Journal of Affective Disorders 243 (2019) 525–530

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Executive dysfunctions and behavioral changes in early drug-naïve patients with Parkinson's disease

Shirong Li[a,b], Ruwei Ou[a], Xiaoqin Yuan[a], Hui Liu[a], Yanbing Hou[a], Qianqian Wei[a], Wei Song[a], Bei Cao[a], Yongping Chen[a], Huifang Shang[a,*]

[a] Department of Neurology, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, China
[b] Department of Neurology, Guizhou Provincial People's Hospital, Guiyang, Guizhou, China

ARTICLE INFO

Keywords:
Parkinson's disease
Executive function
Behavioral change
Early-onset Parkinson's disease
Late-onset Parkinson's disease
Age at onset

ABSTRACT

Objectives: This study aims to explore the clinical profiles and onset age-related difference of executive dysfunctions and behavioral changes in early drug-naïve patients with Parkinson's disease (PD).
Methods: A cross-sectional analysis on 419 early stage drug-naïve PD patients was conducted. The frontal assessment battery (FAB) was used to assess executive functions and the frontal behavioral inventory (FBI) was used to assess behavioral changes.
Results: Executive dysfunctions were detected in 113 patients (27.0%), and 219 patients (52.3%) displayed varied degrees of behavioral changes. The most frequent affected domain for the FAB was lexical fluency (31.7%), while the three most frequent affected domains for the FBI were apathy (26.0%), irritability (24.3%) and inattention (20.8%). Compared to the early-onset PD (EOPD) patients, the late-onset PD (LOPD) patients exhibited significantly higher frequent damage in FAB especially similarities, motor series, and conflicting instructions as well as lower frequent damage in lexical fluency. The frequencies of FBI-abnormal were not different between the two groups. Multivariate analyses indicated that age at PD onset was independently associated with FAB total score and its subscores including lexical fluency, motor series, conflicting instructions and go-no go task, but it has no relationship with FBI total score and its subscores.
Conclusions: Executive deficits and behavioral changes are common in the early stage of PD. Age at PD onset is independently associated with the performance of executive functions. However, behavioral changes in PD may be not affected by onset age.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by rest tremor, bradykinesia, rigidity and postural instability (Kalia and Lang, 2015). These motor dysfunctions of PD are associated with the degeneration of dopaminergic neurons in the substantia nigra pars compacta (Kalia and Lang, 2015), which contributes to a drastic reduction of dopamine in the basal ganglia, particularly the posterior putamen, at early stage of the disease. As the disease progresses, the degeneration can extend to anterior striatum, limbic nuclei and neocortical regions (Chaudhuri and Schapira, 2009), which contributes to a host of non-motor symptoms (NMSs) such as neuropsychiatric disturbances and cognitive deficits (Chaudhuri and Schapira, 2009).

Neuropsychiatric symptoms and executive deficits are common throughout the course of PD and may precede and exceed motor symptoms as major factors affecting the disease course and patients' quality of life (Szatmari et al., 2017). They often occur and progress simultaneously from the onset of PD, suggesting they are strongly related to each other. For example, a two-year follow-up study (Santangelo et al., 2015) indicates that the poor executive function in drug-naïve PD patients may predict the development of future apathy. However, in the early stage of PD, these symptoms are frequently unrecognized and untreated (Chaudhuri and Schapira, 2009). In the post-levodopa era, dopamine replacement therapy, particularly dopamine receptor agonists that cause hyperdopaminergic states, has been associated with some neuropsychiatric symptoms such as psychosis, impulse control disorders (ICDs), excessive daytime sleepiness (EDS), and hallucinations (Burn and Troster, 2004). In addition, according to the dopamine overdose hypothesis (Gotham et al., 1988), a dose of dopaminergic medication can lead to adverse behavioral and cognitive consequences in specific executive function tasks, which can make

* Corresponding author.
E-mail address: hfshang2002@126.com (H. Shang).

https://doi.org/10.1016/j.jad.2018.09.052
Received 7 March 2018; Received in revised form 6 August 2018; Accepted 15 September 2018
Available online 17 September 2018

these NMSs difficult to be recognized and managed. It is reported that side of onset of parkinsonian motor symptoms does not influence the neuropsychiatric and neuropsychological performances in drug-naïve PD (Pellicano et al., 2015), also suggesting that onset side related-differences reported by previous reports may be at least secondary to dopamine replacement therapy. Furthermore, a recent study (Antoniades et al., 2015) found that certain cognitive domains are already significantly impoverished in newly diagnosed PD patients, even before the initiation of medication. Above evidences suggest that it is necessary to study the neuropsychiatric symptoms and cognitive dysfunctions in drug-naïve PD patients.

To date, some studies have focused on the integral prevalence of neuropsychiatric symptoms and cognitive dysfunction in the untreated PD patients. For example, a Norwegian study (Aarsland et al., 2009) found that neuropsychiatric symptoms are more common in patients with PD (56%) than those in individuals without PD (22%). A subsequent American study (Weintraub et al., 2015) found approximately 10% of early, untreated PD patients had cognitive impairments, and PD patients experienced more depression, anxiety and apathy than general population. Another study from Mexico (Isais-Millán et al., 2016) found that 41.3% PD patients had different degrees of cognitive impairments and more than 10% subjects exhibited varied degrees of neuropsychiatric symptoms. In addition, a study from England (Foltynie et al., 2004) found that the overall cognitive impairments are present in 36% and executive dysfunctions are present in 24% of incident cohorts.

