

NON-MOTOR SYMPTOMS IN PATIENTS WITH PARKINSON'S DISEASE IN BABOL, NORTH OF IRAN

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ABSTRACT

Introduction. Non-motor symptoms (NMS) are common in Parkinson's disease. It can be predominant as the disease advances, thereby constituting a major source of disease burden for patients. Current study was conducted to determine the prevalence of these symptoms in the north of Iran.

Method. This cross-sectional study was performed on 109 patients with Parkinson's disease in Ayatollah Rouhani Hospital in Babol, North of Iran, during 2017-2018. NMS were obtained from a NMS standard questionnaire containing 30 questions plus the clinical and demographic information in a separate checklist of patients. NMS were then classified into nine distinct categories. The association of NMS with clinical and demographic variables was evaluated by the SPSS software version 23. In all cases, the significance level of the tests was less than 0.05.

Results. The mean age of the patients was 70.59 ± 9.69 years (46-97 years) and 61 (56%) were male. The duration of the disease was 5.61 ± 4.89 years. NMS associated with sleep / fatigue with the prevalence of 76.1% were the most prevalent symptoms. NMS related to mood / cognition with frequency of 65.1%, cardiovascular with 51.4% and miscellaneous with 51.4% frequency were the most commonly reported symptoms in patients. Severity of the disease was significantly correlated with the symptoms of the cardiovascular, attention / memory and GI tract ($P = 0.001$). Age and education of the patients with cardiovascular symptoms and attention / memory had a significant relationship ($P < 0.05$). Occupation and marriage of the patients were significant with attention/memory symptoms ($P < 0.05$).

Conclusions. The sleep-related symptoms and fatigue were the most common NMSs in Parkinson's patients. Also, the severity of the disease and ageing were statistically significant with the prevalence of the NMS in patients. Therefore, consideration should be given to older patients suffering from more severe Parkinson's disease.

Keywords: Parkinson's disease, non-motor symptoms, severity of disease, duration of disease, priority sign

INTRODUCTION

Parkinson's disease (PD) was first described by James Parkinson in 1817 in his book "An essay on the shaking palsy" [1]. It is a progressive neurodegenerative disorder that affects 0.3% of people who are above 40 years old. About 7.5 million people worldwide and one million in North America suffer from the Parkinson disease [2-5].

Non-motor symptoms (NMS) are common in Parkinson's patients to the extent that in two studies approximately 100% of patients had at least two NMSs [6,7]. NMS (NMS) of Parkinson's disease can be predominant as the disease advances, thereby constituting a major source of disease burden for patients and caregivers. However, current understanding of NMS is incomplete, particularly as a result of the absence of standardization of the out-

come definitions and the heterogeneity of the risk factors that are assessed [8]. These symptoms even occur in normal people due to aging (about 68% to 88% of normal people); in older people, at least one case of NMS is seen [6,7]. While people with PD have more NMS than normal, these symptoms will be more severe for them [9]. In some cases, NMS occurs in 20% of the Patients as a primary PD clinical manifestation, and causes a delay to the diagnosis of the disease [10].

Parkinson's NMS is a relatively new issue and in recent years, it has been highly regarded by the researchers and quite distinct from the Parkinson's classic motor symptoms. The other importance of these symptoms is the early onset of them. Before the onset of the classic Parkinson symptoms are shown, the NMS can be considered as screening for these patients. This study is to determine the prevalence of the non-transient symptoms and their occurrence in patients with PD who were referred to Ayatollah Rouhani Hospital in Babol, 2017-2018.

MATERIAL AND METHOD

This descriptive-analytic cross-sectional study was performed on 109 patients with PD who were referred to the clinic at Ayatollah Rouhani Hospital in Babol in 2017-2018. Just as the previous studies, the Movement Disorder Society (MDS) Clinical Diagnostic Criteria for PD was used [11] to diagnose and include the patients in this study [4]. The history check and clinical examination were carried out by the responsible neurologist for this study. Unwillingness of the patients to take part in the study, and the existence of secondary Parkinson's syndromes (such as PD caused by drugs and vascular lesions, etc.) were the exclusion criteria. Patients' data were collected via a checklist and a questionnaire.

