

Bladder Symptoms Assessed with Overactive Bladder Questionnaire in Parkinson's Disease

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Abstract: In Parkinson's disease (PD) the urinary dysfunction manifests primarily with symptoms of overactive bladder (OAB). The OAB questionnaire (OAB-q) is a measure designed to assess the impact of OAB symptoms on health-related quality of life. In this study, we quantified the urinary symptoms in a large cohort of PD patients by using the OAB-q short form. Possible correlations between the OAB-q and clinical features were tested. Three hundred and two PD patients were enrolled in the study. Correlations between the OAB-q and sex, age, Unified Parkinson's Disease Rating Scale part III (UPDRS-III), Hoehn-Yahr (H-Y) staging, disease duration, and treatment were analyzed. Data were compared with a large cohort of 303 age-matched healthy subjects. The OAB-q yielded significantly higher scores in PD patients than in healthy subjects. In the group of PD patients, all the variables tested were similar between men and women. Pearson's coefficient showed a significant correlation between mean age, dis-

ease duration, mean OAB-q scores, UPDRS-III scores, and H-Y staging. A multiple linear regression analysis showed that OAB-q values were significantly influenced by age and UPDRS-III. No statistical correlations were found between OAB-q scores and drug therapy or the equivalent levodopa dose, whilst the items relating to the nocturia symptoms were significantly associated with the equivalent levodopa dose. Our findings suggest that bladder dysfunction assessed by OAB-q mainly correlates with UPDRS-III scores for severity of motor impairment, possibly reflecting the known role of the decline in nigrostriatal dopaminergic function in bladder dysfunction associated with PD and patients' age. Our study also suggests that the OAB-q is a simple, easily administered test that can objectively evaluate bladder function in patients with PD. © 2010 Movement Disorder Society

Key words: Parkinson's disease; bladder dysfunctions; OABq

Growing interest now centers on bladder dysfunction in Parkinson's disease (PD) and parkinsonism first because many patients find these symptoms disabling, and second because increasing evidence suggests a role

of dopaminergic mechanisms in the neural control of the urinary bladder.¹ Bladder dysfunction in PD manifests primarily with symptoms such as urinary urgency without urge incontinence, usually with frequency, and nocturia suggesting overactive bladder (OAB).^{1,2} Neurogenic OAB is secondary to neurogenic detrusor overactivity characterized by involuntary detrusor contractions during bladder filling.^{1–3} Other common complaints include difficulty in initiating micturition and reduced urinary stream. Night-time frequency is among the most troublesome urinary complaints in advanced

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PD.^{4,5} Convincing evidence suggests that OAB associated with PD arises from a decline in nigrostriatal dopaminergic function.⁴ Clinical observations have shown that urinary dysfunction in PD is related to the extent of dopamine depletion, stage of disease and also to patients' general neurological disability.^{4,6-7} Further support for a striatal dopaminergic mechanism comes from a study by Sakakibara et al.⁵ showing lower 2-carbomethoxy-3-(4-iodophenyl)-tropane striatal uptake in PD patients complaining of bladder symptoms than in those without, indicating a correlation between urinary dysfunction and nigrostriatal dopaminergic cell degeneration.⁵ In a similar study, Winge et al.⁷ found that the presence of bladder symptoms is related to the decrease in the total number of dopaminergic neurones in the striatum and that relative degeneration of the caudate correlates with the severity of bladder symptoms. Although loss of cortical inputs from the basal ganglia appears to have a major role as the cause of urinary symptoms in PD, some evidence suggests that alterations in the integrated cortical and subcortical circuits may contribute to bladder dysfunction probably acting by altering the way in which bladder afferent activity is processed.⁷ Studies of bladder function after implantation of a deep brain stimulator for the treatment of advanced movement disorders have shown a reduction in OAB and increased bladder capacity although the effect of this intervention on urinary symptoms appears to be more complex.⁸

The OAB questionnaire (OAB-q) is an 36 item or eight item (short form), condition-specific measure originally designed to assess the impact of OAB symptoms on health-related quality of life.⁹ This instrument has been adopted by the International Consultation on Incontinence Questionnaire committee as the questionnaire module for OAB and has demonstrated internal consistency reliability, validity, and responsiveness.⁹ The eight item OAB-q addresses both the frequency and bother of frequency, urgency, nocturia, and incontinence symptoms. The OAB-q has been validated in multiple clinical and community samples in over 2500 patients and has performed well among patients with a range of mild-to-severe OAB symptoms.¹⁰ Although this questionnaire has already been used for assessing quality-of-life in healthy subjects with OAB, lower urinary tract dysfunction and the efficacy of drug therapy,^{11,12} no data are yet available about its use for assessing bladder dysfunction in patients with central nervous system (CNS) disorders.

