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Clinical Study

Associations between neuropsychiatric symptoms and cognition in Chinese idiopathic Parkinson's disease patients

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ABSTRACT

The associations between neuropsychiatric symptoms and cognition, frontal lobe function and frontal behavioral changes in the Chinese idiopathic Parkinson's disease (PD) population are largely unknown. This study included 348 idiopathic PD patients from southwest China. Neuropsychiatric symptoms were investigated using the Neuropsychiatric Inventory Questionnaire (NPI), and cognition was assessed using Addenbrooke's Cognitive Examination-Revised (ACE-R). The Frontal Assessment Battery (FAB) was used to evaluate frontal function and the Frontal Behavior Inventory (FBI) was used to assess frontal behavioral changes. The mean (± standard deviation) age of the PD patients was 60.24 ± 12.07 years, and the mean disease duration was 3.88 ± 3.34 years. The mean NPI score was 3.49 ± 4.00. The mean score of ACE-R was 76.82 ± 16.73. The mean score of FAB was 15.27 ± 2.90, and the mean score of FBI was 3.18 ± 5.17. Weak negative correlations between the NPI and ACE-R scores as well as FAB score were found in the total sample, the male patient subgroup, the early onset PD subgroup and the late onset PD subgroup. Strong positive correlations were found between the NPI and FBI scores in the total sample ($r = 0.661$, $p < 0.001$), the male patient subgroup ($r = 0.789$, $p < 0.001$) and the late onset PD subgroup ($r = 0.749$, $p < 0.001$). Moderate positive correlations were found between the NPI and FBI scores in the female patient subgroup ($r = 0.536$, $p < 0.001$) and the early onset PD subgroup ($r = 0.462$, $p < 0.001$). Neuropsychiatric symptoms were closely associated with frontal behavioral changes but were not closely related with worse cognition and frontal lobe function in the Chinese idiopathic PD population.

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder characterized by cardinal motor symptoms and numerous non-motor symptoms, including neuropsychiatric symptoms and cognitive impairment [1]. Neuropsychiatric symptoms include delusions, hallucinations, depression and anxiety, which may have significant effects on the quality of life in PD patients and lead to a heavy burden on their caregivers. Cognitive impairment in PD may range from impairment in a single domain to global cognitive decline and dementia [2]. It can often manifest as frontal lobe dysfunction with behavioral changes and executive dysfunction [3].

Although many studies have focused on the features of neuropsychiatric symptoms, cognitive impairment, frontal lobe dysfunction and frontal lobe behavioral changes in PD patients [4,5], studies on the associations between neuropsychiatric symptoms and cognition, frontal lobe function and frontal behavioral changes are limited. A variety of scales were used in these different studies, and the results were not completely consistent. For example, one study from the UK revealed only a weak correlation between cognition assessed by Addenbrooke's Cognitive Examination-Revised (ACE-R) and behavioral changes measured by the carer-completed Cambridge Behavioral Inventory-Revised [6]. A study from Mexico obtained similar results using the Neuropsychiatric Inventory Questionnaire (NPI) to assess neuropsychiatric symptoms [7]. However, one study from Norway found that psychiatric symptoms assessed by NPI were significantly correlated with cognitive impairment assessed by the Mini-Mental State Examination [8]. A prospective study also found a close correlation between hallucinations and frontal lobe function evaluated by the Frontal Assessment Battery (FAB) [9], and another study indicated that hallucination were associated with cognitive impairment in PD patients [10].

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To our knowledge, there are no data regarding associations between overall neuropsychiatric symptoms and cognition, frontal lobe function and frontal behavioral changes in the Chinese idiopathic PD population. Therefore, we conducted this observational and cross-sectional study using accepted scales to clarify this issue.

2. Patients and methods

Three hundred forty-eight idiopathic PD patients were included in this study. All of the PD patients were admitted to the Department of Neurology, West China Hospital of SiChuan University between March 2011 and November 2013. The PD diagnosis was based on the United Kingdom Parkinson's Disease Brain Bank criteria [11]. The demographic and clinical data of all included PD patients such as sex, age, age of onset, years of education, disease duration and anti-parkinson medication were recorded by neurologists during face-to-face interviews. Disease duration was defined as the time from disease onset to evaluation. Early onset Parkinson's disease (EOPD) was defined as PD onset before the age of 50 years and late onset Parkinson's disease (LOPD) as onset after the age of 50 years [12]. Hoehn and Yahr stage (H–Y stage) [13] was used to assess the severity of PD, and the Unified Parkinson's Disease Rating Scale part III (UPDRS III) [14] was used to evaluate the motor symptoms. Motor complications were assessed by the UPDRS part IV. Neuropsychiatric symptoms were investigated using the NPI [15], which was completed by the caregivers. The NPI is a convenient instrument that assesses both the frequency and severity of the following 12 domains of neuropsychiatric symptoms: delusions, hallucinations, agitation/aggression, dysphoria/depression, anxiety, euphoria, apathy, disinhibition, irritability/lability, aberrant motor behavior, sleep disturbances and appetite. Each domain is rated on the presence and severity of the symptoms (frequency $\times$ severity). A higher score indicates greater behavioral disturbance. Cognition was evaluated by the Chinese version of ACE-R [16]. The ACE-R consists of five cognitive domains including attention/orientation (18 points), memory (26 points), verbal fluency (14 points), language (26 points) and visuospatial ability (16 points), totaling up to a maximum score of 100. Higher ACE-R scores represent better cognition. Frontal lobe function was evaluated by the FAB [17], which includes the following six domains: similarities, lexical fluency, motor series, conflicting instructions, go-no-go, and prehension behavior (environmental autonomy). Frontal behavior changes were assessed using the 24 item Frontal Behavior Inventory (FBI) [18] with two subscales for negative (FBI-A) or positive behaviors (FBI-B), completed by the caregivers. The quantitative measure for each item was determined using a 0–3 Likert scale and by accounting for a total FBI score range of 0 to 72. Higher scores indicate more severe frontal behavioral disorders. Patients who could not complete the clinical features assessment FAB, ACE-R or whose caregivers could not complete the NPI or FBI assessment were excluded. Patients with atypical parkinsonism were also excluded.

