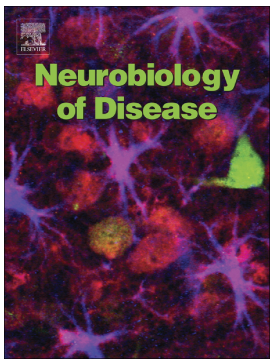

Autonomic dysfunction in Parkinson's disease: Implications for pathophysiology, diagnosis, and treatment

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Autonomic dysfunction in Parkinson's disease: Implications for pathophysiology, diagnosis, and treatment

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Abstract

Parkinson's disease (PD) is a neurodegenerative disease with a 200 year-long research history. Our understanding about its clinical phenotype and pathogenesis remains limited, although dopaminergic replacement therapy has significantly improved patient outcomes. Autonomic dysfunction is an essential category of non-motor phenotypes that has recently become a cutting edge field that directs frontier research in PD. In this review, we initially describe the epidemiology of dysautonomic symptoms in PD. Then, we perform a meticulous analysis of the pathophysiology of autonomic dysfunction in PD and propose that the peripheral autonomic nervous system may be a key route for α-synuclein pathology propagation from the periphery to the central nervous system. In addition, we recommend that constipation, orthostatic hypotension, urinary dysfunction, erectile dysfunction, and pure autonomic failure should be viewed as prodromal dysautonomic markers in PD prediction and diagnosis. Finally, we summarize the strategies currently available for the treatment of autonomic dysfunction in PD and suggest that high-quality, better-designed, randomized clinical trials should be conducted in the future.

Keywords: autonomic dysfunction; Parkinson's disease; epidemiology; pathophysiology; diagnosis; treatment

1. Introduction

Autonomic dysfunction is an important non-motor phenotype of Parkinson's disease (PD) (Schapira et al., 2017). Recently, an increasing number of studies have focused on the role of autonomic dysfunction in the prediction and early diagnosis of PD, making this one of the top research frontiers in the PD field (Berg et al., 2015; Fereshtehnejad et al., 2019; Schrag et al., 2015). Autonomic dysfunction in PD includes gastrointestinal malfunction, cardiovascular dysregulation, urinary disturbance, sexual dysfunction, thermoregulatory aberrance, and pupillo-motor and tear abnormalities (Berg et al., 2015; Postuma et al., 2013; Schrag et al., 2015). Our knowledge of the epidemiology of dysautonomic symptoms in PD is limited by insufficient attention, a lack of unambiguous definitions, and the inadequacy of objective methodologies to measure them (Schapira et al., 2017).

Although α-synuclein pathology and autonomic nerve denervation have been widely observed in the peripheral sympathetic, parasympathetic, and enteric nervous systems, the specific culprit or mechanism that leads to autonomic failure in PD has not yet been identified (Orimo et al., 2008b; Phillips et al., 2008). Pure autonomic failure (PAF) is a rare autonomic disease that was recently revealed to have a high risk of leading to the development of PD-related neuropathology and motor dysfunction during disease progression (Kaufmann et al., 2017; Singer et al., 2017). The breakthrough suggested that autonomic dysfunction might be one of the aetiological origins of PD pathophysiology, although most cases of PD might not be associated with autonomic dysfunction.

In previous decades, the international Movement Disorder Society (MDS) recommended that multiple clinical rating scales (shown in Table 1 and Section 4) should be used for the evaluation of autonomic dysfunction in PD which may improve the measurement of dysautonomic symptoms in PD (Evatt et al., 2009; Pavy-Le Traon et al., 2011; Pavy-Le Traon et al., 2018). Nevertheless, only limited objective assessments of dysautonomic symptoms are available in previous studies, highlighting the importance of applying functional, imaging, pathological, and electrophysiological techniques in future studies of autonomic dysfunction in PD. Although autonomic dysfunction is one of most common non-motor phenotypes in PD, it is very challenging to manage it (Palma and Kaufmann, 2018). The limited treatment options available

for autonomic dysfunction in PD make it one of the key issues in PD management. In this review, we make a sophisticated summary of recent research progress into autonomic dysfunction in PD with the hope of providing an integrated and prospective picture for future basic and clinical research.

2. Epidemiology

At least four categories of dysautonomic symptoms occur in PD patients, which include gastrointestinal malfunction, cardiovascular dysregulation, urinary disturbance, sexual dysfunction, thermoregulatory aberrance, and pupillo-motor and tear abnormalities (Figure 1). In addition, pupillo-motor and tear abnormalities due to the destruction of the ocular autonomic nervous system are also prevalent in PD (Figure 1). In this section, we describe the epidemiology of dysautonomic symptoms in PD patients to establish the importance and necessity of studying autonomic dysfunction in PD.

2.1. Gastrointestinal dysfunction

The frequency of gastrointestinal symptoms is very high in PD, even during the premotor phase of the disease. It has been reported that 88.9% of PD patients will develop gastrointestinal symptoms prior to the onset of Parkinsonian motor symptoms (Sung et al., 2014).

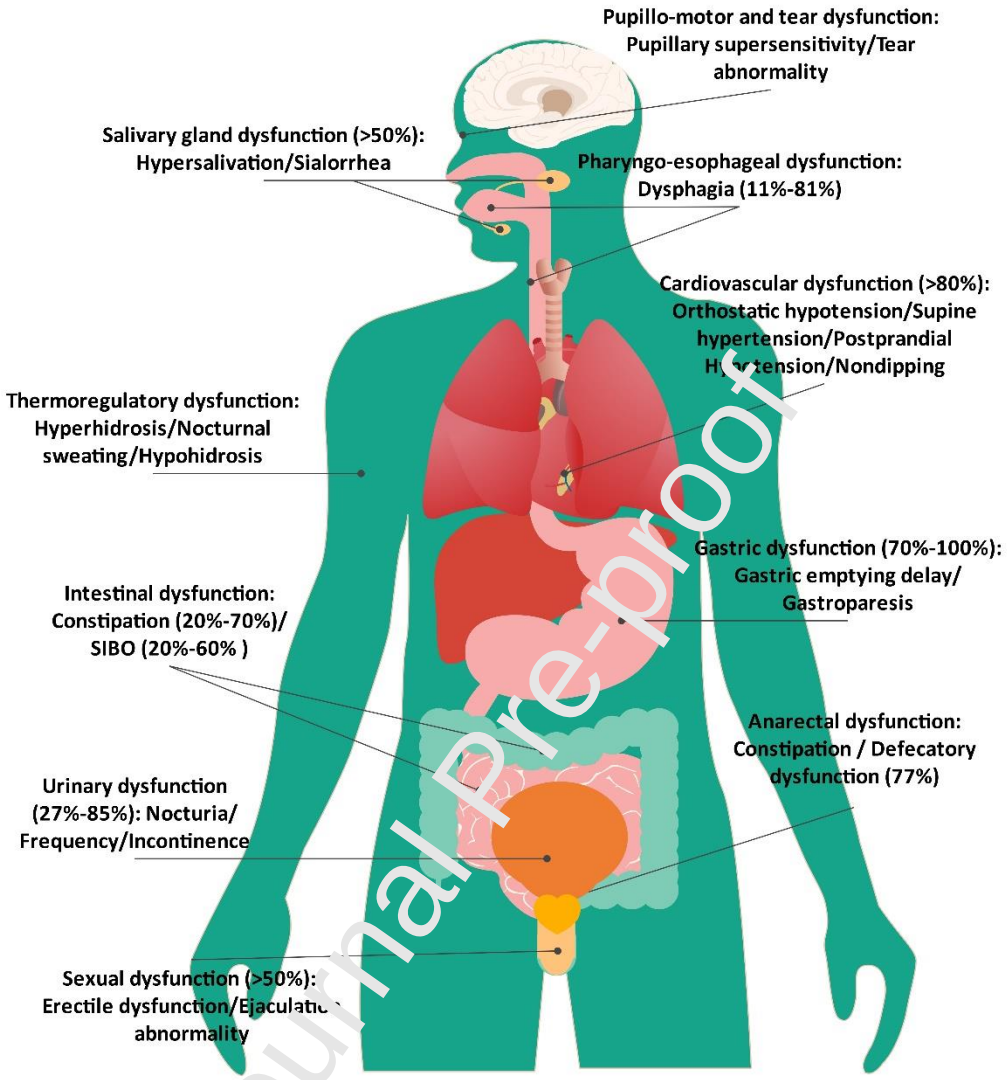

Figure 1. The distribution and frequency of dysautonomic symptoms in PD patients. This figure illustrates the most common dysautonomic symptoms observed in PD patients. Our findings indicate that autonomic dysfunction should be viewed as an important phenotype in the definition and characterization of PD.