Our aim in this study was to use the OAB-q short form to quantify the urinary symptoms associated with PD and to evaluate possible correlations between the

bladder dysfunction as quantified by the OAB-q and sex, age, disease severity scored by Hoehn-Yahr (H-Y) staging,¹³ severity of motor dysfunctions tested by the Unified Parkinson's Disease Rating Scale motor section part III (UPDRS-III), disease duration, and drug therapy in a large cohort of patients with PD. To compare OAB-q scores in patients and healthy subjects, we recruited a large cohort of healthy controls.

PATIENTS AND METHODS

Subjects

Three hundred and two patients with idiopathic PD were consecutively recruited from the outpatient clinic at the Department of Neurological Sciences, Department of Neurology and Otolaryngology, University of Rome "Sapienza", and the Neurology Units of Sant'Eugenio Hospital. All patients fulfilled the UK Parkinson's Disease Society Brain Bank criteria for idiopathic PD, which require that patients have bradykinesia and at least one of the other three cardinal features (rigidity, rest tremor, and postural instability), none of 16 exclusion criteria and at least three of eight supportive features (relating to asymmetric onset and progression, levodopa (L-dopa) or dopamine agonist (DA) responsiveness, and chronic progression of clinical features).¹⁴ Patients showing abnormalities compatible with secondary parkinsonism or clinical symptoms possibly related to progressive supranuclear palsy (PSP) or corticobasal degeneration (CBD), and those with cognitive impairment (mini mental state examination, MMSE $\leq 26/30$) were excluded. Because it was difficult to exclude patients with possible multisystemic atrophy (MSA) from a study on urinary dysfunction in PD, patients with concomitant symptoms suggesting an MSA, such as autonomic failure, cerebellar ataxia, corticospinal dysfunction, and poorly L-dopa responsive parkinsonism were not enrolled in the study. Finally patients with a history of urological (such as prostatic hyperplasia or cancer, prostatitis, previous lower urinary tract surgery) or pure gynecological disorders were also excluded from the study. Any patients have been treated with anticholinergic drugs. The group of patients comprised 168 men and 134 women (range age 40–93 years, mean age \pm SD 69.4 ± 9.16 years). Illness duration ranged from 8 months to 37 years (average 6.88 ± 5.1 years). The motor dysfunction severity was evaluated with the UPDRS-III in the on condition during their usual dopaminergic therapy (mean score 18.7 ± 10.5 ; range 3–50). The severity of disease was evaluated with H-Y staging (Table 1).

TABLE 1. *Patients: Clinical details of the 302 patients with Parkinson's disease*

| Clinical details | Patients | |
|-----------------------|----------------|-----------------|
| | Men (n = 168) | Women (n = 134) |
| Age (yr) | | |
| Mean \pm SD | 69.2 \pm 9.1 | 69.7 \pm 9.2 |
| Range | 46–87 | 40–93 |
| Disease duration (yr) | | |
| Mean \pm SD | 7.0 \pm 5.4 | 6.7 \pm 4.6 |
| Range | 0.08–37 | 0.08–20 |
| UPDRS-III on therapy | | |
| Mean \pm SD | 18.4 \pm 9.9 | 18.5 \pm 10.5 |
| Range | 0–46.5 | 3–50 |
| Drug therapy (%) | | |
| No therapy | 7.1 | 5.2 |
| L-Dopa | 47.6 | 51.1 |
| DA | 10.7 | 5.9 |
| Other drugs | 34.5 | 37.8 |
| H-Y staging | | |
| I | 76 (45 %) | 51 (38.1%) |
| II | 54 (32 %) | 50 (37.3%) |
| III | 38 (23 %) | 32 (23.9%) |
| IV | — | 1 (0.7%) |
| V | — | — |
| OAB-q score | | |
| Mean \pm SD | 18.5 \pm 8.7 | 18.9 \pm 9.4 |
| Range | 0–46.5 | 0–46.5 |

Of the 302 patients studied, 149 were receiving chronic drug therapy with L-dopa, 26 patients were receiving DA, 107 patients were receiving L-dopa plus DA, and 19 patients were receiving no drugs. Data for one patient were missing. In patients, who were taking L-dopa and DA we calculated the equivalent L-dopa dose.^{15,16} Clinical details of the 302 PD patients are summarized in Table 1.

