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Non-motor symptoms depending on motor severity in Japanese patients with Parkinson's disease: A multicenter cross-sectional study

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ABSTRACT

Background: Although non-motor symptoms (NMS) in patients with Parkinson's disease (PD) often worsen as the severity of motor symptoms (MS) increases, few studies have assessed the associated factors of non-motor symptoms.

Objective: This study aims to determine whether the presence of NMS in PD patients is associated with or independent from the severity of MS considering confounders.

Methods: The registry of PD patients from seven facilities in Japan was used. Multiple logistic regression was performed with each domain and item of the Non-motor Symptoms Scale (NMSS) as objective variables. Severity of motor symptoms was assessed by Hoehn & Yahr stage (HY stage) as an explanatory variable. The analysis was adjusted for sex, age, disease duration, presence/absence of wearing off and dyskinesia, clinical phenotypes and Levodopa equivalent daily dose.

Results: A total of 1037 patients were analyzed. Analysis by NMSS domain showed higher odds ratios (ORs) in patients with higher HY stages compared with patients with lower HY stages for domains D1 (cardiovascular), D2 (sleep/fatigue), D3 (mood/apathy), D4 (perceptual problems/hallucinations), D5 (attention/memory), and D6 (gastrointestinal) (ORs: 1.54–2.72, $P < .05$). However, only domains D7 (urinary) and D8 (sexual dysfunction) were not associated with HY stage. Item 2 (fainting) and Item 14 (delusions) showed higher ORs in the HY stage 4–5 (ORs: 9.95 and 5.92, $P < .05$).

Conclusions: Most NMS worsened with exacerbation of MS in PD patients, however some NMS domains were also affected with other factors. These findings contribute to the understanding of the clinical picture of PD and may improve personalized medicine and research in PD.

1. Introduction

Diagnoses and severity classifications in Parkinson's disease (PD) are defined based on motor symptoms (MS), where the majority of PD treatment is focused [1,2].

However, non-motor symptoms (NMS) [3,4] have a greater impact on reducing the Quality of life (QOL) of PD patients compared with MS [5–12]. The results of several studies have led to the notion that NMS must be also therapeutically addressed with appropriate measures [13]. However, NMS are not always self-reported by PD patients [14,15]. Because many of these symptoms are subjective, efforts to increase symptom awareness among healthcare professionals are needed: these would be questionnaire surveys and patient interviews. Moreover, there is less evidence in the field regarding the treatment of NMS than there is for MS [16,17], and NMS are often overlooked in clinical settings. In most cases, MS progression and the appearance of NMS seem to be

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related. Assessing this relationship may help healthcare professionals consider treatments that take into account both MS and NMS.

While the rate of NMS appearance has been reported in some studies to increase as MS severity worsens [6,18–21], most of these studies assessed the association between the two using univariate analysis. Other than MS severity, factors such as age, sex, and disease duration [20–36] have also shown a relation to NMS. However, univariate analysis may not sufficient to detect a true association considering these confounding factors [37].

The current study assessed the association between MS severity and the presence/absence of NMS in PD patients while adjusting for confounding factors.

2. Materials and methods

2.1. Study population/design

This was a cross-sectional study of 1054 PD patients registered consecutively in a multicenter study in Japan. This registry was developed through a collaboration between two university hospitals and five regional general hospitals and included PD patients who underwent treatment in the neurology outpatient department of each facility for three months continuously on a voluntary basis between 2011 and 2012. Diagnoses were made by neurologists according to the United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria [1]. Patients who had other neurological disorders or could not answer questions due to severe dementia were excluded. Informed consent was obtained from all recruited patients from all facilities, and the patients were registered after obtaining approval from the ethics committee at each participating facility. The following information was obtained: age, sex, medical history, family history, age at onset, received deep brain stimulation (DBS) or not, disease duration, duration of drug treatment, Parkinson's medications, Mini-mental State Examination, and Hoehn & Yahr stage (HY stage). Clinical records and interviews were conducted by physicians with patients and their families. Of the registered patients, those who underwent DBS were excluded, leaving 1037 patients in the final analysis.