The demographic data (age, sex, education, housing status, marital status, economic status), the clinical information (duration of Parkinson's disease diagnosis, degree of disease, severity of disease, type of medication and duration of use), and the type of NMS (cardiovascular, memory impairment, depression, smoking, gastrointestinal symptoms, psychosis, sexual dysfunction, salivation, salivary disorder, olfactory, irritable pain, weight

loss, swelling and sweating) according to the standard questionnaire [12] and the time of occurrence of those symptoms were obtained from the patients and entered into the checklist.

The Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) was used to assess the clinical condition of the enrolled cases [13]. Using the NMS questionnaire prepared by this association and the criterion it suggests, scoring was performed on the information gathered from the patients.

The collected data were analyzed using the SPSS v.23 software. Data were analyzed with the t-test and the chi-square test. Spearman correlation coefficient was also calculated for the correlation between the severity of the disease and the motor symptoms. The quantitative continuous variables were expressed as the mean \pm standard deviation and the distribution of qualitative frequency in percentage. The significance level of all tests was less than 0.05.

RESULTS

This cross-sectional study was performed on 109 patients with PD, the mean age of the patients was 70.59 ± 9.69 years (46-97 years of age) and 61 cases (56%) were male. The duration of the disease was 5.61 ± 4.89 years. Four patients had no NMS. Table 1 shows that 61 patients (56%) were illiterate. 31 patients (28.4%) farmers and 42 cases (38.5%) were housewives. Eighty four cases (77.1%) were married. Also, 40 patients (36.7%) were urban and 98 cases (89.9%) were non-smokers. In Table 2, the severity of the disease and the symptom indexes were respectively expressed in frequency and frequency percentile of patients. The severity of the illness was 1-2 for 41.3%, 44% had 2/5-3 and 14.7% had more than 3. The indicator markers of the tremor cases were 76.1%, 17.5% bradykinesia, 3.7% rigidity and 2.8% had Gait impairments.

Table 3 shows that symptoms associated with the sleep / fatigue with the prevalence of 76.1% were the most NMS. Symptoms related to the mood / cognition with the frequency of 65.1%, the cardiovascular with 51.4% and miscellaneous symptoms with 51.4% were the most commonly reported symptoms in the patients.

TABLE 1. Demographic information of patients with Parkinson's disease

Variables	Category	Frequency(Percentage)
Age (year)	45-64	26(23.9)
	65-79	64(58.7)
	≥80	19(17.4)
Gender	Male	61(56)
	Female	48(44)
Education	illiterate	61(56)
	Under-diploma	31(28.4)
	Diploma	12(11)
	Upper-diploma	5(4.6)
Job	Employee	16(14.7)
	Self-administered	18(16.5)
	Farmer	31(28.4)
	housekeeper	42(38.5)
	Unemployed	2(1.8)
Marital	Bachelor	17(15.6)
	Married	84(77.1)
Residence	Urban	40(36.7)
	Rural	69(63.3)
Smoking	Non smoker	98(89.9)
	Smoker	3(2.8)
	Cessation	8(7.3)
Total	–	109(100)

TABLE 2. Frequency of clinical information and severity of disease in patients with Parkinson's disease

Variables		Frequency (%)
Illness severity	1-2	45(41.3)
	2.5-3	48(44)
	>3	16(14.7)
	Total	109(100)
Clinical features	Tremor	83(76.1)
	Bradykinesia	19(17.4)
	Rigidity	4(3.7)
	Gait impairments	3(2.8)
Total	–	109(100)

TABLE 3. Frequency of non-motors symptoms in patients with Parkinson's disease and its correlation with disease severity

Variables	Frequency (%)	Spearman	P-value
Cardiovascular	56(51.4)	0.353	<0.001
Sleep / Fatigue	83(76.1)	0.158	0.100
Mood / Cognition	71(65.1)	-0.005	0.960
Perceptual problems / hallucination	53(48.6)	0.185	0.054
Attention / memory	32(29.4)	0.355	<0.001
GI tract	73(67)	0.482	<0.001
Urinary	21(19.3)	0.062	0.524
Miscellaneous	56(51.4)	0.278	0.003

In Table 3, the questions of the NMSS questionnaire were classified into nine categories according to the NMSs standard and Spearman correlation

analysis with the PD severities was studied. Accordingly, the cardiovascular symptoms with the frequency of 51.4%, the attention / memory symptoms with 29.4%, the GI tract symptoms with 67%, and the miscellaneous symptoms with 51.4% frequency had a significant correlation with the PD severities.