The 324 healthy control subjects, who accompanied the PD patients to the outpatients clinic, were consecutively recruited (164 men and 160 women, range age 42–87 years, mean age 68.7 ± 8.57 SD years). Similarly to PD patients, subjects with a history of lower urinary tract disease or gynecological disorders were excluded.

OAB-Questionnaire

The OAB-q short form assessing subjective OAB symptoms was administered to each patient in their usual dopaminergic therapy, and healthy control recruited in the study (Table 2). The OAB-q sought information on how much selected bladder symptoms bothered subjects during the past 4 weeks. There are no right or wrong answers. All participants had to circle the number that best described the extent of urinary disturbances. Patients rate each item on a six point Likert scale ranging from “not at all” to “a very great deal” for the symptom bother items. Each question is scored on a scale ranging from 1 to 6, scores are summed and transformed into a total score ranging from 8 to 48.

All participants gave their written informed consent to the study and the procedures were approved by the Ethical Committee of the Department of Neurological Sciences, “Sapienza” University, Rome.

Statistical Analysis

The χ^2 test was used to analyze differences in the frequency of categorical variables and odds ratios (ORs) with relative 95% confidence intervals (CIs) were estimated if possible. Differences in the means of continuous measurements were determined with Student's *t*-test. To determine relationships between the studied variables we used Pearson correlation coefficients. A multiple linear regression model was run to evaluate the relation between OAB-q scores and the other independent variables including age, disease duration, UPDRS-III, H-Y staging. Possible correlation between individual PD symptoms and OAB were also tested.

The influence of drugs on the urinary function was also tested. Because most of the patients received L-dopa in monotherapy or L-dopa plus DA and only few patients were receiving DA alone or no therapy, the data were also analyzed using the L-dopa equivalent

TABLE 2. *OABq: The overactive bladder questionnaire (OAB-q) assessing subjective overactive bladder disturbances administered to patients and healthy controls recruited for the study*

| During the past 4 weeks, how bothered were you by | Not at all | A little bit | Somewhat | Quite a bit | A great deal | A very great deal |
|--------------------------------------------------------|------------|--------------|----------|-------------|--------------|-------------------|
| 1. Frequent urination during the daytime hours | 1 | 2 | 3 | 4 | 5 | 6 |
| 2. An uncomfortable urge to urinate | 1 | 2 | 3 | 4 | 5 | 6 |
| 3. A sudden urge to urinate with little or no warning | 1 | 2 | 3 | 4 | 5 | 6 |
| 4. Accidental loss of small amounts of urine | 1 | 2 | 3 | 4 | 5 | 6 |
| 5. Nighttime urination | 1 | 2 | 3 | 4 | 5 | 6 |
| 6. Waking up at night because you had to urinate | 1 | 2 | 3 | 4 | 5 | 6 |
| 7. An uncontrollable urge to urinate | 1 | 2 | 3 | 4 | 5 | 6 |
| 8. Urine loss associated with strong desire to urinate | 1 | 2 | 3 | 4 | 5 | 6 |

dose.^{15,16} To test the impact of different DA on the severity of urinary symptoms a further analysis was performed comparing the OAB-q score in patients receiving D1/D2 dopamine agonists (cabergoline) and those assuming D2 dopamine agonists (pramipexole and ropinirole).

Values are expressed as mean \pm SD. *P* values of < 0.05 were considered to be statistically significant. All statistical calculations were done with the statistical package SPSS (version 15.0; SPSS, Chicago, IL, USA).

RESULTS

Sex distribution (χ^2 , $P = 0.1$) and mean age (*t*-test, $P = 0.3$) were similar in the groups of patients and healthy subjects. Mean OAB-q scores were significantly higher in the group of PD patients than in the healthy control group (18.71 ± 8.9 vs 12.37 ± 5.1 ; $P = 0.001$ by Student's *t*-test).

In the group of PD patients, the mean age, disease duration, the OAB-q scores, UPDRS-III scores, and H-Y staging were similar between men and women (mean age, $P = 0.97$; disease duration, $P = 0.61$; OAB-q, $P = 0.72$; UPDRS-III, $P = 0.96$; H-Y, $P = 0.39$) (Table 1). Pearson's coefficient showed a significant correlation between mean OAB-q scores, mean age, disease duration, UPDRS-III scores, and H-Y staging (Table 3). A subsequent analysis with Pearson's coefficient showed a significant correlation between mean OAB-q scores and each item of the UPDRS III (in particular axial subscores $P < 0.001$; tremor $P < 0.001$; rigidity $P < 0.001$; bradykinesia $P < 0.001$).

