

Orthostatic Hypotension in Parkinson's Disease



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Orthostatic hypotension (OH) has been recognised as a feature of Parkinson's disease (PD) for many years, but has, until recently, been largely attributed to a side effect of dopaminergic medication. Recent interest in the 'multisystem' nature of PD has led to wider recognition of the 'non motor' features of PD, including renewed focus on the dysautonomia associated with the disease.

Using the standard definition of OH (20mmHg fall in systolic or 10mmHg fall in diastolic blood pressure within three minutes of standing or head up tilt to at least 60°) between 20-58% of patients with PD have a 'pathological' orthostatic blood pressure drop.² Extending tilting beyond the three-minute guidance will identify an additional 'late OH' group. Correlation of orthostatic symptoms (dizziness, drowsiness and characteristic 'coat-hanger' ache across the shoulders) with objectively measured OH is poor however, regardless of the length of tilt employed.^{3,4} Why symptoms are so poorly correlated with objective signs is unclear: OH is associated with cognitive decline, particularly with impairment in attentional reserve,⁵ and this may in part explain why some patients with objective OH fail to volunteer expected symptoms. Conversely, poor reproducibility of OH may result in a high 'false negative' diagnostic pool, thereby negatively impacting on correlation of blood pressure changes with symptoms.

Fatigue is the most common non motor symptom in PD, affecting nearly 60% of patients.⁶ Studies in non parkinsonian patients have shown an association between autonomic dysfunction and fatigue severity.⁷ Little is known about the potential relationship between OH and fatigue in PD, and given the significant negative impact of fatigue on quality of life in PD this is a high priority area for future research.

Perhaps because of the methodological difficulties in clearly 'capturing' OH in PD, correlation with falls is surprisingly poor. Disease duration, disease severity and history of previous falls remain the strongest individual predictors of future falls. Any association with OH is weaker, some studies supporting an association, others with conflicting results.^{8,9}

Dysautonomia in PD is related to both peripheral and central autonomic pathology. Studies using metaiodobenzylguanidine (MIBG) as a marker of sympathetic nerve activity show reduced uptake in even the earliest stages of clinical PD.¹⁰ Subjects with PD and OH show reduced resting noradrenaline levels,

supersensitivity to exogenous noradrenaline and upregulation of peripheral $\alpha 2$ adrenoceptors, findings consistent with peripheral sympathetic dysfunction.¹¹ Neuropathological studies confirm the presence of Lewy body pathology in peripheral autonomic ganglia and lower brainstem autonomic nuclei in the presymptomatic phase of the disease. As pathological changes 'ascend' through the brainstem and into the cerebral cortex disease severity increases and, alongside the development of neuropsychiatric features of the disease, other 'higher level autonomic centres' become involved.¹² Both the insular cortex and anterior cingulate area are sites of predilection for Lewy body pathology in PD: As sites of integration of autonomic with limbic and motor function respectively, it is likely that involvement of these higher cortical centres will contribute to the severity of OH in PD. Initial studies are supportive of this hypothesis, demonstrating higher cortical Lewy Body counts in patients with PD and OH compared to subjects with PD alone.¹³

Treatments for OH in PD are largely based on strategies to compensate for poor peripheral autonomic function. Non pharmacological therapies such as compression stockings, caffeine, exercise and avoidance of warm weather and hot baths reduce vascular capacitance, whilst reduction of nocturia through elevation of the bed head alongside increasing salt and fluid intake increase plasma volume. A number of different medications are used in the treatment of symptomatic OH in PD, but the evidence to support efficacy in this condition per se is weak, relying primarily on extrapolation of outcomes from studies on patients with other hypotensive conditions: Medications acting on blood volume (erythropoietin), blood vessel tone (etilefrine, midodrine), sympathetic pathways (pyridostigmine) and for the prevention of postprandial hypotension (octreotide) are used within this context.

A double blind cross over trial of the mineralocorticoid fludrocortisone (0.1mg daily), perhaps the most widely used antihypotensive agent, and the D2 antagonist domperidone (10mg three times daily) in subjects with PD and OH has shown some interesting and disease specific results. Both treatments improved symptoms of orthostatic dizziness and although the measured reduction in postural drop did not reach statistical significance, there was a trend towards improved haemodynamic response which was greatest in the domperidone treatment phase.¹⁴

A recent study of the sympathomimetic drug droxidopa has shown encouraging preliminary results. The synthetic catecholamine, which is metabolised to norepinephrine in vivo, appears to be well tolerated by patients with PD and OH and effective in reducing symptoms of orthostatic dizziness.¹⁵

Non motor features, including dizziness and fatigue, have significant impact on the quality of life of patients with PD. With increasing understanding of the interplay between peripheral and central autonomic pathology in PD, it should be possible to target treatment of the autonomic symptoms, including OH, more effectively. There are very few studies of treatments for OH specifically in PD, and larger clinical trials would be welcome. ♦

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