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The Risk Factors for the Wearing-off Phenomenon in Parkinson's Disease in Japan: A Cross-sectional, Multicenter Study

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Abstract

Objective Parkinson's disease (PD) is a common, progressive, neurodegenerative disorder. With progression of PD, the wearing-off phenomenon occurs more frequently as a motor complication, decreasing the patient's quality of life. The aim of this study was to investigate the risk factors for the wearing-off phenomenon in Japanese PD patients.

Methods All of the study participants were clinically diagnosed as having PD. Each patient was assessed for the wearing-off phenomenon based on the findings of clinical assessments and interviews that were conducted during a single visit. The risk factors for wearing-off were analyzed by univariate and multivariate logistic regression analyses.

Results Wearing-off was observed in 101 of the 180 (56.1%) patients who were enrolled in this study. The multivariate logistic regression analysis revealed that the onset of PD at ≥69 years of age (odds ratio [OR], 0.22; 95% confidence interval [CI], 0.05-0.88; p=0.032), female sex (OR, 6.49; 95% CI, 2.34-17.99; p< 0.001), catechol-O-methyltransferase (COMT) inhibitor treatment (OR, 19.59; 95% CI, 3.55-108.11; p<0.001) and a high daily levodopa dosage (≥600 mg/day) (OR, 7.69; 95% CI, 1.41-41.84; p=0.018) were independent predictive factors for wearing-off in Japanese PD patients.

Conclusion Age at the symptomatic disease onset, female sex, COMT inhibitor treatment, and a high daily levodopa dose were associated with the occurrence of wearing-off in Japanese PD patients. Physicians need to consider the risk factors and carefully choose medications for PD patients to postpone the occurrence of this phenomenon for as long as possible.

Key words: age of onset, daily levodopa dosage, Parkinson's disease, female sex, wearing-off

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Introduction

Parkinson's disease (PD), which is one of the most common neurodegenerative disorders, mainly affects the nigrostriatal dopaminergic neurons (1). PD patients show various combinations of clinical symptoms, ranging from motor symptoms to non-motor symptoms (1, 2). Levodopa, which is one of the anti-parkinsonian drugs, is used to treat PD patients throughout the world. Wearing-off (WO), a complication that is frequently induced by levodopa, is defined as the predictable recurrence of motor and non-motor symptoms that precedes the administration of scheduled doses of levodopa. Previous reports from Western countries have demon-

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strated that approximately 40% of PD patients who were treated with levodopa for 4-6 years experienced WO (3-5). The occurrence of WO increases gradually, with almost all PD patients developing WO within 10 years after the initiation of levodopa therapy (5, 6). Since the occurrence of WO is associated with a decreased quality of life (QOL) (5), it is important to identify the occurrence of WO and to start managing it immediately. To postpone the occurrence of WO as much as possible, it is crucial to clarify the potential risk factors for WO.

Several risk factors related to WO have been reported by researchers from Western countries, including a young age at the time of symptomatic disease onset, high scores on the parts II and III of the Unified Parkinson's disease rating scale (UPDRS), female sex, and being located in North America (7). To date, however, only a few reports related to this issue have been published from Asian countries including Japan. The aim of this study was to identify the risk factors for WO in Japanese patients with PD; this study was a post hoc analysis of the data from the validation study of the Japanese version of the 9-item Wearing-off Questionnaire (6).

Materials and Methods

The patients enrolled in this study were diagnosed according to the United Kingdom PD Society Brain Bank criteria. Patients with severe dementia, uncontrolled psychiatric comorbidities, and a history of previous neurosurgery for PD were excluded from the study. This study was conducted at five hospitals in Japan: Fukuoka University Hospital, Juntendo University Hospital, Juntendo Koshigaya Hospital, Juntendo Shizuoka Hospital, and Okayama Kyokuto Hospital. The study protocol was approved by the ethics committee of each hospital. All patients provided their written, informed consent before participating in the study.

WO was defined as "the generally predictable recurrence of motor and non-motor symptoms that precedes the administration of scheduled doses of anti-parkinsonian medication and which usually improves after these doses." (6, 8) The physicians assessed each PD patient for WO based on the findings of clinical assessments and interviews during a single visit. The clinical data, regarding the clinical course of PD, were collected from all subjects. These included the age at examination, the age at the symptomatic disease onset, disease duration, duration of anti-parkinsonian therapy, duration of levodopa therapy, detailed anti-parkinsonian medications, sex, Hoehn and Yahr stage (HY stage), initial symptom, site of onset, and the daily levodopa dosage. All of the physicians who participated in this study had more than 7 years of clinical experience in treating PD patients.

