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Symptomatic orthostatic hypotension in Parkinson's disease patients: Prevalence, associated factors and its impact on balance confidence

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ABSTRACT

Background: Orthostatic hypotension (OH) is a commonly reported sign of the cardiovascular autonomic dysfunctions associated with Parkinson's disease (PD). Patients might suffer from a variety of the clinical symptoms of OH, including dizziness, lightheadedness, or problems with vision and fatigue.
Objectives: To determine the prevalence of, and factors associated with, symptomatic orthostatic hypotension (OH) in Parkinson's disease (PD) and to identify any relationships between the clinical symptoms of OH and balance confidence in this patient population.
Methods: Symptomatic OH was defined as a systolic or diastolic BP fall of ≥ 20 or ≥ 10 mmHg respectively, within 3 min of standing and an Orthostatic Hypotension Questionnaire (OHQ) score of more than zero. Factors related to symptomatic OH were identified from a multivariate logistic regression analysis. Pearson's correlation test was used to reveal any relationships between the clinical symptoms of OH and a patient's confidence in their ability to balance, assessed using the Activities-specific Balance Confidence (ABC) scale.
Results: 100 Thai PD patients were consecutively recruited into this study. The prevalence of symptomatic OH was 18%, asymptomatic OH was 4%, while 78% were patients without OH. Factors associated with symptomatic OH were age (OR, 95%CI: 1.06, 1.003–1.115, p = 0.038) and hypertension (OR, 95%CI: 6.16, 1.171–32.440, p = 0.032). A significant and negative correlation (r = −0.229, p = 0.022) between OHQ composite scores and item 3 of the ABC scale (picking up slippers from floor), one of the movements in a vertical orientation, was found.
Conclusion: Elderly PD patients and with a co-morbidity of essential hypertension should be closely evaluated for the presence of symptomatic OH. In addition, they should be advised to change positions slowly, especially those in a vertical orientation.

1. Introduction

Orthostatic hypotension (OH), a sign of cardiovascular autonomic dysfunction, is one of the commonly occurring nonmotor problems in patients with PD [1], with, according to a meta-analysis, a prevalence of 30.1% (95% CI: 22.9% to 38.4%) [2]. The consensus statement of the American Autonomic Society (AAS) and American Academ y of Neurology (AAN), defines OH as a sustained fall of ≥ 20 mmHg in systolic or ≥ 10 mmHg in diastolic blood pressure (BP) within 3 min of active standing or head-up tilt to at least 60°[3]. The clinical symptoms of OH include dizziness, lightheadedness, problems with vision, generalized weakness, fatigue, trouble concentrating, head/neck discomfort or, in worst cases, syncope [4]. OH has both neurogenic (due to failure of the autonomic nervous system (ANS) to regulate blood pressure in response to postural change, as a result of an inadequate release of norepinephrine (NE) from postganglionic sympathetic nerves) and non-neurogenic causes [5,6]. OH in PD is mostly due to postganglionic sympathetic denervation resulting in efferent baroreflex failure (i.e., neurogenic OH) [7,8]. Other non-neurogenic causes, such as intravascular volume depletion, medications, or cardiac failure, can also contribute to OH in PD [5,9], and should be identified first [5]. In addition, some studies have reported predisposing factors to OH in PD

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patients, including a more advanced disease stage, longer duration of PD [10], male gender [11–13], older age, posture and gait instability, low mini-mental state examination scores and visual hallucinations [14]. Also, the use of antiparkinson medications, including L-DOPA, dopamine agonists, and monoamine oxidase-B (MAO-B) inhibitors have been shown to reduce BP [15]. Higher doses of dopaminergic medication [16] and use of combined therapies [17] increase the risk of OH. This hypotensive effect of antiparkinson medication can be observed at the beginning of therapy and is usually tolerated [18] or can be addressed by dose adjustments [19].

OH is associated with significant morbidity and mortality in both working age adults and elderly people, with or without PD. It has been shown that OH is a predictor of ischemic stroke in middle-aged people (age range of 53–57 year olds) without a history of neurological medical problems and who did not suffer from stroke and/or heart disease at baseline assessments [20]. In addition, Ooi found that OH increased the risk of falls (RR = 2.1) in the elderly [21]. In PD, it was found that PD patients suffering with OH had an increased risk of postural sway when standing compared with those without OH [22]. Also, OH was found to be the direct cause of falls in 4.1% of PD patients [23]. Using the Activities-specific Balance Confidence (ABC) Scale, a 16-item scale used to assess balance confidence when performing activities at home or in areas external to the home environment [24], it has been shown that a lower self-perceived balance confidence level is associated with falls in the elderly [25] and in PD patients [26]. In addition, items 3, 6 and 9 of the ABC scale are predictors of falls in PD patients [27].