2.2. Variables/measurements

NMS were evaluated using the Japanese version of the Non-motor Symptoms Scale (NMSS) [7,38,39]. The NMSS is rated by the health professionals and obtained through interview [38]. Patients with symptomatic NMS had an NMSS score ≥ 1, and for each domain, patients were symptomatic when the score for at least one item was ≥1 [22–27]. The severity of MS was assessed by HY stage, and classified into four categories ("No functional disability" and HY stage 1–1.5 [HY stage −1.5], HY stage 2–2.5, HY stage 3, and HY stage 4–5).

From factors previously reported to be related to NMS [6,21–36], sex, age, disease duration, presence/absence of wearing off (WO), presence/absence of dyskinesia, clinical phenotype and levodopa equivalent daily dose (LEDD) were selected as confounding factors.

Sex (male/female) was set as a binary variable, and age (1 year), disease duration (1 year) and LEDD (per 100 mg) were set as continuous variables. The absence of WO and dyskinesia was defined when the score was 0 for Items 39 and 32 of Part IV of the Unified Parkinson's Disease Rating Scale (UPDRS), respectively, and "presence" when the score was ≥1. Clinical phenotypes were nominal variables calculated from Parts II and III of the UPDRS, and classified into the three categories of Tremor Dominant (TD), Postural Instability Gait Disability (PIGD), and indeterminate [40], with indeterminate set as the reference category.

2.3. Statistical analysis

Patient characteristics were presented as mean and standard deviation (SD) for continuous variables and the percentile for categorical variables. For NMS, the prevalence for each item and domain were presented, as well as mean and SD scores of each item and domain (total score of items belonging to the domain).

Multiple logistic regression analysis was conducted with the presence/absence of symptoms for each item and domain of the NMSS as the outcome. To include independent variables in our model, we evaluated the assumption of each variable in statistical perspective. When there were missing data for each selected variable, multiple imputations were conducted based on predictions from age, sex, disease duration, and HY stage. Sensitivity analysis was performed that excluded patients with missing data for any of the items. The significance level was set at 0.05 (two-sided). Statistical analyses were performed with STATA11.2 software.

Ethical approval

The anonymous data were used for the present analysis. This study was approved by the Institutional Review Board of Kyoto University (E2349, December 2014).

3. Results

Patient characteristics are summarized in Table 1. In this study, 1037 patients were analyzed. Males accounted for 44% of the study population (mean age, 69.9 years; mean age at onset, 63.1 years; mean disease duration, 6.7 years). For severity of MS, 76% of patients had an HY stage of 2–3. The mean levodopa equivalent daily dose (LEDD) was 487.1 mg.

Table 2 shows the prevalence of NMS for the nine domains and 30 NMSS items. The total NMSS score was 36.7 ± 34.6. The prevalence by domain was highest for D7 (urinary) at 87.0%, and lowest for D8

Table 1
Clinical characteristics of patients.

Characteristics	All patients (N = 1037)
Sex, Male n (%)/Female n (%)	457 (44.1)/ 580 (55.9)
Age, years	69.9 ± 8.6
Age at onset, years	63.1 ± 9.7
Disease duration, years	6.7 ± 5.0
Modified Hoehn &Yahr stage	
Stage, n (%)	
No functional disability	9 (0.87)
1	139 (13.4)
1.5	35 (3.4)
2	431 (41.6)
2.5	103 (9.9)
3	258 (24.9)
4	61 (5.9)
5	1 (0.1)
Mean (SD)	2.3 ± 0.8
Wearing off, with (%)/without (%)	341 (32.9) / 696 (67.1)
Dyskinesia	181 (17.5)
Clinical phenotype	
Tremor dominant, n (%)	65 (6.3)
Posture instability/gait difficulty, n (%)	812 (78.3)
Indeterminate patients, n (%)	160 (15.4)
L-dopa equivalent dose, mg	487.1 ± 319.6
UPDRS[a]	
Part I (N = 1034)[b]	1.4 ± 1.9
Part II (N = 965)[b]	11.4 ± 7.8
Part III (N = 996)[b]	20.4 ± 10.9
Part IV (N = 1025)[b]	2.1 ± 2.8
PDQ-39[c] Summary Index (N = 1007)[b]	24.1 ± 17.7
MMSE[d] (N = 1034)*2	26.6 ± 3.9

