DOI: 10.1590/0004-282X20130101

ARTICLE

Urinary dysfunction with detrusor hyperactivity in women with Parkinson's disease cannot be blamed as a factor of worsening motor performance

Disfunção urinária com hiperatividade detrusora não é fator de risco para progressão do desempenho motor em mulheres com doença de Parkinson

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ABSTRACT

Introduction: Detrusor hyperactivity is the leading cause of urinary dysfunction in Parkinson's disease (PD). There are few studies correlating PD clinical aspects with this autonomic feature. **Methods:** A cohort of 63 women with PD were prospectively examined for assessment of clinical aspects and disease severity using unified Parkinson's disease rating scale and Hoehn-Yahr scale, respectively. The urologic function was evaluated by the urodynamic study. Two groups were categorized at this time – groups with and without detrusor hyperactivity. After seven years, the same parameters were re-evaluated. **Results:** Progression of the disease on mental scores was found in the group with detrusor hyperactivity. On follow-up, clinical symptoms and severity did not show significant worsening between the groups. **Conclusion:** Detrusor hyperactivity is a frequent urodynamic finding in PD, and even though it is associated with dopaminergic dysfunction, it cannot be blamed as a factor of worsening motor performance, but is probably associated with poor cognitive and mental prognosis.

Key words: detrusor overactivity, detrusor hyperreflexia, Parkinson's disease, urinary symptoms.

RESUMO

Introdução: Hiperatividade detrusora (HD) é a principal causa de disfunção urinária na doença de Parkinson e poucos estudos correlacionam aspectos clínicos da doença com este componente autonômico. **Métodos:** Foi avaliada uma coorte de 63 pacientes com DP quanto aos aspectos clínicos e gravidade global da doença utilizando as escalas UPDRS e Hoehn-Yahr. A função urológica foi avaliada através de estudo urodinâmico. Foram então categorizados dois grupos: pacientes com e sem HD. Após sete anos os mesmos parâmetros foram reavaliados. **Resultados:** Houve progressão da doença quanto aos escores mentais no grupo com HD. Na reavaliação dos grupos os sintomas motores não evidenciaram piora significante. **Conclusão:** HD é um achado urodinâmico frequente em pacientes com DP. Embora associada à disfunção dopaminérgica, HD não pode ser considerada fator de risco para piora do desempenho motor, mas provavelmente está associada com pior prognóstico mental e cognitivo.

Palavras-Chave: hiperatividade detrusora, hiperreflexia detrusora, doença de Parkinson, sintomas urinários.

Multiple clinical manifestations, besides movement disorders, are seen in Parkinson's disease (PD), presently considered a multisystem disease[1,2]. These manifestations include sexual, psychiatric, cognitive, and autonomic dysfunctions. Usually, autonomic features such as gastrointestinal and urinary disturbances increase with age, illness severity, drug use, postural instability, cognitive impairment, and visual hallucinations[3,4]. In association with the classic motor symptoms, these nonmotor manifestations are a signal of the pathological involvement of several circuits and neurotransmitters, which reach far beyond the striatal dopaminergic system[5,6], compromising cortical areas, midbrain, spinal cord, and peripheral autonomic nervous system[5,7], thus explaining the heterogeneity of PD with its different clinical forms in relation to the severity of motor and nonmotor symptoms[8].

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Conflict of interest: There is no conflict of interest to declare.

Received 26 November 2012; Received in final form 10 April 2013; Accepted 17 April 2013.

Urinary tract symptoms are highly prevalent in patients with advanced disease. It is estimated that 50% of the patients have significant symptoms of the lower urinary tract, with hyperreflexia or hyperactivity of the detrusor muscle or of the bladder[9]. Nevertheless, Uchiyama et al.[10] reported that urinary dysfunctions are common even in younger patients in the initial stages of the illness and not treated as yet. In this study, 64% of the patients had urinary dysfunctions. Considering only the PD women group, 50% had urinary symptoms. Bladder hyperactivity includes irritative urinary symptoms[11,12], increase in daytime urinary frequency, nocturia, and urgency with or without urge incontinence[13,14]. Such symptoms usually become more pronounced in PD due to the bradykinesia, thus leading to a decrease in patients' quality of life[15]. PD patients with lower urinary tract symptoms require urodynamic evaluation to establish the neurologic origin of the urinary dysfunctions[16]. Detrusor hyperreflexia or detrusor hyperactivity (DH) is determined by autonomic mechanisms that cause spontaneous involuntary contractions of the bladder detrusor muscle, being the most common urodynamic finding in PD patients with urinary dysfunction[17] and can be detected by cystometry during the bladder filling phase[18,19].