Statistical analysis

The differences in the clinical and demographic characteristics were tested using Fisher's exact test or a one-way analysis of variance, as appropriate. The age at examination, age at symptomatic disease onset, disease duration, duration of anti-parkinsonian therapy, and duration of levodopa therapy of all patients were divided into four groups (age at examination: <65 years, 66-69 years, 70-73 years, ≥74 years; age at the symptomatic disease onset: <56 years, 56-62.4 years, 62.5-68 years, ≥69 years; disease duration: <3.5 years, 3.5-5 years, 6-8 years, ≥9 years; duration of anti-parkinsonian therapy: <2 years, 2-4.4 years, 4.5-6 years, ≥7 years; duration of levodopa therapy: <1.3 years, 1.3-2 years, 3-5 years, ≥6 years; daily dose of levodopa: <300 mg, 300-349 mg, 350-500 mg, ≥600 mg). A univariate logistic regression was performed. Factors with p values of <0.05 were included in a multivariate logistic regression analysis to determine the independent risk factors for WO. A multivariable logistic regression analysis was then performed to determine the odds ratios (ORs and 95% confidence interval [CI]) for each group. All of the statistical analyses were performed using the SAS software program (version 9.3.1; SAS Institute, Cary, USA).

Results

The demographic characteristics of PD patients

The demographic characteristics of the participants have already been described elsewhere (6). Briefly, 180 PD patients (80 men and 100 women) were enrolled in the study. One hundred one of the 180 (56.1%) PD patients had symptoms of WO. In comparison to PD patients without WO, the PD patients with WO showed the following characteristics: younger age, a greater female predominance, an earlier age at the time of symptomatic disease onset, the administration of dopamine agonists and COMT inhibitors, a longer duration of anti-parkinsonian and levodopa treatment, and higher daily doses of levodopa (Table 1).

The risk factors for WO

The results of univariate logistic regression analyses of the factors that were related to the occurrence of WO are shown in Table 2. The age at examination, disease duration, duration of anti-parkinsonian treatment, duration of levodopa therapy, sex, HY stage, daily dose of levodopa, dopamine agonist treatment, and COMT inhibitor treatment were found to be significant risk factors for WO in the univariate logistic regression analysis. Initially, a multivariate logistic regression analysis could not be performed due to the large number of categories; thus, the categories of duration of anti-parkinsonian therapy and HY stage were changed (duration of anti-parkinsonian therapy: <4.5 years, 4.5-6 years, ≥7 years; HY stage: 1-3, 4-5). The results of the multivariate logistic regression analysis, with adjustment for potential confounders, are shown in Table 3. First, a younger age at the time of symptomatic disease onset increased the risk of developing WO. The OR for WO in the oldest onset group (≥69 years) was 0.22 (95% CI, 0.05-0.88, p=0.032) in comparison to the youngest onset group (<56 years). Second,

Table 1. Demographic Characteristics of the PD Patients.

	Overall	Wearing-off	Non-wearing-off	p value
Number of patients	180	101	79	
Male : female	80 : 100	38 : 63	42 : 37	p=0.049*
Age (y)	68.8±8.5	67.6±9.4	70.3±6.9	p=0.027*
Age of onset (y)	61.7±9.6	59.3±9.9	64.9±8.1	p<0.001**
Disease duration (y)	7.0±4.8	8.3±5.1	5.4±3.8	p<0.001**
Hoehn & Yahr stage	2.6±0.8	2.7±0.9	2.4±0.7	p=0.214
Medication				
Anti-parkinsonian treatment duration (y)	5.5±5.0	7.0±5.6	3.7±3.5	p<0.001**
L-dopa treatment duration (y)	4.5±4.1	5.6±4.5	3.0±2.9	p<0.001**
Daily L-dopa dosage (mg)	441.9±237.4	520.8±273.0	341.1±124.2	p<0.001**
Dopamine agonist (n)	111 (61.7%)	64 (69.3%)	41 (51.9%)	p=0.004**
MAOB inhibitor (n)	64 (35.6%)	39 (38.6%)	25 (31.6%)	p=0.351
COMT inhibitor (n)	45 (25.0%)	43 (42.6%)	2 (2.5%)	p<0.001**
Anticholinergic (n)	22 (12.2%)	15 (14.9%)	7 (8.9%)	p=0.258
Amantadine (n)	21 (11.7%)	13 (12.9%)	8 (10.1%)	p=0.645
Zonisamide (n)	26 (14.4%)	14 (13.9%)	12 (15.2%)	p=0.833
Droxidopa (n)	4 (2.2%)	3 (3.0%)	1 (1.3%)	p=0.632

