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Autonomic disorders predicting Parkinson's disease

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SUMMARY

It is now well recognized that there is a premotor phase of Parkinson's disease (PD) with hyposmia and REM sleep behavior disorder caused by degeneration of specific CNS neurons. Most patients with PD describe autonomic symptoms at the time of diagnosis suggesting that these features may have potential sensitivity as clinical biomarkers of the premotor phase. The recognition that damage to peripheral autonomic neurons is present in the early stages of PD has led to a search for specific abnormalities in autonomic function that could serve as predictive biomarkers. There is evidence that constipation, urinary and sexual dysfunction and more recently decreased cardiac chronotropic response during exercise, are part of the premotor parkinsonian phenotype. The sensitivity and specificity of these features has yet to be accurately assessed. We briefly review the evidence for autonomic dysfunction as biomarker of premotor PD.

1. Introduction

Hallmark characteristics of Parkinson's disease (PD) include motor signs and symptoms, such as resting tremor, rigidity, bradykinesia, and gait disturbance. In addition, PD patients frequently exhibit non-motor features, such as sleep disturbances, impaired sense of smell (hyposmia), visual changes, neuropsychiatric, and autonomic abnormalities. Among these non-motor features, autonomic abnormalities are now recognized as a cardinal feature of PD, with characteristic deficits in cardiovascular, gastrointestinal (GI), genitourinary, and thermoregulatory functions.

Non-motor manifestations of PD are receiving increased attention, in part because they may be present at very early stages of the disease, sometimes years before the classic motor signs and symptoms become apparent [1]. Therefore, non-motor features may potentially predict the future development of PD years or even decades earlier than a motor-based diagnosis. Detecting this prodromal, premotor threshold by clinical examination, symptoms screening, or other tests is an important goal of research.

The presence of rapid eye movement (REM) sleep behavior disorder (RBD), and olfactory dysfunction, are already recognized to markedly increase the future risk of developing PD. In this review we will focus on the autonomic abnormalities that may occur in the premotor phase of PD, as a result of involvement of the peripheral autonomic nervous system, with emphasis on their potential relevance as putative clinical predictors of the disease (Table 1).

Table 1
Clinical biomarkers of premotor Parkinson's disease

Central nervous system	Peripheral and enteric nervous systems
Olfactory loss	Cardiovascular dysfunction
REM sleep behavior disorder	Gastrointestinal disturbances, constipation
Depression and mood disorders	Urinary dysfunction
	Sexual impairment, erectile dysfunction

2. Pathophysiological basis of using autonomic dysfunction as predictor of PD

Involvement of the dopaminergic nigrostriatal neurons underlies the motor deficits of PD. However, as shown by the staging system proposed by Braak and colleagues [2], the first stage of PD in the central nervous system (CNS) involves deposition of α-synuclein in the anterior olfactory nucleus and dorsal motor nucleus of the vagus. Peripheral autonomic ganglia may also be involved in this early Stage 1. Stage 2 is characterized by involvement of the medulla oblongata and the pons. Stage 3 affects midbrain (including the substantia nigra), and at Stages 4–6 cortical structures are affected. Additional studies suggest that peripheral postganglionic sympathetic denervation may occur even earlier [3,4], thus constituting the earliest stage of the disease, at least in certain patients [1,5]. The fact that incidental LB may be present in peripheral autonomic neurons before a diagnosis of PD is made [6] suggests that screening for specific autonomic abnormalities may detect the earliest stages of PD before it spreads to the CNS (Fig. 1). This raises the possibility that tests of peripheral autonomic function may be used as clinical predictive biomarkers for PD.

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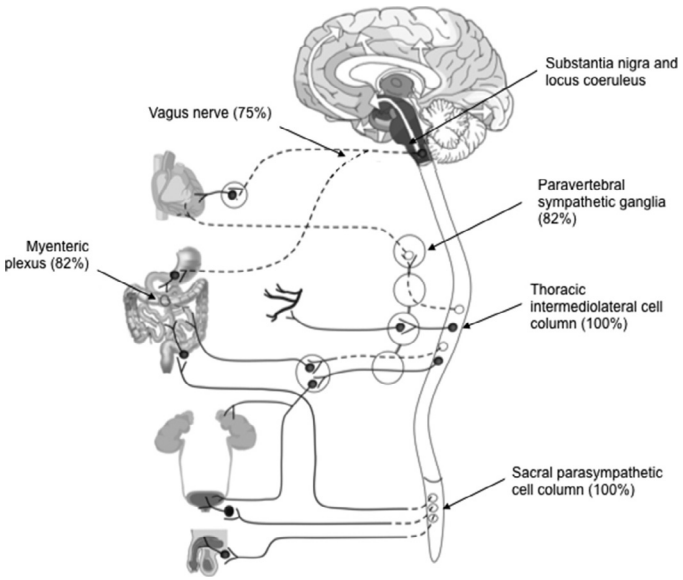

Fig. 1. Distribution of incidental Lewy bodies in elderly subjects without clinical evidence of parkinsonism or dementia. Data are those reported by Bloch and colleagues [6]. Interestingly, the localization of Lewy bodies in this group was strikingly similar to those reported in PAF patients [7]. Information regarding non-motor symptoms (orthostatic hypotension, erectile dysfunction or urinary problems) was not collected by Bloch et al.

