Current Trends in Internal Medicine
Oikonomou P and Jost WH. Curr Trends Intern Med 7: 1876.
www.doi.org/10.29011/2638-003X.100087
www.gavinpublishers.com

Research Article

Orthostatic Hypotension and Parkinson's Disease: A Review about Epidemiology, Pathophysiology and Clinical Management

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Citation: Oikonomou P, Jost WH (2023) Orthostatic Hypotension and Parkinson's Disease: A Review about Epidemiology, Pathophysiology and Clinical Management. Curr Trends Intern Med 7: 187. DOI: 10.29011/2638-003X.100087

Received Date: 21 February 2023; **Accepted Date:** 27 February 2023; **Published Date:** 02 March 2023

Abstract

Orthostatic Hypotension (OH) may cause unexplained falls, syncope, blurry vision, dizziness, fatigue, shoulder and neck pain and is confronted daily by colleges in internal medicine. OH is also an important non-motor feature of Parkinson's Disease (PD) and considerably contributes to worse outcomes and disability in everyday life. However, the pathogenesis of OH in PD is different from OH with a different aetiology, can be ultimately distinguished through the medical history and cardiovascular autonomic function tests, and requires specific management. In this review, we outline the epidemiology of OH in PD with detailed reference to relevant studies, summarize the prominent pathophysiological mechanisms and the current clinical management.

Keywords: Orthostatic Hypotension; Parkinson's Disease; Epidemiology; Pathophysiology; Current Clinical Management

Introduction

PD is a progressive neurodegenerative disease presenting with bradykinesia and rigidity or tremor and a variety of non-motor symptoms, affecting about 1% of the population over 60 years, is characterized neuropathologically by degeneration of the substantia nigra pars compacta as well as other parts of the central and Autonomic Nervous System (ANS) accompanied by neuronal inclusions composed of α- synuclein (Lewy bodies) [1,2]. Dysautonomia is an important non-motor feature of PD and the most common cardiovascular autonomic dysfunctions is Orthostatic Hypotension (OH) with or without clinical symptoms [3,4].

OH is conventionally defined by a reduction of >20 mmHg in Systolic Blood Pressure (SBP) or >10 mmHg diastolic BP (DBP) of standing or head-up tilt-table testing within three minutes [5]. OH can by manifested with a variety of symptoms and signs such as blurry vision, dizziness, fatigue, shoulder, neck, or low-back pain, which develop upon standing, and recover by lying down and syncope with or without trauma [6,7]. Furthermore, labile blood pressure, Postpandial Hypotension (PH), Supine Hypertension (SH), and a phenomenon called nondipping, defined as the absence of a decrease in pressure during the night, belong to other cardiovascular abnormalities, which can coexist in PD and are related to each other [8,4]. In PD OH is mostly neurogenic (nOH), i.e., due to post-ganglionic noradrenergic denervation, but non neurogenic aetiology such as cardiac origin, hypovolemia and medication should also be taken into consideration [9].

In this review we will focus on the epidemiology, pathophysiology and clinical management of OH in PD with the purpose of providing an updated literature overview.

Methods

We conducted an electronic search of human studies published on PubMed in the English language as of October 2022 using the following keywords: "Orthostatic Hypotension" AND "Parkinson's Disease" We selected the relevant reviews and original studies regarding epidemiology, pathophysiology and clinical management based on the scopes of our article.

Epidemiology of OH and PD

In a meta-analysis study from 2011, which included 25 studies and 5,070 patients with PD, the estimated prevalence of OH in PD was 30.1% [10]. In a study conducted in 2015 on a cohort of 210 patients with PD, although the prevalence of classically defined OH, was relatively high (i.e. 50%) only a third of patients (~16%) had symptoms [11]. In a retrospective analysis on 106 patients with PD over a period of almost 16 years and overall 212 evaluations, no significant correlation between severity of OH, defined as maximal drop of SBP after postural challenge, and duration of the disease was found. The p value of 0.064 is interpreted to be associated merely with aging [12]. In a recent study using longitudinal data of 660 patients with PD with disease duration up to 12 years from the Parkinson's Progression Markers Initiative Cohort, male sex, lower supine DBP, and lower total proteins helped to identify the only 18 patients with low ΔSBP that increased continuously during the follow-up [13].

