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Functional neurological disorders in Parkinson disease

Benjamin D. Wissel, BS[1], Alok K. Dwivedi, PhD[2], Danielle Chin[1], Aristide Merola, MD, PhD[1], Cara Jacob, MD[1], Andrew P. Duker, MD[1], Jennifer E. Vaughan, MD[1], Lilia Lovera, MD[1], Kathrin LaFaver, MD[3], Ariel Levy, MD, FRCPC[4], Anthony E. Lang, MD, FRCPC[4], Francesca Morgante, MD, PhD[5,6], Melissa J. Nirenberg, MD, PhD, FAAN[7], Christopher Stephen, MB, CHB[8], Nutan Sharma, MD, PhD[8], Alberto Romagnolo, MD[9], Leonardo Lopiano, MD, PhD[9], Bettina Balint, MD[10,11,12], Xin X. Yu, MD[13], Kailash P. Bhatia, MD, DM, FRCP[10], Alberto J. Espay, MD, MSc, FAAN[1]

[1]Gardner Family Center for Parkinson's Disease and Movement Disorders, Department of Neurology, University of Cincinnati, Cincinnati, OH, USA

[2]Division of Biostatistics & Epidemiology, Department of Biomedical Sciences, Texas Tech University Health Sciences Center, El Paso, TX, USA

[3]Department of Neurology, University of Louisville, Louisville, KY, USA

[4]Morton and Gloria Shulman Movement Disorders Clinic and the Edmond J. Safra Program in Parkinson's Disease, Toronto Western Hospital and the Department of Medicine University of Toronto, Toronto, ON, Canada

[5]Dipartimento di Medicina Clinica e Sperimentale, Università degli Studi di Messina, Messina, Italy

[6]Institute of Molecular and Clinical Sciences, St George's University of London, London, United Kingdom

[7]Department of Neurology, NYU School of Medicine, New York, NY, USA

[8]Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

[9]Department of Neuroscience "Rita Levi Montalcini", University of Turin, Torino, Italy

[10]Sobell Department of Motor Neuroscience and Movement Disorders, University College London, United Kingdom

[11]Department of Neurology, University Hospital, Heidelberg, Germany

[12]Autoimmune Neurology Group, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK

[13]Cleveland Clinic Center for Neurological Restoration, Cleveland, OH, USA

All correspondence to:

Dr. Alberto J. Espay

University of Cincinnati Academic Health Center

260 Stetson St., Suite 2300

Cincinnati, OH 45267-0525, USA

Phone 513-558-4035

Fax 513-558-7015

alberto.espay@uc.edu

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ABSTRACT

Objective: To ascertain demographic and clinical features of Parkinson disease (PD) associated with functional neurological features.

Methods: A standardized form was used to extract data from electronic records of 53 PD patients with associated functional neurological disorders (PD-FND) across eight movement disorders centers in the US, Canada, and Europe. These subjects were matched for age, gender, and disease duration to PD patients without functional features (PD-only). Logistic regression analysis was used to compare both groups after adjusting for clustering effect.

Results: Functional symptoms preceded or co-occurred with PD onset in 34% of cases, nearly always in the most affected body side. Compared to PD-only subjects, PD-FND were predominantly female (68%), had longer delay to PD diagnosis, greater prevalence of dyskinesia (42% vs. 18%; $p = 0.023$), worse depression and anxiety ($p = 0.033$ and 0.025, respectively), higher levodopa equivalent daily dose (972 ± 701 vs. 741 ± 559 mg; $p = 0.029$), and lower motor severity ($p = 0.019$). These patients also exhibited greater healthcare resource utilization, higher use of [(123)I]FP-CIT SPECT, and were more likely to have had a preexisting psychiatric disorder ($p = 0.008$) and family history of PD ($p = 0.036$).

Conclusions: A subtype of PD with functional neurological features is familial in one fourth of cases and associated with more psychiatric than motor disability and greater use of diagnostic and health care resources than those without functional features. Functional manifestations may be prodromal to PD in one third of patients.

