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Diagnosis and treatment of orthostatic hypotension in Parkinson's disease

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Diagnosis and Treatment of Orthostatic Hypotension in Parkinson's Disease

Review Article

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Abstract Orthostatic hypotension (OH) is a frequent comorbidity affecting between 23 and 38% of Parkinson's disease (PD) patients. Several pieces of evidence suggest that OH is related to faster cognitive decline and more frequent falls, and has been also connected to increased mortality. OH can be arbitrarily defined as a drop of systolic and/or diastolic blood pressure of 20 or 10 mmHg or more in the first three minutes after passing from decubitus to an upright position. Till test appears to be the most reliable tool for assessing the orthostatic response. On the other hand, the standing test and evaluation of orthostatic symptoms should be regarded as screening tests. The key physiopathological aspect of OH is an altered baroreflex function resulting from cardiac and vascular sympathetic denervation. Nonetheless, OH can be aggravated by heat, alcohol consumption or by drug treatments, such as antihypertensives, dopamine agonists or amantadine. Treatment should begin with re-considering drug treatments. After treatment is optimized, non-pharmacological measures may be employed. Drugs treatment should be reserved for patients in whom other strategies have failed. Midodrine and fludrocortisone are the most frequently used treatments, even though evidence about their efficacy and safety is weak.

Midodrine has a shorter duration of action and thus avoidance of evening dosing may help keep nocturnal blood pressure dipping intact. Promising alternatives may include droxidopa and fipamezole.

Keywords Orthostatic Hypotension, Treatment, Parkinson's Disease, Midodrine, Integrative Medicine

1. Introduction

Autonomic disturbances including orthostatic hypotension, constipation, hypersalivation or excessive sweating are frequent features of Parkinson's disease (PD) [1, 2]. They can impair a patient's quality of life, worsen caregiver burden, lead to hospitalization and institutionalization, and increase the cost of care of patients with PD [1]. Their management and treatment have been recognized by the UK National Institute for Clinical Excellence as unmet needs in PD [3].

A variety of neurocirculatory abnormalities have been noted in PD, orthostatic hypotension (OH) being the most

frequent and incapacitating one [4]. OH can cause falls and increase the risk of cognitive dysfunction [5] and is a predictor of all-cause mortality [6]. These data emphasize the importance of its prompt recognition and treatment.

In this review we will deal with the epidemiology, clinical evaluation and treatment of orthostatic hypotension in PD. We will begin by briefly discussing its physiopathology.

2. Physiopathology

In PD, orthostatic hypotension may results from the disease process as well as from extrinsic influences [4]. General extrinsic factors include older age and drug treatments [7, 8, 9]. Excessive heat has been related to more frequent and more severe OH-related events, such as syncope [10]. Alcohol elicits hypotension during orthostatic stress because of impairment of vasoconstriction, as has been shown in healthy young volunteers [11]. Other risk factors include female gender, diabetes, low body mass index or smoking.

As mentioned, exposure to drugs can either cause or aggravate OH. For example, we have recently observed that OH was more frequent in subjects exposed to diuretics or amantadine and those exposed to five or more drugs at the same time (i.e., polypharmacy) [8]. Some studies have also suggested that OH is more frequent in patients on dopamine agonists [12, 13] but not on levodopa [12, 14].

In any case, orthostatic hypotension is also present in recently diagnosed "de novo" PD patients, suggesting that it is independent of dopaminergic replacement therapy [15]. OH is also related to PD severity [16], further suggesting that disease-related factors also play a role in OH development.

Altered baroreflex appears to be the hallmark of OH in PD. The baroreflex is the main short-term compensatory mechanism to buffer blood pressure changes and maintain circulatory homeostasis. Briefly, blood pressure variations are sensed by arterial or venous baroreceptors (Figure 1) [17]. The information is conveyed to the brainstem, where autonomic nervous system activity is modified to revert blood pressure fluctuations. Patients with PD and OH have low baroreflex-cardiovagal gain compared to healthy controls [4, 18]. Altered baroreflex function results mainly from postganglionic sympathetic denervation [19] (Figure 1). Such lesions result in altered autonomic control of cardiac function as shown by the reduction in heart rate variability observed in PD [20]. Reduced sympathetic tone is also observed in blood vessels, which is the other effector of baroreflex [4, 21]. The alterations leads to impaired haemodynamic responses to blood pressure drop, which would normally induce increased cardiac output by increased heart rate and myocardial contractility and peripheral resistance by vasoconstriction.

