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Comparison of clinical features among Parkinson's disease subtypes: A large retrospective study in a single center

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ABSTRACT

Introduction: Tremor dominant (TD), postural instability/gait difficulty (PIGD), and akinetic-rigid (AR) subtypes are widely used in classifying patients with Parkinson's disease (PD).

Methods: We compared clinical characteristics between PD subtypes in a large retrospective cohort. Between 1998 and 2016, we included a total of 1003 patients with PD in this retrospective study. Six hundred ninety-four patients had more than one visit. Data were collected regarding motor/non-motor symptoms at the initial/final visits. Based on the prominent symptom at the initial visit, we classified patients into one of the four subtypes: TD, AR, gait difficulty, and mixed. Rapid progression was defined by emergence of falls, dementia, or dependency within 5 years after onset.

Results: TD was the most prevalent subtype (44%), followed by AR (29%), mixed (18%), and gait difficulty (9%). Rapid progression was observed more frequently in gait difficulty compared to AR (OR: 3.59 $P < 0.001$). Hallucinations at the final visit were more likely to occur in AR (OR: 2.36, $P = 0.005$) and mixed (OR: 3.28, $P < 0.001$) compared to TD.

Conclusions: Our findings provide support for a distinction of four different PD subtypes: TD, AR, gait difficulty, and mixed. The gait difficulty subtype was distinguishable from the AR subtype.

1. Introduction

Parkinson's disease (PD) is a clinically heterogeneous neurodegenerative disorder [1]. Tremor may be present dominantly in some patients, but it may be less obvious than other cardinal signs [2,3]. While PD usually occurs after age 60, some patients experience their PD symptoms earlier than 40 years of age [4]. This clinical variability indicates that pathophysiological distinctions underlie diverse phenotypes of PD. In the past three decades, researchers have attempted to classify PD patients into clinical subtypes in several ways, using either an empirical approach based on observation [5], or a data-driven approach using cluster analysis [6–8]. The resulting classifications have the potential to provide us with subtype-specific information including etiology, prognosis and responsiveness to therapies. For example, patients who have tremor dominantly are likely to exhibit slower progression and better response to levodopa than others [9,10]. Not only motor signs, but also non-motor symptoms may differ between PD subtypes [11]. These subtypes may represent different stages of PD rather than being independent of each other [12].

The empirically assigned classification is recommended to be used in clinical research because of its simplicity of implementation and the small number of subtypes [1]. Traditionally, the empirical approach leads to three different PD subtypes, and these are classified in one of two ways: (1) tremor dominant (TD), postural instability/gait difficulty (PIGD), and indeterminate [3,5], or (2) TD, akinetic-rigid (AR), and mixed [13,14]; these classifications are widely used. PIGD and AR are similar entities and have been used without being clearly distinguished [1,15]; however, these are intrinsically different because items for rigidity and bradykinesia are not always used for classifying PIGD subtype, and those of postural instability and gait disturbance are not used

Abbreviations: AR, akinetic-rigid; OR, odds ratios; PD, Parkinson's disease; PIGD, postural instability/gait difficulty; UPDRS, the Unified Parkinson's Disease Rating Scale; TD, tremor dominant

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for AR according to the rating method using the Unified Parkinson's Disease Rating Scale (UPDRS) [14,16]. An early factor analysis indicated that rigidity and bradykinesia did not contribute to the characterization of subtypes [3], and there is little knowledge about clinical differences between these two subtypes.

We performed clinical subtyping in a large cohort of PD patients who were seen at our institution. In contrast to the previous studies, we considered AR and gait difficulty as different subtypes, as we hypothesized that their clinical characteristics may differ. Specifically, we empirically classified patients into one of the following four subtypes: TD, AR, gait difficulty, and mixed. The aim of this study was to compare clinical information between these four PD subtypes in order to advance our understanding of PD heterogeneity.

2. Methods

2.1. Study population

This study was approved by the Mayo Clinic Institutional Review Board Committee. All participants provided written informed consent upon recruitment to this study. All patients were seen at Mayo Clinic, Florida between July 1998 to December 2016 by movement disorder specialists (JAVG, RJU, and ZKW). We only included patients who fulfilled the clinical diagnostic criteria of PD [17] and had detailed clinical information available. In addition, the current study is part of an ongoing clinico-genetic study, and therefore all included patients agreed to give blood for genetic analysis. Since the diagnosis of PD made at the initial visit could be changed, if new clinical information or symptoms appeared in subsequent visits (694 patients of our cohort had more than one visit), all PD diagnoses at the patients' final visits were verified. Patients who had non-PD diagnosis at their final visits were excluded from our analysis (e.g. drug-induced parkinsonism, vascular parkinsonism, normal pressure hydrocephalus, progressive supranuclear palsy, corticobasal syndrome, multiple system atrophy). We excluded patients who had developed dementia within one year from onset because in that case their clinical diagnosis was considered to be dementia with Lewy bodies [18].

2.2. Collection of clinical data

We retrospectively reviewed medical records of the patients and extracted data regarding their demographic information and motor and non-motor symptoms at initial and final visits, and date of death (if available). Demographic information included age of onset (defined as the time that a PD-related motor sign initially appeared), gender, and family history of PD (defined as at least one relative with PD diagnosis). Motor signs included bradykinesia, rigidity, postural instability, resting tremor, postural tremor, kinetic tremor, dystonia, and dyskinesia. Non-motor symptoms were dementia, orthostatic hypotension, other autonomic dysfunction (gastrointestinal [GI], and urogenital [UG] dysfunction), impulse control disorder, hallucinations, depression, rapid eye movement sleep behavior disorder, and restless legs syndrome. Since diagnostic procedures (e.g. tilt-table test, polysomnography) were not always performed, patients were considered as having symptoms if suspected by the movement disorder specialists. In addition, we collected information regarding levodopa use and response to levodopa at initial and final visits.

2.3. PD subtype classification

All research subjects had very extensive descriptive Mayo Clinic historical records including detailed clinical history and a full Mayo Clinic semi quantitative neurological examination [19]. However, information regarding UPDRS and Hoehn and Yahr stage was not collected. We classified each patient based on initial evaluation into one of four clinical subtypes: TD, AR, gait difficulty, and mixed. If tremor was the most prominent clinical feature, the patient was classified as having TD subtype. If rigidity and bradykinesia were the prominent phenotypic characteristic, the patient was classified as having AR subtype. If gait difficulty was the prominent abnormality, the patient was classified as having a gait difficulty subtype. If there were mixed signs and no prominent feature could be identified, such patient was classified as having a mixed subtype. The prominent feature had to be internally consistent with the patient's history, neurological examination findings, and final physician's diagnosis at the time of initial visit. Three of authors (TK, AD, and MO) independently reviewed full medical documents of patients' initial visit and classified each patient into one of the four aforementioned subtypes. Disagreements were resolved by consensus through discussion with one of the movement disorder specialists (ZKW) as needed. Patients were considered to be a rapid progressor if they had fallen, developed dementia, or become dependent (i.e. requiring assistance for activity in daily life such as eating, dressing, and maintaining hygiene, or living in a nursing home) within 5 years from PD onset; if none of these criteria has been met and the patient had not been followed for 5 years after onset, progression information was considered to be unavailable.

2.4. Data analysis

Tests of overall difference in clinical features across the four PD subtypes were performed using multivariable regression models as follows. Features assessed at the initial/final visit were compared across PD subtypes using logistic regression models adjusted for age at initial/final visit, disease duration at initial/final visit, levodopa use at initial/final visit, and gender. Age at PD onset was compared between PD subtype groups using a linear regression model adjusted for gender and family history of PD. Gender, family history of PD, and rapid progression were compared between subtypes using logistic regression models adjusted for age of PD onset, gender, and family history of PD. Survival after PD onset was estimated using the Kaplan-Meier method and was compared between the PD subtypes using Cox proportional hazards regression models adjusted for age at PD onset, gender, and family history of PD. When there was a statistically significant difference across the four subtypes for a given feature (which only occurred for binary outcomes), pair-wise comparisons between subtypes were made using the aforementioned logistic regression models; odds ratios (ORs) and 95% confidence intervals were estimated.

To account for the number of statistical tests performed regarding overall tests of difference between subtypes, we utilized a Bonferroni correction when considering the 17 different clinical features that were examined at the initial and final visit, the three baseline features (age of PD onset, gender, family history of PD), rapid progression and its three components, and survival after onset. After adjusting for these 25 independent overall tests, P-values of 0.0020 or lower were considered as statistically significant. For pair-wise comparisons that were made only when a significant ($P \leq 0.0020$) overall difference was identified, these were also adjusted for using a Bonferroni correction. After adjustment for all six pair-wise comparisons made for a given clinical feature, P-values of 0.0083 or lower were considered as statistically significant. All statistical analysis was performed using SAS (version 9.4; SAS Institute, Inc., Cary, North Carolina) and R Statistical Software (version 3.1.1; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

We identified 1003 patients with PD from our records. 694 patients had more than one visit at our clinic, with a median length of time of 3.7 years (Range: < 0.1–22.9 years) between initial and final visits. A summary of the clinical features of the overall cohort is provided in Table 1. Median age at PD onset was 64 years (Range: 22–94 years). TD was the most frequent PD subtype (44%), followed by AR (29%), mixed (18%), and gait difficulty (9%) (Fig. 1). Median disease duration was