. In view of the fact that we aimed to obtain information on the full spectrum of the disease, a recruitment strategy based on age-at-onset (onset of PD specific complaints as perceived by the patient; ≤/>50 years) and disease duration (≤/> 10 years) was applied. We intended to recruit at least 100 patients in each of the four strata. Patients who had undergone brain surgery, either at baseline or during follow-up ($n = 41$), were excluded. Data of the 261 patients who took part in both the first and the last assessment (70.0% of the remaining population) were used in the present example. This involved 165 men and 96 women with a mean ± standard deviation (SD) age at last follow-up of 63.4 ± 9.9 years and a mean ± SD disease duration at last follow-up of 14.6 ± 6.0 years. The distribution across H&Y stages at last follow-up was: 1: $n = 0$; 2: 98; 3: 65; 4: 82; 5: 7 (9 missing).

2.2. Instruments

To illustrate our example we used data from 2 subscales of the SPES/SCOPA: the SPES/SCOPA-Motor scale (range: 0–42) and the SPES/SCOPA-ADL (activities of daily living) scale (range 0–21) [12]. A score of '0' in these subscales indicates absence of abnormality and scores >0 are theoretically indicative of pathology, although it cannot be ruled out that some elderly individuals have non-zero scores, as was found in a study where the UPDRS motor scale was administered to normal elderly of 70–90 years old, and where a mean of 4.1 ± 2.8 was found [13]. Instruments whereby a range of scores is consistent with 'normal functioning' – such as the MMSE or the Beck Depression Inventory, and, to a lesser extent, autonomic symptoms or sleep complaints – cannot be used to demonstrate the discrepancy between both methods (and are also not used for this purpose in the literature), because it is unclear which particular score (from the possible range of 'normal' scores) should be used.

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 [14].

2.3. Statistical analyses

For the SPES/SCOPA-Motor and ADL scales we analyzed 2 scenarios: one in which progression rates were calculated on the basis of a cross-sectional approach (PR_{CROSS}), using scores obtained at last follow-up, i.e., last follow-up SPES/SCOPA-Motor or ADL score divided by disease duration at last follow-up; the other calculated from the difference in scores over time (PR_{LONG}), i.e., where baseline SPES/SCOPA-Motor or ADL scores were subtracted from SPES/SCOPA-Motor or ADL scores obtained at last follow-up, and where these score differences were divided by the amount of time that passed between both assessments. The rank order correlation between both approaches was next calculated with Spearman's rho.

Two linear regression analyses with the SPES/SCOPA-Motor or ADL scores obtained at last follow-up selected as dependent variables and disease duration at last follow-up as independent variable were performed to obtain an estimate ('best guess') of the approximate severity of motor and ADL scores at disease onset.

In an additional analysis we used linear mixed models (LMM) to calculate the average annual progression rate. LMM takes into account that repeated measures in the same subject are not independent but correlated. An advantage of this method is that it can deal with missing data in the outcome, and therefore this analysis does not have to be restricted to patients with a complete follow-up, as in the PR_{LONG} approach. A restricted maximum likelihood (REML) model with an autoregressive (heterogeneous) covariance structure type was used in all LMM analyses; this assumes that measurements that are closer in time are more strongly correlated than those that are further apart. Since heterogeneity between patients was expected in baseline levels and in change over time, random intercepts and random slopes were used. Two models were calculated for both scales, one without covariates and one in which baseline age, disease duration and total LDE were entered as covariates.

The PROPARK study was approved by the medical ethics committee of the Leiden University Medical Center and written informed consent was obtained from all participants.

3. Results

The mean ± SD score of the SPES/SCOPA-Motor score obtained at last follow-up was 15.72 ± 5.60 (available for $n = 258$), while the mean ± SD of the ADL score at last follow-up was 10.72 ± 3.63 ($n = 260$). The mean ± SD disease duration at last follow-up was 14.62 ± 6.00 years.

The mean ± SD of the annual progression rate based on the cross-sectional approach calculated on the data from the last follow-up was 1.23 ± 0.62 for the SPES/SCOPA-Motor ($PR_{CROSS\text{-}MOTOR}$) and 0.82 ± 0.36 for the SPES-ADL ($PR_{CROSS\text{-}ADL}$). The distributions of $PR_{CROSS\text{-}MOTOR}$ and $PR_{CROSS\text{-}ADL}$ versus disease duration are shown in Fig. 1A and B.

The mean ± SD annual progression rate based on the longitudinal approach for the SPES/SCOPA-Motor scale ($PR_{LONG\text{-}MOTOR}$) was 0.63 ± 1.04, whereas this was 0.53 ± 0.58 for the SPES/SCOPA-ADL scale ($PR_{LONG\text{-}ADL}$). The distributions of $PR_{LONG\text{-}MOTOR}$ and $PR_{LONG\text{-}ADL}$ versus disease duration are shown in Fig. 2A and B.

The rank order correlation between $PR_{CROSS\text{-}MOTOR}$ and $PR_{LONG\text{-}MOTOR}$ was 0.48 ($P < 0.001$). The rank order correlation between $PR_{CROSS\text{-}ADL}$ and $PR_{LONG\text{-}ADL}$ was also 0.48 ($P < 0.001$).

The linear regression model with the SPES/SCOPA-Motor scores obtained at last follow-up as dependent variable and disease duration at last follow-up as independent variable yielded an intercept of 12.96 and a regression coefficient of 0.19 (SPES/SCOPA-Motor score = 12.96 + 0.19 * disease duration in years). With the SPES/SCOPA-ADL score as dependent variable, the model yielded an intercept of 8.12 and a regression coefficient of 0.18 (SPES/SCOPA-ADL score = 8.12 + 0.18 * disease duration in years).

The mean progression rate based on the LMM analysis for the SPES/SCOPA-Motor scale ($PR_{LMM\text{-}MOTOR}$) without covariates was 0.65, whereas this was 0.67 for the model with the covariates age, disease duration and total LDE (Table S1). The mean progression rate based on the LMM analysis for the SPES/SCOPA-ADL scale ($PR_{LMM\text{-}ADL}$) without covariates was 0.55, whereas this was 0.56 for the model with the covariates age, disease duration and total LDE (Table S1).

4. Discussion

The present analysis shows that cross-sectional and longitudinal methods of calculating progression rates in PD yield very different results, but that both longitudinal methods result in quite similar findings. The small differences between the results of both longitudinal approaches are in part due to the fact that in LMM all time points are used instead of the two time points in the PR_{LONG} approach, and that the PR_{LONG} analysis is based on complete data, whereas the LMM procedure can deal with missing data in the outcome variable and thus is applied on a larger sample.

If cross-sectional and longitudinal methods would have been similar, this would have resulted in a similar rank order and a Spearman's correlation coefficient value close to 1, which clearly was not the case. One might argue that the measurement error of the scales should be taken into account and that perfect correlation therefore cannot be expected. However, the interrater reliability of the sumscores of the SPES/SCOPA motor and ADL scale, measured with an intraclass correlation coefficient, are 0.86 and 0.89 [12], respectively, and therefore a much higher correlation than 0.48 would have been expected if the methods were equivalent. With the cross-sectional method, the rates are 1½ (ADL scale: 0.82 vs 0.53) to 2 (Motor scale: 1.23 vs 0.63) times higher than the values obtained with the longitudinal methods. The discrepancy is caused by the fact that the cross-sectional method does not take the actual score at disease onset into account. In the cross-sectional approach, the implicit assumption is that at disease onset this score is zero,