[a] UPDRS, Unified Parkinson's Disease Rating Scale.
[b] There were missing data.
[c] PDQ-39, 39-item Parkinson's Disease Questionnaire.
[d] MMSE, Mini-Mental State Examination.

Table 2
Non-motor symptoms prevalence and scores of each item and domain.

	Prevalence					Mean ± SD	Range
	HY stage					All	All
	−1.5	2–2.5	3	4–5	All		
D1. Cardiovascular	38.3	42.9	56.2	69.4	47.0	1.2 ± 2.2	0–17
1. Light-headedness	38.3	42.3	55.4	69.4	46.5	1.1 ± 1.9	0–12
2. Fainting	1.6	3.2	7.8	24.2	5.3	0.1 ± 0.7	0–9
D2. Sleep/fatigue	81.4	86.0	93.4	95.2	87.6	6.7 ± 7.4	0–45
3. Daytime sleep	48.6	55.6	70.9	75.8	59.4	1.5 ± 2.1	0–12
4. Fatigue	51.9	60.5	69.8	80.7	62.5	2.0 ± 2.8	0–12
5. Difficulty falling asleep	48.1	49.3	57.4	62.9	51.9	1.8 ± 2.8	0–12
6. Restress legs	36.6	41.2	53.5	59.7	44.6	1.4 ± 2.4	0–12
D3. Mood/apathy	58.5	70.0	78.3	88.7	71.0	5.5 ± 8.8	0–72
7. Lost interest in surroundings	16.4	28.5	42.3	58.1	31.5	0.8 ± 1.8	0–12
8. Lack motivation	35.0	47.8	56.2	69.4	48.9	1.4 ± 2.5	0–12
9. Feel nervous	26.2	31.7	36.1	43.6	32.5	0.8 ± 1.8	0–12
10. Seem sad	23.0	31.7	34.1	62.9	32.6	0.8 ± 1.8	0–12
11. Flat mood	19.1	26.8	39.5	53.2	30.2	0.7 ± 1.6	0–12
12. Difficulty experiencing pleasure	23.5	32.6	44.2	58.1	35.4	0.9 ± 1.9	0–12
D4. Perceptual problems/hallucinations	17.5	29.4	44.2	60.0	32.8	1.5 ± 3.7	0–36
13. Hallucinations	9.3	19.1	33.3	45.2	22.5	0.6 ± 1.7	0–12
14. Delusion	2.2	6.7	13.6	27.4	8.9	0.3 ± 1.2	0–12
15. Double vision	9.3	18.2	24.4	30.7	18.9	0.6 ± 1.8	0–12
D5. Attention/memory	63.9	78.7	86.1	80.7	78.0	3.9 ± 5.6	0–36
16. Concentration	34.4	45.1	53.1	58.1	46.0	1.2 ± 2.2	0–12
17. Forget things or events	48.6	62.7	72.5	69.4	63.1	1.5 ± 2.2	0–12
18. Forget to do things	47.0	53.2	63.2	62.9	55.2	1.2 ± 2.0	0–12
D6. Gastrointestinal	67.2	79.4	88.4	87.1	79.9	4.9 ± 5.6	0–36
19. Saliva	14.8	28.1	45.7	54.8	31.7	1.0 ± 2.1	0–12
20. Swallowing	14.2	26.2	39.9	53.2	29.1	0.8 ± 1.9	0–12
21. Constipations	61.2	69.9	77.1	82.3	70.9	3.2 ± 3.6	0–12
D7. Urinary	78.7	86.9	90.7	96.8	87.0	7.1 ± 7.7	0–36
22. Urgency	42.1	55.4	64.0	75.8	56.4	2.0 ± 3.0	0–12
23. Frequency	57.4	68.5	72.1	75.8	67.9	2.2 ± 2.8	0–12
24. Nocturia	61.8	72.3	81.4	87.1	73.6	3.0 ± 3.2	0–12
D8. Sexual dysfunction	27.9	27.7	27.9	33.9	28.2	2.0 ± 4.2	0–24
25. Interest in sex	26.2	23.8	24.8	30.7	24.9	1.0 ± 2.1	0–12
26. Problems in sex	20.8	18.2	20.5	30.7	20.0	1.0 ± 2.4	0–12
D9. Miscellaneous	59.0	61.8	65.1	71.0	62.7	3.9 ± 5.7	0–32
27. Pains	25.7	27.0	32.6	38.7	28.8	1.2 ± 2.8	0–12
28. Taste or smell	23.0	23.4	28.7	30.7	25.1	1.0 ± 2.3	0–12
29. Weight change	21.9	22.9	27.1	40.3	24.8	0.6 ± 1.7	0–12
30. Excessive sweating	32.8	29.2	32.6	38.7	31.2	1.0 ± 2.3	0–12
Total						36.7 ± 34.6	0–259