OH in PD can be symptomatic or asymptomatic, depending on the magnitude of the reduction in BP and an individual patient's ability to compensate for the reduction. Most people who are symptomatic for OH have a much greater fall in BP on standing and those who have an impairment of the compensatory systems in the body, including activation of the sympathetic nervous system, the renin-angiotensin system, and/or the aldosterone system are more likely to be symptomatic for OH [1]. Recently it has been shown that symptomatic OH is also associated with an impairment of activities of daily living (ADL), instrumental activities of daily living (iADL), and the Ambulatory Capacity Measure (ACM) [28]. However, little information related to symptomatic OH is available in PD and, so far, only one study has investigated its prevalence and characteristics [29]. In this study, we aimed to expand the knowledge about symptomatic OH in terms of its prevalence, associated factors and the correlation of its clinical symptoms with the level of balance confidence in PD patients.

2. Methods

2.1. Subjects

A cross-sectional study was conducted at Chulalongkorn Center of Excellence for Parkinson's disease and Related disorders, King Chulalongkorn Memorial Hospital. We consecutively recruited 100 PD patients during the period between May and August 2015. Inclusion criteria included idiopathic PD meeting the United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB) diagnostic criteria; Hoehn and Yahr (H&Y) stage 1–4; and stable on drug therapy or had not received any drug modifications (dopaminergic treatment and other medications) for at least four weeks prior to enrollment. We excluded bedridden idiopathic PD patients or those in the nursing homes; patients with other neurogenic OH, including pure autonomic failure (PAF), multiple system atrophy (MSA), progressive supranuclear palsy (PSP) or an autonomic neuropathy; and patients who were treated with antihypotensive drugs (fludrocortisone, droxidopa or midodrine). Diagnosis of patients was performed by the movement disorder neurologists. The local institutional review boards approved the study, and all participants gave written informed consent prior to the study. Demographic data, medical conditions, list of medications, and the daily doses of all current medications were recorded.

2.2. Procedures

Blood pressure (BP) was recorded by autonomic sphygmomanometer (Omron® HEM-7200). BP was measured after 10 min resting in a sitting or supine position, then patients were asked to stand and, within 3 min, BP was recorded while the patient remained in a standing position. OH was defined by consensus as a fall in systolic BP (SBP) or diastolic BP (DBP) of ≥ 20 or ≥ 10 mmHg after standing within 3 min [3]. All patients took their regular morning treatment and had a regular breakfast or lunch at least 2 h before the BP measurement. The Orthostatic Hypotension Questionnaire (OHQ) was used to assess the presence of OH symptoms and the impact of OH symptoms on daily activities in the past seven days [30]. The OHQ had been translated into Thai language and used in this study (Cronbach's alpha reliability of the questionnaire was 0.759). In this study, the researcher asked the patients in Thai and recorded the scores.

The OHQ consists of two parts: OHSA (Orthostatic Hypotension Symptom Assessment) and OHDAS (Orthostatic Hypotension Daily Activities Scale). The OHSA assesses symptoms of OH using six subjective items; 1) Dizziness, lightheadedness, feeling faint, or feeling like you might black out, 2) Problems with vision (blurring, seeing spots, tunnel vision), 3) Generalized weakness, 4) Fatigue, 5) Trouble concentrating, and 6) Head/neck discomfort. The OHDAS assesses the impact of OH symptoms on daily activities and consists of four items (impact on standing for short (item 1) or long (item 2) periods of time, impact on walking for short (item 3) or long (item 4) periods of time). Each item was scored on an 11-point scale from 0 to 10, with 0 indicating no symptoms/no interference and 10 indicating the worst possible symptoms/complete interference. The composite OHQ score was calculated by averaging the OHSA and the OHDAS [30].

Using BP measurement and OHQ score, patients were categorized into 4 different groups. “symptomatic OH” was acknowledged when the subject had a BP fall according to manometric definition and composite OHQ score of more than zero, while “asymptomatic OH” was defined when the subject had a BP fall according to manometric definition, but composite OHQ score was zero. The other 2 groups were subjects who did not have BP fall according to manometric definition and their composite OHQ score can be zero or more than zero. These 2 groups were classified in this study as “patients without OH” because they did not have BP fall according to manometric definition regardless of composite OHQ score.

The self-perceived balance confidence level was measured using the Activities-specific Balance Confidence (ABC) scale [24]. The Thai validated ABC scale (Cronbach's alpha 0.952) was used in this study [27]. Patients rated their level of balance confidence from 0 (no confidence at all) to 100 (full confidence) if they were to complete each of 16 activities of daily living. Scores for each activity and collectively for all 16 activities were calculated, with a minimum score of 0 to a maximum of 100. Low ABC scores reflect a low level of balance confidence or increased fear of falling [24].

