Sakarya Tıp Dergisi
Sakarya Med J

E-ISSN: 4146-409X
Yayıncı / Publisher: Sakarya Üniversitesi

Cilt/Vol. 14, Sayı/No. 1, 47-53, 2024
DOI: http://doi.org/10.31832/smj.1273461

Research Article/ Araştırma Makalesi

Evaluation of the Frequency of Non-Motor Symptoms in Idiopathic Parkinson's Disease by Gender and Disease Stage

Sena Boncuk Ulaş[1*], Yeşim Güzey Aras[2]

[1] Keşan State Hospital, Neurology, Edirne, Türkiye
senaboncuk@gmail.com

[2] Sakarya University, Faculty of Medicine, Neurology, Sakarya, Türkiye
yesimguzeyaras@hotmail.com

*Corresponding Author

Received Date:
08.04.2023
Accepted Date:
11.08.2023
Available Online Date:
15.03.2024

Purpose: Idiopathic Parkinson's Disease (PD) is a chronic, progressive, neurodegenerative disease affecting basal ganglia, especially the substantia nigra pars compacta, and dopaminergic neurons in the brain stem. Although PD is defined as a movement disorder with motor symptoms, it also affects many systems such as limbic, autonomic, gastrointestinal, and genitourinary systems. The aim of our study is to evaluate the frequency of NMS in PD, which is often overlooked in clinical practice and has serious effects on patients' quality of life

Method: A total of 97 patients were included in the study, 31 of whom were in the mild stage, 30 in the moderate stage, and 36 in the severe stage. REM sleep behavior disorder (RBD), constipation, presence of hyposmia-anosmia, history of appendectomy and excessive daytime sleepiness, depression, orthostatic hypotension, apathy, forgetfulness, hallucinations, sleep problem, pain, fatigue, dizziness, and frequent urination findings have been noted from patients files.

Results: There was no significant difference ($p > 0,05$) between the rates of appendectomy, prodromal stage symptoms, and NMS between genders (Table 2). Only forgetfulness, dreaming and fatigue were found to be statistically significantly ($p<0,05$) lower in mild-stage PD patients than in the moderate and severe stages.

Conclusion: In conclusion, NMS consists of many neuropsychiatric, autonomic, and sensory symptoms that can be seen in every stage of PD from the prodromal stage to the severe stage, and they increase the disability caused by the motor findings of PD and decrease the quality of life.

Keywords: Parkinson's disease, Non-motor symptoms, Disease stage, Gender

1.INTRODUCTION

Idiopathic Parkinson's Disease (PD) is a chronic, progressive, neurodegenerative disease affecting basal ganglia, especially the substantia nigra pars compacta, and dopaminergic neurons in the brain stem in the central nervous system.[1,2] Among neurodegenerative diseases, it is the second most common disease following Alzheimer's disease.[3] The cardinal motor signs of PD are resting tremor, rigidity, and bradykinesia, while autonomic signs, and cognitive, behavioral, and psychiatric symptoms called non-motor symptoms (NMS) are often accompanied.[4] Although PD is defined as a movement disorder with motor symptoms, it also affects many systems such as limbic, autonomic, gastrointestinal, and genitourinary systems. Accordingly, NMS such as anxiety, apathy, depression, sleep disorders, cognitive disorders, constipation, and frequent urination may accompany the manifestation of PD. Although NMS is seen from the early stage of the disease, they become more prominent in the severe stage, become more disabling than motor symptoms, and are often overlooked in clinical practice.[5] The fact that NMS can be seen before motor symptoms appear also suggests that they may be important markers in the early diagnosis of PD. However, the fact that dopamine replacement therapies used in the treatment of PD target

Cite as: Boncuk Ulaş S, Güzey Aras Y. Frequency of Non-Motor Symptoms in Idiopathic Parkinson's Disease Stage Frequency of Non-Motor Symptoms in Idiopathic Parkinson's Disease, Sakarya Med J 2024; 14(1): 47-53 DOI: 10.31832/smj.1273461

motor symptoms put NMS into the background.[6] The aim of our study is to evaluate the frequency of NMS in PD, which is often overlooked in clinical practice and has serious effects on patients' quality of life.