In Table 4, the NMSs were analyzed by the mark of the index. No significant association was found in any of the categories of the NMS and the symptom of the disease index. In Table 5, the NMS were evaluated in relation with the duration of the disease. No significant association was found between any categories of the NMS and the duration of the disease.

In this study, NMSs were also evaluated in accordance with the age factor. Cardiovascular symptoms in the age group of 65-79 years (frequency= 67.9%) were significantly higher than those of other ages ($P = 0.017$). Also, the attention / memory symptoms were significantly higher with 53.1% and 37.5% in the age group of 65-79 and over 80 years ($P = 0.001$). The NMSs were also analyzed in accordance with the gender. No significant association was found in any categories of the NMS and gender. Frequency of the NMSs in terms of education was also studied. Cardiovascular symptoms with a high frequency of 69.6% were significantly higher among the illiterate subjects than other educational levels ($P = 0.004$). Also, the attention / memory symptoms were 75% more common in the illiterate people than other levels of education ($P = 0.013$). The NMSs were evaluated then in accordance with the occupation of the patients. The symptoms of attention / memory with a frequency of 46.9% and 40.6% in farmers and housewives were significantly higher than other occupations ($P = 0.023$). The NMSs were analyzed in relation with the marital status as well. Symptoms of attention / memory with the frequency of 65.6% were significantly higher in married people ($P = 0.016$). The NMSs as related with the residency factor were also studied. No significant relationship was found in any categories of the NMSs. Also, no significant difference was found between any categories of the NMS and smoking.

DISCUSSIONS

Based on the findings of this study, 109 patients with PD were studied. The most NMSs were sleep/

TABLE 4. Frequency of non-motor symptoms by cardinal symptoms in patients with Parkinson's disease

cardinal symptoms non-motor symptoms	Tremor N(%)	Bradykinesia N(%)	Rigidity N(%)	Gait instability N(%)	P-value
Cardiovascular	43(76.8)	9(16.1)	3(5.4)	1(1.8)	0.703
Sleep / Fatigue	63(75.9)	14(16.9)	4(4.8)	2(2.4)	0.690
Mood / Cognition	53(74.6)	13(18.3)	3(4.2)	2(2.8)	0.955
Perceptual problems / hallucination	37(69.8)	11(20.8)	2(3.8)	3(5.7)	0.224
Attention / memory	23(71.9)	7(21.9)	1(3.1)	1(3.1)	0.878
GI tract	53(72.6)	14(19.2)	4(5.5)	2(2.7)	0.436
Urinary	14(66.7)	5(23.8)	1(4.8)	1(4.8)	0.710
Miscellaneous	42(75)	10(17.9)	2(3.6)	2(3.6)	0.957

Table 5. Frequency of non-motor symptoms by disease duration in patients with Parkinson's disease

disease duration non-motor symptoms	5> N(%)	5-9 N(%)	10 ≤ N(%)	P-value
Cardiovascular	25(44.6)	16(28.6)	15(26.8)	0.081
Sleep / Fatigue	42(50.6)	24(28.9)	17(20.5)	0.620
Mood / Cognition	40(56.3)	17(23.9)	14(19.7)	0.511
Perceptual problems / hallucination	28(52.8)	12(22.6)	12(24.5)	0.304
Attention / memory	15(46.9)	8(25)	9(28.1)	0.318
GI tract	40(54.8)	20(27.4)	13(17.8)	0.840
Urinary	10(47.6)	7(33.3)	4(19)	0.790
Miscellaneous	28(50)	17(30.4)	11(19.6)	0.753