HY stage, Hoehn & Yahr stage; SD, Standard deviation.

(sexual function) at 28.2%. Regarding the prevalence of NMS by HY stage, more than half of the patients were symptomatic from an early stage (HY stage −1.5) for Item 4 (fatigue), Item 21 (constipation), Item 23 (frequency), and Item 24 (nocturia).

Table 3 shows the results of multiple logistic regression. Odds ratios (ORs) for HY stage categories 2–2.5 (n = 534), 3 (n = 258), and 4–5 (n = 62), with HY stage −1.5 (n = 183) as the reference, were significant for domains D1 (cardiovascular), D2 (sleep/fatigue), D3 (mood/apathy), D4 (perceptual problems/hallucinations), D5 (attention/memory), and D6 (gastrointestinal). Domains D7 (urinary) and D8 (sexual dysfunction) were not significantly associated with HY stage.

For the 30 NMSS items, HY stage categories 2–2.5, 3, and 4–5 were significantly associated with NMS for 18 items (Fig. 1, Supplemental data 1). A trend showed increased ORs for NMS as HY stage severity increased for the following items: Item 8 (lack motivation), and Item 20 (swallowing). In HY stage category 4–5, Item 2 (fainting) and Item 14 (delusions) had high ORs (9.95 [P = .001] and 5.92 [P = .004], respectively) (Supplementary data 1). Similar trends were observed in the sensitivity analysis.

4. Discussion

We assessed the prevalence of NMS and the associations with MS considering confounding factors based on more than one thousand patients with PD in Japan. The ORs were higher in PD patients with more severe MS compared with those with mild MS in NMSS domains D1 (cardiovascular), D2 (sleep/fatigue), D3 (mood/apathy), D4 (perceptual problems/hallucinations), D5 (attention/memory), and D6 (gastrointestinal), but no significant associations were found in domains D7 (urinary) and D8 (sexual dysfunction).

Based on multivariable analysis, ORs for domains D1-D6 were lower compared with ORs determined by univariate logistic regression analysis that used HY stage category as the explanatory variable and the presence of NMS by domain as the objective variable (Supplementary data 2). Moreover, in the univariate analysis, the association observed between MS and NMS in domain D7 (urinary) was not observed in the multivariable analysis. The difference between both analyses suggested confounding factors need to be adjusted for when considering the independent association between MS severity and the presence of NMS. Our findings are largely similar in trend to previous studies reporting an association between MS and NMS, although we were able to further clarify differences by the nine NMSS domain. For domains D1-D6, HY stage, which could be objectively evaluated, may predict the presence of NMS. However, for domains D7 (urinary) and D8 (sexual dysfunction), our findings suggested that patients should be questioned about the presence/absence of symptoms regardless of MS severity.