There are findings from cardiac sympathetic neuroimaging that support that OH belongs to the prodromal non-motor signs of PD and could be easily distinguished from other synucleinopathies such as Multiple system atrophy (MSA) [9]. In a study published in 2021, however, OH was measured on general population with 6,910 participants with an average age of 69.0 ± 8.8 years at baseline and a median follow-up age of 16.1 years (8.5-22.7 years) and it was found that the patients with incident PD at baseline were significantly more likely to have OH (odds ratio [OR], 1.88; 95% confidence interval [CI], 1.09-3.24), but OH was not associated with an increased risk of PD, indicating that OH is not a prodromal marker of PD in the general population [14]. In the update of the Movement Disorder Society (MDS) Research Criteria for Prodromal PD however, published in 2018, the nOH has been calculated to have a positive likelihood ratios of 18,5 therefore being the third in the list after polysomnography (PSG)-proven Rapid Eye Movement (REM) sleep behaviour disorder (RBD) and clearly abnormal dopaminergic PET/SPECT (2 SD below mean) [15].

Furthermore, several studies provide evidence that OH is common in early stages of PD and is associated with worse outcome: In a prospective population-based study, with 185 initially drug-naive patients with PD, the relative risk of OH was found to be 3.0 (95% CI 1.6–5.8; $p < 0.001$) at baseline and 4.9 (95%). CI 2.4–10.1; $p < 0.001$) after 7 years. OH was independently associated with older age (OR 1.06 per year; 95% CI 1.03–1.10), lower Mini–Mental State Examination (MMSE) score (OR 0.91 [0.85–0.97] per unit), and longer follow-up time (OR 1.12 [1.03–1.23] per year). Clinically significant OH was associated with the same characteristics, in addition to higher levodopa equivalent dosage (OR 1.16 [1.07–1.25] per 100 mg) [16]. In a study in which neuropsychological and hemodynamic parameters in 87 patients with early PD were analysed, a clear association of cognitive impairment with OH and SH was found [17]. In a prospective cohort study with 80 PD patients without dementia, orthostatic BP drop was strongly associated with dementia risk (OR = 1.84 per 10 mm Hg, $p < 0.001$); having a systolic dropof >10 mm Hg increased dementia odds 7-fold (OR = 7.3, p = 0.002) [18]. Moreover, in a prospective cohort study of a total of 113 patients with PD, the presence of OH was a core parameter for a cluster analysis for subtyping PD in diffuse/malignant, and intermediate subtype as distinct from the mainly motor/slow progression subtype [19].

Pathophysiology

Physiologically, upon standing up (i.e. orthostasis), blood pools in the legs, pelvis and gut, resulting in (1) reduced blood volume return to the right heart, (2) in decrease of cardial output and (3) a reduction of BP. Then the baroreceptors in the aorta and carotid sinus and mechanoceptors in the lungs and heart detect the reduction of BP, resulting in sympathetic nervous system activation releases Noradrenaline (NE) into plasma with splanchnic/lower-limb vasoconstriction and an increase in HR [20,21].

In nOH, this physiologically compensatory mechanism in orthostasis is impaired. By contrast to non- neurogenic OH, HR does not increase or only in small amount, despite the reduction of BP and consequently: Unless this is corrected by sitting or lying supine, with persistent decrease in cardiac output, cerebral hypoperfusion with the corresponding symptoms may occur [20,22].