3. Epidemiology

Several studies have investigated the prevalence of OH in PD. A recent systematic review and meta-analysis assessed the prevalence if OH in PD in retrospective, cross-sectional, or prospective cohort studies involving undemented PD patients [22]. The prevalence rate across the 25 studies included in the analysis ranged from 9.6% to 64.9% with a pooled prevalence of 30.1% (95% CI: 22.9-38.4%). Study characteristics, such as methodological quality, risk of selection bias, sample size, OH definition and the complexity level of the centre where the study was carried out did not influence prevalence figures. These results lie in the range stated in previous non-systematic reviews concerning this subject [23].

In some cases, OH can precede PD diagnosis [23, 24], but the prevalence of OH as a presenting symptom remains unknown.

4. Clinical evaluation of OH in PD

OH can be operationally defined as a sustained reduction of systolic blood pressure of at least 20mm Hg or diastolic blood pressure of 10mm Hg within three minutes of standing (i.e., Schellong test) or head-up tilt to at least 60° on a tilt table [25]. Tilt testing for up to ten minutes appears to be the most reliable method for evaluation of OH [26]. On the other hand, the presence of orthostatic symptoms and results from the standing test can only be considered as screening tools.

Beat-to-beat blood pressure using non-invasive measurement during a Valsalva manoeuvre can be of help during the evaluation of neurogenic OH. Systolic blood pressure decreases progressively during the manoeuvre, increasing slowly toward the baseline value with no pressure overshoot after release of the manoeuvre [27]. BP responses to deep breathing can also be analysed. Plasmatic norepinephrine change after and the orthostatic test can be used to assess denervation of blood vessels. Cardiac responses can be assessed by analysing heart rate variability.

OH can be symptomatic or asymptomatic. When present such symptoms may include light-headedness, dizziness, presyncope and syncope [25, 28]. Weakness, fatigue, cognitive slowing, leg buckling, visual blurring, hearing disturbances, headache, hanger-coat pain, orthostatic dyspnoea or chest pain can also sometimes be observed [28].
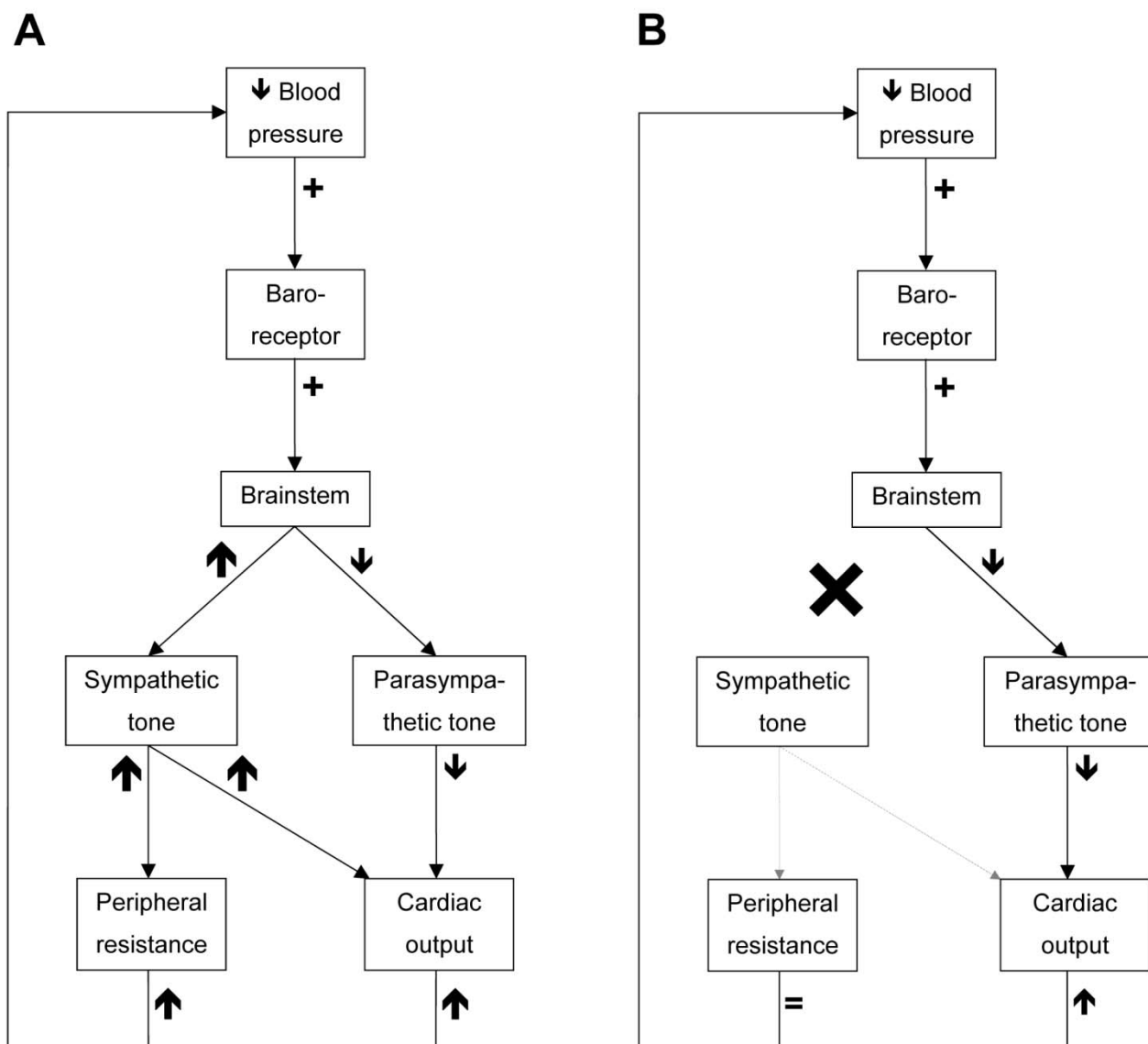
Figure 1. Baroreflex function in healthy subjects (A) and in PD patients (B). In PD, post-ganglionic sympathetic denervation leads to blunted responses to reduced blood pressure, which would otherwise lead to increased cardiac output and peripheral resistance.