Table 3
Multiple logistic regression[a]: Domains.

		D1. Cardiovascular			D2. Sleep/fatigue			D3. Mood/apathy		
		OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
HY stage	−1.5	Reference			Reference			Reference		
	2–2.5	0.96	0.66, 1.38	0.823	1.13	0.70, 1.81	0.624	1.31	0.90, 1.90	0.153
	3	1.30	0.84, 2.01	0.234	2.14	1.08, 4.26	0.030	1.52	0.95, 2.43	0.083
	4–5	2.09	1.06, 4.11	0.033	2.56	0.70, 9.35	0.154	2.72	1.11, 6.66	0.028
Sex (Male)		1.44	1.11, 1.87	0.005	0.99	0.68, 1.46	0.972	1.08	0.81, 1.43	0.598
Age		1.01	0.99, 1.02	0.439	1.01	0.99, 1.04	0.279	1.02	1.00, 1.04	0.013
Disease duration		1.02	0.98, 1.05	0.332	0.97	0.92, 1.03	0.295	1.02	0.98, 1.07	0.239
Wearing off		1.11	0.79, 1.55	0.563	2.48	1.34, 4.58	0.004	1.05	0.71, 1.54	0.816
Dyskinesia		1.05	0.71, 1.57	0.807	1.33	0.61, 2.91	0.476	1.76	1.08, 2.86	0.024
Clinical phenotype	TD	1.07	0.56, 2.02	0.840	0.76	0.33, 1.72	0.506	0.61	0.33, 1.13	0.113
	PIGD	2.06	1.18, 3.58	0.011	0.99	0.46, 2.10	0.969	1.21	0.70, 2.12	0.496
LEDD		1.03	0.98, 1.09	0.192	1.06	0.98, 1.16	0.157	0.99	0.93, 1.05	0.697

		D4. Perceptual problems			D5. Attention/memory			D6. Gastrointestinal		
		OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
HY stage	−1.5	Reference			Reference			Reference		
	2–2.5	1.37	0.87, 2.16	0.170	1.54	1.04, 2.28	0.029	1.37	0.92, 2.05	0.121
	3	1.72	1.04, 2.84	0.035	1.93	1.15, 3.25	0.013	2.04	1.17, 3.54	0.012
	4–5	2.25	1.11, 4.56	0.024	1.15	0.53, 2.49	0.730	1.36	0.56, 3.30	0.491
Sex (Male)		1.35	1.01, 1.79	0.040	1.52	1.10, 2.08	0.010	1.63	1.17, 2.27	0.004
Age		1.03	1.02, 1.05	<0.001	1.04	1.02, 1.05	<0.001	1.01	0.99, 1.03	0.356
Disease duration		1.08	1.04, 1.12	<0.001	0.99	0.95, 1.04	0.772	1.08	1.03, 1.14	0.003
Wearing off		1.09	0.76, 1.56	0.640	0.98	0.65, 1.50	0.940	1.51	0.94, 2.40	0.085
Dyskinesia		0.98	0.64, 1.48	0.906	1.45	0.86, 2.43	0.159	0.77	0.44, 1.34	0.351
Clinical phenotype	TD	0.68	0.32, 1.47	0.327	0.69	0.35, 1.35	0.279	0.66	0.34, 1.31	0.238
	PIGD	1.53	0.82, 2.85	0.177	1.23	0.67, 2.27	0.497	1.19	0.64, 2.22	0.583
LEDD		1.04	0.99, 1.10	0.145	1.03	0.97, 1.10	0.326	1.01	0.95, 1.09	0.697