A multiple linear regression analysis showed that OAB-q scores were significantly influenced by age and UPDRS-III ($R^2 = 0.139$; age $P = 0.006$, UPDRS-III $P = 0.002$; disease duration $P = 0.76$; H-Y staging $P = 0.16$), showing that older patients or higher UPDRS-III scores had worse OAB-q scores than younger or less affected patients.

A categorical statistical analysis to test the influence of drugs on the urinary function showed that the OAB-q scores were similar in patients receiving drug therapy with L-dopa, DA, L-dopa plus DA, and patients without therapy (χ^2 , $P = 0.9$). No significant differences in the urinary functions as assessed by each OAB-q item were found between patients receiving D1/D2 vs D2 dopamine agonists.

The L-dopa equivalent dose ranged between 100 and 1500 mg (mean 615.02 ± 324.45 mg) and was similar between men and women (mean \pm SD 636.0 ± 356.74 mg, 588.36 ± 277.10 mg; $P = 0.22$). Neither

TABLE 3. Statistical analysis: Statistical results of the Pearson's correlation analysis and significance (2-code) of the age, unified Parkinson's disease rating scale part III (UPDRS-III) values, overactive bladder questionnaire (OAB-q) scores, disease duration, and Hoehn-Yahr (H-Y) staging

| | | Age | UPDRS-III | OAB-q | Disease duration | H-Y staging |
|------------------|-------|-----|--------------|--------------|------------------|--------------|
| Age | r_p | – | 0.34 0.01 | 0.25 0.01 | 0.24 0.01 | 0.23 0.01 |
| UPDRS-III | r_p | – | – | 0.30 0.01 | 0.37 0.01 | 0.45 0.01 |
| OAB-q | r_p | – | – | – | 0.16 0.01 | 0.25 0.01 |
| Disease duration | r_p | – | – | – | – | 0.24 0.01 |
| H-Y staging | r_p | – | – | – | – | – |

Pearson analysis nor categorical analysis showed a correlation or association between the L-dopa equivalent dose and the OAB-q scores (Pearson correlation coefficient $P = 0.23$, $r = 0.071$; χ^2 $P = 0.2$). A subsequent correlation analysis between each OAB-q item and the L-dopa equivalent dose showed that the items 2, 5, and 6, relating to the nocturia symptoms, were significantly associated with the L-dopa equivalent dose (item 2: $r = 0.140$ $P = 0.049$; item 5: $r = 0.174$, $P = 0.014$; item 6: $r = 0.164$, $P = 0.021$) (Table 2).

Pearson analysis showed a significant correlation between the L-dopa equivalent dose and the UPDRS-III values ($P = 0.001$, $r = 0.194$) showing that patients with higher UPDRS-III score took a higher L-dopa equivalent dose.

In the group of healthy subjects Pearson's coefficient showed a significant correlation between mean OAB-q scores and age ($P = 0.038$) showing that older subjects had worse OAB-q scores than younger subjects.

DISCUSSION

In this study enrolling a large cohort of patients, we found that the OAB-q scores were significantly higher in patients with PD than in healthy subjects. An interesting finding came from the multiple linear regression analysis showing that OAB-q values in PD patients were significantly influenced by age and motor dysfunction assessed by the UPDRS-III. We found no statistical correlation between OAB-q scores and drug therapy or the equivalent L-dopa dose.

Our findings do not reflect differences between patients and healthy controls because the two groups had similar sex distribution and mean age. Nor do they reflect gender-related anatomical or disease differences

because men and women had similar mean age, OAB-q scores, disease severity calculated by H-Y staging, the UPDRS-III and disease duration. To exclude the possible influence of confounding factors on bladder symptoms, we also explicitly excluded healthy controls with a history of lower urinary tract or gynecologic disease and concomitant neurological diseases. In the group of patients, we included only subjects with a diagnosis of PD excluding secondary parkinsonism and other neurological diseases such as CBD and PSP. Finally, because it was difficult to exclude patients with possible MSA considering the context of the study on the urinary dysfunction, patients with concomitant other symptoms suggesting MSA were not enrolled. Moreover the significant correlation between OAB and disease duration we found, makes unlikely the possibility that the number of patients here tested with possible MSA was significant.