The presence and severity of orthostatic symptoms in PD may be evaluated by the AUTonomic SCale for Outcomes in PArkinson's disease (SCOPA-Aut) or the COMPosite Autonomic Symptom Scale (COMPASS) [29]. The SCOPA-AUT is a brief, reliable, validated and easily self-administered questionnaire for assessing the frequency and burden of autonomic dysfunction in PD patients. On the other hand, COMPASS is a complex and long questionnaire, which has not been specifically validated for use in PD. As mentioned earlier, assessment of OH symptoms can only be considered as a screening test since the agreement between blood pressure decreases during an orthostatic challenge and OH symptoms is very poor both in PD [8, 26] and in the general population [30].

5. Treatment

Identification of the mechanism of orthostatic hypotension (disease, drug or other causes) is the first step in the treatment, followed by non-pharmacological measures. Exposure to diuretics, amantadine and polypharmacy, dopamine agonists, alpha-adrenergic blockers used for prostatic hyperplasia, clonidine or many antidepressants should be appraised and reconsidered [8, 9, 31]. Patients should also be advised to avoid precipitating factors such as sudden postural change, large meals, hot baths, alcohol and vasodilating medications [32]. Other non-pharmacological methods for treating OH include addition of salt to the diet, exercise, compression stockings or physical manoeuvres that help to raise blood pressure.

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Drug	Status	Dose	Effect duration	Safety
Midodrine	Approved for neurogenic OH in USA and Europe	5-10 mg/day	2-4 hs	supine hypertension, paresthesias and goose-bumps
Fludrocortisone	Approved in USA and Europe, but used off-label in OH	0.1-0.3 mg/day	days	nausea, chest discomfort, nocturnal hypertension, hypocalcaemia, postural oedemas, Addison syndrome
Droxidopa	Experimental. In PD it reduced risk of fall but not OH	200-300 mg/day	hours	tachycardia, hypertension, nausea and vomiting, headache
Fipamezole	Experimental, in Phase III	30-90 mg/day	hours	hypertension, atrial fibrillation, presyncope and tachycardia

Table 1. Pharmacological treatment of orthostatic hypotension in PD.

