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Autonomic dysfunction in Parkinson's disease and other synucleinopathies: introduction to the series

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In his 1817 seminal essay, James Parkinson captured with astonishing clarity numerous clinical aspects of what came to be called Parkinson's disease (PD) in his honor, including key elements of its natural history, several of the prominent motor features, and some of its non-motor autonomic features, such as constipation, urinary dysfunction, and dysphagia.¹ He did not describe orthostatic hypotension (OH), though. Indeed, Parkinson did not have the opportunity to carefully question or even examine his patients, as five of the six patients included in his essay were only casually observed on the street.

Today, dysfunction of the autonomic nervous system - including neurogenic OH, among other signs and symptoms, is a well-known characteristic non-motor feature of patients with PD and other synucleinopathies that can occur at all stages of the disease. Moreover, there is strong evidence that autonomic dysfunction can be the one of the earliest, prodromal manifestations of the disease, occurring years or even decades before any of the defining motor characteristics are evident.²⁻⁴ The overlap between autonomic dysfunction and REM behavior disorder is increasingly apparent, which further supports their role as prodromal features of PD and other synucleinopathies.^{5, 6} In this issue of *Movement Disorders*, expert authors review the neuropathological, genetic, therapeutic, and natural history aspects of autonomic dysfunction in patients with PD and other synucleinopathies such as multiple system atrophy (MSA) or pure autonomic failure (PAF).

Autonomic dysfunction in the synucleinopathies results from variable involvement of the central and peripheral autonomic networks. The traditional notion is that autonomic dysfunction in patients with Lewy body disorders (i.e., PD and dementia with Lewy bodies) is caused by peripheral autonomic damage, whereas autonomic dysfunction in MSA is due to central autonomic dysfunction. And, although pathological studies usually confirm it,⁷

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ETHICAL COMPLIANCE STATEMENT

I confirm that I have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Coon, Cutsforth-Gregory and Benarroch⁸ show that this is not always the case. as Approximately 30% of patients with MSA have peripheral autonomic involvement, particularly as the disease progresses, and central autonomic involvement can also be seen in patients with PD. Recent discoveries also challenge the classification of MSA as an oligodendroglial synucleinopathy. We now know that neuronal pathology also plays an important role in the development and progression of MSA.⁹

Although sporadic forms are the most frequent, the growing description of genetic mutations causing synucleinopathy offers a window into understanding the physiopathology of these disorders, as reviewed by Chelban and colleagues.¹⁰ Patients with PD caused by mutations of the *SNCA* gene typically develop autonomic dysfunction, many times before the emergence of motor signs, similarly to sporadic forms. Interestingly, autonomic dysfunction is much less frequent in PD caused by mutations of genes unrelated to alpha-synuclein accumulation (e.g., *PARK2*), highlighting the preferential affinity that the protein alpha-synuclein has for the autonomic nervous system.

The morbidity of autonomic dysfunction in general, and of OH in particular, is noteworthy in patients with synucleinopathies. Patients with PD and OH generate more hospitalizations, emergency room visits, and telephone calls/e-mails to doctors, and they have a shorter survival than those with PD without OH.^{11, 12} Overall, the health-related cost in patients with PD and OH is 2.5-fold higher compared to patients with PD without OH.¹² Therefore, early diagnosis and treatment of autonomic dysfunction in patients with PD and other synucleinopathies should be a priority. As Palma and Kaufmann discuss in their review on treatments,¹³ improved understanding of the pathophysiology of autonomic dysfunction in neurodegenerative synucleinopathies has led to identification of therapeutic targets and development and recent approval of effective drug therapies. This review provides an updated overview of available options for treatment of autonomic disorders and offers practical algorithms for treatment of OH, constipation, and neurogenic bladder.

The development of novel treatments for autonomic dysfunction in synucleinopathies faces many challenges which contribute to difficulties in powering studies. For instance, the natural history of autonomic dysfunction in PD is poorly understood (e.g., does it remain stable, or worsen over time?), and the ability to detect clinically meaningful outcomes requires understanding of its evolution and variability. In this regard, the contribution by Merola and colleagues,¹⁴ shows that prevalence of OH increases in PD patients by 15%, and its symptomatic burden worsens by 20% over 12 months. This is an important step in understanding the natural history of these patients.

We hope this series is helpful to readers in order to increase awareness, expedite diagnosis, and optimize management of autonomic dysfunction in patients with PD and other synucleinopathies.

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