2.1.1. Weight Loss

Almost half of PD patients show weight loss during disease progression (Cersosimo et al., 2018). However, weight loss can be associated with levodopa usage, rigidity, tremor, and other factors; thus, assessing the frequency of weight loss due to disease progression may be much

more accurate during the initial diagnosis of the disease, when patients have not yet started drug therapy. Because of a lack of sufficient attention, no accurate assessment of the frequency of weight loss that occurs during the pre-diagnosis or premotor phase of PD is available.

2.1.2. Sialorrhea

Sialorrhea occurs in over 50% of early PD patients (Malek et al., 2017). Sialorrhea can cause both day and night-time drooling. In PD, the frequency of drooling ranges from 32% to 74%, and the pooled drooling prevalence was estimated to be 56% in a systematic review (Kalf et al., 2009). Frequent drooling appears in approximately 25% of PD patients. Over 20% of PD patients exhibit diurnal drooling. Drooling causes social embarrassment and increases the risk of aspiration pneumonia; thus, it is a key clinical issue in the management of PD patients.

2.1.3. Dysphagia

According to a systematic review, dysphagia occurs in 11-81% of PD patients (Takizawa et al., 2016). Among newly diagnosed PD patients, over 15% may have dysphagia (Owolabi et al., 2014). As the disease progresses, the frequency and severity of dysphagia increase. Sex, age, disease duration and dementia are reported to be independently associated with the occurrence of swallowing disturbances in PD. Dysphagia significantly impairs patient quality of life and is a predictor of poor outcomes in late-stage PD.

2.1.4. Gastroparesis

The exact prevalence of gastroparesis in PD is still unknown. Among the causes that can lead to gastroparesis, PD accounts for 7.5% of all cases (Marrinan et al., 2014). A systematic review reported that the prevalence of gastric emptying delay in PD ranged from 70% to 100%, although many cases may be asymptomatic (Heetun and Quigley, 2012). In the premotor phase, gastroparesis may occur; however, its prevalence is not significantly different from that of the average population. Gastroparesis has the potential to affect nutrition and quality of life. It has also been reported to cause plasma levodopa peak delay, which would be an unavoidable concern in PD.

2.1.5. Small intestinal bacterial overgrowth syndrome

Small intestinal bacterial overgrowth (SIBO) is defined as an excessive amount of bacteria in the small intestine. The frequency of SIBO in PD ranges from 20% to 60% (Niu et al., 2016; Tan et al., 2014). SIBO may exacerbate gastrointestinal symptoms and motor functions, making it a key issue in PD management.

2.1.6. Constipation

According to previous studies, 20% to 70% of diagnosed PD patients have constipation symptoms (Kaye et al., 2006; Malek et al., 2017). Because constipation also occurs frequently in the premotor stage of PD, it has been incorporated into the MDS diagnostic criteria of prodromal PD (Berg et al., 2015). Multiple factors may contribute to constipation in PD; these include reduced water intake, mobility, and disease progression (Ueki and Otsuka, 2004).

2.1.7. Defecatory dysfunction

Defecatory dysfunction has been reported for decades in PD patients (Mathers et al., 1989). The prevalence of defecatory dysfunction in PD patients is nearly 77% (Edwards et al., 1994). PD patients with defecatory dysfunction usually exhibit diffuse lower abdominal discomfort, constipation, and fecal incontinence.

2.2. Cardiovascular dysfunction

2.2.1. Orthostatic Hypotension

Orthostatic Hypotension(OH) is a frequent cardiovascular symptom of PD. According to one systematic review and meta-analysis, the estimated prevalence of OH is approximately 30% in PD (Velseboer et al., 2011). In another study, 40% of early stage PD patients with no prior medication treatment were reported to have OH (Bae et al., 2011). Thus, OH is prevalent in early stage PD patients. OH may have a negative influence on disease progression and quality of life in PD patients, in whom it increases health care utilization, disrupts cognitive abilities, impairs daily

living activities, and increases the rate of medically attended falls. In addition, PD patients with OH have more severely impaired motor function. Even in the asymptomatic stage, OH is associated with impaired daily living activities.

2.2.2. Postprandial Hypotension

Postprandial hypotension occurs early in PD, in which the prevalence of postprandial hypotension is over 30% (Yalcin et al., 2016). The odds ratio (OR) of postprandial hypotension in PD is 3.49 according to a recent systematic review and meta-analysis (Pavelic et al., 2017). The prevalence of postprandial hypotension in PD was higher in patients with OH than in those without (Yalcin et al., 2016). Postprandial hypotension is associated with marked worsening of parkinsonian motor symptoms and is thought to be a predictor of all-cause mortality in older, low-level care residents.

2.2.3. Nondipping

Nondipping is defined as the loss of or any decrease in nocturnal blood pressure fall. Currently, only a few studies have reported on nondipping in PD. One reported that 88% of PD patients have nondipping (Sommer et al., 2011), and nondipping was found to be more prevalent in PD patients with OH than in those without (Sommer et al., 2011), consistent with a study conducted by Berganzo et al. (Berganzo et al., 2013). In a recent study, over 80% of PD patients were revealed to be pathological dippers (Arici Duz and Helvaci Yilmaz, 2019). Additionally, reverse dipping has been demonstrated to be a biomarker of dysautonomia in PD, indicating that nocturnal blood pressure is dysregulated in PD (Milazzo et al., 2018).

2.2.4. Supine Hypertension

Supine hypertension is a common characteristic of cardiovascular autonomic dysfunction that often accompanies OH (Goldstein et al., 2003). The prevalence of supine hypertension in PD is 34% (Fanciulli et al., 2016). Supine hypertension is associated with the occurrence of cardiovascular comorbidities, cognitive dysfunction, and a greater fall in systolic and diastolic orthostatic blood pressure. Supine hypertension also increases the risk of stroke, dementia, and

myocardial infarction in the long-term.

2.3. Urogenital dysfunction

2.3.1. Urinary dysfunction

According to previous studies, urinary dysfunction occurs in 27-85% of PD patients, with most symptoms classified as irritative (McDonald et al., 2017; Winge and Nielsen, 2012). It has been estimated that 64% of PD patients complain of urinary symptoms (Uchiyama et al., 2011). Urinary dysfunction also occurs in the early stage of PD. The most common irritative symptom in PD is nocturia, followed by frequency and urinary incontinence. Approximately 25% of affected patients present functional obstructive symptoms (Campos-Sousa et al., 2003). The most frequent obstructive symptom is incomplete emptying of the bladder. An increase in post-void residual urine volumes was observed in a small percentage of early drug-naïve PD patients (Lee et al., 2018b). Urinary dysfunction is associated with falls, cognitive impairment, and worse motor and non-motor impairment in PD patients. Lower tract urinary symptoms can jeopardize relationships, intimacy, and participation in social activities and cause embarrassment, all of which have a profound impact on quality of life.

2.3.2. Sexual Dysfunction

Sexual dysfunction occurs in over 50% of early stage PD patients (Malek et al., 2017). Dopamine replacement-induced hypersexuality and aberrant sexual behaviour, which are not due to dysautonomia itself but instead to impaired impulse control, have also been reported in PD (Giladi et al., 2007; Meco et al., 2008). A common presentation of sexual dysfunction in PD patients of both sexes is reduced sexual drive and arousal. Hypersexuality, erectile dysfunction, and ejaculation abnormality occur specifically in male PD patients, while female patients may experience loss of lubrication and involuntary urination during sex. Sexual dysfunction produces an extremely negative influence on the quality of life and emotional moods of PD patients.

2.4. Thermoregulatory dysfunction

Hyperhidrosis, especially nocturnal sweating, is one of the most common features of

thermoregulatory dysfunction in PD (Schestatsky et al., 2006; van Wamelen et al., 2019). Patients with hyperhidrosis usually exhibit higher dysautonomia burden than those without (van Wamelen et al., 2019). They also tend to present higher dyskinesia symptoms and have a worse quality of life and higher levels of anxiety and depression (van Wamelen et al., 2019).