The Thammasat University Non-Motor Symptoms Questionnaire (TU-NMSQuest) was used to determine the presence of non-motor symptoms (NMS) in the PD patients. TU-NMSQuest is the Thai validated NMS questionnaire (Cronbach's alpha 0.835) consisting of 40 non-motor symptoms (items) grouped into 10 domains [31]. Patients chose the response “yes” or “no” to indicate if they do or don't experience each item of the NMS domains. The number of yes responses for each domain and for all of the domains was determined.

All measurements (BP, OHQ score, ABC score and TU-NMS score evaluations) were collected from individual patients at one point in time. Factors analyzed for an association with symptomatic OH were: age; gender; duration of PD symptoms; disease severity (Hoehn & Yahr stage); co-morbidities; antiparkinson drug use; levodopa daily dose; levodopa equivalent daily dose (LEDD); dopamine agonist levodopa

equivalent daily dose (DALEDD); and polypharmacy (intake ≥ 5 medications).

Protocol and consent forms were approved by the Human Subjects Ethics Committee of the Faculty of Medicine, Chulalongkorn University on April 2015. All subjects gave their written informed consent in accordance with the declaration of Helsinki.

2.3. Statistical analysis

Statistical analyses were performed using SPSS version 21.0. Categorical data were analyzed using Chi-square analysis. For bivariate comparisons between symptomatic OH and patients without OH groups, categorical data were analyzed using Chi-square analysis and numerical data were analyzed using unpaired Student's *t*-test. Univariate logistic regression analysis was used to calculate odds ratios with 95% confident intervals for each variable, and the potential factors (p-value ≤ 0.25) were entered into the multivariate analyses. Multivariate logistic regression analysis with backward stepwise procedure was performed to determine the concomitant independent factors relating to symptomatic OH. Model's goodness of fit was explored by the Hosmer & Lemeshow score and multicollinearity was absent. Pearson's correlation test was used to assess the correlation of ABC score versus OHQ composite score. A p-value < 0.05 was considered as statistically significant.

3. Results

One hundred patients (53 women and 47 men) with an average age (± SD) of 65.5 ± 11.6 years entered the study. The average (± SD) age of disease onset and PD duration were 56.3 ± 13.4 and 9.2 ± 6.1 years, respectively. The average H&Y stage (± SD) was 2.4 ± 0.7. The number of PD patients in each H&Y stage were 7 (stage 1), 5 (stage 1.5), 16 (stage 2), 40 (stage 2.5), 26 (stage 3), and 6 (stage 4), with no significant difference in the number of each category of patients at those stages. In terms of antiparkinson medication, the average (± SD) number of medications received by patients was 3 ± 1 items, with mean (± SD) daily levodopa dose of 658 (± 319) mg, a levodopa equivalent daily dose (LEDD) of 836 (± 438) mg, and dopamine agonist levodopa equivalent daily dose (DALEDD) of 175 (± 194) mg. Twenty three percent of patients were taking monotherapy (levodopa), and 77% were on combination therapy, including two-drug (32%), three-drug (34%), four-drug (10%) and five-drug (1%) combinations. Co-morbidities found in patients were hypertension (26%), diabetes mellitus (13%), depression (11%), psychosis (8%), ischemic heart disease (9%), ischemic stroke (2%) and dementia (6%).

3.1. Prevalence of symptomatic OH, blood pressure, and OHQ score

According to the characterization of patients using BP measurement and OHQ score, there were 18 patients with symptomatic OH, 4 patients with asymptomatic OH and 78 patients without OH. Therefore, the prevalence of OH was 22%, composing of a symptomatic OH prevalence of 18% and an asymptomatic OH prevalence of 4%, and a prevalence of patients without OH of 78%. Of the 78 patients who had a BP change that did not meet manometric definition, 42 patients had OHQ score more than zero and 36 patients had OHQ of zero.

