

## Non Motor Symptoms and their Impact on Quality of Life in Moroccan Patients with Parkinson Disease

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### Abstract

Patients with Parkinson disease are more impaired by Non-motor symptoms (NMS) than motor symptoms, especially in advanced stages. Unfortunately, in most cases, it is unrecognized. NMS are important determinant of disability and quality of life in patients with Parkinson disease (PD). This is a prospective observational study conducted in the neurology department of Mohammed VI university hospital, on NMS in Moroccan patients with Parkinson disease. We report 115 patients (Males 61.5% mean age 59.1years) diagnosed over a period of 18 months. Patients were administered detailed questionnaires by a neurologist. The mean age of onset was 53.71 (ranged from 23 to 76 years). Pain (60.3%), constipation (59%), urinary urgency (52.6%), sleep disturbances mainly insomnia (57.7), and depression (47.4%), were the most frequent NMS in our cohort, while hallucinations (29.5%), diplopia (12.8%) and memory impairment (30.8%) were less frequent.

There was a difference between males and females on the distribution of NMS, depressed mood, anxiety and sleep problems were more common in females, while urinary disorders, constipation, sexual dysfunction were more common in males. NMS are positively correlated to the H&Y stage and to duration of the disease.

We used the Parkinson's disease quality of life questionnaire Summary Index score (PDQ39IS) to assess the impact on quality of life in patients. Our results showed that the impact affected mainly the emotional well-being (47, 81%). Mobility was affected in second place (44.13%), followed by daily activities (42.9%).

**Keywords:** Parkinson Disease; Non-Motor Symptoms; Quality of Life; NMSS; PDQ3; Moroccan Cohort

### Abbreviations

NMS: Non Motor Symptoms; PD: Parkinson Disease; PDQ39IS: The Parkinson's Disease Quality of Life Questionnaire Summary Index Score; QoL: Quality of Life; UKPDSBB: The United Kingdom Parkinson Disease Brain Bank Criteria; H&Y: Hoehn and Yahr Staging; UPDRS-III: The Unified Parkinson's Disease Rating Scale Part III; NMSQ: Non Motor Symptoms Questionnaire; SD: Standard Deviation; RBD: Rapid Eye Movement Sleep Behavior Disorder

### Introduction

Parkinson's disease (PD) is a neurologic pathology characterized by the presence of cardinal motor symptoms. A progressive loss of nigrostriatal neurons, leading to striatal dopaminergic denervation is the main feature of the disease [1].

The association with non-motor signs (NMS) is frequent, but often goes unrecognized in 50% of cases [1,2].

These non-motor signs include sensory symptoms, autonomic failure, sleep disorders and neuropsychiatric disorders [3,4]. NMS can be more disabling for the patient than motor disorders and may be responsible for a significant decline on quality of life (QoL) in the absence of the appropriate treatment for each symptom [5-7].

This work is the second study done in Morocco, and concerns rather the south of Morocco, the first study was conducted in Rabat.

The objectives of this study are to evaluate the frequency of NMS in our patients, to describe the relationship of NMS to demographic parameters and motor function and specially the stage of the disease, as well as the evaluation of the impact of these non-motor signs on the quality of life.

We used the NMS questionnaire to assess NMS, and the 39-item Parkinson's disease quality of life questionnaire Summary Index score (PDQ-39IS) for the quality of life (QoL).

### Methods

In this observational prospective study, we have included 115 PD patients attending the neurology department of Mohammed VI university hospital of Marrakesh.

The recruitment period was from February 2017 to July 2018. The diagnosis of patients was based on the United Kingdom Parkinson Disease Brain Bank Criteria (UKPDSBB). The exclusion criteria were other forms of parkinsonism. A neurologist accomplished a detailed interview and a neurologic examination to acquire clinical characteristics of patients. We evaluated the motor function in the ON state using the modified Hoehn and Yahr staging (H&Y) and the unified Parkinson's Disease Rating scale part III (UPDRS-III).

We evaluated the non-motor signs using the non-motor symptoms questionnaire (NMSQ), containing items detailing the age and sex of the patients and 30 questions to be answered by yes or no. To figure out the impact on QoL, we used the 39-item Parkinson's disease quality of life questionnaire Summary Index score (PDQ-39IS).