2.5. Pupillo-motor and tear abnormalities

The pupillary light reflex has been known to be impaired in PD for decades (Giza et al., 2011). Pupillary unrest has also been found to be associated with both motor and non-motor features of PD (Jain et al., 2011). Pupillary supersensitivity to both parasympathomimetic agents and sympathomimetic agents has been reported in PD (Hori et al., 2008). Impaired tear function was first reported in PD patients in 2005 (Tamer et al., 2005). The clinical significance of pupil and tear abnormalities in PD is unknown.

3. Pathogenesis

3.1. Neuropathology

The two core hallmarks of autonomic neuropathology in PD are autonomic neuronal destruction and α-synuclein accumulation. Neuronal destruction is characterized by neuron loss, nerve fibre degeneration, and synapse loss. The accumulation of α-synuclein is characterized by the formation of Lewy bodies. The central autonomic control centres include the cortex, insula, hypothalamus, brain stem, and spinal cord, and both neuronal destruction and α-synuclein accumulation have been observed in these regions (Christopher et al., 2014; De Pablo-Fernandez et al., 2017; Del Tredici and Braak, 2012; Muntane et al., 2008; Oinas et al., 2010; Orimo et al., 2008b). In the peripheral autonomic nervous system, structures such as the vagus nerve, sympathetic nerve fibres, and enteric neural plexus exhibit neuronal destruction, and α-synuclein pathology is also common and can even precede central neuropathology (Bloch et al., 2006; Braak et al., 2007; Gold et al., 2013; Orimo et al., 2008b).

The neuropathology of the autonomic system, including both α-synuclein accumulation and neuronal destruction, has been reproduced in animal models of PD. Chronic exposure to rotenone induced a robust increase in α-synuclein aggregates that were similar to the enteric Lewy bodies found in idiopathic PD (Drolet et al., 2009). In addition, a rotenone-induced PD

model exhibited a significant loss in small intestine myenteric neurons, which also occurs in PD patients (Drolet et al., 2009). PD-related neuropathologies including α-synuclein aggregation and enteric neurodegeneration were also replicated in a PD mouse model that expressed human α-synuclein (Chen et al., 2018; Kuo et al., 2010), a 1-methyl-4-phenyl-1,2,3,6-tetrahydroxypyridine (MPTP) model (Anderson et al., 2007; Lai et al., 2018), and a 6-hydroxydopamine (6-OHDA) Rhesus monkey model (Shultz et al., 2016). In addition, 6-OHDA induced a reduction in cardiac sympathetic nerve fibres in nonhuman primates (Joers et al., 2014).

3.2. Genetic factors

Genetic factors affect multiple phenotypes of PD, including both motor and non-motor symptoms. A few studies have reported that autonomic dysfunction is associated with genetic factors. Gene variants that cause familial PD are associated with autonomic dysfunction in PD. Family PD patients usually present autonomic dysfunction in the early stage of the disease, in some cases in the premotor stage. It has been reported that SNCA gene duplication and triplication are both associated with cardiac sympathetic denervation in PD (Orimo et al., 2008a; Singleton et al., 2004). In addition, both symptomatic and asymptomatic SNCA E46K carriers exhibit cardiac sympathetic denervation (Tijero et al., 2013a; Tijero et al., 2010). In patients with GBA mutations, both colonic Lewy body pathology and cardiac sympathetic denervation have been observed (Brockmann et al., 2011; Lebouvier et al., 2014). In contrast, autonomic dysfunction is less prevalent and severe throughout the course of the disease in familial PD patients with PARK2 (parkin RING-Between-RING E3 ubiquitin protein ligase) and PARK9 (ATPase Cation Transporting 13A2) mutations (Kanai et al., 2009; Tijero et al., 2015). For carriers of the LRRK2 mutation, the earlier studies reported they tend to exhibit higher cardiac MIBG uptake, less gastrointestinal dysfunction, and relatively intact heart rate variability (HRV) as compared with idiopathic PD patients (Tijero et al., 2013b; Trinh et al., 2014; Visanji et al., 2017). However, recent studies showed that LRRK2 G2019S mutation carriers had increased beat-to-beat HRV and LRRK2 R1441G mutation carriers had higher scores of dysautonomia as compared to noncarriers (Carricarte Naranjo et al., 2019; Pont-Sunyer et al., 2017). Further studies were required to clarify

how the LRRK2 variants affect autonomic functions in PD. Therefore, autonomic dysfunction in PD can be modified by genetic factors.

3.3. Environmental factors

Only a few studies have investigated how environmental toxins cause PD-like pathology and PD-related autonomic dysfunction. Gastrointestinal tract is the major interface where external factors interact with internal environment. Gut microbiota alterations play a key role in the pathogenesis of PD. The imbalance of the gastrointestinal microbiota has been reported in PD patients by using 16s ribosomal RNA gene amplicon sequencing analysis (Barichella et al., 2019; Li et al., 2019; Pietrucci et al., 2019; Scheperjans et al., 2015). Scheperjans et al. (2015) reported that the intestinal microbiome was altered in PD and associated with the motor phenotype (Scheperjans et al., 2015). Barichella et al. (2019) found that decreased Lachnospiraceae and increased Lactobacillaceae and Christensenellaceae were significantly associated with worse cognitive impairment, gait disturbances, and postural instability in PD patients (Barichella et al., 2019). Pietrucci et al. (2019) reported reduced Lachnospiraceae and increased Enterobacteriaceae families were correlated with worse disease severity and motor impairment (Pietrucci et al., 2019). However, most studies have not found a correlation between altered microbiota and gastrointestinal symptoms, therefore, whether microbiota dysbiosis affects gastrointestinal symptoms in PD patients remains unknown. In a chronic MPTP model, researchers found that gastrointestinal dysfunction and intestinal pathology occurred prior to motor dysfunction (Lai et al., 2018). They found significant changes in the abundance of Lachnospiraceae, Erysipelotrichaceae, Prevotellaceae, Clostridiales, Erysipelotrichales and Proteobacteria (Lai et al., 2018). In rotenone induced-PD model, PD-like microbiome traits have been identified (Johnson et al., 2018). It was also revealed that gut microbiota were required for motor deficits, microglia activation, and α-synuclein pathology (Sampson et al., 2016). However, they all did not demonstrate that alterations in the gut microbiota were associated with gastrointestinal dysfunction in animal models. Previously, an epidemiological and genetic overlap between PD and inflammatory bowel disease (IBD) has been reported (Hui et al., 2018; Park et al., 2019; Villumsen et al., 2019; Zhu et al., 2019). It was shown that IBD patients had a 22%

increased risk of PD as compared with non-IBD individuals (HR=1.22) (Villumsen et al., 2019). In the past decades, microbiota alterations in IBD have been demonstrated to disrupt intestinal barrier, trigger intestinal inflammation, and induce autoimmune response (Chu et al., 2016; Iyer et al., 2018; Levy et al., 2015), therefore, it is very likely that microbiota dysbiosis may also induce gastrointestinal inflammation and functional impairment in PD. Future studies are required to identify the correlations between gastrointestinal dysfunction and microbiota dyshomeostasis in PD.

SIBO is among the most common gastrointestinal phenotypes of PD and may be associated with gastrointestinal dysfunction. However, it has been reported that SIBO is not related to worse gastrointestinal symptoms, indicating that SIBO is likely a parallel consequence but not the cause of gastrointestinal symptoms (Tan et al., 2014). Interestingly, bile acid abnormality and altered lipid metabolism in PD have been found to be associated with gut microbiota dysbiosis (Hasuike et al., 2019). Thus there is possibility that gut microbiota may induce gastrointestinal dysfunction by affecting biochemical metabolism of gut tract of PD patients.

The question of whether gastrointestinal infection is associated with autonomic dysfunction in PD remains unresolved. A study conducted by Tan et al. (2014) reported that nearly one-third of PD patients are infected with *Helicobacter pylori* (HP) (Tan et al., 2015). Although they found that HP positivity was associated with worse motor function, HP infection had no effect on the gastrointestinal symptoms of patients (Tan et al., 2015). Recently, intestinal Gram-negative bacteria infection has been demonstrated to induce mitochondrial antigen presentation and cytotoxic mitochondria-specific CD8+ T cells in both periphery and the brain in Pink1$^{-/-}$ mice (Matheoud et al., 2019). Thus it is possible that autoimmune and inflammatory responses may mediate the intestinal dysfunction and autonomic dysfunction in PD.