		D7. Urinary			D8. Sexual dysfunction			D9. Miscellaneous		
		OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
HY stage	−1.5	Reference			Reference			Reference		
	2–2.5	1.13	0.71, 1.82	0.605	0.82	0.54, 1.23	0.334	0.95	0.66, 1.38	0.804
	3	1.15	0.61, 2.18	0.661	0.73	0.44, 1.19	0.205	0.89	0.57, 1.39	0.602
	4–5	2.55	0.56, 11.64	0.227	0.98	0.47, 2.02	0.950	1.07	0.53, 2.13	0.857
Sex (Male)		2.68	1.76, 4.08	<0.001	2.71	2.03, 3.64	<0.001	1.14	0.88, 1.49	0.325
Age		1.04	1.02, 1.07	0.001	0.96	0.94, 0.98	<0.001	0.99	0.97, 1.01	0.230
Disease duration		1.07	1.01, 1.14	0.033	1.04	1.01, 1.08	0.019	1.00	0.97, 1.04	0.889
Wearing off		1.31	0.76, 2.27	0.326	0.78	0.53, 1.15	0.208	1.38	0.97, 1.97	0.076
Dyskinesia		2.13	0.99, 4.57	0.052	1.07	0.69, 1.66	0.756	1.53	0.98, 2.38	0.062
Clinical phenotype	TD	0.45	0.18, 1.10	0.081	0.46	0.23, 0.91	0.026	0.69	0.38, 1.25	0.223
	PIGD	0.75	0.32, 1.73	0.497	0.89	0.50, 1.58	0.683	1.10	0.65, 1.87	0.723
LEDD		0.98	0.90, 1.06	0.561	1.07	1.01, 1.13	0.026	1.06	1.00, 1.12	0.047

OR, Odds ratio; 95% CI, 95% Confidence Interval; P, P value; HY stage, Hoehn & Yahr stage; TD, Tremor dominant; PIGD, Postural instability/gait difficulty; LEDD, L-dopa equivalent daily dose.
[a] Adjusted sex, age, disease duration, wearing off, dyskinesia, clinical phenotypes and LEDD.

Unlike most previous studies, we also assessed NMS by each of the 30 items. For some (e.g., Item 9. feel nervous, Item 18. forget to do things, Item 28. taste or small) of the 12 items which were not associated with MS severity, NMS may have already been present prior to the PD diagnosis. This presence could potentially be attributed to the fact that the pathology of PD involved not only the degeneration of nigrostriatal neurons, but also the aggregation of neurotransmitters and proteins, other than Lewy bodies throughout the nervous system [2]. Braak et al. suggested a model in which changes in Lewy bodies began from the peripheral nervous system, olfactory bulb, and anterior olfactory nucleus and progressed to the lower brainstem [41]. Changes to the lower brainstem are thought to appear as NMS, such as sleep abnormalities, depression, dementia, pain, constipation, and autonomic symptoms [4], and the Braak model may explain the mechanism underlying the pre-motor/prodromal period [3,41]. Previous studies have categorized NMSS Item 5 (difficulty falling asleep), Item 9 (feel nervous), Item 15 (double vision), Item 21 (constipation), and Item 28 (taste or smell) as pre-motor symptoms [42]. The present study confirmed that these items were not associated with MS severity, suggesting that they appeared much earlier than MS did. NMSS Item 6 (restless legs) has been reported to be a pre-motor symptom in previous studies [2,16,42]. However, NMSS Item 6 was found to be associated with MS severity in our study, as ORs were higher in HY stage categories 3 and 4–5 compared with HY stage category −1.5 ($p < .05$). These higher ORs suggested the need to understand that some items tended to appear in early stages of the disease and increase in prevalence as MS severity increased. Item 8 (lack motivation) and Item 20 (swallowing) increased in prevalence as MS severity increased, and Item 2 (fainting) and Item 14 (delusions) showed high ORs in HY stage category 4–5 (at high MS severity). These symptoms should be noted and considered when MS worsens.

