Parkinsonism and Related Disorders 38 (2017) 54–60

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Clinical manifestations of nonmotor symptoms in 1021 Japanese Parkinson's disease patients from 35 medical centers

Tetsuya Maeda, MD, PhD [a, b, *], Yasushi Shimo, MD, PhD [c], Shih-Wei Chiu, MS [d], Takuhiro Yamaguchi, PhD [d], Kenichi Kashihara, MD, PhD [e], Yoshio Tsuboi, MD, PhD [f], Masahiro Nomoto, MD, PhD [g], Nobutaka Hattori, MD, PhD [c], Hirohisa Watanabe, MD, PhD [h], Hidemoto Saiki, MD, PhD [i], on behalf of the J-FIRST group

[a] Division of Neurology and Gerontology, Department of Internal Medicine, School of Medicine, Iwate Medical University, 19-1 Uchimaru, Morioka, Iwate 020-8505, Japan
[b] Department of Neurology and Movement Disorder Research, Research Institute for Brain and Blood Vessels-Akita, 6-10 Senshukubotamachi, Akita 010-0874, Japan
[c] Department of Neurology, Juntendo University School of Medicine 3-1-3 Hongo, Bunkyo-ku, Tokyo 113-8431, Japan
[d] Division of Biostatistics, Tohoku University Graduate School of Medicine, 2-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi, 980-8575, Japan
[e] Department of Neurology, Okayama Kyokuto Hospital, 567-1 Kurata, Okayama, 703-8265, Japan
[f] Department of Neurology, Faculty of Medicine, Fukuoka University, 3-1-1, Maidashi, Higashi-ku, Fukuoka City, 812-8582, Japan
[g] Department of Neurology and Clinical Pharmacology, Ehime University Graduate School of Medicine, 454 Shizukawa, Tohon, Ehime 791-0295, Japan
[h] Brain and Mind Research Center, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8602, Japan
[i] Department of Neurology, Kitano Hospital, The Tazuke Kofukai Medical Research Institute, 2-4-20 Ohgimachi, Kita-ku, Osaka 530-8480, Japan

ARTICLE INFO

Article history:
Received 27 October 2016
Received in revised form
27 December 2016
Accepted 19 February 2017

Keywords:
Parkinson's disease
Nonmotor symptoms
Japan
Quality of life

ABSTRACT

Introduction: We aimed to investigate the prevalence and severity of nonmotor symptoms (NMSs) and to identify factors affecting NMSs and the health-related quality of life of Japanese patients with Parkinson's disease (PD).

Methods: A total of 1021 patients with PD who had one or more NMS and showed wearing-off under anti-parkinsonian treatment were enrolled from 35 medical centers in Japan for this observational study. The primary measurements were the Movement Disorder Society unified Parkinson's disease rating scale (MDS-UPDRS) part I and the Parkinson's Disease Questionnaire (PDQ-8). The relationships of MDS-UPDRS and PDQ-8 with the patient's clinical background and undertaken medical interventions were determined. Here, we report baseline data of our 52-week ongoing study.

Results: The mean MDS-UPDRS part I and PDQ-8 scores were 10.9 and 7.3, respectively. The most common NMSs were constipation problems (85.4%), sleep problems (73.7%), pain and other sensations (72.7%) and daytime sleepiness (72.0%). Fatigue was an NMS that affected 79.6% of females but only 72.6% of males, whereas features of dopamine dysregulation syndrome affected only 5.6% of females and 10.8% of males. Positive correlations were found between the MDS-UPDRS part I and the PDQ-8 ($p < 0.0001$, $r = 0.56$) and between the number of NMSs and the PDQ-8 score ($p < 0.0001$, $r = 0.47$).

Conclusions: This study revealed distinctive patterns of NMSs in Japanese patients with PD and suggested that the prevalence and severity of NMSs vary between sexes, and that the NMSs are important factors affecting the long-term quality of life of PD patients.

* Corresponding author. Division of Neurology and Gerontology, Department of Internal Medicine, School of Medicine, Iwate Medical University, 19-1 Uchimaru, Morioka 020-8505, Japan.
E-mail addresses: maeda@iwate-med.ac.jp (T. Maeda), yshimo@juntendo.ac.jp (Y. Shimo), chiu@med.tohoku.ac.jp (S.-W. Chiu), yamaguchi@med.tohoku.ac.jp (T. Yamaguchi), kkashi@kyokuto.or.jp (K. Kashihara), tsuboi@cis.fukuoka-u.ac.jp (Y. Tsuboi), nomoto@m.ehime-u.ac.jp (M. Nomoto), nhattori@juntendo.ac.jp (N. Hattori), nabe@med.nagoya-u.ac.jp (H. Watanabe), saiki@kuhp.kyoto-u.ac.jp (H. Saiki).

http://dx.doi.org/10.1016/j.parkreldis.2017.02.024

1. Introduction

Parkinson's disease (PD) is characterized by some cardinal motor features, including resting tremor, muscle rigidity, akinesia and postural instability. Alleviation of motor symptoms directly improves clinical prognosis and health-related quality of life (HrQOL). In addition to motor symptoms, PD can cause nonmotor symptoms (NMSs), such as autonomic failure, sensory problems, mood disorders and sleep disorders [1], which can have a significant impact on patients' HrQOL [2–4], especially in the advanced stage in clinical practice. Because dopamine replacement therapy is generally ineffective against NMSs [5,6], physicians must carefully assess patients on a case-by-case basis and determine the appropriate treatment based on their NMSs. In practice, there is relatively little evidence regarding clinical management of NMSs compared with motor symptoms. Because PD patients typically have multiple NMSs, the number of NMSs may have a subclinical importance. Therefore, this observational study was planned to gain a better understanding of the NMSs affecting Japanese patients with PD, taking into consideration other factors that may affect patients' NMSs and/or HrQOL, including clinical backgrounds and anti-parkinsonian medical interventions. In this paper, we describe the clinical manifestations of NMSs and their effects on HrQOL.

