Parkinsonism and Related Disorders 33 (2016) 65–71

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Orthostatic hypotension in Parkinson's disease: Does it matter if asymptomatic?

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ARTICLE INFO

Article history:
Received 31 July 2016
Received in revised form
31 August 2016
Accepted 10 September 2016

Keywords:
Parkinson's disease
Autonomic
Syncope
Orthostatic hypotension
Supine hypertension

ABSTRACT

Introduction: Orthostatic hypotension (OH) may frequently be asymptomatic in patients with Parkinson's disease (PD). However, the relationship between symptomatic/asymptomatic status and functional disability remains unclear.

Methods: Using orthostatic blood pressure (BP) measurements and the Orthostatic Hypotension Symptom Assessment (OHSA) questionnaire, 121 consecutive PD patients without history of chronic hypertension and not taking alpha-adrenergic antagonists for bladder disorders were classified according to (1) OH symptomatic status, based on presence/absence of orthostatic symptoms (symptomatic OH: OHSA item 1 $\geq$ 1), and (2) OH severity, based on the magnitude of BP fall on the lying-to-standing test: OH- (<20/10 mmHg); moderate OH+ ($\geq$20/10 mmHg but < 30/15 mmHg); and severe OH+ ($\geq$30/15 mmHg). The primary endpoints were the activities of daily living/instrumental activities of daily living (ADL/iADL) and the Ambulatory Capacity Measure (ACM). Secondary endpoints included PD quality of life (PDQ-8) and prevalence of falls.

Results: The overall prevalence of OH+ was 30.6% (37/121 patients), with 62.2% symptomatic (23/37) and 37.8% asymptomatic (14/37). Symptomatic and asymptomatic OH + patients had similar impairments in ADL/iADL and ACM, significantly worse than OH- ($p \leq 0.035$). There was a trend for worse ADL/iADL and ACM scores in severe OH + compared to moderate OH+, but both were worse than OH- ($p \leq 0.048$). Symptomatic and asymptomatic OH + showed similar impairment in PDQ-8 and higher prevalence of falls compared to OH-.

Conclusions: Asymptomatic OH+ was associated with similar impairments in ADL/iADL and ACM than symptomatic OH+. These findings support screening for OH in PD patients regardless of postural lightheadedness.

1. Introduction

Orthostatic hypotension (OH) may predate or follow the onset of motor symptoms in Parkinson's disease (PD), with an estimated prevalence of 30–50% [1,2]. Only one half of PD patients with OH report the classic orthostatic symptoms, namely "dizziness, lightheadedness, feeling faint, or feeling like you might black out while standing", as recorded in item 1 of the Orthostatic Hypotension Symptoms Assessment [OHSA] [3], which is used to define symptomatic OH. Most cases remain asymptomatic or experience these symptoms only under conditions of increased orthostatic stress, such as the postprandial state, raised ambient temperature, and physical exercise [2]. Asymptomatic OH, often recognized serendipitously, is managed less aggressively than symptomatic OH, first because of its unclear clinical relevance and, second, due to the risk of treatment-induced and baroreflex impairment-related supine hypertension (SH) [4]. The complex relationship between OH-

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http://dx.doi.org/10.1016/j.parkreldis.2016.09.013
1353-8020/

associated symptomatic status, functional impairment, and the magnitude of blood pressure (BP) fall remains to be clarified. In this cross-sectional study we assessed the impairment on activities of daily living (ADL) and ambulatory capacity measure (ACM) in patients with and without OH (OH+ and OH-) according to their symptomatic state (symptomatic vs. asymptomatic), and OH severity (moderate [≥ 20/10 mmHg but < 30/15 mmHg] vs. severe [≥ 30/15 mmHg]). Our aim was (1) to examine the differential severity and disability between symptomatic and asymptomatic OH, as compared to OH-; and (2) to evaluate the correlation between the severity of OH and the extent of ADL/iADL and ACM functional impairment.

2. Materials and methods

2.1. Participants and study design

We consecutively screened 160 patients between April 2015 and March 2016 from two specialized Movement Disorder Centers (University of Cincinnati and University of Turin). Inclusion criteria were idiopathic PD, meeting UK Brain Bank criteria [5]; Hoehn and Yahr (H&Y) stage I-IV; age between 30 and 85 years old; and stable doses of dopaminergic treatment for at least four weeks prior to enrollment.

Exclusion criteria were diabetes mellitus or other diseases potentially associated with autonomic dysfunction; treatment with antihypertensive drugs and/or treatment with alpha-adrenergic antagonists for bladder disorders; and any atypical features lowering the diagnostic certainty of PD. The local institutional review boards approved the study and all participants gave written informed consent.

2.2. Clinical evaluations

Patients were evaluated by means of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [6] and a battery of clinical scales/questionnaires assessing the following domains: ADL impairment: ADL scale [7], iADL scale; gait impairment: Ambulatory Capacity Measure (ACM) [8], a construct already used in previous clinical trials (NET-PD) [9] calculated as the sum of items 13, 14, 15, 29, 30 of the UPDRS; Freezing of Gait Questionnaire (FOGQ) [10]; non-motor symptoms: Non-Motor Symptom Scale (NMSS) [11]; autonomic symptoms: Scale for Outcome in Parkinson's disease-Autonomic (SCOPA-AUT) [12]; Orthostatic Hypotension Questionnaire (OHQ = Orthostatic Hypotension Daily Activities Scale [OHDAS] + Orthostatic Hypotension Symptom Assessment [OHSA]) [3]; fatigue: Parkinson's fatigue scale (PFS-16) [13]; quality of life: PD Quality of life questionnaire (PDQ-8) [14]; cognitive function: Montreal Cognitive Assessment (MoCA) [15]; and mood: Beck Depression Inventory (BDI) [16]. Lastly, subjects underwent a structured diagnostic interview, aiming at assessing for the presence of falls in the previous 6 months, dopamine agonists and levodopa equivalent daily dosage (LEDD), and medications taken in the previous 4 weeks.

2.3. Blood pressure measurements

BP measurements were performed using an automated sphygmomanometer (HEM-7200 – Omron Healthcare Co. Kyoto Japan) placed at heart level on the left arm, evaluating patients in the following conditions: a) while sitting in a chair after at least 10 min of rest (average of two measurements); b) after a minimum of 10 min of supine rest (supine BP was calculated as the average of two measurements); c) after 1 and 3 min of standing. All patients were evaluated in the morning in their best ON state, defined as a period of perceived maximal efficacy of dopaminergic medications, at least 2 h after the assumption of the last medication and 3 h after the last meal.

Criteria and definitions: OH was defined as a fall in systolic BP of at least 20 mmHg or diastolic BP of at least 10 mmHg within 3 min of standing [17]. OHSA item 1 (severity of dizziness, lightheadedness, feeling faint, or feeling like you might blackout resulting from low blood pressure; score 0–10) was used to define symptomatic OH (OHSA item 1 ≥ 1) and asymptomatic OH (OHSA item 1 = 0). In addition, patients were classified as moderate OH + or severe OH + according to the magnitude of BP fall: Moderate OH+ was defined as a fall in systolic BP ≥ 20 mmHg but <30 mmHg, or diastolic BP ≥ 10 mmHg but <15 mmHg within 3 min of standing; Severe OH+ was defined as a fall in systolic BP ≥ 30 mmHg or diastolic BP ≥ 15 mmHg within 3 min of standing [2,18]. In the absence of consensus criteria, diurnal SH was defined as supine systolic BP ≥ 150 mmHg or diastolic BP ≥ 90 mmHg [19] in patients without hypertension while sitting. Supine BP and OH data were used to subcategorize patients into: OH+/SH+, OH-/SH+, OH-/SH- or OH+/SH-.

2.4. Outcome measures and statistical analyses

Primary endpoints included ADL/iADL impairment and ACM. Analysis of covariance (ANCOVA) was used to evaluate differences in dependent variables (ADL/iADL and ACM), adjusted for MoCA score and disease duration (covariates), with the following independent variables: (a) symptomatic state: OH-; asymptomatic OH+; symptomatic OH+; (b) OH severity: OH-; moderate OH+; severe OH+. Secondary endpoints included MDS-UPDRS sections 1-4, PDQ-8, prevalence of falls, PFS-16, BDI, NMSS, OHQ, and SCOPA-AUT, sub-classifying patients in accordance with: (a) symptomatic state; (b) OH severity; and (c) presence/absence of comorbid diurnal SH. Moreover, ANCOVA analysis was also used to evaluate differences in MoCA scores (adjusted for age and disease duration) between patients with and without OH (symptomatic and asymptomatic). Mann-Whitney, Kruskal Wallis, and Fisher's test were used for comparisons between groups. Bonferroni's correction was applied in post-hoc analyses and ANCOVA assumption of homogeneity of regression slopes was verified. Statistical tests were performed using SPSS 21.0 for Macintosh. The significance threshold was at 0.05 using two-tailed p-values.

3. Results

3.1. Patients

The cohort consisted of 121 consecutively consenting PD patients (57.0% males; 43.0% females) treated with L-dopa (76.0%), dopamine agonists (38.0%), MAO-B inhibitors (9.1%), and COMT inhibitors (7.4%). The overall prevalence of OH+ was 30.6% (37/121 patients), with 62.2% symptomatic OH+ (23/37) and 37.8% asymptomatic OH+ (14/37). Among OH + patients, 48.6% (18/37) had moderate OH+, and 51.4% (19/37) severe OH+ (BP fall range: 20/10–65/32 mmHg), with a prevalence of OH symptoms of 50.0% (9/18 patients) in moderate OH+ and 73.6% (14/19 patients) in severe OH+ ($p = 0.138$). The prevalence of diurnal SH was 27.3% (33/121 patients).

3.2. ADL/iADL impairment

3.2.1. Symptomatic state (OH- vs. symptomatic OH + vs. asymptomatic OH+)

ADL and iADL scores differed in the three groups (Fig. 1A) (ADL: $F(2, 116) = 6.7$; $p < 0.001$; iADL: $F(2, 116) = 11.4$; $p = 0.006$). In post-hoc analyses, both symptomatic and asymptomatic