Regarding the postural BP change of the 18 symptomatic OH, there were 5 patients whose both SBP and DBP reductions met the manometric OH criteria, while there were 4 patients met the SBP reduction criteria only and 9 patients who met the DBP reduction criteria only. The symptomatic OH group had a mean SBP (± SD) decrease of 15.8 (± 8.5) mmHg (p = 0.001) and mean DBP (± SD) decrease of 10.3 (± 5.7) mmHg (p = 0.001) following the postural change from sitting/supine to standing, while SBP and DBP increases of 1.4 (± 8.4) mmHg and 2.8 (± 6.6) mmHg were found in the group of patients without OH (Table 1). Postural changes in SBP and DBP with symptomatic OH were also significantly greater than those in the group of patients without OH (p < 0.001). In addition, symptomatic OH patients had SBP and DBP in the sitting/supine position which were significantly higher than those of patients without OH (p = 0.021 for SBP and p = 0.017 for DBP), and the OHQ composite score for symptomatic OH patients was significantly higher than that of patients without OH (1.20 ± 0.85 and 0.53 ± 0.74 (p < 0.001)), as shown in Table 2. Similar results were found for the OHSA, OHDAS average scores, and specific items of OHSA (item 1 and 4) and OHDAS (item 1). This suggests that the clinical symptoms of OH and their impact on the daily activity of symptomatic OH patients was significantly greater than that of patients without OH.

For the 4 asymptomatic OH patients, their standing BP was significantly reduced from sitting/supine position, and those SBP and DBP reductions were also comparable to those of symptomatic OH patients (Table 1). However, the OHQ scores of the 4 asymptomatic OH patients were zero.

3.2. Correlation study of the OHQ and ABC scale

The highest OHQ score in PD patients was found for item 1 of both the OHSA and OHDAS. This suggested that dizziness, lightheadedness, feeling faint, or feeling like you might black out are the most common OH symptoms and standing for short periods of time was the daily activity most affected in PD patients. With regard to self-perceived levels of balance confidence, the average (± SD) ABC total score of PD patients was 67.0 ± 25.1, and symptomatic OH patients tended to have lower total scores compared to patients without OH (63.0 ± 23.9 vs 67.4 ± 25.9, p = 0.419). This pattern was reflected in almost all the individual scores of the 16 items, however, these differences did not reach statistical significance. Correlation analysis showed that balance confidence for item 3 of the ABC score (picking up slippers from floor) had a negative relationship with OHQ composite score with a correlation coefficient of − 0.229 (p = 0.022) (Table 3). This suggests that picking up slippers from floor was an activity for which PD patients had less balance confidence and this lack of confidence could be related to the occurrence of clinical symptoms of OH.

3.3. Clinical data of symptomatic OH versus patients without OH

Symptomatic OH patients were older than patients without OH (69.7 ± 8.3 vs 64.8 ± 12.2 (mean ± SD) years, p = 0.047). However, there was no significant difference between symptomatic OH (n = 18) vs patients without OH (n = 78) for the number of patients for each H&Y stage (stage 1: 1 vs 6, stage 1.5: 0 vs 5, stage 2: 3 vs 11, stage 2.5: 6 vs 32, stage 3: 8 vs 18, stage 4: 0 vs 6), average number of antiparkinson medications received (2.7 vs 3.0 items), levodopa daily dose (624 vs 632 mg/day), LEDD (811 vs 820 mg/day), and DALEDD (154 vs 179 mg/day). In addition, there was no significant difference between symptomatic OH vs patients without OH in terms of number of patients diagnosed with hypertension (6 vs 24), and the average number of antihypertensive medications received (1.3 vs 1.2 items). There was no significant difference in regards to the types of antihypertensive medications received by those two groups of patients: angiotensin converting enzyme inhibitor (enalapril; 3 vs 5 patients), angiotensin II receptor blocker (losartan, valsartan or telmisartan; 1 vs 5 patients), calcium channel blocker (amlodipine or verapamil; 0 vs 7 patients), beta-blocker (propranolol, atenolol or carvedilol; 1 vs 6 patients) and diuretics (hydrochlorothiazide, furosemide; 1 vs 3 patients). Other medications received by those two groups of patients were also not significantly different: antipsychotics (quetiapine, olanzapine; 5 vs 7 patients), alpha-blocker (tamsulosin; 1 vs 1 patient), and antidepressants: SSRIs (sertraline, escitalopram, fluoxetine; 1 vs 7 patients), SNRIs (venlafaxine, desvenlafaxine, duloxetine; 2 vs 1 patients) and tricyclic antidepressants (nortriptyline; 0 vs. 2 patients). None of the patients had taken any medications to treat the OH (fludrocortisone, droxidopa or midodrine). A TU-NMS mean total score of 8.3 ± 4.5 was

Table 1
Sitting/supine BP and standing BP of PD patients.

