Original Article

The Relationship Between Fatigue and Other Non-Motor Symptoms in Parkinson's Disease in Chinese Population

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A R T I C L E   I N F O

S U M M A R Y

Background: The aim of our study was to explore in detail the relationship between fatigue and other non-motor symptoms in Parkinson's disease (PD).
Methods: One hundred and four PD patients took part in our study. The Fatigue Severity Scale (FSS) was used to measure the severity of fatigue and a cut-off of 4 was used to define the presence of fatigue. Patients who scored more than 4 were divided into the "fatigue group" while the other patients were allocated to the "no fatigue group". The Non-motor Symptoms Scale (NMSS) was used to screen other non-motor symptoms. The Parkinson's disease Sleep Scale (PDSS), Rapid Eye Movement Sleep Behavior Disorders Scale (RBD) and Epworth Sleepiness Scale (ESS) were used to measure different kinds of sleep disorders, and the affective sphere were measured with the Hamilton Anxiety Scale (HAMA) and the Hamilton Depression Scale (HAMD).
Result: Patients with fatigue in PD had higher levels in domain 2 (sleep disorders) ($p < 0.001$) and domain 3 (mood/anxiety) ($p < 0.05$) of the NMSS. The severity of fatigue was positively associated with excessive daytime sleepiness ($r_s = 0.254$, $p = 0.009$), anxiety ($r_s = 0.268$, $p = 0.006$) and depression ($r_s = 0.264$, $p = 0.007$).
Conclusion: Forty patients (42.4%) showed notable complaints of fatigue with FSS scores > 4. Among the patients with fatigue, the severity of fatigue in PD patients was related to sleep and affective disorders. Of the disorders, excessive daytime sleepiness, anxiety and depression were particularly linked to fatigue in PD.
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1. Introduction

The characteristic symptoms that develop in patients with Parkinson's disease (PD) are traditionally considered to be motor symptoms.[1] However, more recently, the important contribution of non-motor symptoms (NMS) has drawn a great deal of attention.[2] A study of 92 PD patients showed that almost all patients suffered from at least one type of non-motor symptoms.[3] Non-motor symptoms constitute the main source of adversity to patients and have a negative impact on their quality of life (QoL).[4,5]

Fatigue can be defined as "a sense of tiredness, lack of energy, and a feeling of total exhaustion" and consists of mental fatigue and physical fatigue in PD.[6,7] The prevalence ranges from 33% to 58% in patients with PD, contrast to a prevalence of only 20% in the general population.[8–10] It is likely to be one of the most troublesome symptoms for patients and limits their ability to enjoy social activities. Despite this, it is often overlooked during routine follow-up.[7] Previous studies have reported that fatigue in PD patients is related to sex, disease duration, anxiety and depression.[11–14] Although several previous studies have shown a relationship between fatigue and other non-motor symptoms in PD patients, the nature of the relationship has not been systemically examined and its associations with other non-motor symptoms are unclear. Only one study reported by Solla et al. showed that among all other non-motor symptoms, sleep disorders and affective sphere were thought to contribute to the severity of fatigue.[15]

Therefore, the aim of our study was to evaluate the prevalence of fatigue in Chinese PD patients, and explore its relationship with other non-motor symptoms in details.

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2. Methods

2.1. Patients

One hundred and four PD patients who satisfied the UK PD Brain Bank Criteria for the diagnosis of idiopathic PD were collected for our study.[16] Patients with Mini-Mental State Examination (MMSE) < 24,[17] as well as those who had corticobasal degeneration, progressive supranuclear palsy, dementia with Lewy bodies, vascular parkinsonism, or other forms of parkinsonism were excluded from our study. Moreover, any patients with heart disease, pulmonary disease, renal failure, hepatic failure or cancer were also excluded. The basic characteristics of PD patients including age, disease duration, Unified Parkinson's disease Rating Scale (UPDRS) I, II, III score, levodopa equivalent daily dose (LEDD), etc. were also collected.[18,19]

Our study was approved by the ethics committee of the First Affiliated Hospital of Nanjing Medical University and written informed consent was obtained from each patient.

2.2. Defining fatigue in PD patients

The patients were divided into two groups: patients with and without fatigue. As there is no recognized standard in the diagnosis of fatigue in PD patients, we used the Fatigue Severity Scale (FSS) to measure fatigue in our study.[20] The FSS is widely used for its high internal consistency and reliability. The FSS is a self-administered 9-item scale for measuring fatigue. Each answer is scored from 0 to 7, with a higher score meaning greater fatigue. Although it is not a scale specifically designed for PD, a number of studies have used the FSS to assess the severity of fatigue in patients with PD, and a cut-off of 4 has been used to define the presence of fatigue.[21] Patients who scored greater than four were allocated to the "fatigue group" while the other patients were allocated to the "no fatigue group".