fatigue. Then symptoms associated with the mood/cognition (frequency = 65.1%), cardiovascular with 51.4% frequency, and miscellaneous symptoms (including olfactory disorder, irreparable pain, weight change, foot swelling and sweating) with 51.4% frequency were the most reported symptoms by the patients. Severity of the PD in patients with cardiovascular symptoms, attention/memory symptoms, GI tract symptoms, and miscellaneous symptoms were significant. In the study of age-related association with the NMSs in PD, the cardiovascular symptoms with the frequency of 67.9% were significantly higher in the age group of 65-79 years. Symptoms related to the attention/memory in the age group of 65-79 years and over 80 years, with the frequencies of 53.1% and 37.5% respectively, were significantly higher than the younger ages. The cardiovascular and attention/memory symptoms were significantly higher in the illiterate patients. In the study of the relationship between occupation and the NMSs in agricultural businesses ($f = 46.9\%$) and the housewives ($f = 40.6\%$), the attention/memory related symptoms were significantly higher than other occupations. In the study of the relationship between mar-

ital status and the NMSs, married patients ($f = 65.6\%$) had significant attention/memory related symptoms. The NMSs in Parkinson's patients were not statistically significant in any of the 9 categories of patients with their sex, habitation, smoking as well as the sign of the disease indexes and their duration of the disease. Berganzo et al. reported a direct correlation between the NMSs and the axial signs, which was significant for bradykinesia and rigidity [14]. The sign of the disease index, in our study, did not have a significant relationship with the NMSs in our patients.

Yoritaka et al. studied the duration of the involvement of the PD patients and the occurrence of various symptoms. They reported symptoms such as sleep disorders, pain, and orthostatic hypotension in patients with multiple years of disease [15]. Duration of the disease was not a significant factor in our study, and it contradicted previous findings.

Relationship between the NMSs with jobs, marital status, and smoking was investigated in other studies as far as possible, but there was no clear analysis of the Parkinson's patients. The cause of increased symptoms associated with the memory and attention in housewives and farming business-

es as well as in married individuals, are subject to further investigation in future studies. Also, smoking and residence factors in our study did not play a role in the frequency of the NMSs.

According to Nicoletti et al. study, the NMSs were associated with the severity of the Parkinson disease, which was also confirmed in Martinez-Martin, Krishnan and Khedr studies [7,16,17]. In our study, severity of the Parkinson's disease was significantly increased in cardiovascular symptoms, the attention / memory related symptoms as well as the GI tract and miscellaneous symptoms. Findings of this study are inline with the Martinez-Martin, Krishnan and Khedr research. Parkinson's disease is associated with multiple neurotransmitter pathologies including cholinergic, noradrenergic and serotonergic [18,19]. Signs such as the depression can be related to the loss of the dopaminergic and noradrenergic transmissions in the limbic system, and anxiety and apathy can be related to the reduced dopaminergic transitions [20]. This can justify the increase in NMSs due to the increased severity of the disease in patients with the Parkinson's disease. As it is assumed, with the increase in the severity of the disease, neurotransmitter disturbances become more intense and, therefore, the disorders associated with the involved part will be manifested more.

Nicoletti et al. noted that age was the main cause of the NMSs' development not only in patients but also in healthy subjects, which has been confirmed in other studies [7,16,17,21]. Findings of this study coincide with these studies in that the age had a direct correlation with the cardiovascular symptoms and attention / memory related symptoms. It is conceivable that with the increase in age and the occurrence of the aging phenomena, the function of the various parts of the body will be disturbed and the speed of the tissue repair will be reduced. Also, the risk of cardiovascular disease and the cognitive impairment increase with age, therefore, our finding can be justified with this regard.

Several studies, such as the one of Nicoletti et al., have indicated the gender differences in terms of the development of NMSs, in which the prevalence of the NMSs was higher in women [16,22-24]. In our study, there was no significant difference in the NMSs between the two genders, which was contradictory to the aforementioned studies.

However, consistent with the results gained from this study, in some other studies, there were also some studies in which no difference was found between the genders in terms of the incidence of the NMSs [7,17]. It should be noted that the NMSs were more prevalent in men in our study except for the symptoms associated with the mood / cognition, which was slightly higher in women. This finding was not statistically significant.