This relatively obvious pathophysiology indicates insufficient arterial baroreflex. The neuronal structures involved are the vagus nerve, the central autonomic control centres including the cortex, insula, hypothalamus, brain stem, and spinal cord as well as the sympathetic nerves and in PD they show neuronal destruction (neuron and synapse loss, nerve fibre degeneration) and α-synuclein accumulation, which leads to a lack of catecholamines and, accordingly, an insufficient adrenergic and noradrenergic response [4,21]. OH in PD is characterised thus by severe dysfunction of both the sympathetic and parasympathetic (vagal nerve) components of ANS. The lower baroreflexive cardiovagal gain could be demonstrated experimentally, showing that (1) the proportionate increment in plasma NE is blunted during orthostasis, reflecting the sympathetic component and that (2) the extent of decrease in the time between heartbeats is low during the Valsalva manoeuvre, reflecting the parasympathetic component. The degeneration of cardiac, and less extensively extra-cardiac, sympathetic post-ganglionic noradrenergic nerves with functional affection due to α-synuclein deposits and fiber loss, is proven by a variety of sympathetic neuroimaging and pathological studies [9]. In the first international symposium on cardiac sympathetic neuroimaging, in 2009, the very important finding presented was that all examined patients with PD and OH have markedly reduced sympathetic noradrenergic innervation

of the left ventricular myocardium. The fact that in patients with central neurodegeneration and OH, neuroimaging evidence for normal myocardial noradrenergic innervation excludes PD, implies a pathognomonic character of this finding [23]. Indeed, in an experimental study on 95 patients with PD and 17 normal controls it was found that the reductions in SBP during orthostasis resulted in an insufficient increase in total peripheral resistance in patients with cardiac sympathetic denervation. However, patients without cardiac denervation exhibited a positive inotropic response against vasodilatation [24]. The insufficient noradrenergic stimulation to the blood vessels in patients with nOH and PD is indicated also by the absence of the physiological BP exceed at the end of a Valsalva maneuver [25]. These multifactorial mechanisms may explain the co-incidence and co-interaction of all the forms of cardiovascular autonomic dysfunctions in PD, i.e. PS, SH, and non-dipping.

Clinical management

Identifying and managing OH in PD is important because it impacts on activity of daily living and, if untreated, increases the risk of injurious falls. The aim of management is to reduce symptoms and improve standing time, physical function and activity of the patients [22].

Diagnosis

The first step is making a correct diagnosis. Patients with symptoms of OH and additional signs of PD should be referred to a neurologist for further investigation. Vice versa, all patients with PD should be actively screened for OH because of the possibility of asymptomatic cases and unspecific symptoms. Regarding screening for orthostatic symptoms in PD, the MDS suggest the self-completed Non-Motor Symptoms Questionnaire [26].

Although there are more sophisticated ways to test the pathophysiology of orthostasis, a simplified version of the Schellong-test, or standing test (i.e. the evaluation of HR and BB changes from the supine to upright position) is still recommended as a bedside screening measure. There is no universal standardized protocol for performing a standing test, although this usually consists of a supine phase of 5–10 min, followed by an active standing phase of at least 3 min, ideally 5–10 min. BP and HR are measured at the end of the supine phase and at 1-minute intervals during the orthostatic challenge [27]. If the patient is unable to stand up from the supine position, a sitting-to-standing protocol is acceptable [28]. Pragmatically, a non-specialised clinic bedside screening should be performed by measuring the BP and heart HR in the supine position (after 10 minutes of rest) and over 10 minutes (every minute) upon standing.

Non-neurogenic causes and exacerbating factors such as dehydration, anaemia, and infection should be excluded and a careful medication review should be performed including not only anti-hypertensive agents, but also dopaminergic drugs, tricyclics, opioids, neuroleptics or alpha-blockers [22].

Afterwards, a distinction between neurogenic and non-neurogenic OH should be obtained, using cardiovascular autonomic function tests, such as the standing test, the head-up tilt test, the cold pressor test, deep breathing tests, Valsalva manoeuvres, the isometric contraction test, 24-h ambulatory BP monitoring, 24-h Holter monitoring, hyperventilation tests, and R-R interval variation [29].