Current treatment strategies for patients with PD are needed to

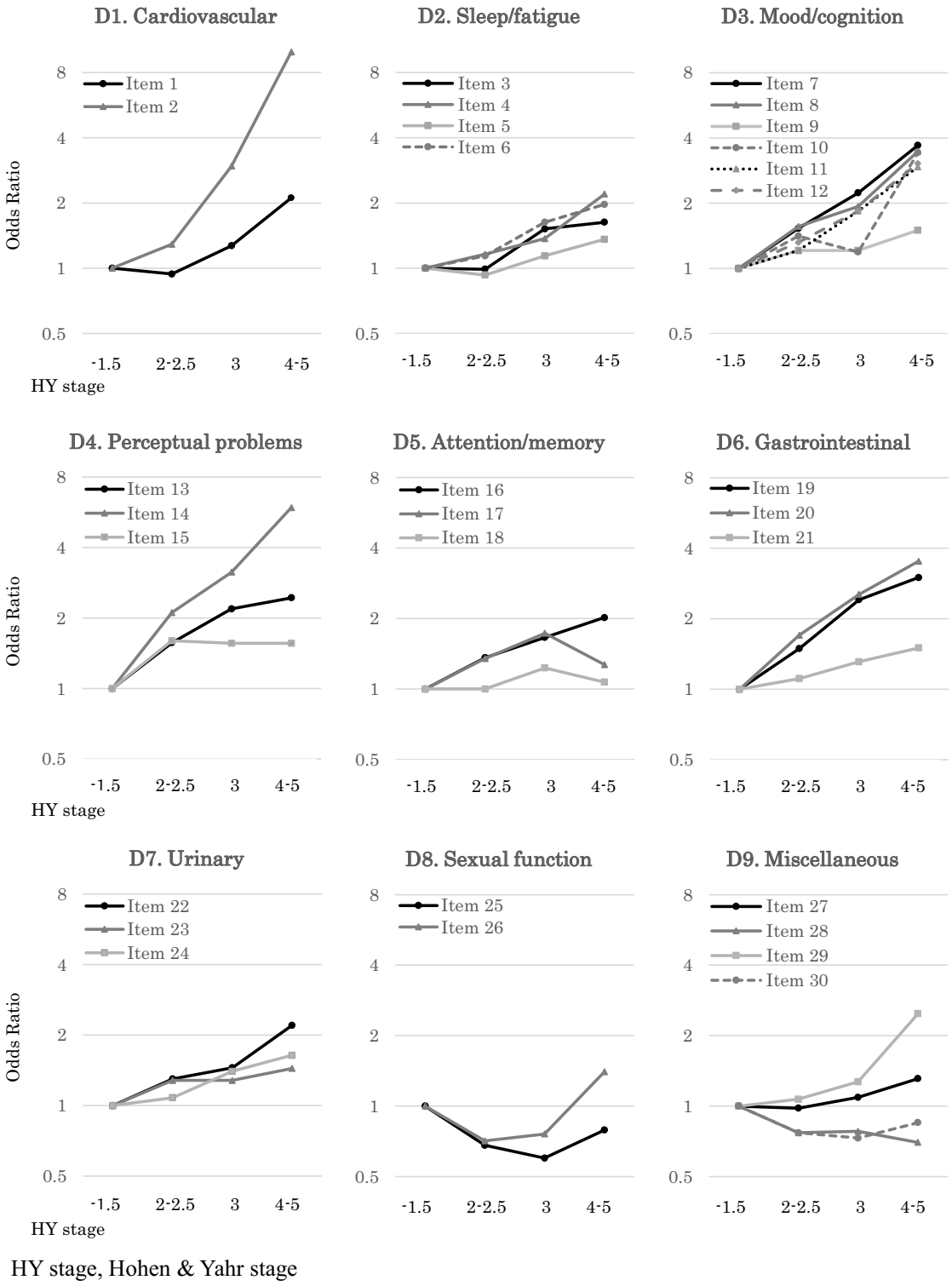

Fig. 1. Odds ratios of multiple logistic regression for each non-motor symptom by motor symptom.

