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Clinical features and varieties of non-motor fluctuations in Parkinson's disease: A Japanese multicenter study

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ABSTRACT

Objective: This multicenter cross-sectional study aimed to investigate the clinical features and varieties of non-motor fluctuation in Parkinson's disease (PD).
Methods: To identify motor and non-motor fluctuation, we employed the wearing-off questionnaire of 19 symptoms (WOQ-19) in 464 PD patients. We compared the frequency of levodopa-related fluctuation as identified by the WOQ-19 with recognition by neurologists. We compared patients with both motor and non-motor fluctuations with those who only had motor fluctuations. Non-motor fluctuations were separated into psychiatric, autonomic, and sensory categories for further analysis.
Results: The patients' average age was 70.8 ± 8.4 years (mean ± SD) and disease duration was 6.6 ± 5.0 years. The frequency of motor fluctuations was 69% and for non-motor fluctuation 40%. Fifty-three percent of patients with motor fluctuations also had non-motor fluctuations, whereas 93% of patients with non-motor fluctuations also had motor fluctuations. The WOQ-19 showed a sensitivity of 82% but a specificity of only 40%. The patients with both non-motor and motor fluctuations exhibited more severe motor symptoms, more non-motor symptoms and higher levodopa daily doses ($p < 0.05$). Patients had

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significantly higher fluctuation rates if they had psychiatric (49%) and sensory (45%) symptoms than patients with autonomic symptoms (32%, $p < 0.01$). Forty-eight percent of patients with non-motor fluctuations exhibited more than one type of non-motor fluctuation.
Conclusion: Forty percent of PD patients presented with non-motor fluctuations, and almost half of these exhibited more than one type. Appropriate recognition of levodopa-related fluctuations, both motor and non-motor, can lead to treatment modifications in PD patients.

1. Introduction

Most patients with PD develop motor fluctuations (MF), related to chronic levodopa therapy. It is estimated that each year approximately 10% of all PD patients develop MF [1]. Levodopa-related fluctuations are common in motor symptoms (MS), but also occur in various non-motor symptoms (NMS). Previous studies focusing on NMF have reported a wide range of prevalence, between 17% [2] and 100% [3], among PD patients showing MF. Although non-motor fluctuations (NMF) were described 30 years ago [4], their presentation has not been well researched. In some patients NMF may cause greater discomfort than MF [3,5]; nevertheless, this entity has been under reported and under-diagnosed in clinical practice and consequently remains untreated [6]. In this multicenter cross-sectional observational study, we investigated the clinical features and types of NMF in Japanese PD patients using the wearing-off questionnaire of 19 symptoms (WOQ-19) developed by Stacy et al. [7]. The Movement Disorder Society (MDS) Task Force has recommended the WOQ-19 as a diagnostic tool for screening the presence of wearing-off in PD patients [8]; furthermore, the WOQ-19 identified symptoms of wearing-off more frequently than did standard assessments conducted by physicians [9,10]. As the WOQ-19 includes 9 motor symptoms and 10 non-motor symptoms, it can assist the clinical management of both MF and NMF. We classified non-motor fluctuation into three categories: sensory (3 questions), autonomic (3 questions) and coginitive/psychiatric (4 questions) [11]. We also determined the sensitivity and specificity of the WOQ-19 compared with physician assessment. Early and accurate recognition of NMF could result in patients receiving optimal treatment adjustments to reduce wearing-off and improve symptoms.

2. Patients and methods

2.1. Subjects

A total of 610 patients with PD who attended one of the 13 hospitals participating in the Keio PD database between May 2008 and February 2009 agreed to participate in this study. The study was approved by the ethics committee of each hospital, and informed consent was obtained from all patients. Patients with less than one year of disease duration ($n = 22$) or no levodopa treatment ($n = 59$) were excluded. Patients with dementia ($n = 72$), as diagnosed by neurologists using DSM-IV criteria, were also excluded because their self-reporting on the WOQ-19 would likely be unreliable. After these exclusions, 464 patients were included in the study. The diagnosis of PD was made according to the UK Parkinson's Disease Society Brain Bank clinical diagnosis criteria [12].