3. Cardiovascular dysfunction

Changes in cardiovascular physiology are virtually universal in PD, and they may precede the development of motor features and the diagnosis of PD. Post-mortem studies of patients with incidental Lewy body (LB) disease, i.e., patients with LB in the CNS but no clinical features of PD during life, which is thought to be a presymptomatic stage of PD, showed α-synuclein-containing neuronal inclusions (Lewy pathology) in epicardial nerve fascicles [8]. In addition, LB restricted to the heart and stellate ganglia have been reported in post-mortem studies of patients without LB in the CNS or in neuronal somata of the paravertebral sympathetic ganglia [9], supporting the notion that α-synuclein deposits in cardiac postganglionic sympathetic nerve can precede involvement of other structures.

3.1. Cardiac sympathetic neuroimaging

The sympathetic innervation of the heart can be visualized in vivo using radiolabeled molecules that are substrates for the neuronal membrane norepinephrine transporter and for the vesicular monoamine transporter. ^{123}I-metaiodobenzylguanidine (MIBG) is widely available and combined with scintigraphy (single-photon emission computed tomography, SPECT) has been used in a large number of studies of patients with PD. 6-[^{18}F]fluorodopamine with positron emission tomography (PET) has also been used. 6-[^{18}F]fluorodopamine and MIBG uptake are consistently reduced in most PD patients, even at early stages, suggesting either functional abnormalities of the neuronal reuptake system or degeneration of cardiac sympathetic nerves.

No large studies have specifically evaluated whether impaired cardiac MIBG uptake can identify premotor PD. A recent study of asymptomatic carriers of a point mutation resulting in glutamic acid substitution by lysine in position 46 (E46K) of the α-synuclein gene (SNCA) disclosed reduced cardiac MIBG uptake with normal plasma norepinephrine levels and normal BP values [10]. Previous reports showed that patients with SNCA gene duplication and triplication [11] develop cardiac denervation, as measured by cardiac MIBG, with normal plasma catecholamines, suggesting a cardiac-specific involvement in these patients.

3.2. Chronotropic insufficiency

The clinical phenotype of cardiac sympathetic denervation in patients with PD has not been fully defined. It is likely to include chronotropic insufficiency, a finding that has been documented during treadmill exercise stress testing in patients with an established diagnosis of PD [12]. In a recent cohort study of 2,539 patients without a history of neurological disease who had undergone cardiac stress testing [13], 18 patients developed PD after a mean of 4 years. Retrospective analysis of the cohort revealed that patients who subsequently developed PD had a blunted heart rate response during stress testing (i.e., their maximum heart rate was significantly lower than expected for age and gender) when compared to those who did not develop motor symptoms. These findings suggest that chronotropic insufficiency may be an early sign of premotor PD, which might serve as potential biomarker.

3.3. Orthostatic hypotension

Orthostatic hypotension (OH) (i.e., fall in blood pressure of ≥20 mmHg systolic or 10 mmHg diastolic when moving from supine to standing) is present in up to 52% of PD patients [14]. OH in PD is likely a consequence of sympathetic denervation of the vasculature, as cardiac sympathetic denervation does not impair orthostatic tolerance. Normally, baroreflex-mediated sympathetic activation causing vasoconstriction maintains blood pressure in the standing posture. This compensatory vasoconstriction is absent or attenuated in patients with PD, resulting in OH. Interestingly, OH can occasionally precede the development of the disease. In a retrospective evaluation of the clinical data of 35 patients with PD and OH, 21 (60%) had documented early-onset OH (i.e., OH before, concurrent with, or starting within 1 year after the onset of motor symptoms). In 4 of these patients (i.e., 11% from the total of 35), OH had preceded the onset of parkinsonism [15]. However, a large prospective cohort study with a 14-year follow-up period involving more than 5,000 adults aged 65 years and older failed to show OH as a predictor of PD. Of 214 cases of incident PD that were identified during the follow-up period, OH was documented in 27 (18%) before the onset of motor symptoms while OH was documented in a similar percentage of patients who did not develop PD (970 patients, 17.9%) [16]. On the other hand, a recent study by Postuma and colleagues that prospectively assessed the autonomic symptoms in 91 patients with idiopathic RBD without parkinsonism or dementia showed that, after a mean follow-up period of 3.3 years, 32 developed a neurodegenerative disease [17]. 66% of patients with parkinsonism or dementia had OH at disease diagnosis compared with 0% of patients with “still idiopathic” RBD. The systolic blood pressure drop from lying to standing predicted the conversion to a defined neurodegenerative disorder with a sensitivity of around 60% up to 3 years before diagnosis. However, the severity of orthostatic symptoms, as measured by the *Unified Multiple System Atrophy Rating Scale* (UMSARS), was not a predictable biomarker.

3.4. Heart rate variability

Heart rate variability (HRV) is also being explored as a potential tool to screen for individuals at risk for PD. Some HRV variables, namely the standard deviation of the R–R intervals (SDNN), the very-low frequency (VLF) and low frequency (LF) spectral components, and the LF/HF ratio, are consistently decreased in patients with PD [18]. In patients with RBD, many of whom will develop PD, HRV is also