assess the various symptoms of each patient [43]. Revealing the association between MS, the focus of PD studies, and the presence/absence of NMS may increase NMS awareness in busy clinical settings. Our findings also suggested that each NMSS domain had unique features in factors other than HY stage (e.g., age, sex, disease duration) that were associated with NMS. Future studies should determine which factors have a greater impact than others on NMS in each domain and item. PD is understood to be a neurological disease affecting the entire body rather than being limited to the central nervous system. Furthermore, there are proposals to redefine PD [44]. In this case, the ability to predict the presence of NMS based on MS might be useful in clinical settings because of its contribution to early diagnosis and interventions.

4.1. Limitations

This study has some limitations. First, we adopted a cross-sectional

design and did not consider changes in disease condition over time. Second, we did not take into account details of treatments for MS and each individual NMS. These, as well as unassessed confounders, could have influenced the results. Third, dichotomous presence/absence of NMS was adopted in this study, so the NMS was not evaluated quantitatively.

Finally, the study population consisted of patients seen by neurologists at specialty outpatient clinics and thus represented a population of patients with well-controlled symptoms. So, the present results should be applied carefully for the other patient groups. Future longitudinal studies are warranted that examine various cases of PD patients including quantity (severity and frequency) and progression of NMS.

5. Conclusion

After adjusting for confounders, most non-motor symptoms were found to increase as motor symptoms worsened in PD patients, however some of them increased independent of motor symptoms. In an analysis that adjusted for confounding factors, six NMSS domains (cardiovascular symptoms, sleep/fatigue, mood/cognition, perceptual problems, attention/memory, gastrointestinal symptoms) were found to increase as MS progressed in PD patients, but not of urinary symptoms and sexual function. Item 8 (lack motivation) and Item 20 (swallowing) increased in prevalence as MS became more severe, and Item 2 (fainting) and Item 14 (delusions) had higher ORs at a higher HY stage category (stage 4–5). Items for which the association with MS was unclear may have been present when MS severity was low or prior to the appearance of MS. These findings contribute to the understanding of the clinical picture of PD and may improve treatment and research of PD.

Declaration of Competing Interest

Dr. Okuma reports personal fees from Otsuka pharmaceuticals, Abbvie Pharmaceuticals, Dai-Nippon Sumitomo Pharmaceuticals, and Kyowa-Hakko Kirin Pharmaceuticals., other from Otsuka pharmaceuticals, Abbvie Pharmaceuticals, Dai-Nippon Sumitomo Pharmaceuticals, Kyowa-Hakko Kirin Pharmaceuticals, Eisai Pharmaceuticals, Nippon Behringer Ingerheim, FP Pharmaceuticals and Nihon Medi-physics., outside the submitted work;. Dr. Kashihara reports grants from AMED, personal fees from Kyowa Hakko Kirin Co. Ltd., personal fees from Novartis Pharma K.K., personal fees from Sumitomo Dainippon Pharma Co. Ltd., personal fees from AbbVie GK., personal fees from Otsuka Pharmaceutical Co. Ltd., personal fees from FP Pharmaceutical Co. Ltd., personal fees from Daiichi Sankyo Co. Ltd., personal fees from Esai Co. Ltd., personal fees from Novartis Pharmaceutical Co. Ltd., outside the submitted work;. Dr. Nakayama reports personal fees from Otsuka Pharmaceutical co., other from Nakamura hospital, other from Japan Medical Data Center, personal fees from Dainippon Sumitomo Pharmaceutical co., personal fees from Ono Pharmaceutical co., personal fees from Chugai Pharmaceutical co., personal fees from Dentsu co., personal fees from Lixil co., personal fees from Takeda Pharmaceutical co., personal fees from Janssen Pharmaceutical K.K., outside the submitted work;.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.116641.

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