INVITED EDITORIAL

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Significance of dysautonomia in Parkinson's Disease and atypical parkinsonisms

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Parkinson's Disease (PD) and atypical parkinsonisms vary in the context of prevalence, age at onset, and initiation of autonomic failures [1–5] (Tab. 1). In Multiple System Atrophy (MSA), dysautonomia is associated with disruption within the central autonomic pathways, while in PD and Progressive Supranuclear Palsy (PSP), the deterioration is linked to the parasympathetic system [6–7]. Sympathetic system disturbance, though present in PD, is not as pronounced in PSP [6–7]. Autonomic failures, especially in tauopathic parkinsonian syndromes, are difficult to verify due to cognitive impairment which can intensify the risk of gait disorders. In MSA, orthostatic hypotension (OH) additionally increases the risk of falls. In PSP and PD, the presence of autonomic failures not bounded to OH is interpreted as a predictor for falls (e.g. in PSP constipation and dysuria) [8, 9]. The treatment of coexisting diseases may also be a cause of certain manifestations of dysautonomia e.g. OH in alpha-adrenoceptor blockers treatment commonly used in prostatic hypertrophy.

Dysautonomia is a core clinical feature in the criteria of MSA [10]. It is defined by voiding disturbances, urinary urge incontinence which cannot be linked to other causes, and neurogenic orthostatic hypotension (NOH). In PD, the manifestations of autonomic failure have been linked to cognitive deterioration [11]. In PSP, among the mandatory exclusion criteria can be mentioned predominant autonomic failure, which cannot be otherwise explained [12]. In Corticobasal Degeneration (CBD), significantly pronounced dysautonomia is indicated as an exclusion criterion, more suggestive of MSA when accompanied by cerebellar syndrome [13]. Dysautonomia has been indicated as one of the features enabling differential diagnosis of PSP-predominant cerebellar ataxia (PSP-C) and MSA with predominant cerebellar features (MSA-C) in a study concentrating on pathologically confirmed diseases [14]. Regardless of the clinical boundaries, the manifestations of MSA and PSP, especially in its Parkinsonism Predominant (PSP-P) subtype, may overlap [15, 16]. In the examination of PSP-P with MSA, PD and Dementia with Lewy Bodies (DLB), dysautonomia has been indicated as one of the primary features feasible in the examination [17]. Malkiewicz et al. [18] stressed the significance of dysautonomia in synucleinopathic and tauopathic parkinsonism, although they emphasised that the manifestation of autonomic failure differs, and may be feasible as a tool in differential diagnosis. The authors implemented a SCOPA-AUT questionnaire, a 5-minute tilt test and 5-minute heart rate variability (HRV) in the evaluation of autonomic failure of 76 patients with PD, 25 with PSP, 12 with MSA, and 20 healthy controls. This revealed decreased HRV among patients in all groups. However, when the PSP group was divided into PSP-Richardson's syndrome (PSP-RS) and PSP-P, the observation was not confirmed in the PSP-P group. Although NOH was present in PD and absent in PSP, the subanalysis indicated that more symptoms of dysautonomia were observed among PSP patients.

The fact that decreased HRV is linked with PSP-RS and MSA, but not with PSP-P, may suggest that subtypes of PSP may be associated with different mechanisms affecting the autonomic nervous system [19]. Previous evaluations of HRV, though lacking the division into PSP subtypes, revealed ambiguous results, which could be partly caused by the small number of patients [20]. Moreover, previous evaluations of R-R interval variability revealed contradictory outcomes, as in PSP certain studies showed a lack of significant abnormalities compared to controls [21, 22]. NOH was not detected in the PSP group, which aligns with most previous studies, although the outcomes of other studies were affected by differing methods of OH assessment [23, 24].

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Table 1. Epidemiological data

	Incidence	Age at onset	Prevalence of certain manifestations of autonomic failures through course of disease (e.g. dysuria)
Parkinson's Disease	17 per 100,000 [1]	Differing depending on subtype of disease	0–80%*
Multiple system atrophy	0.6 per 100,000 [4]	Average age 61.5 in MSA-P, 57.4 in MSA-C	Core clinical feature [10]
Corticobasal syndrome	0.6 per 100,000 [3]	Mean age at onset 64	
Progressive supranuclear palsy	0.6 per 100,000 [2]	Median age at diagnosis 72 (median time from primary symptoms to diagnosis = 4.2 years)	40–55%
Dementia with Lewy Bodies	3.8% new dementia cases [5]	Mean age at onset 75	

*Rate depending on stage of disease

The work by Malkiewicz et al. [18] suggests that cardiovascular symptoms and OH are a feasible tool in the differential diagnosis of PSP and MSA, whereas gastrointestinal and urinary evaluation may seem more beneficial in the differential diagnosis of PD and parkinsonism-plus. The results concerning the significance of gastrointestinal and urinary symptoms accord with the outcomes of autonomic failure manifestations of PSP presented in another study [9]. Dysautonomia in parkinsonisms has also been evaluated in supplementary examinations e.g. electrophysiological evaluation and neuroimaging [25–27]. A work evaluating dysautonomia in PD, MSA and PSP revealed common clinical dysautonomia in MSA, although it also found frequent subclinical autonomic failure in PSP [25]. Moreover, regional atrophy within the anteriotemporal and mediotemporal regions was linked to more severe OH when compared to non-severe in DLB [26]. Resting state functional magnetic resonance imaging assessment of PD patients showed a link between abnormalities within the thalamo-striato-hypothalamic functional connectivity and dysautonomia [27].

The treatment of autonomic failure in parkinsonisms is complex. In PD midodrine, droxidopa and fludrocortisone are commonly indicated treatments for OH [11]. In MSA, due to the spared noradrenergic fibres, the use of norepinephrine transporter inhibitors leading to an increase of norepinephrine levels in the synaptic gaps, may be feasible in the treatment of autonomic failures [28]. Interestingly, FTY720-Mitox, a derivative of the FTY72 drug approved for multiple sclerosis, has shown improvement in the context of autonomic failures, and was found to reduce alpha-synuclein accumulation and microglial activation [29]. Sialorrhea, the common manifestation of various parkinsonisms, has been linked to possibly beneficial treatment using botulin toxin injections into salivary glands [30].

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