

# Constipation associated with Parkinson's disease in Morocco. A report on the clinical experience in Morocco

Constipation associated to Parkinson's disease in Morocco

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## Abstract

**Aim:** Constipation is the most frequent symptom of autonomic dysfunction in patients with Parkinson's disease. The objective of this work is to study the prevalence and clinical features of constipation symptoms.

**Material and Methods:** A cross-sectional descriptive study was conducted on a selected cohort of 180 patients, previously diagnosed with PD.

**Results:** The frequency of constipation in patients with Parkinson's disease was 69.4%, and 96 % of Parkinson's disease patients had constipation before the onset of motor symptoms. Patients with Parkinson's disease with constipation had significantly longer duration of the disease and more advanced stages of Hoehn and Yahr scales. We also found that the group of patients with Parkinson's disease with constipation sign had less significant symptoms of bradykinesia compared to the non-constipation group.

**Discussion:** The improvement of the management of patients with Parkinson's disease requires the integration of the search for non-motor signs during consultation and the validation of evaluation scales in Arabic.

## Keywords

Parkinson's Disease; Constipation; Premotor symptom; Hoehn and Yahr scale

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## Introduction

Parkinson's disease (PD) is the most common neurodegenerative disorder after Alzheimer's disease [1], affecting 1% of the population older than 60 years [2]. Clinically, most patients suffer from the motoric disorder, including bradykinesia, rest tremor, rigidity, and postural and gait impairment. However, a number of patients also suffer from non-motor disorders, including olfactory, cognitive impairment dysfunction, anxiety, depression, sleep disorders, autonomic disturbances, pain, fatigue, and dementia [3, 4]. In fact, both mood disorders and constipation have been shown to increase an individual's risk for subsequently developing Parkinson's disease[5]. They are associated with neuropathological lesions commencing in the dorsal vagus nucleus, in the bulb and in the anterior olfactory nucleus, and will progressively propagate in the overlying structures [6, 7].

Constipation remains the most common symptom of dysautonomic and gastrointestinal symptoms, reported by 70-80 % of patients with Parkinson's disease [8], may also appear many years before the onset of motor symptoms and, therefore, in combination with the other non-motor symptoms, can be a predictive marker. The accumulation of  $\alpha$ -Synuclein and associated neurodegeneration in the enteric nervous system, characterized by increased intestinal permeability, oxidative stress and local inflammation, explain constipation in these patients [9]. Early screening for such symptoms may constitute an important approach for early pre-clinical diagnosis. This study was conducted to determine the prevalence of constipation symptoms in PD compared to patients with Parkinson's disease without constipation and to evaluate the relationship between these pre-motor symptoms and the clinical features of PD.

## Material and Methods

### *Patients and criteria of inclusion*

This is a cross-sectional study on a cohort of 180 patients (males and females), previously diagnosed with Parkinson's disease. Patients were recruited from both private and public neurology centers in the city of Agadir in South-western Morocco. All the selected patients gave their written consent, according to the recommendation of the Ethics Committees of the Faculty of Medicine and Pharmacy of Marrakech.

### *Data collection*

The data were collected between January 2017 and July 2018 using a detailed clinical questionnaire filled up by the clinicians through an interview with the patients. In order to distribute individuals into a number of classes, a k-means clustering algorithm was used to define 2 age clusters of disease onset (early-onset Parkinson's  $\leq$  at age 50 and late-onset Parkinson's  $>$  at age 50).

### *Statistical analysis*

Data are presented as means  $\pm$  standard deviation (SD) or percentage. Independent sample t-tests, non-parametric test and Variance test were used. Variations in the distribution of categorical data were evaluated using the Chi-square test or Fisher exact test. A p-value below 0.05 was considered statistically significant. Statistical correlation was performed using the IBM SPSS statistics 22 software

## Results

Patients diagnosed with Parkinson's disease were recruited both in private and public neurology services. The size of the sample reached 180 individuals, including 117 males (65%) patients and 63 females (35%). The mean age of the patients included in the cohort was estimated to be around  $68.1 \pm 11.3$  years old. The results showed that the age at the onset of the disease, in the sample ranged between 35 and 80 years old. The mean age at the onset of symptoms for male and female population was  $60.3 \pm 9.78$  years.