In our study, OAB-q scores were significantly higher in patients with PD than in healthy subjects, confirming previous findings that parkinsonian patients frequently have symptoms of bladder dysfunction the most frequent finding being detrusor hyperreflexia.¹⁷⁻²⁴ Urethral obstruction has also been described and attributed to poor sphincter relaxation.¹⁷⁻¹⁹ As expected, owing to the complexity of the urinary dysfunction in PD patients, when we first analyzed the statistical significance of our data for patients, we found a significant correlation between the OAB-q scores with age, disease duration, UDPRS-III scores, and H-Y staging. A subsequent linear regression analysis to investigate the role of the single variables on urinary dysfunction showed that in patients the OAB-q was significantly influenced by the UPDRS-III and age.

The correlation between OAB-q scores and age, though weaker in healthy subjects than in PD patients, confirms the age-related lower urinary tract dysfunctions described by others.²⁵⁻²⁸ A previous study comparing PD patients and age-matched subjects with urinary symptoms without neurological diseases²⁹ showed that apart from bladder capacity, which was reduced in both men and women with PD, all the other changes in bladder function were similar in both groups again suggesting that the alterations in urinary tract function are associated with age. PD patients also had higher OAB-q scores than age-matched healthy subjects and UPDRS-III scores had a significant influence on OAB-q scores strongly suggesting that another factor influencing urinary problems is the severity of motor dysfunction without different impact of the individual PD symptoms.

Our multiple linear regression model considering the correlation between OAB-q scores and the other inde-

pendent variables studied showed that the UPDRS-III scores significantly influenced the OAB-q score thus confirming that urinary dysfunction depends also on the severity of motor symptoms. Our findings agree with previous reports⁵ that the urinary dysfunction in PD is commonly noted along with motor disturbance (higher UPDRS total score and H-Y staging).³⁰

We found no correlation between OAB-q scores, drug therapy and L-dopa equivalent dose. Published reports yield inconsistent data on how dopamine affects detrusor hyperreflexia. For example, whereas some,²⁰ found a random effect of L-dopa on detrusor hyperreflexia or an inconsistent effect of apomorphine,¹⁹ others found that apomorphine and L-dopa improved hyperreflexia but left hyporeflexia unchanged,³¹ suggesting that urinary dysfunction in PD depends also on factors other than dopamine deficiency. Studies of animals with experimentally-induced parkinsonism have shown that depletion of dopaminergic neurones induces OAB and that D1-receptor agonists inhibit the micturition reflex in a dose-dependent manner, whereas D2-receptor agonists stimulate micturition.³²⁻³⁴ It may be speculated that detrusor hyperreflexia associated with Parkinson's disease results from activation failure of D1 receptors and that administration of D2 receptor agonists might worsen the condition. These findings may suggest that concurrent activation of D1/D2 receptors, rather than selective stimulation of D2 receptors, might be beneficial for treating urinary symptoms caused by detrusor hyperreflexia in PD. However, our data did not show significant differences in the urinary dysfunction between patients receiving D1/D2 vs D2 dopamine agonists. This result is in line with previous studies³⁵ demonstrating an unpredictable effect of the dopaminergic therapy on urodynamic parameters in PD. Moreover, the most of the patients here studied received more than one drug, therefore the heterogeneity and the combinations of drugs in our study group probably influenced the results making unlikely the estimation of differences in pharmacodynamics. Moreover, our study provides no information on dopamine-induced effects on urinary dysfunction given that unlike previous studies we did not compare the urinary symptoms in each subject before and after therapy. Finally, the significant correlation between the items of OAB-q relating to the nocturia symptom and L-dopa equivalent dose nevertheless confirms the main result of this study that the urinary symptoms are related to the severity of motor dysfunction as suggested by the significant correlation we found between the UPDRS-III scores and the L-dopa equivalent dose.

The large patient cohort considered in this study confirms the importance of urinary disorders in patients with PD and the usefulness of the OAB-q in assessing bladder symptoms in PD. Our observations reinforce the concept that the diagnostic work up of patients presenting with PD should include a detailed history to seek possible visceral symptoms. This diagnostic approach may help to clarify the pathophysiology of visceral dysfunction and could help to limit the development of severe bladder dysfunction that can severely worsen the patients' quality of life.

Our data also suggest that the OAB-q is a simple, easy, objective, and reliable test for evaluating urinary bladder function in patients with central nervous system diseases.

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