Blood pressure	Overall	Symptomatic OH	Patients without OH	Asymptomatic OH	P-value[a]	P-value[c]
(mmHg)	(n = 100)	(n = 18)	(n = 78)	(n = 4)		
Sitting/supine SBP	133.4 ± 21.3	144.4 ± 28.2	131.6 ± 19.0	120.3 ± 8.0	0.021	0.129
Standing SBP	130.1 ± 22.9	125.7 ± 29.0	133.0 ± 19.8	105.8 ± 12.1	0.423	0.150
Δ SBP	− 2.4 ± 11.0	− 15.8 ± 8.5[b]	1.4 ± 8.4	− 14.5 ± 8.7[d]	< 0.001	0.715
(min, max)	(− 35.0, 24.0)	(− 35.0, − 3.0)	(− 14.0, 24.0)	(− 21.0, − 2)		
Sitting/supine DBP	77.4 ± 13.7	85.1 ± 15.7	75.2 ± 11.6	72.8 ± 12.1	0.017	0.093
Standing DBP	76.5 ± 2.6	72.4 ± 10.7	78.1 ± 12.6	65.0 ± 12.2	0.081	0.285
Δ DBP	0.1 ± 8.2	− 10.3 ± 5.7[b]	2.8 ± 6.6	− 7.8 ± 2.9[d]	< 0.001	0.481
(min, max)	(− 21.0, 26.0)	(− 21.0, 7.0)	(− 11.0, 26.0)	(− 10.0, − 4.0)		

Negative symbol indicated the reduction of BP.
[a] Comparison of Symptomatic OH versus Patients without OH.
[b] p = 0.001 for BP reduction from sitting/supine to standing position of Symptomatic OH patients.
[c] Comparison of Asymptomatic OH versus Symptomatic OH.
[d] p < 0.05 for BP reduction from sitting/supine to standing position of Asymptomatic OH patients.

Table 2
OHSA, OHDAS and OHQ of PD patients.

	Overall	Symptomatic OH	Patients without OH	P-value[a]
	(n = 100)	(n = 18)	(n = 78)	
OHQ score	0.62 ± 0.80	1.20 ± 0.85	0.53 ± 0.74	**0.001**
OHSA score				
Item 1	2.14 ± 2.35	3.67 ± 2.54	1.85 ± 2.13	**0.009**
Item 2	0.47 ± 1.54	0.72 ± 1.71	0.44 ± 1.55	0.334
Item 3	0.54 ± 1.50	0.89 ± 1.75	0.49 ± 1.47	0.224
Item 4	0.24 ± 1.12	0.67 ± 1.57	1.01 ± 0.11	**0.017**
Item 5	0.03 ± 0.30	0.00 ± 0.00	0.04 ± 0.34	0.631
Item 6	0.11 ± 0.67	0.22 ± 0.94	0.09 ± 0.61	0.513
OHSA score	0.56 ± 0.83	1.06 ± 0.85	0.47 ± 0.80	**0.001**
OHDAS score				
Item 1	1.92 ± 2.21	3.61 ± 2.17	1.60 ± 2.05	**0.001**
Item 2	0.19 ± 0.86	0.44 ± 1.34	0.14 ± 0.73	0.209
Item 3	0.43 ± 1.33	0.83 ± 1.95	0.36 ± 1.17	0.288
Item 4	0.34 ± 1.18	0.83 ± 1.92	0.24 ± 0.96	0.127
OHDAS score	0.72 ± 0.94	1.43 ± 1.24	0.59 ± 0.79	**0.001**

Data were shown as mean ± SD. Bold signifies p-values < 0.05.
[a] Symptomatic OH versus Patients without OH was analyzed by Mann-Whitney *U* test.

Table 3
ABC scores and their correlation with the OHQ composite score.

	Overall	Correlation coefficient with OHQ composite score	Pearson's correlation
	(n = 100)		
Item 1	81.8 ± 25.6	0.000	0.999
Item 2	75.0 ± 31.5	0.054	0.594
Item 3	77.3 ± 31.5	**− 0.229**	**0.022**
Item 4	88.6 ± 24.9	− 0.048	0.638
Item 5	68.0 ± 35.7	0.043	0.668
Item 6	48.3 ± 38.5	0.007	0.942
Item 7	68.6 ± 39.4	− 0.023	0.819
Item 8	65.5 ± 39.6	0.085	0.403
Item 9	71.9 ± 31.3	0.088	0.384
Item 10	67.8 ± 36.8	0.074	0.465
Item 11	77.2 ± 33.3	0.077	0.446
Item 12	57.8 ± 36.4	− 0.183	0.069
Item 13	43.3 ± 36.0	− 0.014	0.887
Item 14	67.1 ± 37.0	0.007	0.944
Item 15	45.2 ± 33.9	0.033	0.747
Item 16	69.2 ± 27.0	− 0.075	0.459
Average ABC score	67.0 ± 25.1	− 0.005	0.957

Bold signifies p-values < 0.05.

found for all PD patients with all multitudes of dysfunction identified, including neuropsychiatric symptoms, sleep disorders, autonomic nervous system function, gastrointestinal, and sensory function. However, no difference in either total score or individual domain scores were found between symptomatic OH patients and those from the patients without OH group.