3.4. Mechanisms and hypothesis

3.4.1 Peripheral nerve dysfunction

Most dysautonomic symptoms can be attributed to the functional or structural impairment of peripheral nerves of the autonomic nervous system, including the sympathetic nervous system, the parasympathetic nervous system, and the enteric neural plexuses. In a clinical setting, PD patients with autonomic dysfunction usually present with extremely severe degeneration of

autonomic nerve fibres and neurons in both the early and late stages of the disease.

With regard for gastrointestinal dysfunction, dysautonomic symptoms can be attributed to the degeneration of the autonomic nervous system that innervates the gut, including the peripheral sympathetic nerve, vagus nerve, sacral parasympathetic nerve, and enteric plexuses. Most gastrointestinal dysfunction observed in PD may reflect an impairment in the mobility of the digestive tracts from the oral outlet to the anal outlet; these impairments can include dysphagia, gastrin emptying delay, gastroparesis, intestinal dysmotility, constipation and so on. Generally, the parasympathetic nervous system drives gastrointestinal mobility, and the sympathetic nervous system antagonizes the mobility induced by the parasympathetic nervous system. The vagus nerve system is the major parasympathetic nervous system important to the regulation of gastrointestinal motility functions. In PD patients, vagus nerve degeneration is very common and has been associated with the development of PD (Breen et al., 2019; Pelz et al., 2018; Phillips et al., 2008; Tsukita et al., 2018). Pelz et al (2018) revealed that vagus nerve (VN) axons were significantly smaller in PD patients than in controls by using high-resolution ultrasound (Pelz et al., 2018), which was also found by Walter et al (2018) (Walter et al., 2018). The deposition of α-synuclein has been observed in vagus nerve in PD patients and PD animal models (Kalaitzakis et al., 2008; Mu et al., 2013; Noorian et al., 2012; Phillips et al., 2008; Uemura et al., 2018). In animal experiments, the vagus nerve has been demonstrated to be an essential route for the transmission of α-synuclein pathology from the periphery to the central nervous system or from central regions to peripheral nervous system (Holmqvist et al., 2014; Kim et al., 2019; Uemura et al., 2018; Ulusoy et al., 2017; Van Den Berge et al., 2019). The enteric neuropathology observed in PD patients has been reproduced in PD models and is thought to be associated with gastrointestinal dysfunction (Colucci et al., 2012; Greene et al., 2009; Zhang et al., 2015). In a MPTP mouse model, changes in colon motility were associated with the loss of enteric dopaminergic neurons (Anderson et al., 2007). In a rotenone-induced PD model, delayed gastric emptying was reported to be mediated by enteric nervous system dysfunction (Greene et al., 2009). In a 6-OHDA-induced PD rat model, intestinal dysmotility was shown to be related to neurochemical changes in the enteric system (Colucci et al., 2012).

With regard for cardiovascular dysfunction, the destruction of both the sympathetic nervous system and the parasympathetic nervous system may contribute to the imbalances observed in

blood pressure and heart rate variability (HRV). Under physiological conditions, the baroreflex modulates the homeostasis of blood pressure under stressed situations, such as an increase in blood volume or shock. However, the baroreflex is not the only mechanism involved in maintaining stable blood pressure within a physiological range. Balanced cardiac contraction and relaxation, a normal blood volume, enough peripheral vascular resistance, and the elastic reservoir ability of the aorta all contribute to the maintenance and stability of blood pressure. Changing from the supine position to the standing position causes a decrease in the volume of blood that flows back to the right heart from the peripheral organs, resulting in a subsequent decrease in cardiac output and a decline in blood pressure. In a physiological situation, the carotid sinus baroreceptor senses that less mechanical pressure is produced by the blood, and this results in a reduction in parasympathetic activity and an increase in sympathetic activity in the cardiovascular system. A reduction in afferent transmission of the baroreflex and an increase in sympathetic activity complement the decline of blood pressure caused by the orthostatic position change. In PD, OH may be related to the abnormal response of the cardiovascular regulatory centre to a reduction of blood pressure due to a body position change. Goldstein et al. (2005) proposed that lower baroreflexive cardiovagal gain during valsalva maneuver and orthostatism, sympathoneural failure, and cardiac and extracardiac noradrenergic denervation revealed by septal myocardial ^{18}F-dopamine radioactivity and plasma norepinephrine levels are strongly related to OH in PD (Goldstein et al., 2005). In fact, it has been shown that low baroreflex sensitivity is strongly associated with supine hypertension and OH in PD patients (Blaho et al., 2017). Nakamura et al. (2014) demonstrated that the failure to increase total peripheral resistance that results from impaired sympathetic innervation leads to large reductions in systolic blood pressure in OH in PD (Nakamura et al., 2014). In addition to the cardiac sympathetic system, a study has also revealed that cardiac parasympathetic dysfunction is observed in PD and associated with the development of OH, indicating that cardiac parasympathetic dysfunction and cardiac sympathetic denervation are concurrent with each other (Shibata et al., 2009).

The peripheral pelvic plexus and inferior hypogastric plexus control both bladder and sexual function, respectively, in humans. It remains unknown how the dysfunction of these sympathetic and parasympathetic nerves, which innervate the bladder and reproductive organs, contributes to urinary dysfunction. The degeneration of the peripheral pelvic plexus and inferior hypogastric

plexus have rarely been studied in PD.

The thermoregulatory dysfunction observed in PD may be mediated by peripheral mechanisms. The peripheral sympathetic and parasympathetic nervous system both participate in maintaining the stability of body temperature. In PD patients, sympathetic sudomotor and vasoconstrictive functions become impaired in parallel with a reduction in intraepidermal nerve fibre density and an increase in skin α-synuclein deposition (Asahina et al., 2014; Kass-Iliyya et al., 2015; Kuzkina et al., 2019). Therefore, skin neuropathy may be a potential cause of thermoregulatory dysfunction in PD.

In pupil function, pupillary parasympathetic and sympathetic postganglionic impairments both occur in PD (Hori et al., 2008), and these are thought to be the mechanism that mediate pupil abnormalities in this patient population.

3.4.2. Central autonomic dysregulation

The autonomic dysfunction observed in PD can be caused by the degeneration of the central nuclei or central neural networks that control physiological autonomic functions. Both cortical and subcortical structures are involved in the regulation of autonomic function in humans. The degeneration of central autonomic regulatory centres has been reviewed recently (Coon et al., 2018). The insular cortex plays a key role in autonomic and limbic integration, and neuropathological studies have revealed that α-synuclein pathology occurs in the insula in PD patients (Papapetropoulos and Mash, 2007). Papapetropoulos et al. (2007) found that the severity of PD-related neuropathology in the insular cortex was associated with OH in PD (Papapetropoulos and Mash, 2007), indicating the involvement of central mechanisms in cardiovascular dysfunction of PD. In the spinal cord, α-synuclein pathology was found in spinal cord lamina I neurons, in the parasympathetic preganglionic projection neurons of the vagal nerve, and in sympathetic preganglionic neurons of the spinal cord (Braak et al., 2007; Del Tredici and Braak, 2012). A new study published in 2019 revealed that the central network that modulates parasympathetic outflow was impaired in early PD by combining heart-rate-variability based methods and resting-state fMRI (Tessa et al., 2019).The degeneration of the nigrostriatal network may participate in the occurrence of autonomic dysfunction in PD. Anselmi et al. (2017)

identified a nigro-vagal monosynaptic pathway that regulates gastric tone and motility. Interestingly, this nigro-vagal pathway was impaired in a paraquat-induced model of Parkinsonism (Anselmi et al., 2017). Recent studies have shown that impaired cortical activation and functional connectivity shown in fMRI are associated with dysautonomia in PD. Suntrup et al. (2013) provided the first evidence showing that the cortical activation associated with swallowing is significantly reduced in PD patients (Suntrup et al., 2013), a finding that was further supported by a recent study that showed that changes in functional connectivity in swallowing-related cortices can contribute to dysphagia in PD (Gao et al., 2019). In addition, central cholinergic dysfunction has been reported to be associated with dysphagia in early PD (Lee et al., 2015). Therefore, central mechanisms may be involved in the cardiovascular and gastrointestinal dysfunction observed in PD.