INTRODUCTION

Parkinson disease (PD) and functional neurological disorders (FND) are considered distinct disorders with non-overlapping pathophysiologic mechanisms. However, the coexistence of FND is well recognized in organic neurological disorders. Patients with "functional overlay" are reported to have more anxiety and depressive symptoms.[1] Certain neurobiological features in organic disorders may explain a predisposition to developing comorbid FND.[2]

Recently, FND have been reported to co-occur with PD and related neurodegenerative disorders.[3 4] Some features such as gastric symptoms, anxiety, and pain are difficult to correctly classify as FND[3-5] and may instead represent non-motor features of PD. Nevertheless, in a series of 11 patients with PD and FND, 4 exhibited functional manifestations predating PD diagnosis.[6] Most of these functional symptoms led to significant disability and escalation of PD treatment, including requests for consideration of deep brain stimulation.

We sought to determine the clinical and demographic features associated with an increased prevalence of functional complications in PD (PD-FND), in particular motor lateralization and dopaminergic medication usage. We hypothesized that these clinical features would differ from those of age-, gender-, and disease duration-matched PD patients without FND (PD-only).

METHODS

We conducted a multi-center case-control study involving nine movement disorder centers in the US, Canada, UK, and Italy. Investigators utilized a standardized data collection sheet using de-identified clinical information extracted from electronic medical records. The study was approved by all local ethics review boards. The Institutional Review Board of the University of

Cincinnati acted as central for all sites (# 2016-1518).

Study population and data collection

Standardized chart review collected demographic (age and gender) and clinical data for both patient groups. Investigators were asked to search electronic medical records of all PD patients within their clinic for key words or phrases such as “psychogenic”, “functional”, “variable severity”, “deliberately effortful”, or “inconsistent with Parkinson disease”. In addition, investigators from each center also were asked to consider additional patients whose symptoms were recalled as excessive or disproportionate to objective impairment to enhance the odds of finding additional subjects with comorbid functional symptoms who may have met inclusion criteria. Inclusion criteria for PD included the diagnosis of idiopathic PD according to UK Brain Bank criteria[7] at least 18 years of age, and Hoehn & Yahr Stage I-IV in the ON state.[8] Patients with PD who had documentation of any (motor or non-motor) FND, meeting criteria for clinically definite FND according to Gupta and Lang criteria (for functional movement disorders), were included as PD-FND cases.[9] Comorbid functional symptoms such as nausea, cognitive symptoms, pain and fatigue, meeting criteria as Somatic Symptom Disorder in DSM-5, were also included. The available clinical scales taken during routine clinical practice included the motor subscale of the Movement Disorders Society-Unified Parkinson Disease Rating Scale (MDS-UPDRS-III) in the ON dopaminergic medication state, Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Parkinson’s Disease Questionaire - 39 (PDQ), Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE). However, only standardized scales and objective data (gender, age, age of onset, treatment and their dosages, etc.) were included. Non-motor functional symptoms were included if they met DSM-5 criteria for functional neurological disorder, which included: a) symptoms of altered voluntary motor or

sensory function; b) clinical findings that provided evidence of incompatibility between the symptom and PD or it's treatment; c) the symptom was not better explained by PD; and d) the symptom caused clinically significant distress or impairment in social, occupational, or other important areas of functioning.[10] Other neurological and psychiatric comorbidities were also recorded if a formal diagnosis was documented. Data were entered and stored in a secure collection system, Research Electronic Data Capture (REDCap). The most updated clinical data were retrieved, and data not available for each patient were omitted from the analysis.

Cases were only included if the PD-FND diagnosis was confirmed after full review of all chart notes and video documentation. In cases of uncertainty, the case was excluded. A second investigator at a different site reviewed all eligible cases, and both parties had to agree to allow inclusion. PD-FND cases (N = 53) were individually matched for gender, age, and disease duration (within three years) to PD-only controls within each originating center. Matched PD-only controls were selected proportionally to the number of PD-FND at each center. Controls were selected from a consecutive cohort based on the patients who fit match criteria that most recently visited the clinic. Data from these de-identified pairs were then submitted to the University of Cincinnati for collation into a single spreadsheet for data analysis.

FND was considered to have a rapid onset if symptoms fully appeared within a six-month period, and was considered static if they did not progress after documentation of the initial onset. Cognitive decline was measured using MMSE and MoCA scores and compared between groups. Health care utilization data, including number of movement disorders office visits, hospitalizations, phone calls, and messages since joining the movement disorders clinic were collected. Data were available only for events within the providers' respective health care

system. Year of symptom onset and clinical diagnosis for PD and FND were recorded. Neurological and psychiatric comorbidities and FND symptom onset were analyzed in relation to timing of PD diagnosis.[6] Dosage of dopaminergic therapy, history of deep brain stimulation (DBS), and outcome of [(123)I]FP-CIT SPECT (DATscan®) were also recorded, when available. LEDD was calculated according to the conversion table proposed by Tomlison et al.[11] PD and FND symptoms were categorized and analyzed separately.

Statistical Analysis

Appropriate summary measures (mean and standard deviation [SD]) were used for quantitative variables, and frequency and proportion for categorical variables. Clinical variables were compared between groups using logistic regression analysis after adjusting for clustering effect. Further, non-normal quantitative data were compared between two groups using non-parametric rank sum test for clustered data. Robust variance was estimated to account for matching age, gender, and disease duration. In the sub-group analysis, the prevalence of functional phenotype was estimated and reported along with 95% confidence interval (CI). All continuous variables were compared using unpaired t-test or Wilcoxon rank sum test while Kruskal Wallis test was used for comparing data between more than two groups. In addition, Fisher's exact test was used for comparing categorical data between groups. P-values of <0.05 were considered significant. Correction for multiple comparisons was not conducted given the exploratory nature of the study. Spearman rank correlation analysis was explored for age, timing of diagnosis and delays in diagnosis with health care utilization by groups. Sample size was computed based on two aims: (1) determine the prevalence of functional phenotype (such as tremor, dystonia, myoclonus, parkinsonism) among PD-FND patients, and (2) compare clinical scales (MDS-UPDRS) and characteristics (psychiatric disorders, and dyskinesia) with PD controls. A

previous study estimated the prevalence of tremor (48.5%), dystonia (15.2%), myoclonus (15.2%) and parkinsonism (7.6%) among functional movement disorders (FMD) and compared disability and psychopathology with PD patients.[12] We postulated that we would obtain similar distributions of functional phenotypes in PD-FND patients with 20%-30% confidence width, depending on the prevalence. Based on this, at least 50 cases of PD-FND were required to produce a two-sided 95% confidence interval with proposed width sizes. Further, this study reported moderate (0.55) to large effect sizes (0.80) for quality of life, psychiatric distress, anxiety, depression, and somatization. Based on this assuming a moderate effect size (0.6), a sample size of 64 (32 per group) was found to be sufficient to detect a significant change in MDS-UPDRS with 80% power and at 5% level of significance using a paired t-test/clustered logistic regression. Thus, we proposed to include at least 50 patients per group which allowed detection of significant differences for moderate effect sizes for most of the clinical outcomes due to matched study design. All analyses were carried out using STATA 13.

RESULTS

We examined a total of 106 patients (72 women [68%]), including 53 PD-FND (age, 62 ± 10 years; PD disease duration, 9 ± 5 years) and 53 PD-only patients (63 ± 10 years; duration, 9 ± 5 years) (Table 1). PD diagnosis was more likely to be confirmed by DATscan in the PD-FND group (58% vs. 30%; $p < 0.001$) than the PD-only group. PD-FND patients had a higher proportion of family history of PD (25% vs. 8%; $p = 0.036$) and higher frequency of psychiatric disorders, both before (67% vs. 40%; $p = 0.008$) and after onset of the first PD symptom (85% vs. 72%; $p = 0.033$).

Clinical features

Compared to PD-only, PD-FND was associated with higher BAI and BDI scores (34 ± 8 vs. 17 ± 7 and 21 ± 10 vs. 14 ± 8; p = 0.033 and 0.025, respectively) (Table 1) and higher total LEDD (972 ± 701 mg vs. 741 ± 557 mg; p = 0.029) (Table 2). The PD-FND cohort had a greater prevalence of dyskinesia during motor evaluation (42% vs. 18%; p = 0.023) and lower MDS-UPDRS-III scores (25 ± 14 vs. 30 ± 11; p = 0.019) (Table 1). MoCA and MMSE scores were similar between the two groups.

Characteristics of the functional phenotype

In the PD-FND cohort, FND symptom onset antedated PD diagnosis by <3 years (N = 5), 3-5 years (N = 3), 6-10 years (N = 4), or >10 years (N = 2) in 14 patients (26%). FND occurred simultaneously to PD in 4 (8%), after in 30 (57%), and was unknown in 5 (9%). For cases whose FND symptoms antedated PD diagnosis, there was a longer delay reaching a diagnosis of PD compared to those whose FND symptoms began after PD diagnosis (3.5 ± 2.4 vs. 2.1 ± 2.4 years; p = 0.017) (Table 3).

The onset of functional symptoms was rapid in 55% of cases. Gait/balance impairment and tremor were most frequent, at about 40% each, and 60% of cases had at least two functional manifestations (Figure 1). Violent dyskinesia/shaking spells and non-motor functional symptoms (subcategorized as: pain (N = 8); cognitive decline (N = 2); nausea (N = 2); fatigue (N = 1); and other (N = 2)) were each present in 25%, as well as functional parkinsonism in 21%, dystonia in 15%, speech impairment in 11%, and myoclonus in 6% of cases. Functional symptoms fluctuated with levodopa intake in 12 cases (23%) and did not in 16 (30%) (response unavailable in 25 cases [47%]). Of the patients whose functional symptoms entered remission (N = 24), 71% had at least one relapse of functional symptoms over the course of a mean of 3.5 years of after-

diagnosis data. The course of symptoms was static in 55% and progressive in 30% of cases (unknown in 15%). Overall, symptoms worsened in 7 (13%), improved in 12 (23%), resolved in 5 (9%), and did not change in 23 patients (43%) (unknown in 11%).

Health care utilization

Compared with PD-only, patients with PD-FND utilized more health care resources (Table 4). Patients called their physician's office more (34 ± 45 vs. 17 ± 23 calls; $p = 0.007$) and had more hospitalizations (1.2 ± 1.9 vs. 0.9 ± 2.6 visits; $p = 0.007$). There were no significant between-group differences in the number of office visits or electronic messages captured.

DISCUSSION

We found that PD patients with functional features were on higher dopaminergic medication dosages, had more dyskinesia, exhibited greater depression and anxiety symptoms, and required more attention by clinicians than age-, gender-, and disease duration-matched PD patients without functional complications. Importantly, functional manifestations antedated the diagnosis of PD in 26% and were noted at time the of PD diagnosis (confirmed by DATscan during an evaluation in patients with only suspected FND) in 8%, nearly always manifesting on the more affected PD side. Gait/balance impairment and tremor were the most common functional phenotypes in PD-FND patients, with a prevalence of about 40% each. Incongruent ballistic dyskinesia (with descriptions from source documents ranging from "severe shaking spells," to "restless body syndrome," to "arm flailing," to non-epileptic seizures), which may have initially been confused with levodopa-induced (dose-dependent) peak-dose or diphasic dyskinesia, were described in 25% of the PD-FND cohort.

While the study was not designed to address the prevalence of functional complications in PD, we calculated the prevalence of PD-FND among the patients presented at the University of Cincinnati corresponded to 1.4% of all active patients. More liberal inclusion criteria estimated the prevalence of functional symptoms in PD as high as 7.5%.[4] Nevertheless, the recognition of cases may be lower than actual as reflected by a longer delay to PD diagnosis and more frequent use of DATscan. In addition, 7 (13%) of PD-FND patients underwent DBS surgery, arguing that the disability of these patients, while disproportionally psychiatric over motor in nature, may force consideration of advanced treatments at a higher rate than in the absence of functional manifestations, as recently reported in one patient.[13]

In contrast to the left-sided predominance of motor symptoms (right hemispheric involvement) ascertained for patients with epileptic seizures complicating their course with non-epiletic seizures (PNES),[2] no differences on lateralization of symptoms was demonstrated in our PD-FND cohort. Right-sided PD onset was more common across both groups but there was similar frequency of left and right sided onset of functional symptoms and these were more likely to appear in the more affected side. More intriguingly, while patients with both epileptic and PNES almost universally develop PNES after epilepsy,[2 14] functional features predated or co-occurred in a substantial proportion of PD patients.

Recent data suggest a higher frequency of somatoform disorders, defined as conversion motor or sensory disorders, among patients with PD (7.5%) and dementia with Lewy bodies (18%) compared to patients with other neurodegenerative disorders, followed for up to four years,[4] as well as a more prevalent family history among PD patients with functional complications compared to those without, which may suggest a genetic component for the PD-FND subtype.

Higher somatization scores, as recorded by the Symptom Checklist 90 Revised (SCL-90R), have been reported in PD by women (70% vs. 46%) with higher UPDRS scores ($p<0.01$).[15] The PD-FND cohort had lower UPDRS scores, possibly due to higher LEDD as the result of the initially unrecognized functional features, with the overall behavior characterized as undertreatment. Alternatively, the high LEDD may have directly predisposed to FND (the study design precludes ascertaining the direction of causality). With regards to FND co-occurring or antedating PD in one third of the PD-FND cohort, it is possible a selection bias could have occurred if patients with FND already were receiving care from a neurologist, making PD onset more easily recognized. On the other hand, other prodromal symptoms, such as depression and anxiety, could have influenced the onset of FND.

Although this is the largest study of PD-FND, our study has several limitations worth highlighting. Recall and selection biases, inherent to retrospective case-control studies, could have influenced enrollment despite the strict enrollment criteria and selection methods aimed to reduce these as much as possible. Data were retrospectively recorded from electronic medical records and, thus, systematic clinical interviews could not be structured to obtain data for each patient. Data on non-motor PD symptoms was not available for analysis as most sites did not employ a standardized instrument for these symptoms. Any data that were not available for each subject, including the number of phone calls, which were not regularly collected at European centers, were omitted from the analysis. Data for health care utilization outside of the provider's health care system was also not available. As with the clinical scales, which varied in completion according to the submitting center's standard practice, the reduced power was reflected in the p-values, whose calculations are dependent on sample size. The number of patients analyzed were provided in tables 1-4. Still, data based on low counts should be interpreted with caution.

Additionally, laboratory-supported definite FND diagnosis was not available for most phenotypes beyond tremor and myoclonus, which may have underestimated PD-FND identification. Because of this shortcoming, and the lack of DATscans for most PD patients, some subjects may have been miscategorized. In addition, we did not include patients with PD dementia, which may have increased the prevalence of FND cases given the higher reported prevalence of FND among patients with dementia with Lewy bodies compared with PD (18% vs. 7.5%).[4] Interestingly, it has been reported that patients worked up for functional symptoms tend to overreport family history of neurological disorders.[16] This may have contributed to our findings that PD-FND patients have a higher proportion of family history of neurological disease. However, in our study many family histories were extracted from medical records before FND was recognized. Also, participating sites used MoCA or MMSE in lieu of a complete battery of neuropsychological testing, which further limited the sensitivity to subtle cognitive differences between the groups. Our study design precluded any evaluation of the effect of sex, age, and disease duration, which were used to match cases to controls. Nevertheless, age at onset in both groups was consistent with epidemiologic studies of PD but women were disproportionately more prevalent in the PD-FND cohort, which is at odds with the known male predominance of PD, and suggests that female sex may be an independent risk factor for the development of FND in PD, as it is with most isolated functional disorders.

In conclusion, a subtype of PD with prior and current psychiatric comorbidities and family history of PD, is associated with (or may be preceded by) functional neurological features. Recognition of functional neurological features in PD, which should be suspected in cases of unexplained deterioration or treatment-refractory symptoms (particularly dyskinesia), may warrant avoidance of iatrogenic harm and consideration of non-pharmacologic strategies, such as

cognitive behavioral therapy. Further studies will be necessary to ascertain the neurobiological underpinning of the PD subtype that is followed or preceded by FND.

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Figure legend

Figure 1. Clinical characteristics of functional symptoms

(1)Two or more functional symptoms. (2)Gait/balance functional phenotypes were subcategorized as: excessive retropulsion (N = 6); astasia-abasia (N=6); deliberately effortful (N = 4); knee buckling (N = 4); and other (N = 8). (3)"Other" functional phenotypes included severe dyskinesia/shaking spells (N = 13). (4)Non-motor functional phenotypes were subcategorized as: pain (N = 8); cognitive decline (N = 2); nausea (N = 2); fatigue (N = 1); and other (N = 2). (5)Parkinsonism with very clear functional features distinct from the "organic" aspects found in the same patient (i.e., "functional overlay").

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Table 1. Demographics and clinical characteristics of the study cohort

	PD-FND			PD-only			
	N	**%**	**Mean ± SD**	**N**	**%**	**Mean ± SD**	**P-value***
Age (matched by design)	53	100	61.9 ± 9.8	53	100	62.4 ± 10.1	
PD Onset	53	100	52.5 ± 11.1	53	100	53.1 ± 11.7	0.29
PD disease duration (matched by design)	53	100	9.4 ± 4.6	53	100	9.3 ± 4.7	
Clinical Scales							
MDS-UPDRS-III	43	81.1	25.1 ± 13.8	46	86.8	29.7 ± 11.1	**0.019**
MoCA	26	49.1	25.7 ± 4.8	27	50.9	26.3 ± 3.7	0.875
MMSE	22	41.5	28.9 ± 1.2	17	32.1	28.4 ± 1.7	0.341
BDI	15	28.3	20.9 ± 9.7	15	28.3	14.1 ± 7.6	**0.025**
BAI	5	9.4	34 ± 7.9	5	9.4	16.8 ± 7.3	**0.033**
PDQ	13	24.5	59.6 ± 15.7	13	24.5	51.2 ± 24.6	0.208
Family history of neurological disorder							
None	25	47.2		21	39.6		0.476
Parkinson disease	13	24.5		4	7.5		**0.036**
Dementia NOS	8	15.1		11	20.8		0.472
Tremor	4	7.5		7	13.2		0.325
Neurodegenerative disease NOS	4	7.5		5	9.4		0.658
Other	12	22.6		5	9.4		**0.020**
Unknown	2	3.8		2	3.8		
Family history of psychiatric disorder							0.103
No	20	69.0		33	84.6		
Yes	9	31.0		6	15.4		
Psychiatric disorder antedating PD							**0.008**
No	16	32.7		27	60.0		

Yes	33	67.3	18	40.0	
Current psychiatric disorder					**0.033**
No	8	15.1	15	28.3	
Yes	45	84.9	38	71.7	
Body side at onset for PD					0.380
Right	28	54.9	36	69.2	
Left	20	39.2	14	26.9	
Bilateral	3	5.9	2	3.8	
Dyskinesia					**0.023**
No	18	58.1	23	82.1	
Yes	13	41.9	5	17.9	

NOS: not otherwise specified; SD: standard deviation; PD-FND: Parkinson disease with functional neurological disorder; PD: Parkinson disease

*P-values were obtained using rank sum test for clustered data where data were heavily skewed or logistic regression accounting for clustering effect

Table 2. Dosage of dopaminergic treatments

	PD-FND		**PD-only**		
	N	**Mean ± SD**	**N**	**Mean ± SD**	**P-value**
Levodopa	44	679.5 ± 528.0	38	588.8 ± 426.0	0.274
LCIG	2	1460 ± 367.7	2	1115 ± 357.8	0.439
Levodopa CR	15	273.3 ± 153.4	9	188.9 ± 92.8	0.084
Rytary	3	1453.3 ± 1231.4	1	1470.0	0.747
Stalevo	4	625.0 ± 375.3	3	500.0 ± 100.0	0.648
Entacapone	6	833.3 ± 463.3	5	780.0 ± 319.4	0.875
Pramipexole	10	2.4 ± 1.2	17	2.2 ± 1.2	0.571
Ropinirole	7	8.4 ± 3.2	9	8.5 ± 8.4	0.648
Rotigotine	6	3.8 ± 2.4	3	4.0 ± 3.5	0.917
Selegiline	2	10 ± 0	3	10 ± 0	
Rasagiline	5	0.9 ± 0.3	8	1 ± 0	0.344
Amantadine	7	257.1 ± 53.5	8	225.0 ± 70.7	0.375
Apomorphine	1	20	1	0.7	
LEDD	53	971.9 ± 701.4	53	740.6 ± 559.4	**0.029**
Medication Class	**N**	**%**	**N**	**%**	
L-Dopa	50	81.13	43	87.74	**0.043**
Dopamine Agonist	22	41.51	29	54.72	0.145
COMT Inhibitors	10	18.87	8	15.09	0.531
MAO-B Inhibitors	7	13.21	11	20.75	0.352
Others	7	13.21	9	16.98	0.531

DBS	7	13.21	4	7.55	0.183
DATscan	31	58.49	15	30	**<0.001**
Before FND onset	9	16.98			
After FND onset	16	30.19			
Unknown	6	11.32			

SD: standard deviation; LCIG: Levodopa-carbidopa intestinal gel; CR: sustained release; LEDD: levodopa-equivalent daily dose; DBS: deep brain stimulation**;** PD-FND: Parkinson disease with functional neurological disorder; PD: Parkinson disease; DATscan: [(123)I]FP-CIT SPECT

P-values were obtained using rank sum test for clustered data or logistic regression accounting for clustering effect.

Table 3. FND onset in relation to PD diagnosis

	FND before/with PD		**FND after PD**		
	N	**Mean ± SD**	**N**	**Mean ± SD**	**P-value**
PD diagnosis age (yrs)	12	55.3 ± 10.3	37	53.6 ± 10.8	0.5926
First PD symptom (yrs)	12	51.8 ± 10.8	37	51.5 ± 10.7	0.8981
FND diagnosis (yrs)	12	50.9 ± 13.6	37	59.8 ± 9.7	**0.0212**
First FND symptom (yrs)	11	49.6 ± 14.0	35	57.9 ± 12.0	**0.0403**
PD diagnosis delay	12	3.5 ± 2.4	37	2.1 ± 2.4	**0.0172**
FND diagnosis delay	11	1.4 ± 1.1	35	2.2 ± 5.1	0.5546

SD: standard deviation; FND: functional neurological disorder; PD: Parkinson disease

P-values were obtained using t-test or Wilcoxon rank sum test

Table 4. Health care utilization

	PD-FND		PD-only		
	N	**Mean ± SD**	**N**	**Mean ± SD**	**P-value**
Years in clinic	53	5.1 ± 3.5	53	4.9 ± 2.9	0.958
Office visits	53	15.1 ± 12.8	53	11.8 ± 8.6	0.288
Hospitalizations	53	1.2 ± 1.9	53	0.9 ± 2.6	**0.007**
Phone calls	38	34.7 ± 45.4	38	16.9 ± 23.1	**0.029**
Messages	37	10.2 ± 29.8	37	6.4 ± 13.9	0.454

SD: standard deviation; PD-FND: Parkinson disease with functional neurological disorder; PD: Parkinson disease

P-values were obtained using rank sum test for clustered data or logistic regression accounting for clustering effect.