The Ethics Committee of West China Hospital of SiChuan University approved this study, and all of the participants were made aware of the purpose of the study and provided informed consent before enrollment.

2.1. Statistical analysis

All analyses were performed using the Statistical Package for the Social Sciences version 11.5 (SPSS, Chicago, IL, USA). All continuous variables, such as age, disease duration, H–Y stage, UPDRS-III, daily dose of levodopa, years of education, mean scores of ACE-R and each domain of ACE-R, NPI, FAB and FBI are presented as mean ± standard deviation. All categorical variables such as sex are presented as numbers or percentages. Comparisons of continuous variables between the male and female subgroups as well as EOPD and LOPD subgroups were performed by Student's *t*-test when the variables met the normal distribution and by the Mann–Whitney test when the variables did not meet the normal distribution. Comparisons of categorical variables were performed using a chi-squared test or Fisher's exact test. The differences in the scores of NPI, ACE-R, FAB and FBI between the male and female subgroups as well as EOPD and LOPD subgroups were studied by analyses of covariance with adjustments for age, disease duration, education and UPDRS III score. The partial correlation coefficient was calculated to study the associations between total NPI scores and the scores of ACER, FAB and FBI while controlling for age, disease duration, education and UPDRS III, which may influence the neuropsychiatric symptoms and cognition. A partial correlation coefficient (r) $\geqslant$ 0.8 indicates very strong correlation, r = 0.60 to 0.79 corresponds to strong correlation, r = 0.4 to 0.59 indicates a moderate correlation, r = 0.20 to 0.39 denotes a weak correlation, and r $\leqslant$ 0.19 corresponds to a negligible correlation. A p value of less than 0.05 (unless multiple comparisons were performed) was considered to be statistically significant.

3. Results

The demographic and clinical characteristics of all included PD patients are presented in Table 1. Compared with female patients, male PD patients had a higher level of education (9.41 ± 4.44 years *versus* 7.99 ± 4.69 years, $p = 0.008$), higher score of UPDRS III (29.66 ± 13.00 *versus* 24.96 ± 12.37, $p = 0.003$) and higher daily dose of levodopa (348.11 ± 264.52 mg *versus* 272.07 ± 188.87 mg, $p = 0.013$). Compared with EOPD patients, LOPD patients were older (66.07 ± 6.71 years *versus* 45.16 ± 9.54 years, $p < 0.001$), had a lower level of education (8.37 ± 4.85 years *versus* 9.89 ± 3.89 years, $p = 0.014$), a higher H–Y stage (2.37 ± 0.68 *versus* 2.05 ± 0.74, $p < 0.001$) and a higher UPDRS III score (29.09 ± 12.69 *versus* 22.70 ± 12.38, $p < 0.001$).

The neuropsychiatric and cognitive features of PD patients are listed in Table 2. Two hundred and fifty (71.8%) patients presented with at least one neuropsychiatric symptom. The most common neuropsychiatric symptoms were dysphoria/depression (53.2%) and anxiety (44.8%). Female patients had more frequent delusions (5.5% *versus* 1.1%, $p = 0.028$) and anxiety (51.8% *versus* 38.6%, $p = 0.017$) than male patients. The overall mean FAB score was 15.27 ± 2.90, the mean FBI score was 3.18 ± 5.17, and the mean ACE-R score was 76.82 ± 16.73. After adjusting for age, disease duration, education and UPDRS III, there were no significant differences in the mean scores of NPI, FAB, FBI, ACE-R and each domain of ACE-R between EOPD and LOPD patients. After adjusting for age, disease duration, education and UPDRS III, there were no differences in the mean scores of NPI, FAB and FBI between male patients and female patients. However, male patients performed better on ACE-R (80.01 ± 14.18 *versus* 73.24 ± 18.60, $p < 0.001$), especially in the domains of attention/orientation, verbal fluency, language and visuospatial ability, than female patients (Table 2).

The correlations between total NPI score and scores of FAB, FBI and ACE-R are shown in Table 3. There were weak negative correlations between NPI score and scores of FAB and ACE-R in the total sample, the male subgroup, EOPD subgroup and LOPD subgroup. Strong positive correlations were found between NPI score and FBI score in the total sample (r = 0.661, $p < 0.001$), the male subgroup (r = 0.789, $p < 0.001$) and LOPD subgroup (r = 0.749, $p < 0.001$). Moderate positive correlations were found between NPI score and FBI in the female subgroup (r = 0.536, $p < 0.001$) and EOPD subgroup (r = 0.462, $p < 0.001$).