(adapted from reference 6)

there was a sex difference in the risk factors for WO. The OR for WO in female PD patients was 6.49 (95% CI, 2.34-17.99, p<0.001) in comparison to male PD patients. Third, the risk of WO was increased in a dose-dependent manner according to the levodopa dosage. The OR for WO with a daily levodopa dosage of 600 mg/day was 7.69 (95% CI, 1.41-41.84, p=0.018) in comparison to a daily levodopa dose of <300 mg/day. Furthermore, the OR for WO in patients receiving COMT inhibitor treatment was 19.59 (95% CI, 3.55-108.11, p<0.001).

Discussion

Many studies have reported that young age at the onset of PD is a risk factor for the development of WO. Several previous Japanese studies demonstrated that the hazard ratio for WO was significantly lower in patients with old-onset PD than it was in those with young-onset PD (9, 10). Ferguson et al. compared 22 patients with autopsy-proven early-onset PD (age at onset: 21-50 years) with 44 patients with autopsy-proven late-onset PD (age at onset: ≥65 years), and found that early-onset PD was associated with a higher cumulative incidence of dyskinesia, WO and on-off (11). Several other studies from Western countries also concluded that patients with young-onset PD were more likely to develop WO and dyskinesia (3, 12-14). In the STRIDE-PD study, several predictive factors for WO were identified by a multivariate analysis; among them, young age at the onset of PD was the strongest predictor (7). In the present study, when the ORs for WO in each group were divided by age, the incidence of WO in the oldest onset patient group (≥69 years) was significantly lower than that in the youngest onset patient group (<56 year old). The PD treatment guidelines (2011 version) published by the Japanese Society of Neurology recommended that patients who are older (≥70-75 years) at the onset of PD should start treatment with levodopa. The results of the present study provide further evidence that patients who are ≥70 years of age at the onset of PD should start levodopa treatment.

The present study showed that the risk of WO in female PD patients was higher than that in male patients. A previous Japanese retrospective study demonstrated that the OR for WO in females was 2.13 in comparison to males (9). The results of a multivariate analysis in the STRIDE-PD study (a prospective study) also revealed that female sex was associated with an increased risk of WO (7). Another study indicated that female PD patients experienced more fluctuation in their motor and non-motor symptoms than male patients (15). Taken together, these results suggest that female PD patients are at high risk for experiencing WO. Several causes for the increased risk of WO in female patients have been discussed. Chen et al. analyzed the risk factors for WO in Chinese PD patients by a multivariate analysis and concluded that a high levodopa dosage (adjusted to weight) was associated with WO (16). Because female patients generally have a lower body weight than male patients, they tend to receive a higher daily levodopa dose per kg of body weight than male patients. Second, other environmental factors may be associated with the occurrence of WO. Female hormones and uric acid (UA) may influence the occurrence of WO, as well as the rate of PD progression (17, 18). The neuroprotective effect of UA increases in a dose-dependent manner, and the serum UA concentration in female patients is generally lower than that in male patients; thus, the protective effect of UA is assumed to be weaker in female patients (17, 19, 20). Furthermore, estrogen changes after menopause, and its neuroprotective effect may decrease (18).

Table 2. Results of Univariate Logistic Regression Analysis.

