

LETTER TO EDITOR

## DYSAUTONOMIA IN INHERITED PARKINSON DISEASE

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Dear Editor,

We read with great interest the excellent article by Dutkiewicz and Friedman [1]. The authors critically reviewed the available literature for the diagnosis of autonomic dysfunction, also known as *dysautonomia*, in Parkinson disease (PD). Dysautonomia includes many different medical conditions caused by autonomic nervous system failure, and is among the most important nonmotor symptoms in PD, present in 14% to 80% of PD cases [2-4].

Dysautonomia has also been seen in inherited forms of PD, which occur in approximately 5% to 10% of patients with PD [5,6]. Here, we briefly discuss dysautonomia in the most common monogenic forms of PD.

Dysautonomia in PD gene mutations differs among affected patients [6]. Some pathogenic PD mutations have only been reported in a single family, making general assessment difficult. In addition, the description of dysautonomia in these studies is only clinical, without more objective measures such as tilt test, autonomic reflex screening, (123)I-metaiodobenzylguanidine (123MIBG), and others [6].

Dysautonomia is probably best characterized in SNCA mutation carriers. Occurrence of orthostatic hypotension and tachycardia were reported in 11 of 21 patients with SNCA triplications [7]. SNCA duplications are not fully penetrant, but 15 of 44 symptomatic patients with SNCA duplication had orthostatic hypotension with cardiac sympathetic denervation and reduced cardiac 123MIBG uptake [7]. Of the 60 individuals known to be affected with Contursi kindred with p.Ala53Thr SNCA mutation, dysautonomia was reported in only 1. However, later analyses of 22 additional families (dysautonomia data available for 26 patients) that shared the same p.Ala53Thr SNCA mutation revealed that orthostatic hypotension, urinary incontinence, and central hypoventilation were present in 6 of 26 patients [8]. Dysautonomia was reported in most patients with p.Gly51Asp and p.Glu46Lys SNCA mutations. However, data were collected only in single families with these mutations (dysautonomia reported in 3/3 and 4/5) [6].

*LRRK2* mutations are the most common cause of autosomal dominant PD worldwide. The clinical phenotype seen in carriers with the *LRRK2* mutation is similar to that seen in patients with idiopathic PD. In a Japanese study, only 1 patient out of 5 had reduced 123MIBG cardiac uptake, and a Spanish clinical study comparing 33 *LRRK2* patients with 33 sporadic PD patients found no difference in urinary and gastrointestinal dysfunction [9, 10].

A rare mutation associated with autosomal dominant PD is *VPS35* p.Asp620Asn, with reports of orthostatic hypotension and constipation similar to those observed in patients suffering from idiopathic PD [11]. *CHCHD2* mutations are also a rare cause of autosomal dominant PD. In the first Japanese study, 2 of 12 affected family members had orthostatic hypotension [12], which was also observed in another *CHCHD2* study (7/13 patients) [13].

Autosomal recessive PD is characterized by an early age of onset, usually before age 50. *PRKN* is the most frequently reported autosomal recessive PD gene, and patients usually have a tremor-dominant PD subtype. Dysautonomia is uncommon in *PRKN* homozygotes/compound heterozygotes [14]. *PINK1* is the second most frequently reported mutation in autosomal recessive PD. Both clinical phenotype and occurrence of dysautonomia are similar to those in patients with *PRKN*. These patients usually exhibit orthostatic hypotension and urinary dysfunction in about 22% and 44% of cases, respectively [14]. In yet another extremely rare form of autosomal recessive PD—in this instance, due to *VPS13C* homozygous/compound heterozygous mutations—affected patients develop urinary dysfunction early in the disease course and usually before 40 years of age [15].

*SNCA* and *VPS13C* are associated with the most severe dysautonomia compared to other forms of genetically inherited PD. Dysautonomia is not the main nonmotor feature in *PRKN*, *LRRK2*, and *VPS35* mutations (Table 1); rather, its presence and frequency is most likely affected by the different cellular mechanisms leading to compromise in cell function in these genes. Systematic and prospective studies of dysautonomia in other genetic forms of PD are warranted.

**Table 1.** Autonomic Dysfunction in Different Monogenic Forms of PD

Gene	Mutation	Dysautonomia	Methodology	Reference
SNCA	p.Ala53Thr	Severe (6/26 patients)	Cardiac sympathetic denervation (6-[18F] fluorodopamine-derived radioactivity)	[6]
	p.Gly51Asp	Severe, early-onset orthostatic hypotension (3/3 patients)	Clinical evaluation	[6]
	p.Glu46Lys	Severe (4/5 patients)	Cardiac sympathetic denervation (123MIBG)	[6]
	Duplications	Mild, similar to sporadic PD (15/44 patients, including orthostatic hypotension with fainting, urinary incontinence, constipation, and erectile dysfunction)	Cardiac sympathetic denervation (123MIBG)	[7]
	Triplication	Severe, similar to multiple system atrophy (11/21 patients [6 orthostatic hypotension, 5 urinary incontinence])	Cardiac sympathetic denervation (6-[18F] fluorodopamine-derived radioactivity); heart-to-mediastinum ratio (123MIBG)	[7]
LRRK2	p.Glu2019Ser	Mild, similar age of onset and frequency to sporadic PD	Cardiac sympathetic denervation (123MIBG)	[10]
VPS35	p.Asp620Asn	Mild, similar age of onset and frequency to sporadic PD	Cardiac sympathetic denervation (123MIBG)	[11]
PRKN	Homozygous/compound heterozygous	Mild, similar age of onset and frequency to sporadic PD	Cardiac sympathetic denervation (123MIBG)	[14]
PINK1	Homozygous/compound heterozygous	Mild, similar frequency to sporadic PD; urinary dysfunction most frequently observed (44% in all autonomic dysfunctions reported); reduced 123MIBG uptake in left ventricle reported	Cardiac sympathetic denervation (123MIBG)	[16]
VPS13C	Homozygous/compound heterozygous	Early age of onset, severe orthostatic hypotension, even ≤40 (2/3 patients)	Clinical evaluation	[15]

Abbreviations: 123MIBG – (123)I-metaiodobenzylguanidine scintigraphy; PD – Parkinson disease.

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Dear Professor Wszolek, dear Doctor Milanowski,  
we are glad that our article "Diagnostics of autonomic disorders in Parkinson's disease" aroused your interest. Your letter added a new aspect of dysautonomia being sometimes related to genetic mutations in PD. Autonomic dysfunction deserves special attention, as it is a troublesome complaints of many of our patients. Thank you for such an interesting response to our article.

Yours sincerely,  
Andrzej Friedman, Justyna Dutkiewicz