Urinary dysfunction is mainly caused by central mechanisms in PD. Under physiological conditions, the basal-frontal ganglia circuit controls the lower sacral micturition reflex. However, in PD, the frontal-basal ganglia D1 dopaminergic circuit is impaired. This alteration results in the disinhibition of the micturition reflex and subsequent detrusor overactivity and overactive bladder symptoms (Sakakibara et al., 2014; Winge et al., 2005). In a study performed by Kitta et al. (2006), the researchers used positron emission tomography to identify the brain regions that were activated during detrusor overactivity in PD. They found that significant activation occurred in the periaqueductal grey, supplementary motor area, cerebellar vermis, insula, putamen and thalamus (Kitta et al., 2006). Urinary functions were also controlled by lower brainstem nuclei, including the pontine micturition centre and the pontine continence centre. Roy et al. (2019) found that brainstem degenerative changes around the pontine continence centre may be associated with bladder storage symptoms in PD (Roy et al., 2019). Sexual dysfunction is a common clinical feature in PD, which is characterized by reduced sexual drive and sexual arousal. Sexual drive and sexual arousal are regulated by neurobiological, endocrinological, and psychological mechanisms. The mechanisms of how central regulatory centres are involved in these sexual behaviour changes in PD remain unknown. Testosterone levels have been reported to be reduced in PD and are associated with non-motor symptoms (Okun et al., 2004a; Okun et al., 2004b). Thus, reduced testosterone levels may contribute to sexual dysfunction in PD. However, little is known about the pathological mechanisms involved in sexual dysfunction in PD.

3.4.3. α-synuclein and other toxicities

The pathology associated with α-synuclein or phosphorylated α-synuclein in the autonomic nervous system and its innervated regions is the hallmark of autonomic dysfunction in PD. However, the mechanism of how α-synuclein or phosphorylated α-synuclein exert neurotoxicity in the autonomic nervous system remains unknown. Generally, α-synuclein can induce multiple neuronal pathological phenotypes, including nuclear dysfunction, mitochondrial dysfunction, endoplasmic reticulum/Golgi dysfunction, autophagy/lysosomal dysfunction, and synaptic dysfunction (Wong and Krainc, 2017). Thus, it is very likely that autonomic nervous dysfunction may also share these common mechanisms of α-synuclein toxicity. Orimo et al. (2008) demonstrated that the axonal aggregation of α-synuclein may precede the degeneration of cardiac sympathetic nerves in PD, indicating a causal relationship between α-synuclein pathology and cardiac sympathetic denervation (Orimo et al., 2008b). In addition, α-synuclein-overexpressing transgenic mice showed intestinal accumulation of proteinase K-insoluble alpha-synuclein and autonomic deficits (Hallett et al., 2012). Moreover, α-synuclein deposition in the sympathetic noradrenergic neurons of skin biopsies has been associated with cardiac noradrenergic deficiency measured by ^{18}F-dopamine radioactivity in neurogenic OH, further supporting the notion that α-synuclein pathology plays a key role in cardiac nerve denervation (Isonaka et al., 2019). Accumulated neuropathological data presented in the literature demonstrates that Lewy body pathology occurs in the enteric plexuses and gastrointestinal tracts (Gold et al., 2013). Although α-synuclein pathologies have been localized in enteric plexuses and gastrointestinal tracts, whether they are associated with gut dysfunction in PD has not been demonstrated. Interestingly, a study performed by Lee et al. (2018) showed that the deposition of α-synuclein in the mucosal enteric nervous system was not associated with the functional impairment of the affected gut segment, indicating that α-synuclein pathology is not likely to be the cause of gastrointestinal dysfunction (Lee et al., 2018a).

3.4.4. Gut or autonomic route of α-synuclein propagation

α-Synuclein pathology and the degeneration of the autonomic nervous system are the two hallmarks of dysautonomia in PD. Previous studies have shown that α-synuclein pathology occurs

in parallel with the degeneration of autonomic neurons and nerve fibres (Orimo et al., 2008b). There is also consensus that α-synuclein pathology is an indicator of neurodegeneration, and degenerated neurons usually exhibit α-synuclein pathology. In the past decade, a dual-hit hypothesis has been proposed by the Braak group to better explain the distribution of α-synuclein pathology during PD development. In this hypothesis, a neurotropic pathogen (probably viral) is thought to enter the brain via two routes: a nasal route, with anterograde progression into the temporal lobe, and a gut or autonomic route, with retrograde propagation into the medulla, pons, and midbrain (Hawkes et al., 2007). Because the second route in this hypothesis is mostly involved in the autonomic nervous system in gastrointestinal tracts, this hypothesis suggests that autonomic dysfunction plays a key role in the development of neuropathology in PD. Previous neuropathological studies suggest that α-synuclein pathology, to some extent, may initially occur in autonomic peripheral nerves, including the peripheral sympathetic plexus, vagus nerve and other parasympathetic plexuses as well as enteric neural plexuses before gradually ascending to the lower brain stem nuclei, substantia nigra, striatum, and cortex (Del Tredici and Braak, 2012). This paradigm of peripheral to central transmission of α-synuclein pathology is supported by the finding that in PD patients, peripheral cardiac sympathetic axons exhibit neurodegeneration earlier than that has been observed in the neuronal somata or neurites in the paravertebral sympathetic ganglia (Orimo et al., 2008b). It is also further supported by direct evidence showing that human PD brain lysates containing different conformations of α-synuclein can be transported into the central nervous system via the vagal nerve following their injection into the intestinal wall (Holmqvist et al., 2014). The propagation of α-synuclein from the dorsal motor nucleus of the vagal nerve to the pons, midbrain, and forebrain was demonstrated in another study. Ulusoy et al. (2013) showed that the selective injection of adeno-associated viral vectors carrying human α-synuclein into the vagus nerve in the rat neck can lead to the progressive spreading of α-synuclein pathology to more rostral brain regions, including the ipsilateral coeruleus-subcoeruleus complex, dorsal raphae, hypothalamus and amygdala (Ulusoy et al., 2013). Recent studies also showed that treatment of α-synuclein-preformed fibrils in the mouse gastrointestinal tract caused Lewy body-like aggregates to form in the brainstem via the vagus nerve, and this effect could be prevented by vagotomy before inoculation (Kim et al., 2019; Uemura et al., 2018). In PD patients, the dorsal

motor nucleus of the vagus nerve shows early α-synuclein pathology; thus, the vagus nerve may be the most likely route for α-synuclein transmission from the peripheral autonomic system to the brain (Uemura et al., 2018). Interestingly, a full truncal vagotomy is associated with a reduced PD risk, further supporting the possibility that vagus nerve-induced α-synuclein propagation occurs in PD (Liu et al., 2017; Svensson et al., 2015). Appendix is innervated by vagus nerve, Killinger et al. (2018) showed that healthy human appendix contained α-synuclein aggregates and PD-associated α-synuclein truncation products (Killinger et al., 2018). Moreover, removal of the appendix was associated with a lower risk for PD and delayed age of PD onset (Killinger et al., 2018; Mendes et al., 2015). According to a recent study, vagus nerve may also be a route for the propagation of α-synuclein from brain to periphery (Van Den Berge et al., 2019). Van Den Berge et al. (2019) reported that α-synuclein can propagate from duodenum to brainstem, then from brainstem to stomach via the vagus nerve (Van Den Berge et al., 2019). A gut or autonomic route for α-synuclein pathology transmission may be further supported by findings related to rare pure autonomic failure (PAF), which was recently recognized as a new prodromal PD marker (Kaufmann et al., 2017; Singer et al., 2017). PAF patients show severe α-synuclein pathology in both the sympathetic and parasympathetic autonomic nervous systems (Hague et al., 1997). The pathology of α-synuclein observed in the periphery also occurs prior to the pathology observed in the central nigrostriatal system in PAF (Arai et al., 2000). As the disease progresses, the neuropathology of the central nervous system becomes evident. Therefore, findings in PAF suggest that in some cases of PD, neurodegeneration may initially originate in the autonomic nervous system and then propagate into the central nervous system. Though most of evidence supporting the autonomic propagation of α-synuclein focused on vagus nerve, it is possible that other parasympathetic and sympathetic pathways may also be possible routes for α-synuclein propagation. Orimo et al. (2008) found that accumulation of α-synuclein aggregates in the distal axons of the cardiac sympathetic nerves precedes that of neuronal somata or neurites (Orimo et al., 2008b). Den Berge et al. (2019) revealed that autonomic ganglia, cardiac autonomic nerves, dorsal motor nucleus of the vagus, and enteric plexus all participated in the propagation of α-synuclein pathology (Van Den Berge et al., 2019). Here, we propose an autonomic nerve-mediated α-synuclein propagation model to explain how the autonomic nervous system contributes to the growth of the α-synuclein pathology tree in PD (Figure 2). Future studies

performed in preclinical animal models and PD patients are required to confirm the reliability of non-vagal autonomic nerve-mediated α-synuclein propagation.