3.4. Factors associated with symptomatic OH

In this study, we aimed to identify factors associated with symptomatic OH, therefore we excluded the 4 patients with asymptomatic OH from the samples used for logistic regression analysis, and analyzed the data from only 96 patients (18 symptomatic OH and 78 without OH). Univariate logistic regression analysis showed that age, Hoehn & Yahr stage 3, co-morbidity of hypertension or psychosis, antipsychotics, and SNRIs were significant factors for symptomatic OH ($p \leq 0.25$). However, backward stepwise multivariate logistic regression analysis only identified hypertension (OR, 95%CI: 6.16, 1.171–32.440, p = 0.032), and older age (OR, 95%CI: 1.06, 1.003–1.115, p = 0.038) as significant factors associated with symptomatic OH. The predictive Model had a goodness of fit with Homer and Lemeshow Chi-Square of 4.649 (p = 0.703) and overall accuracy of 80.2%.

4. Discussion

This study confirms that OH occurs in a sub-set of PD patients, however not all of the patients with manometric OH display clinical symptoms. A prevalence of OH (22%) and symptomatic OH (18%) was found in this study which concurs with the prevalence of 30.1% (95% CI: 22.9%–38.4%) for OH reported by Velseboer [2], of 18% as reported by Ha [10], and of 16% as reported by Palma [29] for the frequency of symptomatic OH, but is lower than the 40.2% for OH found in another group of Thai PD patients [32]. Asymptomatic OH, it was found in 4% of PD patients or 18.2% of the OH patients (4/22 patients) in our study, which is lower than that reported by Merola of 11.6% of PD patients or 37.8% of the OH patients (14/37 patients) [28]. The discrepancies in the prevalence rates could be the result of several factors including selection criteria, study population, study design (cross-sectional versus longitudinal), the criteria used to define OH, and the method of BP measurement [22]. In our study, the most common clinical OH symptoms reported were dizziness, lightheadedness, feeling faint, or feeling like you might black out, and the ability to stand for short periods of time was the daily activity most affected in PD patients. OHQ composite scores represent the severity and the impact OH has on daily activity, and a review by Elgebaly suggests that OHQ composite scores (± SD) in the range of 2.83 (± 2.26) to 6.0 (± 1.5) might need

pharmacological treatment [33]. The OHQ composite score from our symptomatic OH patients (1.20 ± 0.85) was lower than this suggested range, therefore, only non-pharmacological therapy was provided to our symptomatic OH patients, however, they were advised to inform the physicians if their symptoms persisted or got worse. The non-pharmacological therapy provided included: physical manoeuvers, such as toe-raises, crossing legs, and squatting; increasing hydration and salt intake if not contraindicated; raising the head of their bed (10–15 cm); and changing position slowly [15]. Patients without OH and asymptomatic OH were informed about the clinical symptoms of OH as well. In this study, we found 42 patients who did not have a BP reduction, which met the manometric criteria, but did have a OHQ score of more than zero, indicating that they experienced symptoms mimicking hypotension [34]. They reported an inebriation-like syndrome in 3 PD patients suffering from chronic disabling orthostatic lightheadedness which disappeared on lying down, but BP measurements either by prolonged passive head up tilt or ambulatory blood pressure measurement (ABPM) did not show BP reduction, which met the manometric criteria [34]. In addition, neurological examinations did not find cerebral hypoperfusion, vestibular or ophthalmologic abnormalities, and orthostatic myoclonus/tremor in those patients. The term "inebriation-like syndrome" was suggested as a highly descriptive and distinctive from other symptoms such as vertigo, feeling faint, or presyncope and was hypothesized that the syndrome is related to basal ganglia abnormalities, leading to subjective balance/coordination impairment [34].