### *Clinical features of PD patients with constipation*

Among the 180 participants in the current clinical investigation, 125 (69.4%) patients suffered from constipation. To compare the characteristics of patients with constipation, PD patients were divided into two groups: constipated group (constipation group) and non-constipated group (non-constipation group). The main characteristics of the cohort in relation to constipation are presented in Table 1. There was no significant difference in Body Mass Index, and gender between the two groups. The age of PD patients in the constipation group ( $69.4 \pm 11.5$  years) was significantly older than that of PD patients in the non-constipation group ( $65.1 \pm 10.2$  years) ( $P < 0.01$ ). The duration of the illness in the PD group with constipation ( $8.8 \pm 5.6$  years) was significantly longer than in the PD group without constipation ( $5.8 \pm 5.1$  years) ( $P < 0.05$ ).

This result showed that the initial symptom differed from that of the non-constipation group. There was a correlation between the constipation group and the severity of motor symptoms of PD. Indeed, the comparison between the two groups in relation to the initial symptom showed that the non-constipation group experienced more significant symptoms of bradykinesia compared to the constipation group.

The clinical profile of the patients differed slightly between the two groups. Both groups presented three disease phenotypes, however, the percentage of patients with a mixed phenotype in the constipation group (33.4%) was significantly lower than in the non-constipation group (46.7%). The mean daily dose of levodopa was similar in the constipation group ( $420.1 \pm 154.1$  mg/d) compared with the non-constipation group ( $390.5 \pm 154$  mg/d). However, this result remains insignificant. The severity of the Hoehn-Yahr Stage ( $p < 0.05$ ) was significantly different in both groups. The H-Y stages in the PD group with constipation ( $3.62 \pm 1.97$ ) were significantly increased compared with the non-constipation group ( $2.95 \pm 1.08$ ) ( $P = 0.01$ ).

A cluster analysis with a two-cluster solution revealed two profiles. The early-onset Parkinson's group had a mean age at the onset of  $49.8 \pm 5.8$  years, compared to the later onset group (mean age of onset =  $66.1 \pm 5.1$  years). In relation to the age at onset of Parkinson's disease, patients with constipation were significantly older than PD without constipation.

### *Pre-motor constipation*

Among the 125 patients with Parkinson's disease, 120 cases (96%) had constipation before the appearance of motor symptoms. Pre-motor constipation appeared in over half of the patients with a delay of 2 to 10 years for a significant proportion (68. 33%). The average duration of onset of premotor constipation was  $4.6 \pm 3.1$  years (Figure 1).

**Table 1.** Comparison of PD patients with/without constipation

Item	PD with constipation	PD without constipation	Test value	P value
Number of cases	125 (69.4%)	55 (30.6%)		
<b>Gender</b>				
Male	80(64%)	37(67.3%)	$\chi^2 = 0.18$	0.4
Female	45(36%)	18(32.7%)		
BMI	25.2 ±2.8	25.7 ± 5.4	t=-0.71	0.47
Age (mean, Years)	69.4 ±11.5	65.1 ±10.2	t=2.38	0.01
Age at onset of disease (mean, years)	60.7 ±9.6	59.3 ±9.9	t=0.87	0.38
<b>Initial symptom</b>				
Tremor	66 (52.8%)	25 (45.4%)	$\chi^2 = 0.82$	0.2
Rigidity	24 (19.2%)	6(11%)	$\chi^2 = 1.89$	0.12
Bradykinesia	36(28%)	24 (43.6%)	$\chi^2 = 3.78$	0.03
<b>Form of disease</b>				
Trembling form	53(42.4%)	23(41.8%)	$\chi^2 = 0.55$	0.27
Rigid akinetic form	28(22.4%)	6(11%)	$\chi^2 = 1.47$	0.16
Mixed form	44(35.2%)	26(47.2%)	$\chi^2 = 1.15$	0.18
Duration of disease	8.8±5.6	5.8±5.1	t=3.42	0.001
Dose of levodopa (mg/d)	420.1±154.1	390.5±154	t=1.18	0.23
Hoehn-Yahr Stage (mean)	3.62±1.97	2.95±1.08	t=2.43	0.01
Middle stage*	98(78.4%)	50(91%)	$\chi^2 = 4.48$	0.03
Moderate stage **	11(8.8%)	3(5.5%)		
Advanced stage***	16(12.8%)	2(3.5%)		
<b>k-means clustering (age at onset)</b>				
Early-onset Parkinson's disease (49.8 ±5.8years)	39(31.2%)	25(45.4%)	$\chi^2 = 3.38$	0.04
Late-onset Parkinson's disease (66.1±5.1 years)	86(68.8%)	30(54.6%)		

$\chi^2$ . Chi-squared  
 \* mild (1-2 stage of Yoehn and Yahr), \*\*moderate (2.5-3) and \*\*\*advanced (4-5).