2.MATERIALS and METHODS

Patients who were admitted to Sakarya University Training and Research Hospital Movement Disorders Outpatient Clinic between March 2022 and March 2023 and who were diagnosed with PD according to MDS Clinical Diagnostic Criteria for Parkinson's Disease, Postuma et al. 2015, were included in the study.[7] Patients who followed up with the diagnosis of secondary parkinsonism, vascular parkinsonism, and Parkinson's plus syndrome were not included in the study. The files of all patients were checked retrospectively, and the patient's age, gender, educational status, age of disease onset, disease duration, disease type (1-Tremor dominant type, 2-Akinetic rigid type, 3-Mixed type), and the drugs they used were noted from the patients' files. In classification according to disease type, Stebbins et al., (2013), Movement Disorders, article was taken as the source and patients were classified as tremor dominant, akinetic rigid and mixed type according to the ratio of MDS-UPDRS scores.[8] MDS-UPDRS Part III Motor Examination and H&Y scales were documented from patients' files. Afterward, the patients were divided into 3 groups as mild stage, moderate stage, and severe stage. We combined literature and examination findings in staging. We especially used the article that "Parkinson's disease severity levels and MDS-Unified Parkinson's Disease Rating Scale" in Parkinsonism and Related Disorders journal published by Martínez-Martín et al. in 2015.[9] Those with a UPDRS score below 20 and H&Y stage 1 were considered mild stage, those with a UPDRS score between 20 and 30, and H&Y stage 1 and 2 were considered moderate stage, and those with the UPDRS score 30 and higher, and H&Y stage 3 and higher were considered severe stage. At the same time, those without limitations in their daily life activities and not needing levodopa were classified as mild stage, those needing levodopa and with initial daytime motor fluctuations were staged as moderate and finally, those with important dyskinesias and motor fluctuations as well as non-motor symptoms, qualified as severe stage. A total of 97 patients were included in the study, 31 of whom were in the mild stage, 30 in the moderate stage, and 36 in the severe stage. REM sleep behavior disorder (RBD), constipation, presence of hyposmia-anosmia, history of appendectomy and excessive daytime sleepiness, depression, orthostatic hypotension, apathy, forgetfulness, hallucinations, sleep problem, pain, fatigue, dizziness, and frequent urination findings have been noted from patients' files. For the diagnosis of RBD, an RBD screening questionnaire was applied to the patients during their outpatient visits, and those who scored 7 and above were accepted as RBD (+). Before starting the study, approval was obtained from the ethics committee of our university.

In the descriptive statistics of the data, mean, standard deviation, median, min, max, frequency, and ratio values were used. The distribution of the variables was measured by the Kolmogorov-Smirnov test. T-test, Kruskal-Wallis, or MannWhitney U tests were used for the analysis of quantitative independent data depending on the data distribution. In the analysis of qualitative independent data, the chi-square and Fischer's exact test were used as appropriate. The Spearman test was used for correlation analyses. SPSS 28.0 program was used in the analyses.

3.RESULTS

The ages of the cases ranged from 38 to 89, with a mean age of 64,00±10,30, and 51,80% (50) of

them were male and 48,20% (47) were female. Considering the age of onset of the disease, it was seen that 23,60% (22) of those with the disease started under the age of 50, 62,30% (61) who started the disease between the ages of 50-70, and 14,20% (14) who started the disease at the age of 70 and over. The disease duration was the shortest 1 year and the longest 26 years. The UPDRS values of the patients ranged from 5-76, and the mean UPDRS score was 26,41±16,01. H&Y values ranged from 1 to 5, with a mean H&Y of 2,01±0,99. 32,10% (31) of the patients were mild stage, 31,10% (30) moderate stage, and 36,80% (36) severe stage. 50,90% (49) of the patients were akinetic rigid type, 39,60% (38) tremor dominant type, and 9,40% (10) mixed type. The daily total Levodopa doses of the patients ranged from 138 mg/day to 1600 mg/day, and the mean daily total Levodopa dose was 705,40±376,60.

13,20% (12) of the patients had previously undergone appendectomy surgery. 64,20% (62) of the patients had RDB, 63,20% (61) had constipation, and 32,10% (31) had anosmia. The NMS frequencies of the patients are listed in Table 1.

Table 1.