In Simuni et al. study, NMSs were significantly higher in women [25]. An increase in the severity of NMSs within 2 years was significantly associated with the age factor. In our study, NMSs did not have a significant relationship with the gender of the patients. This finding was inconsistent with research of Simuni et al. However, our findings are consistent with the Simuni et al. in that the age has a significant relationship with the cardiovascular symptoms and the attention / memory related symptoms.

Regarding the association of NMS and the degree of patients' education, it was noted that with the increase in education, the prevalence of NMS decreased; this result was specifically significant in relation to the cardiovascular symptoms and the attention / memory findings, but not in relation with the other symptoms. This finding has not been investigated in other studies. Attention to the physical changes in patients and the follow-up for faster treatment can increase with the increasing awareness, and this may lead to a reduction in reports from patients. On the other hand, among patients with Parkinson's disease, in this study, people with higher education included a small percentage, and this could have affected the results.

So far, many studies have been conducted on the Parkinson's disease symptoms for a better diagnosis and adjustment of diagnostic and therapeutic systems [26]. NMSs of Parkinson's disease have also played a significant role in patients' quality of life and healthcare economy, which has been considered remarkably in the recent years. The incidence of NMSs can increase along with the duration of the disease. Symptoms such as the olfactory disorder, the sleep disorder (REM), the constipation, the depression and the pain can be the evidence of a pre-clinical phase of the disease [27,28].

This has been confirmed in studies on the increase in the risk of synucleinopathies in patients

with REM sleep disorder or idiopathic insomnia [29,30].

In the early phases of the disease, many of these NMSs persist in patients. In the Sullivan study, over 21% of patients reported pain, depression, or anxiety [10]. In addition, in many cases at the onset of the disease, patients reported major non-motor impairment more than motor symptoms [31,32]. This study only examined the frequency of the NMSs in people with Parkinson's disease. Comparison of these findings with the healthy subjects was not among the goal of this study.

CONCLUSIONS

Based on this study, the sleep-related symptoms and fatigue were the most common NMSs among patients with the PD. Also, one of the other findings of this study was the association of NMSs with the severity of the disease and the age of the patients in a way that the increase in the severity of the disease

and the age were associated with the prevalence of the NMSs. Therefore, attention to these symptoms in people of higher ages with more severe disease is one of the points that physicians should consider while dealing with these patients. Based on the results of this study, the initial identification of NMSs in Parkinson's patients and the treatment of these symptoms can help these patients, and it is one of the important and necessary symptoms of attention; Based on the results, sleep disturbances and excessive fatigue in these patients and early treatment of these can increase the quality of life in these individuals.