Mak and Pang [35] and Adkin [36] have all reported on the clinical impact of low ABC scores in PD patients. Recurrent fall patients (follow up to 12 month) had lower ABC scores than single fall patients [35], and lower levels of balance confidence (as indicated by lower ABC scores) were related to poorer postural stability, manifested as increased postural sway in the standing position [36] and decline in physical performance [37]. In addition, Foongsathaporn reported that specific items 3, 6 and 9 of the ABC scale (all of which involve movement in a vertical orientation) had strong predictive values for fall in PD patients, with item 9 (getting in/out of car; OR = 4.8) having the highest correlation, followed by item 6 (standing on chair to reach; OR = 3.4), and item 3 (picking up slippers from floor; OR = 2.6) [27]. From our data, it was shown that symptomatic OH tended to have lower ABC scores (for both total score and all items except 2 and 5) compared to patients without OH. We also noted a significant negative correlation of item 3 of the ABC scale and OHQ composite score in this study. Previous studies have not reported the correlation of OHQ score and the ABC score. Our findings fill in the gap by providing further evidence for a connection between the clinical symptoms of OH and a low balance confidence of PD patients, especially for movement in a vertical orientation, such as picking up slippers from floor. The self-perceived balance confidence as evaluated from the ABC scale, although it is not as good as the actual balance, it has been shown to be correlated with the actual static/dynamic balance control [38] and can identify patients at risk of future recurrent falls [39]. We hope that some correlation found in this study for the OHQ score and the ABC score can increase the awareness of the fall in OH patients, especially in those with high OHQ score. However to establish whether or not patients with OH symptoms are at a higher risk of falls compared to those who are symptom free require further investigation. Merola indicated that 37.8% of PD with OH were asymptomatic, however those asymptomatic OH had a prevalence of falls (50.0%) near to that of the symptomatic OH group (47.8%) [28]. Falls in PD may be caused by several independent mechanisms (e.g., postural instability, difficulty with transfers, gait disorders), not just lowered BP, which may explain the similarities in prevalence between the two groups [40]. Also, several predictors of falling in PD (previous falls, PD duration, dementia, and loss of arm swing) needed to be considered in PD patients [41].

Using multivariate logistic regression analysis, the factors found to be significantly associated with symptomatic OH included being elderly and also suffering from essential hypertension. Our findings are consistent with Ha [10] who demonstrated that older age was related to symptomatic OH in PD patients (p = 0.001), Perez-Lloret [19] who reported a relation between Age > 68 years and OH (OR; 95%CI: 3.61; 1.31–9.95), and Palma [29] found that the prevalence of OH and symptomatic OH increased with age (patients with OH were older: 68 ± 10 vs 64 ± 11, p = 0.002). Mechanisms of the age-related changes that can affect normal BP regulation include decreases in baroreflex sensitivity, α-1-adrenergic vasoconstrictor response to sympathetic stimuli, parasympathetic activity, renal salt and water conservation, left ventricular diastolic filling, and increased vascular stiffness [42]. For PD patients, as well as these age-related mechanisms, the impairment of several autonomic nervous systems caused by the disease degeneration can play an important role in the loss of blood pressure control. Goldstein reported that OH in PD is related to impaired baroreflex-cardiovagal functions, sympathetic cardiac and also partially extracardiac denervation, and baroreflex-sympathoneural failure [43]. It was found in this study that a co-morbidity of hypertension was also associated with symptomatic OH, however previous studies have not reported this relationship [2,10,19,32]. A possible explanation for the link is that chronic hypertension may impair cerebral autoregulation, leading to a failure to increase normal cerebral blood flow on standing, as seen in non-PD patients with chronic hypertension where OH was present in 5% to 14.6% of the population [44]. The hypotensive effect from antihypertensive agents is less likely to be a contributory factor for the orthostatic blood pressure change found in symptomatic OH patients because the use of antihypertensive drugs in those two groups of patients (symptomatic OH and patients without OH) were not significantly different. Additionally, orthostatic blood pressure change is less likely to have resulted from the use of other medications (alpha-blocker for benign prostate hypertrophy, antipsychotics, antidepressants and antihypotensive drugs) as again, no significant difference in the use of these drugs between the groups was seen.

In our study, exposure to any antiparkinson medication (e.g., levodopa, dopamine agonists, MAO-B inhibitors), using medication regimens of monotherapy or combination therapy, levodopa daily dose, LEDD and DALEDD were not related to symptomatic OH. Polypharmacy and exposure to other medications were also not associated with symptomatic OH. These results differ from previous studies which have shown selegiline [32], amantadine [19], levodopa daily dose of 1069 mg/day [16], diuretics or taking five or more medications (polypharmacy) [19] were significantly related to the occurrence of OH in PD. This discrepancy might be explained in part by our recruitment of subjects who were previously stable on, and had not changed, any drug regimen for at least four weeks. Looking at our results, levodopa daily dose was not shown to be a significant factor associated with symptomatic OH, but the average levodopa daily dose used was approximately 600–700 mg for both symptomatic OH and patients without OH, which is considerably lower than 1069 mg/day found in a previous study [16]. In addition to antiparkinson medications, the disease (PD) itself can also be a contributor to the OH. Lim and Lang [45] and Fereshtehnejad and Lokk [46] have identified that PD rather than antiparkinson medications as a contributory factor for symptomatic OH.