Demographic data of patients, age of disease onset, duration of disease, disease type, disease stage, total levodopa doses, appendectomy, prodromal stage symptoms and rates of non-motor symptoms

		Min-Max	Median	Avg.±sd/n-%	
Age		38,0-89,0	66,0	64,0 ±10,3	
Gender	Male			50	51,8%
	Female			47	48,2%
Educational Status	Not Literate			7	7,5%
	Literate			3	2,8%
	Primary school			64	66,0%
	Middle school			10	10,4%
	High school			11	11,3%
	University			2	1,9%
Age of Disease Onset	< 50			22	23,6%
	50-70			61	62,3%
	≥ 70			14	14,2%
Age of Disease Onset		37,0 - 83,0	59,0	58,2 ± 10,1	
Disease Duration	< 5 years			42	43,4%
	5-10 years			29	30,2%
	> 10 years			26	26,4%
Disease Duration		1,00-26,00	5,00	6,65 ± 5,33	
UPDRS		5,00-76,00	21,00	26,41 ± 16,01	
HY		1,00-5,00	2,00	2,01 ± 0,99	
Daily Total Levodopa Dose		138,0-1600,0	687,5	705,4 ± 376,6	
Disease Type	Tremor Dominant Type			38	39,6%
	Akinetic Rigid Type			49	50,9%
	Mixed Type			10	9,4%

		Min-Max	Median	Avg.±sd/n-%	
Disease Stage	Mild			31	32,1%
	Moderate			30	31,1%
	Advanced			36	36,8%
Daily Total Levodopa Dose Coefficient	< 400 mg			24	24,5%
	400-800 mg			34	35,8%
	800-1200 mg			29	30,2%
	1200-2000 mg			10	9,4%
Appendectomy				12	13,2%
RBD				62	64,2%
Constipation				61	63,2%
Anosmia				31	32,1%
Excessive Daytime Sleepiness				61	63,2%
Depression				5	5,7%
Orthostatic Hypotension				10	10,4%
Forgetfulness				37	38,7%
Hallucinations				23	24,5%
Anxiety				58	60,4%
Apathy				56	57,5%
Sleep problem				58	60,4%
Pain				56	57,5%
Frequent Urination				62	64,2%
Dizziness				24	25,5%
Fatigue				60	62,3%

Min: Minimum, Max: Maksimum, Avg: Average, Sd:Standart deviation, RBD: REM sleep behavior disorde

There was no significant difference (p >0,05) between the rates of appendectomy, prodromal stage symptoms, and NMS between genders (Table 2).

When the NMS rates according to the disease stage were examined, only forgetfulness, dreaming and fatigue were found to be statistically significantly (p<0,05) lower in mild-stage PD patients than in the moderate and severe stages. No significant correlation was found between other NMSs and disease stages (Table 3).

4.Discussion

PD is the second most common neurodegenerative disease.[3,10] Although the exact cause is unknown, the prevalence of PD has been increasing rapidly in the last few decades. There are currently more than 6 million patients with PD worldwide, and according to the global burden of disease study conducted in 2016, this figure is predicted to double to 12 million in 2040.[11]

Studies to date have shown that there are multiple NMS accompanying motor symptoms in PD. NMS can be seen in every stage of the disease, starting from the prodromal stage. In a review published by Pfeiffer in 2015, it was stated that 100% of PD patients had at least one NMS. Since NMS is very common and responds well to treatment, it is of great importance to raise awareness among clinicians and to question them in all patients.[12] In a study conducted in 2008, anxiety was reported

Table 2.

Mean UPDRS and H&Y scores, and rates of appendectomy, prodromal stage symptoms, and non-motor symptoms by gender

	Male			Female			p	
	Avg.±sd/n-%		Median	Avg.±sd/n-%		Median		
UPDRS	Severe Stage		21,0	26,3 ± 17,3		20,00	0,699	m
HY			2,00	2,01 ± 1,10		2,00	0,739	m
Appendectomy	6	42,9%	4	28,6%	4	28,6%	0,619	X^2
RBD	15	25,0%	19	31,7%	26	43,3%	0,132	X^2
Constipation	17	27,9%	21	34,4%	23	37,7%	0,466	X^2
Anosmia	12	40,0%	9	30,0%	9	30,0%	0,476	X^2
Excessive Daytime Sleepiness	19	30,6%	23	37,1%	20	32,3%	0,192	X^2
Depression	2	40,0%	1	20,0%	2	40,0%	0,851	X^2
Orthostatic Hypotension	3	27,3%	4	36,4	4	36,4%	0,902	X^2
Forgetfulness	3	8,6%	14	40,0%	18	51,4%	0,001	X^2
Hallucinations	2	8,3%	6	25,0%	16	66,7%	0,001	X^2
Anxiety	16	26,7%	21	35,0%	23	38,3%	0,319	X^2
Apathy	14	25,0%	16	28,6%	26	46,4%	0,069	X^2
Sleep problem	17	28,8%	20	33,9%	22	37,3%	0,639	X^2
Pain	13	23,2%	18	32,1%	25	44,6%	0,072	X^2
Frequent Urination	17	27,4%	23	37,1%	22	35,5%	0,188	X^2
Dizziness	6	23,1%	8	30,8%	12	46,2%	0,436	X^2
Fatigue	13	22,0%	22	37,3%	24	40,7%	0,028	X^2