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REFERENCES

- Parkinson J. An essay on the shaking palsy. *The Journal of Neuropsychiatry and Clinical Neurosciences* 2002. 14(2):223-236.
- Bradley WG. Neurology in clinical practice: Principles of diagnosis and management. Vol. 1. 2004: Taylor & Francis.
- Ross GW, Abbott RD. Living and dying with Parkinson's disease. *Movement Disorders* 2014 Nov;29(13):1571-3.
- Tahereh Babajani Roshan, A.B., Seyed Reza Hosseini, Mojgan Bagherzade, Payam Saadat, Mohammad Zamani, The Association between Helicobacter Pylori Infection and Parkinson's Disease: A Case-Control Study. *Journal of Clinical and Diagnostic Research* 2018. 12(10):OC05-OC08.
- Ahmadi Ahangar A et al. The Association Between Low Levels of Serum Vitamin D and the Duration and Severity of Parkinson's Disease. *Arch Neurosci* 2018. 5(3):e61085.
- Kim H-S et al. Non-motor symptoms more closely related to Parkinson's disease: Comparison with normal elderly. *Journal of the Neurological Sciences* 2013. 324(1-2):70-73.
- Krishnan S et al. Do non-motor symptoms in Parkinson's disease differ from normal aging? *Movement Disorders* 2011. 26(11):2110-2113.
- Marinus J et al. Risk factors for non-motor symptoms in Parkinson's disease. *The Lancet Neurology* 2018. 17(6):559-568.
- Khoo TK et al. The spectrum of non-motor symptoms in early Parkinson disease. *Neurology*, 2013. 80(3): 276-281.
- O'Sullivan SS et al. Non-motor symptoms as presenting complaints in Parkinson's disease: A clinicopathological study. *Movement Disorders* 2008. 23(1):101-106.
- Postuma RB et al. MDS clinical diagnostic criteria for Parkinson's disease. *Movement Disorders* 2015. 30(12):1591-1601.
- Postuma R, Romenets SR, Rakheja R. Physician guide non-motor symptoms of Parkinson's disease. *Depression* 2012. 19:20.
- Goetz CG et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Movement Disorders* 2008. 23(15):2129-2170.
- Berganzo K et al. Motor and non-motor symptoms of Parkinson's disease and their impact on quality of life and on different clinical subgroups. *Neurologia* (English Edition), 2016. 31(9):585-591.
- Yoritaka A et al. Motor and non-motor symptoms of 1453 patients with Parkinson's disease: prevalence and risks. *Parkinsonism & Related Disorders* 2013. 19(8):725-731.
- Nicoletti A et al. Gender effect on non-motor symptoms in Parkinson's disease: are men more at risk? *Parkinsonism & Related Disorders* 2017. 35:69-74.
- Khedr EM et al. Prevalence of non motor features in a cohort of Parkinson's disease patients. *Clinical Neurology and Neurosurgery*, 2013. 115(6):673-677.
- Buddhala C et al. Dopaminergic, serotonergic, and noradrenergic deficits in Parkinson disease. *Annals of Clinical and Translational Neurology*, 2015. 2(10):949-959.
- Wolters EC. Non-motor extranigral signs and symptoms in Parkinson's disease. *Parkinsonism & Related Disorders* 2009. 15:S6-S12.
- Thobois S et al. Behavioral disorders in Parkinson's disease: From pathophysiology to the mastery of dopaminergic treatment. *Revue neurologique*, 2010. 166(10):816-821.
- Szewczyk-Krolikowski K et al. The influence of age and gender on motor and non-motor features of early Parkinson's disease: Initial findings from the Oxford Parkinson Disease Center (OPDC) discovery cohort. *Parkinsonism & Related Disorders* 2014. 20(1):99-105.
- Martinez-Martin P et al. Gender-related differences in the burden of non-motor symptoms in Parkinson's disease. *Journal of Neurology* 2012. 259(8):1639-1647.
- Barone P et al. The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. *Movement Disorders* 2009. 24(11):1641-1649.

24. Solla P et al. Gender differences in motor and non-motor symptoms among Sardinian patients with Parkinson's disease. *Journal of the Neurological Sciences*, 2012. 323(1-2):33-39.
25. Simuni T et al. Baseline prevalence and longitudinal evolution of non-motor symptoms in early Parkinson's disease: The PPMI cohort. *J Neurol Neurosurg Psychiatry* 2018. 89(1):78-88.
26. Del Rey NL, Quiroga-Varela A, Garbayo E, Carballo-Carbajal I, Fernández-Santiago R, Monje MHG, Trigo-Damas I, Blanco-Prieto MJ, Blesa J. Advances in Parkinson's Disease: 200 Years Later. *Frontiers in Neuroanatomy*, 2018. 12. *Front Neuroanat*. 2018 Dec 14;12:113.
27. Chaudhuri KR, Healy DG, Schapira AH. Non-motor symptoms of Parkinson's disease: diagnosis and management. *The Lancet Neurology*, 2006. 5(3):235-245.
28. Tolosa E et al. Diagnosis and the premotor phase of Parkinson disease. *Neurology* 2009. 72(7): S12-S20.
29. Boeve BF et al. Association of REM sleep behavior disorder and neurodegenerative disease may reflect an underlying synucleinopathy. *Movement Disorders* 2001. 16(4): 622-630.
30. Postuma RB, Berg D. Advances in markers of prodromal Parkinson disease. *Nature Reviews Neurology* 2016. 12(11):622.
31. Gulati A et al. A clinical observational study of the pattern and occurrence of non-motor symptoms in Parkinson's disease ranging from early to advanced disease. In *Movement Disorders*. 2004. Wiley-Liss Div John Wiley & Sons Inc, 111 River St, Hoboken, Nj 07030 USA.
32. Politis M et al. Parkinson's disease symptoms: The patient's perspective. *Movement Disorders* 2010. 25(11):1646-1651.