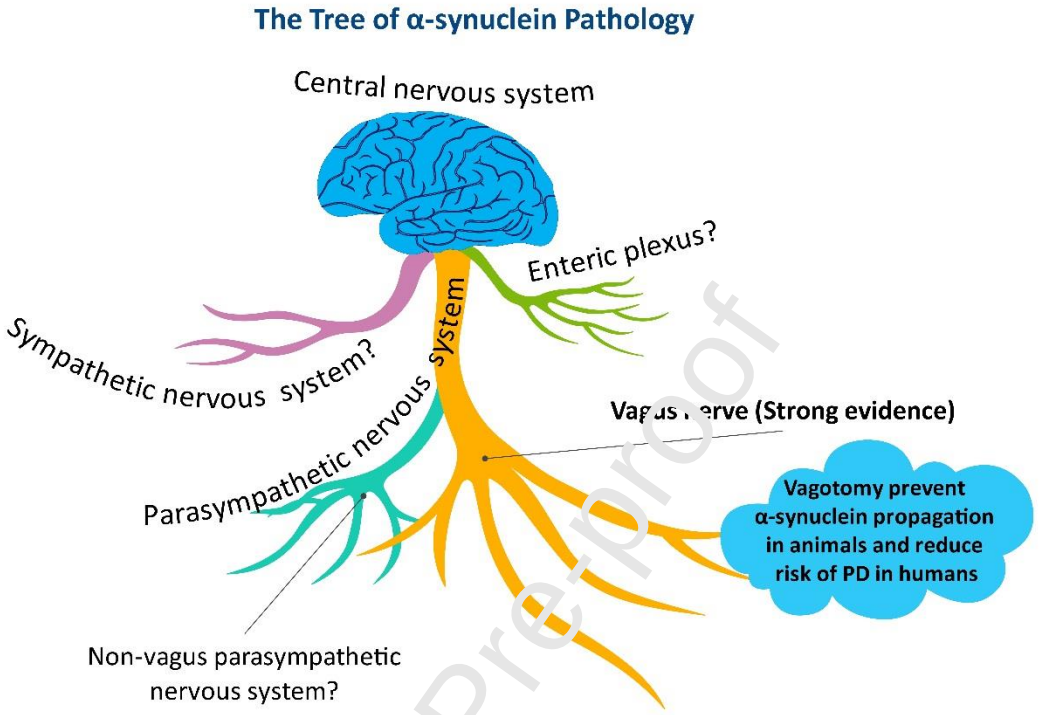

Figure 2. Growth of the "α-synuclein pathology" tree in PD. In this figure, we propose an autonomic nerve-mediated propagation model to illustrate how α-synuclein pathology originates in the peripheral autonomic nervous system and propagates into the central nervous system. According to the dual-hit hypothesis, nasal and gut routes may represent two possible pathways for α-synuclein transmission in PD. Because our review focused on the autonomic nervous system, the nasal route is not discussed in detail. Based on our analysis in this review, we believe there is enough evidence to demonstrate that the propagation of α-synuclein pathology may be partially mediated by the vagus nerve. Whether other autonomic nervous systems also participate in the propagation of α-synuclein pathology should be further investigated in future studies.

4. Clinical evaluation

Table 1

The scales for the evaluation of autonomic dysfunction in PD

Autonomic dysfunction	Scales	References
Global evaluation	SCOPA-AUT	Evatt et al., 2009
	Non-motor Symptoms Questionnaire	
Sialorrhea	Drooling Severity and Frequency Scale	Evatt et al., 2009
	Drooling Rating Scale	
	Sialorrhea Clinical Scale for PD	
Dysphagia	Swallowing Disturbance Questionnaire	Evatt et al., 2009
	Dysphagia-Specific Quality of Life scale	
	Swallowing Clinical Assessment Score	
Constipation	Rome III criteria or Rome II criteria	Evatt et al., 2009
Orthostatic hypotension	SCOPA-AUT	Pavy-Le Traon et al., 2011
	Composite Autonomic Symptom Scale	
	Orthostatic Grading Scale	
	Novel Non-Motor Symptoms Scale	
Urinary dysfunction	Danish Prostatic Symptom Score	Pavy-Le Traon et al., 2018
	International Consultation for Incontinence Questionnaire for Male Lower Urinary Tract Symptoms	
	Overactive Bladder Questionnaire (OABq)/OABq Short Form/8-item OABq score/OAB Symptom Score	
Sexual dysfunction	Quality of Sexual Life Questionnaire	Moore et al., 2002
	Arizona Sexual Experiences Scale	
	Sexual Dysfunction Inventory	

4.1. Clinical rating scales

The recommended global rating scales used for the evaluation of autonomic dysfunction by international MDS are the Scales for Outcomes in PD-Autonomic (SCOPA-AUT) and the Non-motor Symptoms Questionnaire for PD (Evatt et al., 2009). The scales suggested for assessing sialorrhea include the Drooling Severity and Frequency Scale, the Drooling Rating Scale, and the Sialorrhea Clinical Scale for PD. The scales suggested for evaluating dysphagia include the Swallowing Disturbance Questionnaire, the Dysphagia-Specific Quality of Life scale, and the Swallowing Clinical Assessment Score in Parkinson's Disease. Although the Rome III criteria are widely used for the diagnosis of constipation, the early Rome II version is also used in PD studies (Evatt et al., 2009). For the assessment of OH, the MDS task force recommended the SCOPA-AUT and the Composite Autonomic Symptom Scale (Pavy-Le Traon et al., 2011). They also suggested the Novel Non-Motor Symptoms Scale and the Orthostatic Grading Scale for evaluating OH in PD (Pavy-Le Traon et al., 2011). Regarding screening for orthostatic symptoms in PD, the criteria suggest the Self-completed Non-Motor Symptoms Questionnaire (Pavy-Le Traon et al., 2011). The rating scales recommended by the MDS for urinary evaluation include the Danish Prostatic Symptom Score, the International Consultation for Incontinence Questionnaire for Male Lower Urinary Tract Symptoms, the Overactive Bladder Questionnaire (OABq), the OABq Short Form, the 8-item OABq score, and the OAB Symptom Score(Pavy-Le Traon et al., 2018). Most of these scales are well-validated in urological settings, but none are validated specifically in PD. Therefore, they should be studied further and specifically validated in PD. The Quality of Sexual Life Questionnaire (QoSL-Q) is the first questionnaire used for the evaluation of sexual life quality in PD patients (Moore et al., 2002). The Arizona Sexual Experiences Scale and the Sexual Dysfunction Inventory can also be utilized to assess sexual dysfunction in PD. The clinical scales used for evaluating autonomic dysfunction in PD has been summarized in Table 1.

4.2. Objective examinations

4.2.1. Gastrointestinal functions

4.2.1.1. Saliva gland function

Saliva collection and analysis is the most direct methodology for assessing sialorrhea in PD (Tiigimae-Saar et al., 2018). The saliva of the participants is collected into a cup for 5 min in both resting and stimulated situations. The samples are generally taken at 2 hours after breakfast, and the patients are instructed to not brush their teeth before the collection procedure. To measure the amount of saliva under stimulated conditions, the patients chewed a piece of wax for 5 min before the collection of saliva, and this led to the accumulation of saliva in the oral cavity (Tiigimae-Saar et al., 2018). After saliva collection, the quantity and buffering capacity of the saliva were measured. Saliva composition can be analysed using a Saliva-Check BUFFER in Vitro Test or other commercial saliva tests (Tiigimae-Saar et al., 2018). Scintigraphy has been developed to evaluate sialorrhea in PD (Nicaretta et al., 2008). In this study, the uptake and intra-glandular distribution of Tc-99m (pertechnetate) in the parotid gland were not significantly altered in PD, but the speed of parotid excretion was higher in PD patients than in healthy subjects (Nicaretta et al., 2008).