Factor		n	WO (Percentage, %)	Odds ratio	95% CI	p value
Age at examination (y)	<65	44	70.5%	Reference	-	
	66-69	41	48.8%	0.40	0.16-0.97	p=0.044*
	70-73	43	53.5%	0.48	0.20-1.17	p=0.105
	≥74	52	51.9%	0.45	0.19-1.06	p=0.067
Age of onset (y)	<56	42	76.2%	Reference	-	
	56-62.4	48	60.4%	0.48	0.19-1.19	p=0.113
	62.5-68	44	50.0%	0.31	0.12-0.79	p=0.014*
	≥69	46	39.1%	0.20	0.08-0.51	p<0.001***
Disease duration (y)	<3.5	45	31.1%	Reference	-	
	3.5-5.0	33	45.5%	1.85	0.73-4.68	p=0.197
	6.0-8.0	53	66.0%	4.31	1.84-10.07	p<0.001***
	≥9.0	49	75.5%	6.83	2.76-16.91	p<0.001***
Duration of anti-PD treatment (y)	<2.0	34	29.4%	Reference	-	
	2-4.4	56	42.9%	1.80	0.73-4.46	p=0.204
	4.5-6.0	37	64.9%	4.43	1.63-12.04	p<0.001***
	≥7.0	53	81.1%	10.32	3.76-28.30	p<0.001***
Duration of levodopa treatment (y)	<1.3	44	29.5%	Reference	-	
	1.3-2.0	27	48.1%	2.21	0.82-5.99	p=0.117
	3.0-5.0	54	57.4%	3.21	1.38-7.47	p<0.001***
	≥ 6.0	51	82.4%	11.13	4.23-29.30	p<0.001***
Sex	male	80	47.5%	Reference	-	
	female	100	63.0%	1.88	1.04-3.42	p=0.038*
Hoehn and Yahr stage	1	16	43.8%	Reference	-	
	2	66	59.1%	1.86	0.62-5.60	p=0.271
	3	81	48.1%	1.19	0.41-3.51	p=0.748
	4, 5	17	94.1%	20.56	2.17-194.76	p<0.001***
Onset symptom						
Akinesia	negative	71	57.7%	Reference	-	
	positive	109	55.0%	0.90	0.49-1.64	p=0.721
Rigidity	negative	6	50.0%	Reference	-	
	positive	174	56.3%	1.29	0.25-6.57	p=0.760
Tremor	negative	98	56.1%	Reference	-	
	positive	82	56.1%	1.00	0.55-1.80	p=0.997
Daily levodopa dosage (mg)	<300	18	50.0%	Reference	-	
	300-349	67	28.4%	0.40	0.14-1.15	p=0.088
	350-599	48	66.7%	2.00	0.66-6.02	p=0.218
	≥600	47	87.2%	6.83	1.94-24.09	p<0.001***
Dopamine agonist treatment	negative	69	44.9%	Reference	-	
	positive	111	63.1%	2.09	1.14-3.86	p=0.018*
MAOB inhibitor treatment	negative	116	53.4%	Reference	-	
	positive	64	60.9%	1.36	0.73-2.53	p=0.333
COMT inhibitor treatment	negative	135	43.0%	Reference	-	
	positive	45	95.6%	28.54	6.64-122.68	p<0.001***
Anticholinergic drug treatment	negative	158	54.4%	Reference	-	
	positive	22	68.2%	1.79	0.69-4.64	p=0.228
Amantadine treatment	negative	159	55.3%	Reference	-	
	positive	21	61.9%	1.31	0.51-3.34	p=0.570
Zonisamide treatment	negative	153	56.9%	Reference	-	
	positive	27	51.9%	0.82	0.36-1.85	p=0.629
Droxidopa treatment	negative	176	55.7%	Reference	-	
	positive	4	75.0%	2.39	0.24-23.41	p=0.455

n: number, WO: wearing-off phenomenon, CI: confidence interval, MAOB inhibitor: monoamine oxidase B inhibitor, COMT inhibitor: catechol-O-methyltransferase inhibitor

Table 3. Results of Multivariate Logistic Regression Analysis.