2. Methods

2.1. Study design

This is the first-in-Japan large-scale observational study for NMSs and treatment in patients with PD (J-FIRST). A target sample size of 1000 advanced-stage PD patients was planned in light of the feasibility of the study and the number of patients required for identification of the factors related to NMSs. This prospective study is currently being conducted in 35 sites between February 2014 and December 2016 (see Supplementary Information for list of sites and investigators). Patients were enrolled between March 2014 and January 2015 in participating medical centers throughout Japan and are being prospectively examined for 52 weeks. The primary measurements include the interval changes over 52 weeks for the Movement Disorder Society Unified PD Rating Scale (MDS-UPDRS) part I [7,8] and the eight-item PD questionnaire (PDQ-8) [9,10] both of which were translated into Japanese.

The cross-sectional analysis is designed to investigate the prevalence, severity and number of NMSs and the relationship with HrQOL at baseline of the J-FIRST.

Ethics review committees of each study site approved this study. All patients provided written informed consent. The study is registered at clinicaltrials.gov (NCT02073981) and umin. ac.jp/ctr/index-j.htm (UMIN000013161).

2.2. Eligibility criteria

Patients with advanced-stage PD, as diagnosed according to the United Kingdom PD Society Brain Bank clinical diagnostic criteria [11], were eligible for this study if they met the following inclusion criteria: wearing-off of treatment with levodopa-containing drugs (LDs), ≥1 NMS assessed by MDS-UPDRS part I, ≥20 years old at the time of consent, gave written consent and were receiving outpatient care. Patients were excluded if they met the following criteria: dementia or a Mini-Mental State Examination score (MMSE) ≤23, or conditions impairing the proper assessment of the MDS-UPDRS or the PDQ-8, as determined by the investigator.

2.3. Evaluation schedule

A baseline structured interview and a neurological examination were performed to obtain baseline clinical characteristics of patients. The presence and severity of NMSs were evaluated using the MDS-UPDRS part I. Motor complications were also evaluated using the MDS-UPDRS part IV. Overall motor disability was evaluated in on and off states using the modified Hoehn and Yahr scale (mH&Y). Because it was impractical to assess both on and off states directly in office visits for each patient, patients reported their worst state to the attending physician (a neurologist well-versed in the treatment of movement disorders), who then judged the level of H&Y based on the patients' recollections. The HrQOL was evaluated with the PDQ-8. Anti-parkinsonian medical interventions were recorded, including daily dose of LDs, dopamine agonists, dopamine economizers, non-dopaminergic agents and method of functional neurosurgery (if applicable). Patients continue to be evaluated at every subsequent visit during the 52-week study period.

2.4. Statistical analysis

The prevalence is summarized using frequency and percentage, and the MDS-UPDRS part I scores and the PDQ-8 scores are summarized by sample size and mean ± standard deviation. Comparisons between demographic variables and the MDS-UPDRS part I score were performed by *t*-test, analysis of covariance for mean values, Fisher exact test for prevalence, or Mantel–Haenszel test for ordered categorized data. Age, onset age, duration of illness, mH&Y, smoking history and LD dosage were each divided into three or four subcategories and results were compared among them. To determine the relationship between total score for the MDS-UPDRS part I and the PDQ-8, a multivariate linear regression model was used. Associations between the MDS-UPDRS part I score and the PDQ-8, and between total number of NMSs and the PDQ-8 were evaluated using Pearson correlation coefficients. A two-sided p-value with a significance level of 5% was applied. Statistical analysis was performed using SAS software (ver.9.4; SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Baseline clinical backgrounds

In total, 1021 patients were enrolled. Of these patients, three did not meet the eligibility criteria, five withdrew consent, five satisfied the study criteria but were ineligible to continue because of hospitalization, death or difficulty in evaluation, and 12 had no wearing-off under treatment with LDs, as determined by MDS-UPDRS part IV screening at baseline. Therefore, 996 patients entered the observational period (Supplementary Fig. 1). Baseline clinical characteristics are shown in Table 1. Briefly, 624 females and 372 males had a mean age of 68.1 years and median duration of illness of 10 years; mean MDS-UPDRS part I and PDQ-8 scores were 10.9 and 7.3, respectively, and the mean number of NMSs was 6.6. The mean levodopa equivalent dose was 769.5 ± 339.0 mg/day [12].

All patients had previously been treated with LDs; dopamine agonists were used in ~80% of patients. Non-ergot agonists were predominantly used rather than ergot agonists. Selegiline and entacapone were commonly used as adjunctive therapy with LDs. Some non-dopaminergic agents are also used in Japan, such as droxidopa, zonisamide and istradefylline. Functional brain surgery was performed in 3.4% of patients and deep brain stimulation in 3.2% of patients.