Our study had some limitations. Although the presence of essential hypertension in PD patients was found to be a factor associated with symptomatic OH, the low number of patients in this study has led to a wide 95%CI interval. Future studies with a greater number of participants are therefore needed in order to increase the power of the study to detect significance with a lower 95%Cl interval. We did not measure BP after 3 min of postural change, therefore our data could not include any delayed OH that might have been present in the patients. Additionally, as several factors may influence the extent of the orthostatic blood pressure fall, the prevalence of OH or symptomatic OH may differ from what we had reported in the study. The use of

continuous beat-to-beat BP monitoring or 24-hour ABPM which can monitor BP more accurately and a more thorough assessment would increase the chance of detecting the postural BP change, therefore may provide a higher prevalence of OH than what we have reported. In addition, the threshold for determining OH of 20/10 mmHg is quite arbitrary, and the consequences of BP fall might result from a continuous reduction of BP rather than a specific cut-off of the level of BP reduction. The severity of PD can also influence the OH [46], therefore if we had included more patients of the late rather than the early stage of PD, the prevalence of OH or symptomatic OH may increase.

In this study, there were four patients classified as asymptomatic OH. However, it is not possible to extrapolate the consequence of asymptomatic OH from this study due to several factors. Firstly, we only included a sample of patients having OH. Patients with other neurogenic OH were not included. Secondly, although the OHQ has been shown to have good psychometric properties to measure the severity of symptoms and the functional impact of neurogenic OH in a valid and reliably way [30], the scale has not been validated to distinguish symptomatic from asymptomatic OH. Since the present study used the OHQ to classify the patients into symptomatic and asymptomatic OH group, our results may be inadequately recapitulated. Thirdly, the study was not blinded to the patients or physicians or developed with the idea of distinguishing symptomatic from asymptomatic OH.

We suggest further studies should include BP measurements with the patient in a lying position to determine the presence of supine hypertension (SH) in order to investigate its association with symptomatic OH, as our results suggest that patients with symptomatic OH had a higher BP (SBP and DBP) in the sitting/supine position compared those of patients without OH. In addition, it was reported that many patients with neurogenic OH also have SH even before treatment of hypotension is initiated [3]. In OH patients with severe autonomic failure, half also suffer SH, defined as a systolic BP $\geq$ 150 mmHg or diastolic BP $\geq$ 90 mmHg, even though they mostly have normal seated BP [47]. The clinical impact of SH is considerable, including an association of SH with left ventricular hypertrophy [48] and a patient case of hemorrhagic stroke while supine [47]. Umehara studied the clinical characteristics of supine hypertension in de novo PD. The factors found to be associated with SH were older age, preexisting hypertension, and akinetic-rigid motor subtype, and the supine BP was positively and mildly correlated with the degree of orthostatic hypotension (SBP: $r = 0.271$, $p = 0.011$ and DBP: $r = 0.253$. $p = 0.016$) [49]. Similarly, Fanciulli [50] reported that a history of cardiovascular comorbidities, including hypertension, coronary arteries disease, atrial fibrillation, heart failure, diabetes mellitus is predictive of SH at tilt-table examination in PD (OR = 4.06, 95%CI 1.6–10.0, $p = 0.002$) as well as a significant association between SH and progressive systolic and diastolic BP fall upon tilting ($p = 0.007$ for SBP and $p = 0.002$ for DBP). In those two studies [49,50], factors associated with OH were not determined, however with the positive correlation of SH and degree of orthostatic hypotension [49] and the significant association of SH and BP falls upon tilting [50], it could be postulated that those significant factors of SH might play an important role in OH or might be related to OH occurrence. Further studies are needed to clarify these associations. The co-occurrence of SH and OH was found in 10% of PD patients, although it was not as high as the frequency of each condition (SH was 34% and OH developed in 24% of PD patients) [50]. It was also shown that those patients with SH and OH had significantly lower NE_{supine} (224 $\pm$ 111 pg/mL) than those without SH and OH (361 $\pm$ 168 pg/mL, $p < 0.001$). This suggested a significant reduction of peripheral sympathetic denervation in SH and OH [49]. In addition, it was suggested that the presence of SH in PD patients with OH can increase cerebral blood flow. This phenomenon can cause cerebral small-vessel disease and white-matter damage [49], which has been shown to be associated with cognitive decline in patients with PD [51]. We suggest further study should also determine the factors associated with OH and SH from the same patients. The detection and treatment of SH, in addition to OH can be beneficial to PD patients.

In conclusion, our results, which were obtained from PD patients who were not bedridden and who were community-dwellers indicated that symptomatic OH occurs in approximately one out of five Thai PD patients. The factors associated with symptomatic OH included being elderly and co-existing essential hypertension. Although further studies are needed, our study has provided new evidence supporting the clinical importance of symptomatic OH in PD, identifying its impact on balance confidence in these patients. This sub-set of PD patients should be closely monitored and evaluated.

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