2.3. Primary screening tests

In the first phase, non-motor symptoms (NMS) were assessed with the Non-Motor Symptoms Scale (NMSS).[22] The NMSS is a validated, 30-item self-reported questionnaire that has 9 domains: cardiovascular, sleep disorders, mood/anxiety, perceptual problems, attention/memory, gastrointestinal, urinary, sexual function and miscellaneous. Each domain has different items, which are composed of two parts: severity (from 0 to 3) and frequency (from 1 to 4). The domains of this instrument can help us screen specific aspects of non-motor disturbances, which may provide preliminary clues for further exploration.

2.4. Tests for further exploration

After analyzing the NMSS between patients with and without fatigue, our results highlighted domain 2 (sleep disorders) and domain 3 (mood/anxiety) for further analysis. The symptoms of anxiety and depression in patients with PD were assessed with the Hamilton Anxiety Scale (HAMA) and the Hamilton Depression Scale (HAMD), respectively.[23] The Parkinson Disease Sleep Scale (PDSS), Epworth Sleepiness Scale (ESS), and Rapid Eye Movement Sleep Behavior Disorders Scale (RBD) were used to evaluate the different kinds of sleep disorders in PD patients.[24–26]

2.5. Statistical analyses

Statistical analyses were performed with SPSS19.0 (SPSS Inc, Chicago, IL, USA). All continuous variables are shown as the mean ± standard deviation and categorical variables are expressed as percentages. Student's t-test or Mann-Whitney U test was employed to compare groups. Spearman's Rho was used to evaluate the correlations among the severity of fatigue with the clinical data and other non-motor symptoms.

3. Results

3.1. Demographic and clinical characteristics

We collected data from a consecutive series of 104 patients with a mean age of 62.02 ± 11.50 years, and mean disease duration of 2.89 ± 3.11 years. Forty patients (42.4%) showed notably complaints of fatigue with FSS scores > 4. The demographic and clinical characteristics are summarized in Table 1. No significant difference was found in any of the demographic variables between the PD patients with and without fatigue.

3.2. NMSS scores in PD patients with and without fatigue

Table 2 shows the descriptive results for NMS in PD patients, illustrating the severity in each domain of the NMSS in the group. According to the pre-defined FSS cut-off, we divided the PD patients into two subgroups: patients with fatigue and patients without fatigue. Comparing the two subgroups, a significantly higher total score of NMSS was found in the patients with fatigue (40.75 ± 27.51 vs. 29.55 ± 30.81, p < 0.05) than that in the patients without fatigue. Specifically, patients with fatigue, reported more changes in the sleep disorders domain (8.16 ± 6.72 vs. 3.02 ± 6.31, p < 0.001) and the mood/anxiety domain (11.10 ± 12.21 vs. 6.57 ± 9.22, p < 0.05) when compared with patients without fatigue. Furthermore, we explored the correlation between NMSS scores and fatigue. As summarized in Table 3, the severity of fatigue positively correlated with the sleep disorders domain ($r_s = 0.506$, p < 0.001) and the mood/anxiety domain ($r_s = 0.358$, p < 0.001).

3.3. Further assessments for sleep disorders and fatigue

To gain deeper understanding of the correlation between fatigue and the sleep disorders domain, the ESS, PDSS and RBD scales were used to represent the different kinds of sleep disorders and the relationship between fatigue and sleep disorders was further analyzed. Compared to the PD patients without fatigue, the PD patients with fatigue had slightly more complaints about excessive daytime sleepiness (EDS) at a marginal significance (4.89 ± 4.39 vs. 3.32 ± 3.05, p = 0.054). Furthermore, the severity of fatigue positively correlated with excessive daytime sleepiness ($r_s = 0.254$, p = 0.009), as shown in Table 4.

3.4. Further details for affective sphere and fatigue

To obtain the relationship between fatigue and the mood/anxiety domain, more detailed analysis was performed. The HAMA and HAMD scales were used to represent different aspects of the affective sphere. When compared with PD patients without fatigue, the PD patients with fatigue had significantly more complaints about anxiety (8.68 ± 5.00 vs. 6.57 ± 4.89, p = 0.02) and depression (8.91 ± 7.03 vs. 6.43 ± 6.09, p = 0.03). Moreover, the severity of fatigue positively correlated with anxiety ($r_s = 0.268$, p = 0.006) and depression ($r_s = 0.214$, p = 0.007), as shown in Table 4.

4. Discussion

The important results from our observational study are summarized below: