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Original Article

The association of non-motor symptoms with motor symptoms in parkinson's disease

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Abstract

Aim: Idiopathic Parkinson's disease (IPD) is the second most common progressive neurodegenerative disorder and well known with typical motor impairment. Besides motor symptoms, non-motor symptoms (NMS) occur very frequently among patients with IPD. This study aims to assess the presence of non-motor symptoms with the severity of motor symptoms.

Materials and Methods: Alaaddin Keykubat University Training and Research Hospital's database has been screened for identifying patients with IPD from 2015-2019. The patients' motor symptom, NMS, and Hoehn & Yahr stage (H&Y stage) were assessed with the Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS).

Results: A total of 50 IPD patients were analyzed. Analysis by NMS part of MDS-UPDRS (Part I) showed that NMS was present in 99.7% of patients. NMS part score was positively correlated with H&Y stages and total motor scores of MDS-UPDRS (part II-III). The most common symptoms were pain (84%), daytime sleepiness (78%), and urinary problems (76%). Significantly, there was an association between motor impairment, H&Y, and the following NMS items; hallucinations/psychosis, depressed mood, daytime sleepiness, urinary problems, constipation, light-headedness on standing, and fatigue ($p<0.05$, Spearman's rho).

Conclusions: Considering our data suggested that almost all patients with PD experience NMS. NMS are mostly worsened with exacerbation of MS (motor symptoms) and H&Y in cases. These findings will help understand the clinical aspect of PD and may improve personalized medicine and research in PD.

Keywords: Idiopathic parkinson's disease; MDS-UPDRS; motor symptoms; non-motor symptoms

INTRODUCTION

Idiopathic Parkinson's disease (IPD) is a progressive neurodegenerative disorder resulting from depletion dopaminergic neurons in the substantia nigra pars compacta (1). It leads to movement impairment manifested as resting tremor, muscle rigidity, bradykinesia, postural imbalance, and gait disturbance (2). Although PD's motor symptoms dominate the clinical presentation, most PD patients also have non-motor symptoms (NMS) such as cognitive problems, psychiatric disorders, sleep abnormalities, sensory symptoms, and autonomic impairments (3).

Recent studies have shown that NMS are seen among PD patients with high prevalence and affect the quality of life (QoL). Although this impact is often devastating, it has been reported that NMS are being recorded in less than 40% of clinical examinations (4). Case in point, an international survey showed that NMS, such as bowel incontinence, apathy, sexual difficulties, pain, and sleep disorders, may not declare to clinicians up to 62% of cases which could be due that the patients are either feel to be ashamed or do not know that the symptoms are related with PD (5). NMS should be questioned regularly during visits by healthcare professionals for overcoming this clinical failure. Also, such holistic approaches would lessen the negative impact of NMS on the quality of life (QoL) of PD patients (6,7). Thus, in most cases, the progressions of NMS are strongly related to MS; however, it might lead to greater devastation in the quality of life compared with motor symptoms (MS) (4,6,7). For instance, recent studies have indicated that NMS's severity might worsen MS during PD (8-10). MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) is one of the validated and easy-to-use rating scales for assessing and screening NMS and MS in PD patients. This sophisticated tool enables not only to evaluate the PD symptoms but also to monitor NMS-MS symptoms changing with time. We have assessed NMS's frequency and severity and its associations with MS and Hoehn Yahr (H&Y) in this investigation.

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MATERIALS and METHODS

In this retrospective study, 50 patients with well documented were identified from Alaaddin Keykubat University Training and Research Hospital's patient database for the August 2015 and October 2019. The patients who have IPD diagnosis according to Movement Disorders Society (MDS) criteria by a neurologist were included the study (11). We have excluded patients diagnosed with other neurodegenerative disorders and secondary Parkinsonism symptoms such as head injury and stroke. Collected data included patients' gender, age, and PD therapy. For the study, approval has been received from Alaaddin Keykubat University Medical School Ethics Committee (date: 10-03-2021, number: 05-09).

MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) was used to detect NMS, motor symptoms, and H&Y in PD patients. This tool evaluates different aspects of PD with five parts are investigating the effect of PD symptoms on daily life and also examination findings of patients. Besides MDS-UPDRS handy tool in clinical settings, it has also been validated in research studies. (12-14)

UPDRS Part I is related to NMS, which assesses cognition, neuropsychiatric symptoms, and behavior (13 items, range 0–16 points) in the examination. UPDRS Part II and UPDRS III evaluate motor symptoms. While UPDRS II questioning Activities of daily living (ADL) is including the different motor abilities (13 items, range 0-52 points), UPDRS Part III scoring the motor examination (33 items, range 0–108 points) in patients. UPDRS Part IV assessed the motor complications (6 items, range 0-24 points). Each item rates parkinsonian sign or symptom for indicating the degree of severity (ranging from 0 to 4). End of the examination, the sum of item's score has given the total UPDRS score.

In this study, NMS severity was assessed by the non-motor section (Part-I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)) of MDS-UPDRS. This part has been used for comparing NMS features of patients with motor impairment (Part II: Motor Aspects of Experiences of Daily Living (M-EDL) and Part III: Motor Examination) and H&Y stage in MDS-UPDRS.

Statistical Analysis

Patients' clinical characteristics were presented as mean and standard deviation (SD) for continuous variables. For NMS, the prevalence for each item and domain were presented, and mean and SD scores of each item and domain (total score of items belonging to the domain). Main variables in the study showed a non-normal distribution (Kolmogorov-Smirnov test), and these variables were reported as median (interquartile range [IQR]). For testing the main hypothesis, the Spearman test was used for correlation between the mean of NMS and MS. The Mann- Whitney U test for independent samples was used to compare the two groups (H&Y) and detect significant differences in the means of each NMS and MS score. The significance level was set at 0.05 (two-sided). Statistical analyses have been performed with SPSS 20 software.

RESULTS

The sample comprised 50 PD patients (80% male). The main characteristics of the sample are displayed in Table 1.

Table 1. Clinical characteristics of the patients

Characteristic	Mean (±SD)	Median (Range)	95% CI
Age (years)			
Male (n=40)	70 (8)	71 (48-83)	67-72
Female (n=10)	66 (9)	66.50 (52-80)	59-72
Total (n=50)	69.10 (8.3)	70 (48-83)	66-71
MDS-UPDRS			
MDS-UPDRS total	49.02 (22.8)	46 (10-111)	42-55
MDSUPDRS Part-I	10.90 (5.9)	10 (1-29)	9-12
MDSUPDRS Part-II	12.62 (7.2)	12 (2-38)	10-14
MDSUPDRS Part-III	25.50 (12.7)	25 (4-59)	21-29
MDSUPDRS Part-II+III	38.12 (18.9)	35 (6-89)	32-43
MDS-UPDRS Part-IV	1.2 (2.1)	1 (0-2)	0-3
H&Y	**n (%)**	2 (2-3)	2.17-2.43
II	35 (70)		
III	15 (30)		
IPD treatment	**n (%)**		
L-Dopa	15 (30)		
DA	12 (24)		
L-Dopa+DA	16 (32)		
Drug naive	7 (14)		

CI: confidence interval; DA: dopamine agonist; H&Ystage: Hoehn & Yahr stage, IPD: Idiopathic Parkinson's disease, L-Dopa: levodopa; L-Dopa+DA: The combination of levodopa and dopamine agonist; n: number of cases; SD: standard deviation (±)

Among the 50 Parkinson patients reporting age and gender, the median age was 71 years (95% CI, 62-72); 40 (%80) were male, and 10 (%20) were female (66.50; 59-72 years, median age and 95% CI, respectively). According to MDS-UPDRS analyses, the median scores of each part (95% CI); NMS (part-I) was 10 (9 to 12); MS (part II-III) was 35 (32 to 43), and total score was 46 (42 to 55) (Table 1).

Thirty-five patients (%70) were in H&Y II, while 15 patients (%30) in H&Y III.

NMS (part-I) score was positively correlated with H&Y stages and total motor scores of MDS-UPDRS (part II-III) (p=0.000, Spearman's rho). It has been noted that, there was a significant association between the motor impairment (part II-III) and H&Y and the following NMS items: hallucinations/psychosis (item 1.2), depressed mood (item 1.3), daytime sleepiness (1.8), urinary problems (item 1.10), constipation (item 1.11), light-headedness on standing (item 1.12), and fatigue (item 1.13) (p<0.05, Spearman's rho) (Table 2).

Table 2. Non-motor symptoms prevalence and scores of each item and domain. And the correlation of non-motor symptoms' score with Motor symptoms' score and Hoehn & Yahr stage

MDSUPDRS Part-I	Prevalence (%)	Mean (±SD)	Median (Range)	p (MS)	p (H&Y)
1.1 Cognitive impairment	74	1.02 (0.8)	1 (0-4)	0.042*	0.125
1.2 Hallucinations, psychosis	16	0.24 (0.6)	0 (0-3)	0.098	0.027*
1.3 Depressed mood	54	0.80 (0.9)	1 (0-3)	0.035*	0.030*
1.4 Anxious mood	48	0.68 (0.8)	0 (0-3)	0.556	0.909
1.5 Apathy	32	0.40 (0.6)	0 (0-3)	0.451	0.809
1.6 Dopamine dysreg. syndr.	0	0	0	-	-
1.7 Sleep problems	64	1.04 (0.9)	1 (0-3)	0.126	0.256
1.8 Daytime sleepiness	78	1.42 (0.9)	2 (0-3)	0.001*	0.000*
1.9 Pain and other sensations	84	1.34 (0.9)	1 (0-4)	0.013*	0.219
1.10 Urinary problems	76	1.30 (0.9)	1 (0-3)	0.006*	0.005*
1.11 Constipation problems	60	1.00 (1.03)	1 (0-3)	0.048*	0.038*
1.12 Light headedness	60	0.76 (0.7)	1 (0-2)	0.025*	0.062
1.13 Fatigue	60	0.90 (0.9)	1 (0-3)	0.000*	0.001*

MDSUPDRS: Movement Disorder SocietyUnified Parkinson's Disease Rating Scale; MS: Motor Score, H&Y: Hoehn & Yahr stage, SD: standard deviation (±), *p<0.05: relating to differences between in each MDS-UPDRS subscores with motor score and H&Y stage (Spearman correlation and Mann-Whitney U test)

Using part I of the MDS-UPDRS, the most prevalent NMS was pain and other sensations (84%, item 1.9) followed by daytime sleepiness (78%, item 1.8), and urinary problems (76%, item 1.10), while dopamine dysregulation syndrome (0%, item 1.6) was the least reported one. In terms of NMS intensity, items were ranked by means as daytime sleepiness (mean 1.42), pain and other sensations (mean 1.34), and urinary problems (mean 1.30) (Table 2).

Treatment for PD was as follows: 32% received the combination of L-Dopa and dopamine agonists (DA); 30%, L-Dopa; 24%, DA; and 14% none of them (Tablo 1).

There were statistically insignificant NMS (Part-I), MS (Part II-III) MDS-UPDRS scores in both genders (p<0.05, Mann-Whitney U test).

DISCUSSION

NMS have emerged as a critical point of IPD, starting even in the pre-motor phase (15). The burdens of NMS are accepted as a determinant of QoL. Besides its effects on the progression of the disease, it should be considered that the NMS burden is a reason for extended hospitalization and healthcare cost. Despite these events, NMS are often underestimated and under-recognized in PD clinics. Besides motor symptoms, NMS still have low awareness of healthcare professionals (16,17). Notably, most NMS were more likely to be misdiagnosed and to have not enough medical interventions (18).

A large collaborative study has shown that NMS were highly prevalent among PD patients (98.6%) (19). The frequency of NMS increased with disease severity. As the disease advances, NMS can become the most complicated feature, and it seriously decreased the QoL in patients (20,21).

In the current study, we have found that NMS's total score seemed to be associated with the MS total score and H&Y stage.

According to our results, pain and other sensations were the most common NMS (84%). Among the sensory symptoms, pain is the highest reported symptom in PD (40-50%) (22). In this respect, In an NMS investigation study, the pain was reported by 29% (9), while it has been reported that 62% of PD patients had at least one type of chronic pain (23) along the disease process. Our results have indicated that pain severity was associated with motor impairments (p=0.013, Spearman's rho), and we have observed that patients under L-Dopa and L-Dopa+ dopamine agonist (DA) have significantly increased pain scores (p=0.002, Kruskal-Wallis test). Despite our positive results, there are contradictions in studies focusing on the relationship between pain and motor symptoms. For instance, while some studies found no correlation between pain severity and motor symptoms, others suggested a strong correlation between these parameters mentioned above (24). Taken together, it could be suggested that patients who have high motor symptom burden must also be questioned for feeling pain or other unappreciated sensations during their visits by physicians.

The second most common NMS reported in our study was daytime sleepiness (78%) which was observed as the most intense item in the MDS-UPDRS Part-I (mean: 1.42). Accordingly, studies have suggested that almost 75% of patients with PD have this type of sleep disturbance associated with impaired PD progression and decreased quality of life and daily living activities (25, 26). Shortly, we have observed that daytime sleepiness was correlated well with the MS and the H&Y (p=0.001).

The third most common reported NMS in our study were urinary problems (76%) which have been defined as one of the most common autonomic impairments in PD. Studies in this context have revealed different symptoms (e.g., incontinence, nocturia, urgency) ranging from 27% to 85% PD patients (27). Although current investigations are still limited to show a direct correlation between the disease course and the appearance of urinary symptoms in PD, we have observed a significant association between urinary symptoms and motor stages.

Neuropsychiatric symptoms (NPS) have been observed in almost 60% of PD patients, such as depression, anxiety, apathy, hallucinations, and impulse control disorders. It has been found that the most prevalent NPS were reported as anxiety (40%–50%) (2,3) following by depression (20%–40%), dementia (20%–30%), and psychosis (15%–30%) (28).

For the explaining, the reason for NPS's development in PD patients has been suggested several hypotheses. For instance, each NPS have different neuropathological changes, which are might cause varied clinical expressions. According to Braak's hypothesis, the spreading of Lewy body pathology with ascending course in the central nervous system from subcortical areas to cortex reflects as different stage and severity of NMS (29).

Anxiety prevalence was reported 40%-50% (3) is also similar to our data (48%). Anxiety was often associated with increased dyskinesia (28), freezing (29), and motor response fluctuations (30) in PD patients. But, motor complications were relatively less among our patients.

According to two comprehensive studies, there is a strong relationship between depression and anxiety (25,26). Moreover, another link is between anxiety and PD dementia, and it has been found relatively less in patients with PD dementia than other NPS (28). In agreement with this, while anxiety was correlated with depression (p=0.000, Spearman's rho), there was no relation between cognition and anxiety (p=0.120, Spearman's rho) in our results.

The most observed third NPS was apathy (32%) in our study. The prevalence of apathy was reported with pretty different data (16.5 to 40%) (12). Using various assessment tools or study designs might be a cause of this relatively great range. Many studies have suggested a strong link between both NPSs themselves and between motor symptoms (13,27,29). However, sometimes apathy does not show a togetherness with depression or cognitive (31) impairment, which might be related to various neurological conditions, such as stroke associated with some critical neurotransmitter and neurotrophin deficiencies (32). That finding might ensure that its status should be evaluated as a separate clinical syndrome in PD (12).

Our data showed a significant relationship between apathy depression (p=0.014) and anxiety (p=0.001), suggesting their role as a critical component in the NMS spectrum, including its tremendous impact on the QoL. While most NPS showed a significant relationship with MS, this was not constantly confirmed with other studies. It is difficult to estimate what is responsible for this inconsistency; however, it is reasonable to assume that this could be related to different neurotransmitter pathways responsible for apathy, depression, and anxiety, which are located in different non-dopaminergic areas in the brain. Thus, it is not surprising that motor symptoms related to dopaminergic depletion might not occur with NPS simultaneously, and NPS may appear even before the presence of MS in PD patients.

Taken all these findings together with recent data suggesting a significant overlapping between NMS and motor symptoms, it might be hard to separate NPS and rate its severity. Our results indicated that most NMS were associated with MS and H&Y, which fits well with previous similarly designed studies reporting a significant association between MS and NMS. Such a link between MS and NMS may increase the awareness of multifaceted evaluation in busy clinical settings. Since PD is understood to be a neurological disease affecting the entire body rather than being limited to the central nervous system, the ability to predict the presence of NMS based on MS might be useful in clinical settings not only for early diagnosis but also for candidate neuroprotective therapeutic interventions (30,33,34). Although our study provides valuable clinical data, it should be mentioned that we did not take into account the details of treatments, disease duration, and medical history, which could be considered as a weakness.

CONCLUSION

Idiopathic Parkinson's disease course show grift clinical signs with overlapping of NMS and motor disabilities. Nowadays, holistic approaches and multidiscipline therapies still remain unmet needs. In our study, we have found a significant correlation between most of the NMS, MS, and H&Y. In the light of most previous studies showing controversial findings regarding a direct relationship between these parameters; our results might contribute to the understanding of the clinical picture of PD and may raise awareness of health professionals about NMS. Further well-designed studies with larger sample sizes and different examination tools, including the dynamic neuroimaging correlations (i.e., dopamine PET, fMRI), are needed to understand IPD's underlying pathophysiology.

Competing Interests: The authors declare that they have no competing interest.

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Ethical Approval: In this retrospective study, patients's data has been recorded from hospital's database by using Local Ethic Committee. Alaaddin Keykubat University Ethic Committee no:05-09 date:10-03-2021.

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