We used spss 22, to carry out statistical analysis. To express data, we adopted descriptive statistics such as mean, standard deviation, and percentage. We used the univariate analysis of variance for continuous variables, and Chi square tests for categorical variables to compare between various groups. For correlations, we used the Pearson correlation coefficients and linear regression models. We applied a p-value of a significance level of 5%.

### Results

In this study, we report 115 PD patients diagnosed over a period of 18 months.

Clinical details are shown in table 1. In brief, 61.5% of patients were males. Patients' age ranged between 27 and 82 years old, with a mean age of 59.1 years (SD 11.18). Seventeen point nine per cent were younger than 50 years old, while 12.8% were over 70.

The mean age of onset was 53.71 years, within this outcome 32.1% were less than 50 years old. The median duration of illness was 4 years. The mean of UPDRS III score and PDQ-39 was 46.37 and 36.48 respectively. At least, we found one NMS in 98.7% of patients. The mean number of NMS was 12.82 (range 0 - 25).

Behavioural changes were common in our series, especially neuroses as depression (47.4%), followed by anxiety (44.9%). We found less frequently hallucinations (29.5%). Memory impairments were reported in 30.8% of our patients.

Clinical features	Mean ± SD; median %
Age	59.1 ± 11.18
<b>Sex %</b>	
Males	61.5%
Females	38.5%
Duration of disease (median)	4
Age at onset	53.71 ± 11.325
<b>Drugs %</b>	
Dopamine agonists	9%
L-Dopa	48.7%
L-dopa in association with dopamine agonists	42.3%
<b>H&amp;Y stage</b>	
1	15.4%
2	37.2%
3	21.8%
4	25.6%
NMS	12.82 ± 5.864
UPDRS	46.37 ± 25.141
PDQ-39SI	36.49 ± 22.162

**Table 1:** Clinical characteristics of patients.

Abnormalities of sensation were quiet usual, of which pain had the highest rate (60.3%). Olfactory impairment was found in 46.2% of patients.

Autonomic dysfunction were dominated by constipation (59%), followed by urinary urgency (52.6%) and orthostatic hypotension (50%). Sexual dysfunction was found in 46.2% of patients. Sleep disorders were very common in our patients (82.1%), insomnia being the most common (57.7%) (Table 2).

Males (13.04 ± 5,5) reported a higher number of non motor symptoms compared to females (12.46 ± 6,4), but this difference were not statistically significant (p = 0.67).

There was a difference between males and females on the distribution of NMS, depressed mood, anxiety and sleeping disorders were more common in females, while urinary disorders, constipation, sexual dysfunction were more common in males. However, these differences were not statistically significant except for sexual dysfunction and constipation (p = 0,024 and p = 0.026 respectively) (Table 2).

Patients were in different H&Y stages of Parkinson disease (Stage 1:15.4%; stage 2: 37.2%; stage 3: 21.8%; stage 4 and 5: 25.6%).

Linear regression model shows that the number of NMS is positively correlated to the H&Y stage (p = 0.022).

Depression was significantly usual in early stages of the disease (p = 0.001), while memory impairment, hallucinations and excessive sweating were commoner in patients with advanced disease (p = 0.001; 0.02 and 0.033 respectively).

Non motor symptoms items	%	Males %	Females %
Depression	47.4	39.6	60
Anxiety	44.9	37.5	56.7
Apathy	38.5	37.5	40
Hallucinations	29.5	22.9	40
Memory impairment	30.8	29.2	23.3
Difficulties of concentration	37.2	41.7	30
Urinary urgency	52.6	58.3	43.3
pollakiurie	43.6	50	33.3
Low sexual desire	41	41.7	40
Sexual difficulties	41	52.1	23.3
Daytime somnolence	38.5	45.8	26.7
Insomnia	57.7	50	70
Vivid dreams	55.1	56.3	53.3
RBD	47.4	43.8	53.3
Constipation	59	68.8	43.3
Hypotension	50	39.6	66.7
Excessive sweating	47.4	43.8	53.3
Pain	60.3	56.3	66.7
Diplopia	12.8	14.6	10
Olfactory impairment	46.2	43.8	50

**Table 2:** Prevalence of NMS items.

No relation was found between NMS, age on onset and age of patients. On the other hand, NMS are positively correlated to duration of the disease ( $p = 0.024$ ).