		n	WO (Percentage, %)	Odds ratio	95% CI	p value
Age of onset (y)	<56	42	76.2%	Reference	-	-
	56-62.4	48	60.4%	0.45	0.12-1.65	p=0.225
	62.5-68	44	50.0%	0.29	0.07-1.16	p=0.080
	≥69	46	39.1%	0.22	0.05-0.88	p=0.032*
Disease duration (y)	<3.5	45	31.1%	Reference	-	-
	3.5-5.0	33	45.5%	0.7	0.18-2.75	p=0.607
	6.0-8.0	53	66.0%	1.73	0.31-9.64	p=0.531
	≥9.0	49	75.5%	0.28	0.03-2.55	p=0.259
Duration of anti-PD treatment (y)	<4.5	90	37.8%	Reference	-	-
	4.5-6	37	64.9%	1.49	0.29-7.53	p=0.633
	≥7	53	81.1%	6.7	0.42-106.66	p=0.178
Duration of levodopa treatment (y)	<1.3	44	29.5%	Reference	-	-
	1.3-2.0	27	48.1%	1.86	0.49-7.03	p=0.362
	3.0-5.0	54	57.4%	0.62	0.14-2.75	p=0.530
	≥6.0	51	82.4%	0.93	0.10-9.09	p=0.953
Sex	male	80	47.5%	Reference	-	-
	female	100	63.0%	6.49	2.34-17.99	p<0.001***
Hoehn and Yahr stage	1, 2, 3,	163	52.1%	Reference	-	-
	4, 5	17	94.1%	4.75	0.25-90.72	p=0.300
Daily levodopa dosage (mg)	<300	18	50.0%	Reference	-	-
	300-349	67	28.4%	0.4	0.11-1.44	p=0.162
	350-599	48	66.7%	1.49	0.36-6.14	p=0.582
	≥600	47	87.2%	7.69	1.41-41.84	p=0.018*
Dopamine agonist treatment	negative	69	44.9%	Reference	-	-
	positive	111	63.1%	1.15	0.43-3.08	p=0.784
COMT inhibitor treatment	negative	135	43.0%	Reference	-	-
	positive	45	95.6%	19.59	3.55-108.11	p<0.001***

n: number, WO: wearing-off phenomenon, CI: confidence interval, COMT inhibitor: catechol-O-methyltransferase inhibitor

With regard to medications, levodopa treatment and COMT inhibitor treatment were independent risk factors for WO in Japanese PD patients in the present study. Previous reports demonstrated that the daily levodopa dose is a risk factor for WO. The Earlier versus Later Levodopa Therapy in Parkinson's disease (ELLDOPA) study showed that the incidence of WO increased in PD patients who received 600 mg of levodopa per day after only 40 weeks (21). The frequency of another motor complication, dyskinesia, was also significantly increased in PD patients who received 600 mg of levodopa per day (21). The STRIDE-PD study, a large and long-term prospective study, found that the risk of developing WO increased in a dose-dependent manner (7). The present study also showed that the risk of WO was significantly increased in patients who received more than 600 mg of levodopa per day. All of these reports suggest that a high daily levodopa dose is a risk factor for WO. Furthermore, the STRIDE-PD study demonstrated that the time to the onset of dyskinesia in patients receiving levodopa/carbidopa/entacapone (LCE) was a shorter than in patients who received levodopa/carbidopa (LC), and that the time to WO in patients who received LCE tended to be shorter in comparison to patients who received LC (22). These findings are compatible with the results of the present study.

In conclusion, the present multicenter study identified four risk factors for WO in the Japanese PD population: a young age at the time of symptomatic disease onset, female sex, COMT inhibitor treatment, and a high daily levodopa dosage. The results of a number of previous studies show that these risk factors for WO are common to various races. To postpone the occurrence of WO as much as possible, physicians need to keep in mind the risk factors for WO and carefully choose medications for PD patients.

The present study is associated with several limitations. First, recent studies have demonstrated that the daily levodopa dose adjusted for body weight is an important factor for WO (7, 16). Unfortunately, the body weight information was not available for all of the PD patients in this study. Thus, we could not determine whether the increased risk of WO in female PD patients was associated with their lower body weight in comparison to male patients. Second, the levodopa equivalent dose (LED) is a useful evaluation method, but the LED is not appropriate for non-dopaminergic drugs such as anticholinergic drugs, zonisamide, and droxidopa. Since the aim was to analyze the relationships between WO and non-dopaminergic drugs, the

LED was not used in this study. Third, this study was retrospective in nature. The initial anti-parkinsonian drug, its dosage and the timing of the addition of other anti-parkinsonian drugs were unknown. We could not analyze the influence of these factors on the development of WO. Further prospective studies will be necessary to demonstrate that these four factors, as well as young age at the onset of symptomatic disease, female sex, and a high daily levodopa dosage, are associated with the risk of WO in the Japanese population.

The authors state that they have no Conflict of Interest (COI).

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