Increase in prevalence of PD has led to an increase in the number of advanced cases of the disease[20], in which the nondopaminergic symptoms acquire great significance, equal to or even higher than the motor symptoms, in quality of life. Autonomic dysfunction also has impacted significantly on the global progression of PD[6]. Up to now, we have limited knowledge on the demographic or clinical aspects that determine or have influence over the progression rate of PD and its different symptoms. More studies are necessary to analyze prospectively the severity of the illness correlating nonmotor aspects. The presence of autonomic symptoms has not been sufficiently studied as to its value in relation to the prognosis of the disease. We haven't found longitudinal studies about the progression of the disease according to the presence of urinary disturbance. The purpose of this long-term study is to verify the DH prevalence in women affected by PD, to analyze its association with clinical aspects, and, in a prospective way, to evaluate DH as a prognostic factor in the progression of the disease.

METHODS

An observational prospective cohort study of 63 women aged less than or equal to 80 years selected among patients with PD and with lower urinary tract symptoms who were seen consecutively in a public neurologic clinic in 2004 was conducted. Only patients with idiopathic PD who met criteria for diagnosis of the United Kingdom Parkinson's Disease Society (UKPDS) Brain Bank were included[21]. Secondary parkinsonism and other atypical degenerative parkinsonism were excluded. A brain magnetic resonance imaging was performed in all participants as exclusion criteria. Patients who still met criteria for DSM-IV dementia[22] or scale score Schwab and England equal to or less than 60% were also excluded, as well as patients with parkinsonism associated with cerebrovascular disease, early or severe postural instability, lower urinary tract disease, gynecological disorders, and a history of pelvic surgery.

On the initial evaluation in 2004, all patients were examined without levodopa therapy or other dopaminergic medications for at least 15 hours. The unified Parkinson's disease rating scale (UPDRS) and Hoehn-Yahr (HY) scale were used to assess neurological symptoms and the stage of disease severity, respectively. Only the sector I (mental health, cognition, and humor) and sector III (UPDRS motor evaluation) were used for the assessment. Sector I and sector III total scores, the scores of the individual items *(tremor, rigidity, and bradykinesia)*, and the sum of *axial* sign-specific subitems (*posture, gait, and postural instability*) were studied. Lower urinary tract symptoms were assessed by the scale of the American Urological Association, the International Prostate Symptoms Scale (IPSS), always applied with the assistance of the same examiner. Patients scoring 3 or more points in this scale underwent urodynamic evaluation that consisted of uroflowmetry, postmiccional volume measurement, residual urine, and cystometry. The sample was divided into two groups depending on the presence or absence of DH.

In 2011, after a second application of the criteria of the UKPDS, the cohort consisted of 43 patients, with the drop-out of 20 patients due to 7 deaths, 2 cerebrovascular complications, 1 loss of clinical data, 1 refusal to continue in the study, and nonlocation of 9 patients. Thirteen of this drop-out patients had DH. All were reexamined with the UPDRS part I and part III and the HY scale.

We conducted a prospective, longitudinal, and analytical study. For descriptive analysis and frequency tables, measures of location and dispersion were used. In the tables, the data are represented as mean±standard deviation. Differences between groups were compared statistically using the Wilcoxon/Mann-Whitney test. The significance level was 5%. This study was approved by the local ethics committee, and all subjects assigned an informed consent.

RESULTS

Baseline

The cohort study consisted of 63 women with a mean age of 64.1±10 years and mean duration of disease of 5.4±4.4 years. The urinary symptoms quantified by using the IPSS reached the average of 8.1±4.7 points. In this phase of the study, 32 patients had detrusor overactivity (50.8%). The demographic and clinical data of the groups are summarized in Table 1. The

DH group had a mean age of 65.0±9.6, while the nondetrusor hyperactivity (NDH) group had a mean age of 63.1±10.4 (no difference was observed between groups). Disease duration was also similar between groups.

The scores of lower urinary tract symptoms were compared between groups with significant differences (Table 1, IPSS-total), with predominating high scores in the DH group (p<0.001). In relation to disease severity measured by UPDRS III motor, we observed significant difference between groups (p<0.001), higher in the DH group, and also to the stage of PD severity measured by HY scale (p=0.003). The motor symptoms were also studied individually through the cardinal signs of the disease. It has been shown that tremor, rigidity, and bradykinesia were significantly more severe in patients with DH. In this phase of the study, the axial signs (Axial-S in Table 1) showed no difference between groups.

Follow-up

The clinical and demographic data from the cohort reassessed are summarized in Table 2 according to urodynamic findings. The DH group consisted of 19 patients and the NDH group composed of 24 patients. The groups were similar in demographic data. The UPDRS I mental scores and the motor findings quantified by UPDRS III scored significantly higher in the DH group. The key motor symptoms and the axial signs were more severe in the DH group, which was also more affected in the disease severity (HY scale).

Progression

To evaluate the degree of progression of PD, we calculated the differences (*d*-) between the scores in the final evaluation (2011) and baseline (2004). The mean of the differences are summarized in Table 3. The findings revealed that the differences in mental scores by *d*-UPDRS I were significantly higher in the DH group. They also showed that the differences (*d*-UPDRS III motor, *d*-HY and *d*-Axial-S scores) were similar between the groups.

Table 1. Demographic and clinical data obtained at the initial evaluation – 2004.

	Groups (n=63)		p-value
	DH (n=32)	NDH (n=31)	
Age	65.0±9.6	63.1±10.4	0.432
Duration of disease	5.9±4.7	5.02±4.2	0.365
IPSS-total	11.0±4.2	5.1±2.9	<0.001
UPDRS I – mental	2.5±1.3	1.9±1.5	0.107
UPDRS III – motor	39.9±15.7	26.8±13.8	<0.001
Tremor	7.1±4.3	4.3±3.4	0.007
Rigidity	7.4±3.1	5.0±3.0	0.009
Bradykinesia	17.4±7.3	12.2±7.0	0.018
Axial-S	4.2±2.2	3.1±1.5	0.084
Hoehn-Yahr	2.2±0.7	1.7±0.5	0.003

The data are represented as mean±standard deviation. Differences between groups were compared using Wilcoxon/Mann-Whitney test.
DH: detrusor hyperactivity; NDH: nondetrusor hyperactivity.

Table 2. Demographic and clinical data obtained at the final evaluation – 2011.

	Groups		p-value
	DH	NDH	
Age	71.5±8.3	70.3±10.1	0.806
Duration of disease	12.0±4.2	11.7±4.1	0.615
UPDRS I – mental	5.3±2.5	2.8±2.27	0.001
UPDRS III – motor	51.1±18.0	36.8±13.7	0.003
Tremor	9.3±5.5	5.2±4.6	0.003
Rigidity	9.1±4.0	6.2±2.7	0.006
Bradykinesia	22.2±7.3	16.6±6.6	0.013
Axial-S	6.47±2.45	4.91±2.44	0.015
Hoehn and Yahr	2.47±0.6	2.1±0.5	0.036

The data are represented as mean±standard deviation.
DH: detrusor hyperactivity; NDH: nondetrusor hyperactivity.

DISCUSSION

PD is characterized by the presence of clinical forms with various associations of motor and nonmotor signs and symptoms evolving with variable progression rates. The issue of clinical heterogeneity has been studied by analyzing subgroups distinguished by age, progression, and clinical symptoms associated with motor patterns, such as dementia, depression, and autonomic symptoms. In a recent European systematic review conducted by van Rooden et al.[23], clinical forms have been grouped into four subtypes categorized by differences in severity of nondopaminergic aspects and motor complications[23]. Characterization of subtypes and the evolution of the disease can define the prognosis and determine therapeutic strategies, creating a growing demand to identify nonmotor clinical aspects of PD such as urinary dysfunction and determine its role as a prognosis factor. Urinary dysfunction becomes prevalent and disabling with great impact on the quality of life as the disease progresses and can be found even in the early stages of the disease[10].

Table 3. Progression of the disease evaluated through the mean of the differences between scores (2011–2004).

Differences 2011–2004	Groups		p-value
	DH	NDH	
d-UPDRS I – mental	2.6±2.4	0.8±1.8	0.008
d-UPDRS III – motor	12.5±12.2	10.3±13.7	NS
d-Tremor	2.2±4.0	0.9±3.4	NS
d-Rigidity	1.7±2.6	1.2±2.8	NS
d-Bradykinesia	4.7±4.3	4.3±5.6	NS
d-Axial-S	2.2±1.8	1.7±2.5	NS
d-Hoehn–Yahr	0.38±0.5	0.4±0.5	NS

The data are represented as mean±standard deviation.
DH: detrusor hyperactivity; NDH: nondetrusor hyperactivity;
NS: nonsignificant.

In this prospective study of a cohort of women with PD that underwent urodynamic study, DH was present in 50.8% of the sample cases, consistent with findings from studies of prevalence in women[18]. In the initial assessment, the sample was divided in two groups according to the presence or not of DH and who were followed for at least seven years. A long-term assessment estimates progression of degenerative diseases more accurately and it helps to exclude patients with nonidiopathic parkinsonism. On the other hand, part of bladder hyperactivity in the elderly older than 65 years can be a result of latent cerebral vascular changes, which can be a comorbidity in this sample. Also, short duration of follow-up limits the ability to detect important prognostic factors in a disease that often lasts more than a decade. The groups were similar with regard to demographic aspects but differed significantly in the intensity of urinary symptoms in DH which is strongly associated with the findings of DH during cystometry and consistent with previous studies that have demonstrated[24] prevalence of irritating lower urinary tract symptoms in PD.

At the baseline, it was observed that the group with DH was associated with a more advanced stage and a motor performance significantly impaired. When the key symptoms of the disease — tremor, rigidity, and bradykinesia — were compared, there was a significant involvement in the group with overactive bladders, suggesting that DH was associated with greater severity of motor symptoms. This can be attributed to greater dopaminergic depletion. Dopamine that activates the striatal D1 receptors has an indirect inhibitory effect on the micturition reflex and a decrease in inhibition of the reflex results in DH[25]. Axial impairments were similar between the groups. Axial symptoms are not related to dopaminergic depletion, and ambulatory quantitative assessment of gait patterns and postural response is an appropriate tool in trials of PD progression, independent of the medication status. In addition to the PD disease process, ageing appears to play a substantial role in the pathogenesis of these nonmotor symptoms in PD.

In the follow-up, the DH group suffered a greater dropout but remained similar to the group without DH in age and duration of illness. In patients with overactive bladders, the mental performance was compromised linearly in association to the motor performance captured by UPDRS III whose scores, according to Greffard et al. The analysis of the key symptoms of the disease — tremor, rigidity, and bradykinesia — also showed clear and meaningful involvement in these patients who were also categorized as more severe by the stage of Hoehn and Yahr. These data reinforce the thesis of the association between overactive bladder with dopaminergic damage. Otherwise in the follow-up, we found impaired axial symptoms performance in DH group showing involvement of other nondopaminergic systems.

Little is known about the beginning and progression of symptoms and markers in PD. Strategies to analyze the progression of diseases use studies that measure the deterioration or improvement of motor aspects, the presence of nonmotor symptoms, variation in time, and the presence of other clinical comorbidities that influence the overall evolution of the disease. The quick progression of dopaminergic dysfunction in the early years of the disease seems to contrast with the reduction of progression in the later stages and with the increase of nonmotor symptoms. Alves et al. emphasized the need for long-term prospective studies in representative cohorts using standardized rating scales to provide valid information about prognostic factors and the progression of functional decline in patients with PD[27]. For assessment of disease progression, the differences between the scores obtained in the final and the initial assessment were analyzed. The degree of progression of mental functions was analyzed using the differences in the UPDRS I scores. A significant progression of mental impairment in the DH group was observed. The subscale scores used are sensitive though not very specific to detect cognitive impairment and dementia, because they group mental functions of different domains evaluating cognitive functions, thought, mood, and behavior. There are still limitations in sample selection such as the exclusion of patients with dementia based on clinical criteria. Among the patients who dropped out, 65% had DH. It was not possible to obtain a detailed study of the deaths, more frequent in DH, which might have underestimated the actual global progression of the disease.

The degree of global motor dysfunction and severity progression observed in the group with DH was no different in relation to patients without this autonomic cystometric dysfunction. In addition, there was a similarity between the magnitude of the progression of each key symptom — bradykinesia, tremor, and rigidity — as with axial symptoms of disease between the groups. We believe our results are preliminary and need to be replicated in more representative samples of patients studied since the diagnosis and with more frequent and elaborated outcome assessment including motor and nonmotor complications and progression to dementia. The evolution of mental functions will be the subject of a retrospective study using more appropriate scales than those that were applied, to evaluate cognitive outcome and dementia. We conclude that DH is a frequent condition in patients with PD, and even though it is associated with dopaminergic dysfunction, it cannot be characterized as a factor of worsening motor performance, but is probably associated with worse cognitive and mental prognosis.

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