Patients with a longer duration of PD, had more memory problems ( $p = 0.001$ ), apathy ( $< 0.05$ ), hallucinations ( $p = 0.03$ ) and daytime somnolence ( $0.03$ ).

Ninety two percent (92%) of patients were using L-Dopa, within this segment, 48.72% were in monotherapy. Thirty eight percent of patients were using Dopamine agonists most frequently in association with L-dopa. Elevated NMS score were found in patients taking dopamine agonists in monotherapy ( $14.43 \pm 7.59$ ;  $p = 0.046$ ) or in association with L-Dopa ( $14.21 \pm 5.53$ ;  $p = 0.043$ ).

Patients using dopamine agonists in association with L-dopa seems to have more sleep disturbances ( $p = 0.042$ ), pain ( $0.001$ ), and depression ( $p = 0.023$ ), while patients taking dopamine agonists in monotherapy had more hallucinations ( $p = 0.037$ ) and Rapid eye movement sleep behavior disorder (RBD) ( $p = 0.024$ ).

We have also assessed the impact on quality of life in patients using PDQ39-SI. Our results showed that the emotional well-being (mean  $47, 81 \pm 29.13$ ), mobility ( $44.13 \pm 34.63$ ), daily activities ( $42,89 \pm 32.89$ ) were affected respectively, as far as patients' quality of life is concerned.

Multiple linear regression methods showed that health-related QoL (PDQ-39SI) was significantly related to NMS (regression coefficient (R) = 0.688;  $p < 0.0005$ ) and to the H&Y stage (R = 0.281;  $p = 0.006$ ).

Parameters (%)	Hoehn and Yahr stage				p value
	1	2	3	4 and 5	
Whole cohort	15.4	37.2	21.8	25.6	
Depression	75	65.5	35.3	15	0.001
Anxiety	66.7	55.2	35.3	25	0.061
Apathy	8.3	17.2	64.7	65	<0.005
Hallucinations	8.3	17.2	41.2	50	0.02
Memory impairment	8.3	13.8	41.2	60	0.0001
Difficulties of concentration	33.3	41.4	47.1	25	0.517
Urinary urgency	50	48.3	70.6	45	0.404
Pollakiurie	33.3	58.6	47.1	25	0.108
Low sexual desire	25	31	52.9	55	0.166
Sexual difficulties	25	31	64.7	41	0.088
Daytime somnolence	33.3	44.8	17.6	50	0.182
Insomnia	41.7	55.2	70.6	60	0.468
Vivid dreams	25	65.5	70.6	45	0.043
RBD	58.3	44.8	29.4	60	0.248
Constipation	50	62.1	70.6	50	0.546
Orthostatic Hypotension	50	44.8	35.3	70	0.173
Excessive sweating	16.7	44.8	41.2	75	0.012
Pain	33.3	65.5	58.8	70	0.189
Diplopia	8.3	17.	11.8	12.8	0.830
Hyposmia	3.3	37.9	58.8	55	0.346

**Table 3:** Correlation of Hoehn and Yahr with selected non motor symptoms.

PDQ-39SI had also a significant positive correlation to duration of the disease ( $R = 0.45$ ;  $p = 0.00003$ ) and a negative correlation to the age of patients and the age at onset ( $R = -0.204$ ;  $p = 0.036$  and  $R = -0.375$  and  $p < 0.0005$  respectively).

### Discussion

Parkinson disease is the most frequent movement disorder. It represents the second most common degenerative disease of the central nervous system [8].

Non-motor signs are usual in individuals with Parkinson disease, but unfortunately still under diagnosed and consequently under-treated [4].

The physiopathology of Parkinson disease involves the progressive degeneration of the nigrostriatal dopaminergic system. However, this degeneration cannot account for all the clinical manifestations of Parkinson disease, including non-motor signs. Recent studies by BRAAK have changed the classical vision of this disease, suggesting a new theory that lewy bodies progressively affect many brain structures [9].

The frequency of Parkinson disease increases with age [4], in our series the mean age was 59.1 years, and the mean age on onset was 53, 16 years. This result is in keeping with data from the literature, which states that PD affects 1% of the population above 60 years, and remains rare before age of 50 [8,10,11].

Epidemiological studies found that PD affects more frequently males [12-14]. In our study, there was a male predominance too (61, 5% vs 38, 5%), maybe because of the increased susceptibility of this gender to PD [14]. Moreover, recent evidences established gender differences in nigrostriatal dopaminergic innervations, which might influence the PD pathogenesis [15,16-21].