However, at present, the general prevalence of behavioral changes and executive dysfunctions in the Chinese patients with early drug-naïve PD has not yet been systematically reported. Therefore, we conducted this study to describe the executive functions and behavioral profiles in drug-naïve PD based on a large cohort of Chinese patients. In addition, to clarify the onset age-related differences in behavioral changes and executive functions, we also compared their frequencies between different onset age group patients, and further explored the association between age at PD onset and these NMS symptoms.

2. Patients and methods

This study was in accordance with the Ethics Committee of West China Hospital of Sichuan University. All participants had provided written informed consent. A total of 419 patients with PD from the Department of Neurology, West China Hospital of Sichuan University between January 2011 and October 2017 were recruited. All participants met the United Kingdom PD Society Brain Bank Clinical Diagnostic Criteria for PD (Hughes et al., 1992) and presented with no history of antiparkinsonian therapy. Patients with atypical and secondary Parkinsonism and those who reported a history of mental illness or were receiving psychotropic drugs were excluded. All registered patients had been followed-up by a face-to-face interview or a telephone call to ensure the accuracy of PD diagnosis. In addition, we also recruited 181 age, sex and education matched healthy controls (HCs) including 45 young HCs (YHCs) with age < 45 years (range from 30 to 45 years) and 136 old HCs (OHCs) with age > 45 years (range from 45 to 80 years) to measure executive functions. HCs who had any neurological or mental diseases were ruled out, which were determined by neurologists or psychiatrists through medical history reviews and physical examinations.

We divided all patients into early-onset PD (EOPD) group and late-onset PD (LOPD) group based on the cut-off of age of motor symptom onset at 45 years. All participants had undergone a detailed series of interview and clinical assessments. The severity of PD was evaluated by the Unified PD Rating Scale (UPDRS) part III (2003) and the modified version of Hoehn and Yahr (H&Y) stage scale (Hoehn and Yahr, 1967). The severity of depression was evaluated with the 24-item version of Hamilton Depression Rating Scale (HDRS) (Moberg et al., 2001) and the severity of anxiety was evaluated with the Hamilton Anxiety Rating Scale (HARS) (Shear et al., 2001).

The Frontal Assessment Battery (FAB) (Dubois et al., 2000) was used to assess executive functions across six items (similarities, lexical fluency, motor series, conflicting instructions, go-no go task, and prehension behavior), each exploring functions related to the frontal lobes including conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy. The cut-off score for the FAB was defined as a total score of more than 1.5 standard deviations below the mean FAB score compared to that of the HCs. In addition, we also applied the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), a brief cognitive screening instrument, to evaluate the global cognitive functions.

The 24-item version of Frontal Behavioral Inventory (FBI) (Kertesz et al., 1997) was used to assess the frequency and severity of personality and behavioral disturbances. It is a caregiver informant interview with two subscales for negative and positive symptoms covering 24 neuropsychiatric symptom items. A total score of zero suggests absence of behavior changes, a total score of 1–3 corresponds to mild behavior changes, a total score of 4–15 indicates moderate behavior changes, and a total score > 15 corresponds to severe behavior changes (Josephs et al., 2011). We did not conduct the FBI to assess behavioral changes of HCs because it is a caregiver-based tool. In addition, we also performed the Neuropsychiatry Inventory (NPI) (Kaufer et al., 2000), a validated caregiver informant-based interview that is widely used in PD, to describe the global neuropsychiatric symptoms.

3. Statistical analyses

All analyses were performed using the version 19.0 of Statistical Package for the Social Sciences (SPSS). The continuous data with a normal distribution were listed as the mean ± standard deviation and those with a non-normal distribution were described as the median values (quartile), while the categorical variable were presented as number (percentage). Comparisons of the demographic and clinical data between different subgroups were conducted by the chi-square test or student's *T* test, as appropriate. To adjust for the interference of age and UPDRS III, the Cochran's and Mantel-Haenszel statistics test were used to compare the frequencies of FAB-abnormal and FBI-abnormal between EOPD and LOPD groups. To reduce the type 1 error for multiple testing between EOPD and LOPD groups, P values < 0.01 were considered statistically significant based on above analyses.

Furthermore, to explore the association between FAB, FBI and age at onset, a stepwise approach was conducted. We firstly performed a univariate analysis between FAB/FBI scores and age at PD onset, and variables showing a significance level (selection criterion $P < 0.05$) were further chosen to perform the multivariate analyses. In the multivariate regression model, age at testing, sex, age at onset, disease duration, education and UPDRS III score were chosen as independent variables, and FAB/FBI score was set as dependent variable, with P values < 0.05 being considered statistically significant.

4. Results

4.1. Demographic and clinical data

This observational study included 419 PD patients (201 men and 218 women) with mean age of 58.2 ± 12.3 years, mean disease duration of 2.0 ± 1.5 years, mean age at PD onset of 56.2 ± 12.2 years, and median H&Y stage of 2.0 (range from 1 to 2.5) (Table 1). The mean age at testing and mean UPDRS III score of the LOPD patients were significantly higher than those of the EOPD patients ($P < 0.05$) (Table 1). The EOPD patients showed significantly higher mean total score of MoCA than that of the LOPD patients ($P < 0.05$), while both of the EOPD and LOPD patients exhibited lower mean total score of MoCA than that of the HCs ($P < 0.05$)(Table 1).