4.2.1.2. Pharyngo-oesophageal motility

Fiberoptic endoscopic evaluation of swallowing (FEES) is an objective approach to measure dysphagia. Blumin et al. (2004) first evaluated laryngeal functions using FESS in PD patients. They found that PD patients showed significant vocal fold bowing (Blumin et al., 2004). A subsequent study used the FEES revealed swallowing disturbances in PD patients (Manor et al., 2007). In the past decade, FEES has been used to evaluate dysphagia severity, to assess the efficacy of dysphagia therapy and to study the pathophysiology of dysphagia in PD patients. The video-fluoroscopic swallowing study (VFSS) is also widely used to evaluate swallowing capacity in PD (Fukuoka et al., 2019). In VFSS images, PD patients show oropharyngeal bradykinesia, incoordination, reduced anterior hyoid bone movement, and decreased epiglottic rotation angle during swallowing. VFSS can also be used to predict aspiration pneumonia, validate clinical rating scales, and study the mechanisms of dysphagia in PD. High-resolution manometry (HRM) can be used to evaluate swallowing ability and oesophageal motility in PD patients. Researchers have used HRM to evaluate the pharyngo-oesophageal motility of PD patients in randomized clinical trials (Derrey et al., 2015). Radioisotope scintigraphy could be used to assess dysphagia. Potulska

et al. (2003) reported that when dysphagia was evaluated with oesophageal scintigraphy, it was observed in all 18 PD patients (Potulska et al., 2003). Electrophysiological study is an alternative test to evaluate oropharyngeal dysphagia in PD. Electrophysiological abnormalities frequently occur in PD and have been correlated with disease symptoms and pathophysiology (Ertekin, 2014).

4.2.1.3. Gastric emptying

Gastric scintigraphy is the gold standard methodology for the objective measurement of gastric emptying time (GET). In a recent systematic review, compared with healthy control subjects, PD patients showed a non-significant GET delay. However, when they excluded one outlier study, a significant delay was found (Knudsen et al., 2018). The ^{13}C-octanoate breath test has also been used to measure GET. According to the same systematic review, the ^{13}C-octanoate breath test revealed a highly significant GET delay in PD patients (Knudsen et al., 2018). Furthermore, significantly smaller amplitudes of peristaltic contractions were detected in the stomach by functional magnetic resonance imaging in PD subjects (Unger et al., 2010).

4.2.1.4. Intestinal motility

The radio-opaque marker (ROM) technique is an approach used to measure gastrointestinal transit time. A recent study revealed colonic dysfunction in the early to moderate stage of PD patients (Knudsen et al., 2017a). In addition to the ROM technique, colonic volumes derived from CT or MRI scans have been used to assess colonic functions. In PD patients, colonic volume is frequently increased, and this is especially pronounced in distal colonic segments (Knudsen et al., 2017a). A magnetic tracking system was designed to measure gastrointestinal transit time. Knudsen et al. (2017) used an ambulatory 3D-transit system to show that the small intestinal transit time was significantly longer in PD patients (Knudsen et al., 2017b). Intestinal scintigraphy has also been used for the evaluation of intestinal dysmotility in PD, and the duration of small intestine passage was found to be significantly longer in PD patients than in healthy controls (Dutkiewicz et al., 2015).

4.2.1.5. Anorectal function

Anorectal manometry is the most common technique for evaluating anorectal functions in PD. PD patients usually exhibit impaired voluntary sphincter squeeze (Ashraf et al., 1994). Stocchi et al. (2000) used anorectal manometry to show that the straining pattern was abnormal and that anal tone was decreased in PD patients (Stocchi et al., 1999). Recently, high-resolution anorectal manometry was applied in PD patients to evaluate defecatory dysfunction (Su et al., 2016). PD patients can have defecatory dyssynergia, balloon expulsion abnormalities, rectal sensation diminishment, and an absence of rectoanal inhibitory reflex (Su et al., 2016). Electromyography (EMG) is another technique used to measure anorectal function. EMG recordings usually show reduced recruitment of the external anal sphincter and puborectalis muscles in PD patients (Ashraf et al., 1995). Defecography is also a methodology used to evaluate defecatory dysfunction in PD. PD patients usually exhibit increased rectal widening, puborectalis muscle dysfunction, sphincter muscle abnormalities, incomplete emptying, and an elevated postdefecation residual volume in defecography studies.

4.2.2. Cardiovascular functions

4.2.2.1. Cardiovascular autonomic functional tests

Cardiovascular autonomic function tests (CVTs) include orthostatic tests, the head-up tilt test, the cold pressor test, deep breathing tests, Valsalva manoeuvres, the isometric contraction test, 24-h ambulatory blood pressure monitoring, 24-h Holter monitoring, hyperventilation tests, and so on. All of these tests have been used to assess cardiac autonomic functions in PD patients. R-R interval variation (RRIV) is an essential indicator of cardiac autonomic functions. RRIV has been investigated during deep breathing, Valsalva manoeuvres, and standing in PD (Bordet et al., 1996). PD patients may exhibit lower RRIV during deep breathing and the Valsalva manoeuvre. HRV can be measured using echocardiography. Both traditional spectral (very low frequency, VLF; low frequency, LF; high frequency, HF) and non-spectral components can be obtained. The Valsalva ratio, baroreflex sensitivity, and the coefficient of variation of RR intervals in the resting state (resting-CVRR) and during deep breathing (DB-CVRR) are utilized by researchers to study cardiac parasympathetic functions in PD. In these functional tests, PD patients often show

decreased cardiac parasympathetic parameters, and resting-CVRR and DB-CVRR are significantly reduced in the early phase of PD.

4.2.2.2. Cardiac ^{123}I-MIBG or ^{18}F-dopamine uptake

The most common examination used for the evaluation of sympathetic innervation is cardiac iodine-123-labelled metaiodobenzylguanidine (^{123}I-MIBG) uptake. The ratio of the average pixel count corresponding to the heart to that of the mediastinum (H/M) is defined as cardiac ^{123}I-MIBG uptake. Reduced cardiac ^{123}I-MIBG uptake is frequent in PD patients. In addition, reduced ^{123}I-MIBG uptake is intimately correlated with impaired heart functions during exercise, indicating that sympathetic denervation plays a critical role in the pathogenesis of autonomic dysfunction in PD. ^{18}F-dopamine is also a radiotracer used for the measurement of sympathetic dysfunction in PD patients (Goldstein et al., 2018). It has been used to assess cardiac sympathetic denervation in high-risk subjects with a family history of PD olfactory dysfunction, dream enactment behaviour, or OH.

4.2.2.3. ^{11}C-donepezil PET/CT

The PET tracer ^{11}C-donepezil has been validated for the in vivo quantification of acetylcholinesterase density in peripheral organs. Gjerløff et al. (2015) conducted the first study to assess acetylcholinesterase density in the peripheral organs of PD patients. They found that ^{11}C-donepezil binding was significantly decreased in the small intestine and pancreas of PD patients (Gjerloff et al., 2015). In a second study, Fedorova et al. (2017) found that PD patients showed significantly reduced ^{11}C-donepezil uptake in the small intestine, colon, and kidneys (Fedorova et al., 2017).

4.2.2.4. Sympathetic skin response

The abnormal sympathetic skin response (SSR) observed in PD patients was first reported in the 1990s. In that study, 14.5% of PD patients had an abnormal SSR (Wang et al., 1993). The prolongation of latency and reduced amplitudes are the two main presentations in an abnormal SSR in PD. A recent study demonstrated that forehead SSR was more sensitive for the evaluation

of autonomic dysfunction in both the early and late stages of PD (Sariahmetoglu et al., 2014).

4.2.3. Urinary functions

4.2.3.1. Urodynamic tests

PD patients may present detrusor hyperreflexia (67%), hyporeflexia or areflexia (16%), hyperreflexia with impaired contractile function (9%), and hyperreflexia with detrusor-sphincter dyssynergia (3%) in urodynamic tests. It has been reported that over 80% of PD patients have abnormal findings in urodynamic tests (Uchiyama et al., 2011). The urodynamic test is currently used to assess the epidemiology of urinary dysfunction and the efficacy of subthalamic deep brain stimulation (DBS) on bladder function and to study the mechanisms underlying urinary dysfunction in PD (Herzog et al., 2006).