In our PD sample, we found that 97% of patients had at least one non-motor symptom. Which matches the other clinical studies conducted in other countries with prevalence rates ranging from 76, 1% to 100% [6,13,22-26]. Our study reported a median of 13 NMS. Previous studies reported 3.5 to 12 NMS on average [13,22,27-29].

Pain, constipation, urinary urgency, sleep disturbances (mainly insomnia and vivid dreams) and depression were the most frequent NMS in our cohort, while hallucinations, diplopia and memory impairment were less frequent.

In another Moroccan cohort conducted in Rabat, the most common NMS were urinary dysfunctions, sleep, and gastrointestinal disorders [30]. In an Indian cohort of 171 patients [1], anxiety, urinary disorders and constipation were the predominant symptoms. Egyptian and Chinese studies reported similar results [6,31,32]. Urinary symptoms, depression and memory problems were the prevalent NMS found in an international study of 545 patients by Martinez, *et al* [24]. While fatigue (58,1%), anxiety (55,8%) and pain (37,9%) were the most frequent NMS in the PRIAMO study (a multicenter study in Italy with 1325 PD patients) [25].

In the largest prospective clinical study investigating non motor aspects of patients with advanced-stage PD in Japan, named J-First, constipation, sleep problems, pain, fatigue, urinary disorders and anxious mood were the most prevalent [33]. In various other studies, hallucinations have been said to be relatively uncommon [34,35]. As shown, our survey results join the data of literature in the frequency of constipation, sleep disturbances, RBD and pain. It demonstrates also the rarity of hallucinations.

Findings in our series, demonstrated that depressed mood, anxiety and sleep problems were more common in females, while urinary disorders, constipation and sexual dysfunction were more common in males. Previous studies [14,36-39] underlined the frequency of depression and anxious mood in PD female patients. This could be explained by the susceptibility of this gender to develop neuroses. A sardinian study [14] showed that sexual impairment is more frequent in males PD patients, which is comparable to our data. This finding has been explained by the fact that male PD patients present more often compulsive sexual behaviors.

We found a high correlation of the H&Y with NMS. In multiple studies, it was found that the total number of NMS increases with severity, and progression of PD [1,22,24,26,28,33,35]. In our study, patients in earlier stages had more depression, while those in advanced stages had more hallucinations, memory impairment and excessive sweating. Previous studies report the same findings [34,40].

In contrast to other reports [29,24,34], there was no effect of age of patients and age at onset on NMS. On the other hand, NMS are positively correlated to duration of the disease. Among our patients, apathy, memory problems, hallucinations and sleep disturbances were related to a longer duration of PD. Our results are in agreement with those of previous reports [35,41-43].

Regarding treatments used in our patients, those using dopamine agonists in association with L-dopa had more symptoms of sleep disturbances, pain, and depression, while patients taking dopamine agonists in monotherapy had more hallucinations and RBD. Based on the literature, there is increasing evidence that dopamine agonists can ameliorate depression or anxiety. While psychosis or impulse control disorders can be worsened or even be induced by dopaminergic agents [44]. Regarding to Levo-Dopa therapy, it is well known that psychiatric conditions often manifested as compulsive behaviours are emerging as a serious problem [45].

NMS had a direct negative impact on quality of life, and the H&Y stage was correlated to the PDQ-39 score. These findings are similar to other studies [5,7,46,47].

PDQ 39 SI had a significant positive correlation with the duration of the disease, which is consistent with other studies stipulating that patients with a longer duration of PD have a reduced quality of life [48].

In our study, the impact of NMS on QoL affected mainly the emotional well-being (47,81%), mobility (44.13%), and daily activities (42,89%). In several studies, mobility and daily activities were the only parameters disrupted in the QoL of PD patients. This may be in keeping with the fact that the motor aspect is more affected in PD [49,50].

### Conclusion

Beside motor symptoms, Parkinson's disease is characterized by different non motor symptoms, which are actually known, but often go unnoticed in 50% of cases. Their presence help to comfort the diagnosis of PD.

NMS can be very disabling for the patients and should be treated in the different stages of the disease. They can also be responsible of a decreasing on the patient's quality of life.

### Conflict of Interest

We declare that there is no conflict of interest.

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