In patients with insufficient or absent responses, pharmacological options should be offered, midodrine or fludrocortisone being the first line treatments. Nonetheless, a recent systematic review demonstrated that several common pharmacological or non-pharmacological treatments for orthostatic hypotension have been examined only in low-quality trials [33]. Similarly, the Movement Disorders Society Evidence-based medicine (MDS-EBM) review did not identify any clinically useful drugs [34]. Therefore, the treatment of OH in PD still relies on personal experiences or on a low-quality level of evidence. We will briefly review the characteristics of midodrine and fludrocortisone. Some experimental therapies will also be reviewed. A summary can be found in Table 1.

5.1 Midodrine

Midodrine, an alpha1-adrenergic agonist, is considered to be a first line drug for OH treatment [31]. Even if evidence about its efficacy is weak, it is the only drug approved for OH treatment by the FDA and in many European countries [17].

Midodrine is a pro-drug that is metabolized to desglymidodrine, the active compound [17, 35]. Such effects usually last less than two to four hours. The minimum effective dose is 5mg, but patients usually need 10mg or more. Patients should take the drug before getting out of bed or at lunch, to avoid hypotension following postural change and postprandial hypotension and at mid-afternoon [17]. The drug should never be taken after 1800 hours to avoid nocturnal hypertension.

The main side effects are supine hypertension, paresthesias (including troublesome scalp-tingling) and goose bumps. Caution in its use in older males is necessary because of its adverse effects on urinary outflow [28].

5.2 Fludrocortisone

This mineralocorticoid is commonly used for OH management as it increases renal sodium re-absorption and expands plasma volume, thus leading to increased blood pressure [36]. The usual dose is 0.3mg/day. Effects last longer than those of midodrine, thus making it more difficult to avoid nocturnal hypertension.

The efficacy of fludrocortisone is insufficiently documented [36]. Indeed, there is only one study available, in which the efficacy and safety of domperidone or fludrocortisone were explored in PD [37]. Adverse events to fludrocortisone include nausea, chest discomfort, morning headaches, light-headedness and dizziness. With prolonged treatment, nocturnal hypertension, hypocalcaemia, postural oedemas, pulmonary oedema and Addison syndrome can also be observed.

5.3 Experimental therapies.

Droxidopa, an oral pro-drug that is converted to norepinephrine via decarboxylation, is undergoing clinical trials for neurogenic OH [38]. Droxidopa could exert its pressor effect by being converted to epinephrine and activating the sympathetic preganglionic neurons in the spinal cord; by converting to norepinephrine in post ganglionic sympathetic neurons and being released when sympathetic neurons are activated, or it could be converted to norepinephrine outside neurons and released into the blood stream as a circulating hormone [38]. Clinical trials have shown that droxidopa treatment results in reduced orthostatic falls in blood pressure [39], with an overall trend towards improvement in symptoms that did not reach statistical significance. Nonetheless, further studies in PD patients failed to replicate previous results [40]. However, a post-hoc analysis of data coming from clinical trials suggest that the drug may be efficacious to prevent falls [41].

Another promising drug for OH is fipamezole, an alpha 2-adrenergic receptor antagonist [42]. The acute haemodynamic effects of fipamezole were evaluated in a double blind placebo controlled study in 21 PD patients with encouraging results [43]. Further research is, however, needed.

Integrative medicine might represent a valuable alternative as it is for other aspects of Parkinson's disease [44] but further research is needed.

6. Conclusion

Orthostatic hypotension is a frequent and disabling comorbidity in PD. Recent results suggest that it affects about in third of PD patients, which thus have increased risk for falls, cognitive deterioration and death. Till test is essential for the clinical appraisal of OH, with the Schellong test and presence of symptoms serving only as screening tests. OH is the result in PD mainly of altered baroreflex function, which in turn results from cardiac and vascular sympathetic denervation. Treatment should begin with re-considering drug treatments, as many drugs may aggravate OH. After treatment is optimized, non-pharmacological measures may be employed. Drugs treatment should be reserved for patients in whom other strategies have failed. Midodrine and fludrocortisone are the most frequently used treatment, even though evidence about their efficacy and safety is weak. Midodrine has a shorter duration of action and thus avoidance of evening dosing may help keep intact nocturnal blood pressure dipping. Promising alternatives may include droxidopa and fipamezole.

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