As we mentioned in the pathophysiology of nOH, no or only small HR rises are observed despite severe BP fall in contrast to non-neurogenic OH, where HR increases markedly in orthostasis as a compensatory mechanism for the decrease in BP. An increase in HR <0.5 beats-per minute/mmHg of systolic BP fall after 3 minutes of head-up tilt indicates nOH with high diagnostic accuracy [30]. 24 h-ambulatory BP monitoring is also a valuable test and should be obtained to screen and evaluate other, possible concomitant, cardiovascular disorders such as PH, SH, nondipping, or nocturnal hypertention. The MDS recommended the Scales for Outcomes in PD-Autonomic (SCOPA-AUT) and the Composite Autonomic Symptom Scale for the assessment of OH, and the novel Non-Motor Symptoms Scale (NMSS) and the Orthostatic Grading Scale (OGS) for evaluating OH in PD [31]. Validated questionnaires, such as the Orthostatic Hypotension Questionnaire (OHQ) and home BP measurements provide useful additional information on the severity of OH in daily life and monitor for PH and SH [22].

Treatment

The treatment of OH on PD includes patient education, correcting aggravating factors, non- pharmacological measures and pharmacotherapy. An essential facet is first of all general patient education. Patients should be aware of their diagnosis, be advised on hydration and diet, and should be educated to avoid triggers such as hot environments and large carbohydrate-rich meals, because PH can exacerbate symptoms [20]. If clinical assessment reveals dehydration, severe anemia or infections, then a correction should be obtained [22]. Moreover, thyroid disorders, vitamin D and B12 deficiencies should be corrected as these can also contribute to and exacerbate OH [20].

Drugs that may aggregate OH include diuretics, sildenafil, nitrates, α-blockers, centrally acting α2- agonists, and tricyclic antidepressants and should be avoided when treating for OH [32]. A case-by-case risk/benefit evaluation should be performed if the onset of OH is thought to be in temporal relationship with the introduction or increase in dosage of any anti-hypertensive agents. In clinical practice, exacerbation of OH may also occur during the titration of dopamine agonists and, less frequently, of levodopa due to vasodilatory effects and increased renal water and salt excretion. While in some patients orthostatic intolerance may ameliorate

the symptoms without intervention at follow-up, in others OH-specific measures may be necessary to maintain an adequate dopaminergic regimen [22]. However, in a study in 99 patients with PD, who underwent a head up tilt test in the same conditions of a 12-hours period of restriction of food and medication (at the first time without and at the second consecutive to their L-Dopa dosage) no significant statistical difference was found [33].

If no triggered cause or exacerbating factor can be found and OH still persists, specific patients' education, non-pharmacological and pharmacological measures should be applied stepwise depending on the severity of OH symptoms: [22,34]

Patients should be advised:

1. to use specific physical counter strategies such as standing up slowly, especially after resting supine for longer times or they may even pause in the sitting position before standing up (in case of dizziness and inability to sit or lie down), stationary stepping in place, crossing their legs, or tensening the gluteal and abdominal muscles, bending forward or clenching their fists in order to avoid venous pooling;
2. to avoid heat exposure, prolonged standing, alcohol, large, carbohydrate-rich meals and Valsalva-like maneuvers during micturition or bowel movements;
3. to continue physical activity with recumbent exercises (in a stationary bicycle, rowing machine, etc.) or in a swimming pool and to adapt daily routine, such as showering on a chair or (for male patients) urinating in the seated position may be required;
4. to sleep in a 10–20° full-body head-up tilt position in order to stimulate the overnight production of antidiuretic hormone and reduce pressure natriuresis.

A crucial non-pharmacological measure is the increased intake of water (up to 2.5 l/day) and salt (6–10 g/day) and even drinking a bolus of water of 500 m, which significantly raises the BP in the following 30 to 90 minutes in order to expand plasma volume. In patients with known heart, kidney or liver failure, caution in water and salt supplementation should be recommended [22]. High-waist compression stockings producing at least 15–20 mmHg of pressure can increase BP by augmenting venous return, which however may be difficult for elderly patients to put on, and thus limits their usefulness in everyday life. Abdominal binders that inflate automatically only on standing also ameliorate OH by reducing the splanchnic venous pooling [34].

If the specific patient's education and non-pharmacological measurements do not lead to sufficient control of the symptoms, pharmacotherapy should be initiated. The two main strategies used in current clinical practise are to increase the vascular tone with the sympathomimetics midodrine and droxidopa and to expand the intravascular volume with fludrocortisone.