^{m} Mann-whitney u test / $^{X^2}$ Chi-square test (Fischer test)
Avg: Average, Sd: Standart deviation, RBD: REM sleep behavior disorder

Table 3.

Table 3. Frequency of non-motor symptoms by disease stage

	Mild Stage		Moderate Stage		Severe Stage		p	
Appendectomy	6	42,9%	4	28,6%	4	28,6%	0,619	X^2
RBD	15	25,0%	19	31,7%	26	43,3%	0,132	X^2
Constipation	17	27,9%	21	34,4%	23	37,7%	0,466	X^2
Anosmia	12	40,0%	9	30,0%	9	30,0%	0,476	X^2
Excessive Daytime Sleepiness	19	30,6%	23	37,1%	20	32,3%	0,192	X^2
Depression	2	40,0%	1	20,0%	2	40,0%	0,851	X^2
Orthostatic Hypotension	3	27,3%	4	36,4	4	36,4%	0,902	X^2
Forgetfulness	3	8,6%	14	40,0%	18	51,4%	0,001	X^2
Hallucinations	2	8,3%	6	25,0%	16	66,7%	0,001	X^2
Anxiety	16	26,7%	21	35,0%	23	38,3%	0,319	X^2
Apathy	14	25,0%	16	28,6%	26	46,4%	0,069	X^2
Sleep problem	17	28,8%	20	33,9%	22	37,3%	0,639	X^2
Pain	13	23,2%	18	32,1%	25	44,6%	0,072	X^2
Frequent Urination	17	27,4%	23	37,1%	22	35,5%	0,188	X^2
Dizziness	6	23,1%	8	30,8%	12	46,2%	0,436	X^2
Fatigue	13	22,0%	22	37,3%	24	40,7%	0,028	X^2

X^2 Chi-square test (Fischer test) RBD: REM sleep behavior disorder

to be the most common NMS with a frequency of 66% in PD patients.[13] The most common NMS in our study was frequent urination with 64.2%. Anxiety was detected with a frequency of 60.4%. In an article published in 2012, it was reported that NMS is more common in females.[14] In another study, it was reported that excessive daytime sleepiness was observed more frequently in the male.[15] In our study, unlike the literature, no significant difference was found between the genders.

When studies comparing NMS with disease stage are reviewed, it is stated that the frequency of NMS increases in severe stage. In particular, studies have reported that forgetfulness, excessive daytime sleepiness, depression, and apathy are more common in severe stages.[16,17] In another study conducted with newly diagnosed mild stage PD patients, it was stated that all patients had at least one NMS. In the same study, anxiety was the most common NMS in patients with newly diagnosed PD.[18] In our study, when we looked at the NMS rates according to the disease stage, we found that only forgetfulness, hallucinations, and fatigue were statistically significantly lower in patients with mild stages than in the moderate and severe stages. We did not find a significant relationship between other NMS and disease stages. We think that if the study is repeated with larger patient populations, the relationship between NMS and disease stage can be exposed more accurately.

The fact that NMS is seen from the prodromal stage is also important in terms of identifying the patient group at risk for PD. It is stated in the literature that if patients with symptoms of constipation, anosmia-hyposmia, RBD, and depression can be followed up with imaging methods showing dopaminergic neuron loss, there may be a chance for early diagnosis of PD.[6] For this reason, it is of great importance to raise awareness for NMS.

In conclusion, NMS consists of many neuropsychiatric, autonomic, and sensory symptoms that can be seen in every stage of disease from the prodromal to the severe stage, and they increase the disability caused by the motor findings of PD and decrease the quality of life. Therefore, it is important to question, detect and treat NMS in every patient with PD. The small number of patients and the absence of a prodromal stage group are the limitations of our study. Larger, multicenter longitudinal studies including patients in prodromal stages are warranted.

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