2.2. Assessments of variables

All the patients underwent the same clinical assessments and interviews. We examined their clinical features by collecting original clinical survey sheets for PD. Our survey included gender, age at assessment, age at onset of PD, disease duration of PD, Hoehn &Yahr stage (H&Y stage), and the rating of sub-scores on 7 items from the Unified Parkinson's Disease Rating Scale (UPDRS) part III, assessing tremor at rest, finger taps, limb rigidity, arising from chair, gait, posture and postural stability. We employed the WOQ-19 [7] to detect MF and NMF. The Japanese version of the WOQ-19 is available, and linguistic validation has been performed [13]. The WOQ-19 is a self-reporting questionnaire that consists of 19 items assessing 9 motor symptoms and 10 non-motor symptoms. It was designed to identify not only MS/NMS, but also MF/NMF. Patients were asked to indicate whether they experienced any of the 19 symptoms during the day and whether these symptoms improved with their next levodopa medication. When patients gave "positive" answer to any item on the WOQ-19, they were identified as patients with levodopa-related fluctuations. In addition, we compared the frequency of levodopa-related fluctuations as identified by the WOQ-19 with the recognition of fluctuations by participating neurologists. The patients completed the WOQ-19 unassisted. The physicians made their own assessment of whether the patients had levodopa-related fluctuations. The neurologists' assessments were made during a routine consultation. After the patients had completed the WOQ-19 and physicians had made their clinical assessments, the neurologists reviewed each patient's questionnaire to ensure that the questions had been answered appropriately. We compared the clinical characteristics between patients with MF only and those with both MF and NMF. We classified NMS into psychiatric (4 items in the WOQ-19 symptoms: anxiety, mood changes, panic attacks and cloudy mind/dullness of thinking), autonomic (3 items: sweating, abdominal discomfort and experiencing hot and cold), and sensory (3 items: numbness, pain and aching) categories to evaluate the varieties of NMS according to Riley [11].

2.3. Statistical analysis

We used JMP® software version 8.0 (SAS Institute, Japan) for statistical analysis. The level of statistical significance in this study was defined as 0.05. Fisher's exact test was employed to estimate the gender difference between patients with MF only and those with both MF and NMF. Fisher's exact test was also employed to estimate the frequency of fluctuation rates for each NMS and in each category. Wilcoxon/Mann–Whitney's *U* test was performed to estimate the difference in the age at assessment, age at onset of PD, PD disease duration, H&Y stage, subscore on 7 items from UPDRS part III, total levodopa-equivalent daily dose (total LED), levodopa daily dose, and number of MS and NMS between patients with MF only and with both MF and NMF.

3. Results

The study patients included 214 men and 250 women. Their average age at assessment was 70.8 ± 8.4 years old (mean ± SD; 38.0–89.3 years old), age at onset of PD was 64.2 ± 10.1 years old (28.0–84.3 years old), mean disease duration of PD was 6.6 ± 5.0 years (1.0–46.0 years), H&Y stage was 2.6 ± 0.9 (1–5), levodopa daily dose was 310 ± 148 mg/day (50–1100 mg/day) and total LED was 407 ± 200 mg/day (100–1225 mg/day).

3.1. Number of patients with non-motor symptoms and non-motor fluctuations

Three hundred seventy patients (80%) showed at least one kind of NMS, and 368 (79%) showed both MS and NMS. The number of patients who presented with MF was 322 (69%) and with NMF 184 (40%) (Table 1a). The proportion of patients having NMF without MF was 7% (13/184 patients). The WOQ-19 showed that 335 patients had at least one kind of levodopa-related fluctuation, while physicians identified wearing-off in only 254 patients (Table 1b). Of the 210 patients identified as having no wearing-off symptoms by physicians, the WOQ-19 identified 127 patients (60%) having some kind of levodopa-related fluctuation. The sensitivity of the WOQ-19 was calculated to be 82% and the specificity was 40%.

3.2. Comparison of clinical characteristics between patients with both motor and non-motor fluctuations and those with motor fluctuations only

Table 2 shows comparisons of all variables between patients with only MF and those with both MF and NMF. Patients with both MF and NMF had more severe motor symptoms (assessed by H&Y stage, the subscore on 7 items from UPDRS part III and the number