Midodrine is a direct 1-adrenoceptor agonist, whereas droxidopa is a noradrenaline precursor that is converted into noradrenaline by the dopa-decarboxylase. Both sympathomimetic agents are started at the lowest dose 3 times/day and are increased gradually depending on the severity of OH symptoms. Patients with known cardiac disease, kidney failure or urinary retention should not receive sympathomimetic agents [22].

Midodrine is approved for the treatment of symptomatic OH in Europe, U.S. and Asia, whereas Droxidopa is not approved in Europe and was approved in Japan in 1989 for the treatment of nOH in PD, MSA, and familial amyloid polyneuropathy, and in the U.S. in 2014 for the treatment of symptomatic nOH associated with pure autonomic failure, PD, and MSA [34].

Midodrine raises BP in the standing, sitting, and supine positions and its pressor effect is noticeable ~30–45 minutes after consumption, reaching a maximum after ~1 hour, and persists for a total of 2–3 hours. nSH is common, hence patients should not take midodrine less than 3–4 hours before bedtime. Peak plasma concentrations of droxidopa are reached ~3-h after oral administration and in clinical practise the dose of dopa-decarboxylase in patients treated with L-dopa should be low so as to significantly reduce the pressor effect[34]. Unlike midodrine, droxidopa does not cause increased SH, but it should also be avoided at night [22].

Fludrocortisone is a synthetic mineralocorticoid that increases plasma volume by inducing sodium retention. It is used either in monotherapy or in combination with midodrine, but no studies have yet compared the efficacy and safety of single versus combined drug regimens in the long term [22]. Fludrocortisone should be used with extreme caution in the treatment of orthostatic hypotension, preferably for short-term periods, and the dosage should never be higher than 0.2 mg/day [34]. Fludrocortisone is contraindicated in patients with heart or kidney failure and electrolyte monitoring is recommended to exclude hypokalemia, especially in case of fever or diarrhea [22].

In the recommendations of the evidence-based medicine committee of MDS the practice implications for midodrine, fludrocortisone and droxidopa are categorized as "possibly useful", whereas based on the results of a high-quality trial, droxidopa is categorized as "efficacious" for the short‐term treatment of one week of OH in PD classified [35].

As mentioned in the pathophysiology section, due to the same mechanisms, OH and SH and non-dipping are common concomitants, both require treatment, but treating each one risks exacerbating the other, which leads to significant treatment dilemmas [20]. A consensus opinion suggests assessing and balancing risks and benefits. A mean standing BP below 75 mmHg in othostasis appears to be a useful benchmark when deciding whether the benefits of initiating pharmacological treatment of OH

outweigh the risks of exacerbating SH [11]. If antihypertensive are needed they should be short-acting and scheduled in the evening, while during daytime an effective treatment of OH should be prioritized [22].

Conclusion

OH is found in prodromic, early drug-naïve PD with an increased prevalence with age, but irrespective of disease duration, estimated between 30 and 50%. OH in PD is consistently associated with worse outcomes, while a correlation with motor phenotype (i.e. presence of tremor) was not been found in the literature. Whether OH is a prodromal marker of PD in the general population remains controversial.

The prominent pathophysiological mechanisms involved are an insufficient arterial baroreflex as well as a cardiac and extracardiac sympathetic noradrenergic denervation.

OH in PD considerably contributes to disease burden and reduces the quality of life of the patients and requires education and a careful clinical management regarding diagnosis, correcting aggravating factors and treatments. When performed properly patient's education and non-pharmacologic methods are very effective, while many patients still require pharmacotherapy to improve symptoms. Midodrine and droxidopa as sympathomimetics as well as fludrocortisone as intravascular volume expanders are the currently used pharmacotherapy. A titration procedure is recommended, supervised by a clinician and tailored to each patient's needs with evaluation of 24-hour BP monitoring and consideration of possible risks. Biomarkers are needed to predict response to treatment and new efficient and safe treatment options.

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