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The association between non-motor symptoms in Parkinson's disease and age at onset

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ABSTRACT

Objective: Age at onset is likely to be related to a wide range of problems in Parkinson's disease (PD), including cardinal motor features, motor complications and non-motor symptoms (NMS). This study investigated the effect of the age at onset on NMS.
Methods: Two hundred and thirty patients were examined and classified into one of three groups based on age at onset: early onset PD (EOPD) group (<45 years), middle-age onset group (45–64 years) and old-age onset group (≥65 years). The trends relating to NMS were compared across the three groups. The EOPD and old-age onset groups were separately studied to determine their association to the appearance of non-motor features using logistic regression analysis.
Results: There were upward trends in the occurrence of dribbling ($P = 0.009$; all P values are stated for trend), impaired taste/smelling ($P = 0.016$), constipation ($P = 0.006$), urinary urgency ($P = 0.002$), nocturia ($P = 0.018$), hallucinations ($P = 0.016$) and acting out during dreams ($P = 0.011$) with the increase of age at onset. Older age at onset is an independent risk factor for dementia (OR = 8.42, CI 3.16–22.44), dribbling (OR = 4.14, CI 1.93–8.87), impaired taste/smelling (OR = 2.23, CI 1.20–4.13), constipation (OR = 3.42, CI 1.88–6.24), incomplete bowel emptying (OR = 2.23, CI 1.19–4.20), urinary urgency (OR = 2.58 CI 1.46–4.57), nocturia (OR = 2.65, CI 1.49–4.71), hallucinations (OR = 5.32, CI 1.78–15.97), dizziness (OR = 3.03, CI 1.59–5.79), falling (OR = 3.60, CI 1.67–7.77), insomnia (OR = 2.29, CI 1.28–4.11), intense vivid dreaming (OR = 2.10, CI 1.21–3.66) and acting out during dreams (OR = 2.23, CI 1.24–4.01).
Conclusions: PD patients with different ages at onset present clinically different symptoms in terms of NMS. Old-age onset PD is characterized by more olfactory and sensory symptoms, autonomic symptoms, sleep disorders, dementia and psychosis compared to EOPD.

1. Introduction

Parkinson's disease (PD) is an aging-related neurodegenerative disorder, characterized by a wide spectrum of motor and non-motor symptoms (NMS) [1–3]. Motor phenotypes vary from tremor-dominant to postural instability and gait difficulty (PIGD) are related to disease progression and the presence of NMS, such as cognitive decline and rapid eye movement (REM) sleep behavior disorder (RBD) [4–6]. Evidence from both genetic aetiological and clinico-pathological studies showed that pathogenic mutations or the Lewy body pathology of differing distribution and severity are linked to age at onset; this appears crucial to the phenotypes or subtypes of PD [7–9].

According to a number of studies, PD patients with a younger age at onset exhibit slower disease progression, higher risk of dyskinesia and dystonia, lower rate of dementia and worse quality of life compared to older age of PD onset [10–12]. The relationship between age at onset and non-motor features is less clear due to few previous studies. NMS are of great importance in the emergence and progression of PD. Several NMS such as constipation, olfactory deficit and RBD are suggested as preclinical signs of PD [13]. However, NMS and their prevalence by age at onset have not been previously well described. Our study aimed to estimate the effect of the age at onset on NMS.

2. Materials and methods

Consecutive patients diagnosed with PD according to the United Kingdom PD Society Brain Bank (UK-PDSBB) criteria were recruited from the neurology outpatient clinic at Xinhua Hospital of Shanghai Jiaotong University during the period April 2007 to December 2010. Patients of any age and any disease stage were enrolled in the investigation. Exclusion criteria included the inability to understand or

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Table 1
Demographic and clinical characteristics by onset group.

	All $N=230$	<45 years $N=13$	45–64 years $N=103$	≥65 years $N=114$	*P*-value
Gender (male: female)	136:94	5:8	66:37	65:49	0.169
Age (year)	63.1 (10.0)	50.7(4.9)	61.8 (6.2)	75.0 (4.5)	<0.0001
Age at onset (year)	63.0 (10.0)	40.1 (3.3)	56.7 (4.9)	71.3 (4.6)	<0.0001
Motor subtype, *n* (%)					
Tremor	125 (54.3)	7 (53.8)	63 (61.2)	55 (48.2)	0.162
Akinetic-rigid	74 (32.2)	6 (46.2)	34 (33.0)	34 (29.8)	0.487
Gait disturbance	31 (13.5)	0 (0.0)	6 (5.8)	25 (21.9)	0.001
Disease duration (year)	4.6(3.6)	9.3 (5.1)	5.0 (3.9)	3.7 (2.4)	<0.0001
Hoehn and Yahr Scale	2.4 (0.3)	2.4 (0.3)	2.2 (0.8)	2.5 (0.9)	0.07
UPDRS-III score	42.6 (23.0)	41.2 (16.0)	39.5 (23.5)	45.7 (23.0)	0.133
MMSE	26.6(3.9)	28.8(1.5)	27.7(3.1)	25.2(4.4)	<0.0001
HDRS	10.3(7.6)	9.1(7.8)	10.0(7.9)	10.7(7.4)	0.661
HARS	7.7(6.2)	8.7(8.1)	7.3(5.5)	7.9(6.5)	0.661
PDSS	111.7(36.0)	134.2(23.6)	114.8(39.9)	106.3(32.1)	0.015
ESS	4.3(5.5)	0.2(0.8)	4.7(6.2)	4.3(5.1)	0.023
Dopaminergic treatment duration (year)	3.2 (3.7)	7.3 (5.1)	3.5 (4.2)	2.4 (2.5)	0.001
Daily L-dopa dose (mg/d)	343.8 (270.6)	646.2 (290.3)	332.1 (279.0)	328.8 (240.7)	<0.0001
<500 mg/d (%)	166 (72.2)	3 (23.1)	75 (72.8)	88 (77.2)	<0.0001
≥500 mg/d (%)	64 (27.8)	10 (76.9)	28 (27.2)	26 (22.8)	
L-Dopa equivalent daily dose (mg/d)	386.7 (284.3)	719.9 (293.3)	373.6 (286.7)	360.6 (258.5)	<0.0001
<600 mg/d (%)	184 (80.0)	4 (30.8)	84 (81.6)	96 (84.2)	<0.0001
≥600 mg/d (%)	46 (20.0)	9 (69.2)	19 (18.4)	18 (15.8)	

Values expressed as means ± SD (unless otherwise stated).

answer questionnaires and the presence of comorbidity, sequelae or any disorder interfering with assessment of PD manifestation. To ensure accurate recall information, patients were asked to complete the assessment interview with the aid of caregivers, particularly for patients with a score <24 on the Mini-Mental State Examination (MMSE) [14,15]. The local Ethics Committee approved this study, and patients gave informed consent before participation.

Clinical assessments and data collection were performed. In addition to basic demographic data, the following information were noted: age at onset; initial symptoms of PD (tremor, akinetic-rigid, and gait disturbance); the time of dopaminergic therapy initiation; daily dose of each medication at the time of assessment. L-Dopa equivalent daily dose (LEDD) was calculated as described in a previously published systematic review [16].

Activities of daily living and motor function were assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) parts II and III. The Hoehn and Yahr Scale was used to measure disease stage. Postural instability with falling (PIF) and freezing of gait (FOG) are the two main components of axial impairment; they were defined separately as a score of >1 on the UPDRS part II item 13 and a score >1 on the UPDRS part II item 14, according to previously reported studies [17]. All of the above mentioned assessments were conducted in the 'off' status.

To assess the complex range of NMS in PD, the Non-motor Symptoms Questionnaire (NMSQuest) [18,19] was used. Each item contains "yes", "no", and "don't know" answer choices; only the "yes" answers indicating that patients exhibit non-motor features were considered.

Other measures of NMS were also included in the study. Cognitive function was assessed by the MMSE (score <24 indicates dementia). Sleep disturbance was assessed by the Parkinson's Disease Sleep Scale (PDSS) [20,21]. Sleepiness was assessed using the Epworth Sleepiness Scale (ESS) [22,23]. Patients also completed the Hamilton depression (HDRS) [24] and anxiety rating scales (HARS) [25].

2.1. Statistical analysis

Patients were classified into three groups according to age at onset: <45 years, 45–64 years, and ≥65 years. These categories were termed early onset PD (EOPD), middle-age onset group and old-age onset group, respectively. Continuous variables between the three groups were compared by means of a one-way ANOVA or the Kruskal–Wallis test. Categorical data were analyzed using the chi-squared test. To explore trends across the different groups, either ANOVA with polynomial contrasts or the chi-square test for trends was applied.

The EOPD and old-age onset groups were studied separately to determine their association with the appearance of each clinical feature. Multivariate logistic regression analysis was used to adjust for potential confounding factors (duration; dopaminergic treatment duration; LEDD <600 mg/d or ≥600 mg/d; daily L-dopa dose<500 mg/d or ≥500 mg/d). Age was not entered into the regression model due to collinearity with the variable "duration." Analyses were performed using SPSS software, version 17.0. Significance was defined as a P value <0.05.

3. Results

Two hundred and thirty patients participated in the investigation. Patient demographic and clinical variables are shown in Table 1.

The patients had a mean age at onset of 63.0 years, a mean age at examination of 67.7 years and a mean disease duration of 4.7 years. Thirteen (5.7%) experienced the onset of PD before 45 years of age, 103 (44.8%) experienced onset between 45 and 64 years of age, and 114 (49.6%) experienced onset at old age. Three groups differed in age, disease duration, daily L-dopa dose and LEDD; however, they did not differ in gender, the Hoehn and Yahr Scale or the UPDRS-III score.

The prevalence of NMS for each group is listed in Table 2. Patients experienced a high prevalence of constipation, nocturia, impaired memory, daytime sleepiness, intense vivid dreaming, loss of interest and urinary urgency.

3.1. Neuropsychiatric symptoms

Polynomial analyses indicated that there was a significant linear effect between age at onset and the MMSE score ($P=0.001$). Old-age onset was significantly associated with dementia as indicated

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