Parkinson’s Disease
Autonomic Neuronopathy With Impaired Cardiovascular Regulation

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Parkinson’s Disease (PD) is generally considered a movement disorder characterized by loss of dopaminergic neurons in the central nervous system (CNS), most notably in the substantia nigra. The pathogenesis of the neuronal degeneration is not completely understood but is characterized by abnormal protein deposits forming characteristic neuronal inclusions, which are visible by light microscopy of autopsy samples, and termed Lewy bodies. α-Synuclein is one of the proteins found in these inclusions and has attracted interest because mutations of the gene encoding for this protein are found in familiar cases of PD. Most of the disability associated with PD is indeed the result of this CNS defect, and the treatment is aimed at increasing dopamine levels in the CNS, while avoiding as much as possible an increase in the periphery.

Less widely recognized is the fact that orthostatic hypotension can occur in PD patients and can become symptomatic and disabling in a significant proportion of patients. The incidence of documented orthostatic hypotension in PD, in community-based studies, ranges from 10% to 40%.

Orthostatic hypotension in PD is commonly attributed to the known adverse effects of dopaminergic drugs. However, over the last decade there is growing evidence that peripheral nerves, particularly autonomic neurons, are also involved in PD. Lewy body inclusions, containing α-synuclein, have been found in peripheral autonomic neurons in autopsy cases of otherwise classic PD. Microscopically, eosinophilic, or α-synuclein–positive Lewy Bodies and Lewy neurites are not only found in the substantia nigra and locus ceruleus but also are widespread in ganglion cells and axons of the paravertebral sympathetic chain, prevertebral mesenteric, and stellate ganglia. Furthermore, many studies have shown that patients with otherwise classic PD have at least partial loss of noradrenergic neurons innervating the heart, as evidenced by decrease uptake of 123I-labeled metaiodobenzylguanidine and 18fluorine-labeled dopamine. Although there is currently little doubt that sympathetic impairment occurs in PD patients, the incidence of autonomic involvement in PD and its contribution to orthostatic hypotension have not been systematically explored.

In this context, Barbic et al report in this issue of Hypertension that PD patients have measurable impairment of sympathetic vascular modulation, as determined by a reduction in the power of low-frequency variability of blood pressure. These patients had an average duration of disease of 7.5 years but had otherwise mild disease, and, importantly, they included a group of patients who had no clinical evidence of orthostatic hypotension. In these patients, the main defect was an absence of the expected increase in low-frequency variability of blood pressure, an indicator of sympathetic modulation of vascular tone, in response to upright tilt. A limitation in this study, acknowledged by the authors, is that the patients were being treated with dopaminergic agents. It is doubtful, however, that this explains the abnormalities observed. Withdrawal of dopaminergic agents in PD carries significant risks and limits the use of this approach in research.

These results provide additional evidence supporting the concept that PD, in addition to central degeneration of dopaminergic neurons, is also characterized by peripheral degeneration of autonomic nerves involved in cardiovascular regulation. Anecdotal reports indicate that these abnormalities can be seen very early in the disease, but the incidence of subclinical autonomic abnormalities has not been determined. Cardiac imaging of sympathetic neurons using fluorodopamine and metaiodobenzylguanidine uptake are advocated as sensitive methods to diagnose early cardiac sympathetic denervation, but this approach requires imaging techniques that are expensive, available mostly in research institutions, and difficult to apply to large numbers of patients. The study by Barbic et al raises the possibility that spectral analysis may provide a research tool to determine the incidence of autonomic abnormalities in early PD. There are, however, limitations to spectral analysis of heart rate and blood pressure, as with any other research technique.

It is now widely accepted that high-frequency variability of heart rate reflects parasympathetic modulation of sinus node function, and low-frequency variability of blood pressure reflects sympathetic modulation of vascular tone. Studies inducing autonomic withdrawal with ganglionic blockade and observations in patients with different forms of autonomic failure have demonstrated the validity of these indices. Barbic et al found a decrease in both parameters, suggesting impairment of both sympathetic and parasympathetic function, consistent with an autonomic neuronopathy in these patients. High-frequency variability of heart rate in PD patients was half that of controls. This biologically important difference did not reach statistical significance most likely

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**Stepwise Approach to Management of Orthostatic Hypotension**

1. Remove aggravating factors
   - Volume depletion
   - Prolonged bed rest/deconditioning
   - Alcohol
   - Diuretics
   - Tricyclic antidepressants
   - Venodilators (nitrates)
   - Antihypertensives (α-blockers, guanethidine)
   - α-Blockers used to treat prostatic hypertrophy

2. Medical nonpharmacological treatment
   - Liberalize salt intake, salt supplements
   - Head-up tilt during the night
   - Waist-high support stockings
   - Exercise as tolerated, preferable in-water exercises

3. Pharmacological treatment
   - Sodium chloride 1 g per meal
   - Fludrocortisone (Florinef) 0.1 to 0.3 mg/d
   - Short-acting pressor agents:
     - Midodrine (Proamitine) 5 to 10 mg*
     - Yohimbine (Yocon) 5.4 mg*
     - Indomethacin (Indocin) 25 mg*

   *Short-acting pressor agents should be used as needed to improve orthostatic tolerance, on an as-needed basis, rather than at fixed doses. A dose of these short-acting pressor agents, given before exertion, will improve orthostatic symptoms for 2 to 3 hours. In general, administration of >3 doses per day is discouraged to avoid adverse effects and development of tolerance.

Novel therapies under development for the movement disorder of PD may not have orthostatic hypotension as a adverse effect. For example, adenosine A<sub>2A</sub> receptor blockers are being developed as adjunct therapy to levodopa in the treatment of PD. Blockade of A<sub>2A</sub> receptors in the brain stem leads to an increase in blood pressure, and the adenosine receptor antagonist caffeine prevents postprandial hypotension. It is possible, therefore, that this novel treatment may provide a therapeutic benefit not only for the movement disorder of PD but also for the treatment of orthostatic hypotension. This, however, remains speculative.

It is not surprising that PD is associated with autonomic impairment considering that this is also seen in other α-synucleinopathies. Pure autonomic failure, the archetypical disorder of autonomic function, is also characterized by α-synuclein deposits forming Lewy bodies. Furthermore, the spectrum of α-synucleinopathies includes dementia with Lewy bodies, which also has an increased incidence of autonomic impairment. α-Synuclein deposits are also the hallmark of multiple system atrophy, another neurodegenerative disorder with prominent autonomic involvement. In this disease, α-synuclein deposits do not form Lewy bodies but are present in glial cytoplasmic inclusions instead. The one thing all of these α-synucleinopathies have in common is their increased risk of developing symptomatic autonomic failure. It would be of scientific interest to determine the pathogenetic basis for this predisposition.

There is no known effective disease modifying treatment for PD. One would question, therefore, the usefulness of early recognition of subclinical autonomic impairment in individual patients. On the other hand, it is important to recognize patients who are at risk of orthostatic hypotension, particularly in the postprandial period, when they are at higher danger of falls. It may be that a reduction in dopaminergic treatment may be required in some patients to prevent falls, at the expense of worsening of their movement disorder. This, however, may not be necessary if treatment of their orthostatic hypotension with short-acting pressor agents and volume regulators are tried first. A list of potential treatments is shown in the Table, but it should be recognized that controlled studies for the treatment of orthostatic hypotension are lacking in autonomic failure patients in general and PD patients in particular.

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**Disclosures**

None.

**References**