Cardiovascular Autonomic Dysfunction in Parkinson's Disease: Editorial Commentary

Autonomic dysfunction has long been considered a late symptom of Parkinson's disease (PD). However, this has now been proven to be erroneous. Today, autonomic dysfunctions, including neurogenic orthostatic hypotension (OH), are well-recognized nonmotor symptoms of patients with PD of all stages. Strong evidence suggests that autonomic dysfunction can actually present as one of the earliest prodromal symptoms occurring years before motor symptoms appear.[1-3] In this study, the authors find autonomic dysfunction to the tune of 68.3% of patients with early PD with a mean Hoehn and Yahr (H and Y) stage of 2.[4]

Autonomic involvement in PD and other synucleinopathies results from variable involvement of the central and peripheral autonomic systems. Symptoms such as OH, constipation, urinary symptoms, sexual dysfunctions, heat and cold intolerance, sweating, drooling, and swallowing problems likely result from the dysregulation of more than one subdivision of the autonomic nervous system. This has also been supported by neuropathological studies, which found Lewy bodies, the pathological hallmark of PD, at cerebral and spinal levels, in sympathetic trunk ganglia, cardiac nerve cells, gastrointestinal, submandibular, and even in intestinal plexuses, and other areas of peripheral autonomic networks.[5-7]

The discovery of genetic mutations causing different familial forms of PD and other synucleinopathies has thrown up exciting opportunities to understand the pathophysiology of these entities and the evolution of their clinical symptomatology. Similar to the sporadic form, patients of PD with Synuclein Alpha (SNCA) gene mutation develop autonomic dysfunction even before the onset of motor symptoms. On the other hand, autonomic dysfunction was much less in PD caused by mutations of genes unrelated to alpha-synuclein accumulations (e.g., PARK2).[8]

The influence of autonomic dysfunctions on quality of life is immense in all stages of the disease. Cardiovascular involvement has evoked the most clinical interest because of the more frequent severe symptoms and availability of well-standardized, non-invasive investigations. The most frequent cardiovascular symptom among these patients is OH, occurring in more than half of the patients.[9] Goldstein *et al*.[10] reported that PD with OH accounts for more hospitalization, emergency visits, and appointments with doctors and has shorter survival than those with PD without OH. Overall, health care cost has been estimated to be 2.5 times higher among patients of PD with OH compared to PD without OH.[11] Similarly, another serious cardiovascular symptom is neurogenic supine hypertension (nSH) which can occur in up to 50% of patients with PD. The nSH, if left untreated, can cause end organ damage over time.[12] Hence, diagnosing and managing autonomic dysfunctions early in PD patients is paramount.

Autonomic dysfunction can also be evaluated using different clinical questionnaires, for example, Scales for Outcomes in PD—autonomic symptoms, Nonmotor symptoms questionnaire, and the Rome III constipation criteria. Objective autonomic cardiovascular testing can be divided into a) Tests of cardiovagal function such as respiratory mediated variability of heart rate, Valsalva maneuver, and active standing; b) Tests of sympathetic adrenergic function: Blood pressure (BP) response to postural changes like active standing or passive table tilt test, Valsalva maneuver, and sustained isometric muscle contraction; c) Spectral analysis of heart rate fluctuations which reflect modulation of sinus node activity by autonomic and other homeostatic mechanisms; d) Baroreflex analysis: Baroreflex gain or sensitivity calculated by measuring the changes of heart rate related to BP changes; e) 24 h ambulatory blood pressure measurement (ABPM); and f) Cardiac sympathetic imaging with ^{123}I-metaiodobenzylguanide and positron emission tomography scanning.[13] Unfortunately, autonomic laboratories are still very limited and unavailable to most patients. Hence, broadly available clinical tests like supine to standing orthostatic tests, heart rate variability, and 24 h ABPM are usually used to diagnose autonomic dysfunction in many centers. In healthy subjects, BP is lower during nighttime, which is described as "dipping." If BP does not decrease at night, it is termed "non-dipping," and an increase in the night-time BP is termed "reverse dipping." In PD patients, the prevalence of non-dipping and reverse dipping is high in several studies similar to the current study which showed a blood pressure variability of 79.7% and a reverse dipping pattern of 47.5%.[4,14] Iodine meta-iodobenzylguanidine (MIBG) scans can be useful in differentiating autonomic dysfunction in different synucleinopathies. MIBG uptake is impaired in PD patients with autonomic failure, while they are usually present in Multiple System Atrophy (MSA) patients. This indicates that in PD, damage to the postganglionic sympathetic efferents is the main cause of dysautonomia, in contrast to MSA, where postganglionic lesions do not appear. Abnormalities in MIBG scan can precede abnormalities in autonomic reflex.[13] Several studies have reported that cardiovascular dysfunctions do not correlate with the dopaminergic deficit, disease duration, or motor fluctuations.

Finally, the role of antiparkinsonian drugs as a cause of OH in PD patients has been debated for a long time. Earlier literature that described a marked hypotensive effect of L-dopa either had no additional decarboxylase inhibitor in the formulation or was administered at a high dose of one gram or more. Chronic levodopa therapy has not been demonstrated to

cause changes in sympathetic reflex mechanism controlling blood flow when assessed with the 133-Xenon washout technique. It has also influenced the myocardial functional sympathetic nerve terminals detected by myocardial 6-[18F] fluorodopamine-derived radioactivity.[13] Dopamine receptor agonists as PD medication has been attributed to low resting blood pressure and marked fall in orthostatic blood pressure. The OH is usually noted predominantly at the initiation of dopamine agonist therapy.

When orthostatic symptoms are noted in PD patients, non-medical measures are considered the first line of management. They include avoiding sudden changes in body positions; repeated intake of fluids (2–2.5 L/day); intake of a salt-rich diet; having several small meals throughout the day; light exercises such as swimming, aerobic training, and bicycling; and use of elastic stockings. Medical measures include drugs like midodrine, droxidopa, fludrocortisone, and pyridostigmine. Treatment of nSH can be challenging. Avoiding a supine position, resting in a reclining chair, and tilting the head end of the bed by 30–45 degrees at night can be considered. Among pharmacological measures, Nebivolol, Captopril, Clonidine, hydralazine, Losartan, and nitroglycerine patch have also been used.[12]

Cardiovascular autonomic dysfunctions are a common as well as disabling symptom in PD and other synucleinopathies. They can present at any stage of disease and may even precede the motor manifestations and should prompt the clinician for a more concerted attempt at management.

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