**Discussion**

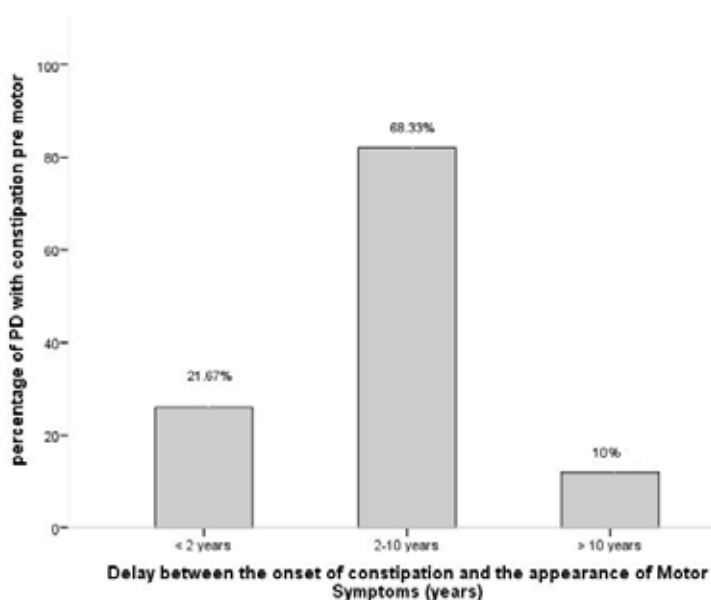
In the present study, 69.4% of Parkinson's disease patients were ascertained to have subjective constipation, in agreement with other reports, in previous studies reporting that constipation affects 70-80% of Parkinson's patients [10-12]. Our results also suggest that constipation in our population had an average of 4 or more years delay before the onset of motor symptoms, which was consistent with previous reports that showed that the prevalence of constipation as a pre-motor sign ranged from 28.19% to 87% depending on the type of the studied population and the constipation criteria [13, 14]. This finding indicates constipation as a prodromal symptom of PD. Early involvement of enteric neurons may explain the discovery that constipation is an early symptom of Parkinson's disease [15].

In previous studies, constipation has been correlated with the time since diagnosis and the severity of Parkinson's disease [16]. In this study, it was observed that the group of Parkinson's patients with constipation had late-onset Parkinson's disease. This confirmed previous findings that showed an influence of old age at the onset of Parkinson's disease on the development of certain symptoms, including constipation [16]. Our results also showed that patients with constipation had significantly longer duration of disease and more advanced stages of the Hoehn and Yahr scale. Presumably, in patients with Parkinson's disease who are more advanced in age and stage of onset, less activity and poorer gastrointestinal motility may cause constipation. This is also supported by our findings that constipated patients are older than non-constipated Parkinson's patients.

Considering the clinical pattern of PD, we found that the group of patients with Parkinson's disease with a sign of constipation had less pronounced symptoms of bradykinesia compared to the non-constipation group. This result might be attributed to the fact that bradykinesia was the most handicapping symptom of Parkinson's disease. This restricts the physical activity and mobilization of patients.

Previous studies have investigated the impact of dopaminergic treatment on autonomic symptoms, such as constipation, in patients with Parkinson's disease [10, 11]. In contrast, in this study, the PD group with constipation received a daily dose of levodopa similar to the PD group without constipation, which is inconsistent with the results of other studies suggesting that autonomic symptom alterations were associated with dopaminergic treatment. This difference may be partially explained because dopaminergic treatment was not initially used to treat patients in our study.

In the literature, constipation has been treated only by a few research papers on Parkinson's disease in Morocco, and to our knowledge, this investigation is the most important to focus on the subjective aspect of the problem. Our study has certain limitations. This is a historical clinical investigation of the onset of premotor symptoms, in which information about the chronology of constipation and other symptoms was collected through patient reminders. Therefore, the subjective bias of the responses could not be ignored and may partially influence the precision of our results.



**Figure 1.** Delay between the onset of constipation and the appearance of Motor symptoms (years)

In conclusion, these results underscore the importance of the clinical and systematic evaluation of constipation in patients with Parkinson's disease. The diagnosis of constipation may allow clinicians to identify PD in their patients at an earlier stage, especially if it is associated with other pre-motor symptoms including sleep and olfactory disorders. The improvement of the management of Parkinson's patients requires the integration of the search for non-motor signs during the consultation and the validation of evaluation scales in Arabic.

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#### Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

#### Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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#### Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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