4.2.3.2. Urinary sonography

To evaluate urinary retention, bladder sonography is performed before and after voluntary voiding. Hahn et al. (2005) initially reported that urinary retention was normal in PD patients but not in those with multiple system atrophy (Hahn and Ebersbach, 2005). Lee et al. (2018) reported that post-void residual urine volumes were higher in PD patients (Lee et al., 2018b). Further studies are required to investigate whether urinary retention can be evaluated based on bladder sonography changes in PD.

4.2.4. Thermoregulatory functions

The sympathetic skin response, sweat response, skin vasomotor reflex, and skin sympathetic nerve activity can be measured in peroneal nerves by microneurography and have been utilized to evaluate sympathetic sudomotor and vasoconstrictive neural function in PD (Shindo et al., 2008). The amplitudes of palmar sweat responses to deep inspiration, mental arithmetic, and exercise are usually lower in PD patients. These patients also exhibit a reduced skin vasomotor reflex and decreased sympathetic sudomotor and vasoconstrictive neural functions.

4.2.5. Pupillary function

Pupillary responses to various stimuli (dark/light adaptation, light reflex, near vision reaction and electrical sural stimulation) have been known to be impaired in PD for decades (Giza et al., 2011; Micieli et al., 1991). Whether the pupillary response observed in PD is specific and deserves investigation should be explored in future studies.

5. The utility for PD prediction and diagnosis

5.1. Prediction utility

Because multiple autonomic symptoms occur prior to motor impairment in PD, dysautonomic symptoms can be utilized to predict the occurrence of PD. In the diagnostic criteria for prodromal PD published in 2015 by MDS, dysautonomic symptoms, including constipation, symptomatic hypotension, severe erectile dysfunction, and urinary dysfunction, were recommended as prodromal markers of PD (Berg et al., 2015). In a recent study performed by the Schrag group, multiple dysautonomic symptoms were used to establish a risk algorithm to predict the diagnosis of PD; these included constipation, urinary dysfunction, hypotension, and hypersalivation (Schrag et al., 2019).

According to a systematic review and meta-analysis, compared to subjects without constipation, those with constipation had a pooled OR of 2.27 (95% CI 2.09 to 2.46) for developing PD (Adams-Carr et al., 2016). Recently, Fereshtehnejad et al. (2019) reported that constipation occurs 10-16 years prior to PD phenoconversion (Fereshtehnejad et al., 2019). Constipation is a frequent feature of iRBD patients and can significantly increase the risk of phenoconversion (Postuma et al., 2019). In addition, constipation also occurs in the premotor stage of Gaucher disease (GD) patients and in heterozygous GBA mutation-positive carriers (Gatto et al., 2016).

Reduced cardiac ^{123}I-MIBG uptake is also a prodromal marker of PD (Kashihara et al., 2010; Tijero et al., 2013a; Tijero et al., 2010). In iRBD patients, a marked reduction in cardiac ^{123}I-MIBG uptake was observed, similar to findings in early stage PD patients (Kashihara et al., 2010). In SCA2 patients with a higher risk of Parkinsonism occurrence, ^{123}I-MIBG myocardial scintigraphy also showed reduced cardiac uptake (Miyaue et al., 2017). In asymptomatic individuals with SNCA

mutations, the reduction in ^{123}I-MIBG uptake precedes nigrostriatal loss and motor impairment (Tijero et al., 2013a; Tijero et al., 2010). Because reduced ^{123}I-MIBG uptake implies impaired cardiovascular function, cardiovascular dysfunction may be a prodromal marker of PD. In fact, the risk ratio for patients with hypotension to develop PD was 3.23 in a study conducted by Schrag et al (Schrag et al., 2015). Thus, cardiovascular dysfunction has substantial value in predicting PD.

Urinary incontinence has been associated with incident parkinsonism and PD-related brain pathology (Buchman et al., 2017). An overactive bladder has been demonstrated to be a premotor biomarker of PD. Erectile dysfunction was incorporated into the diagnostic criteria of prodromal PD proposed by MDS (Berg et al., 2015). Erectile dysfunction can occur 10-16 years before PD phenoconversion. Additionally, erectile dysfunction also markedly increases the rate of phenoconversion in iRBD patients (Postuma et al., 2019).

PAF is a dysautonomic disease with a higher risk of converting into PD. However, it was not recognized as a prodromal marker of PD in the 2015 diagnostic criteria of MDS. PAF showed a pattern of Lewy body deposition similar to that of PD. It has been reported that the Lewy bodies can be observed in the substantia nigra, locus coeruleus, sympathetic ganglia, autonomic axons innervating cardiac tissues, periadrenal adipose tissue, and urinary bladder of PAF patients (Hague et al., 1997). Arai et al. (2000) first reported the association between PAF and synucleinopathy. They showed that PAF patients present a marked increase in α-synuclein deposition in both pre- and post-ganglionic lesions of the sympathetic and parasympathetic nervous systems, while substantia nigra lesions were absent, and no cortical Lewy bodies were observed (Arai et al., 2000). Orimo et al. (2002) revealed that cardiac sympathetic denervation was similar between PAF and PD patients, further indicating that PAF share an autonomic neuropathophysiology similar to that of PD (Orimo et al., 2002). Their results were validated in subsequent studies that showed that both PD patients and PAF patients have reduced noradrenergic innervation in the heart and extracardiac organs (Kashihara et al., 2006; Tipre and Goldstein, 2005). More interestingly, Goldstein et al. (2008) showed that PAF and PD exhibited similar nigral and overall central dopaminergic denervation. However, dopaminergic denervation was more severe in PD than in PAF, and sympathetic noradrenergic denervation was more severe in PAF than in PD (Goldstein et al., 2008). According to a recent study, Kaufmann et al. (2017) revealed that 6 of 74 (8.1%) PAF patients developed PD within a 4-year follow-up period

(Kaufmann et al., 2017). The average age of PAF patients at onset of symptomatic orthostatic hypotension was 65 years, and they obtained PD/DLB diagnosis after 9.5 years later. They also revealed that PAF patients with a supine heart rate over >70 bpm and heart rate response to tilt <10 bpm had higher risk for PD/DLB phenoconversion (Kaufmann et al., 2017). In another study, Singer et al. (2017) reported that 11 of 318 (3.5%) PAF patients converted into PD or dementia with Lewy bodies (Singer et al., 2017). They revealed reduced total Composite Autonomic Severity Score (CASS) and Orthostatic norepinephrine levels in PD/DLB converters as compared with stable PAF patients (Singer et al., 2017). They also found that a total CASS of less than 7 and an orthostatic rise in norepinephrine over 65 pg/mL had the highest risk for developing PD/DLB (Singer et al., 2017). The discrepancy of PD/DLB conversion ratio in these two studies could be due to differences in the diagnostic accuracy of PAF, different durations of follow-up, and differences in the medical conditions present in the PAF patients (Kaufmann et al., 2017; Singer et al., 2017). In summary, PAF is a new prodromal PD characterized by clinical autonomic dysfunction.

5.2. Diagnosis utility

PD is a neurodegenerative disease characterized by motor impairment and non-motor dysfunction. In the diagnostic criteria of PD proposed by MDS in 2015 (Postuma et al., 2015), cardiac sympathetic denervation diagnosed based on ^{123}I-MIBG scintigraphy is listed as a support criterion that can increase the diagnostic accuracy of PD (Postuma et al., 2015). However, these diagnostic criteria do not include other autonomic dysfunctions, such as constipation, OH, erectile dysfunction, and urinary dysfunction, as supportive criteria even though they were also prevalent in PD (Postuma et al., 2015). In contrast, they excluded those patients who exhibited severe autonomic failure in the first 5 years of disease, including those with OH and severe urinary incontinence or urinary retention (Postuma et al., 2015). This was because MSA patients usually develop severe autonomic dysfunction before motor impairment, and ^{123}I-MIBG scintigraphy is specifically altered in PD but not in MSA patients (Kashihara et al., 2006). By excluding subjects with severe autonomic failure, they significantly increased the diagnostic accuracy of established PD to over 90% and that probable PD to over 80%. This diagnostic

criterion may be accurate; however, it may also exclude PD patients with early autonomic dysfunction and those who may present severe autonomic dysfunction concurrent with motor impairment. As discussed above, multiple dysautonomic symptoms have been recognized as prodromal markers of PD, and we do not know why these dysautonomic symptoms are not used to support the diagnosis of PD. Even PAF patients, who have early and severe autonomic dysfunction, can convert to PD during disease progression (Kaufmann et al., 2017; Singer et al., 2017). Therefore, we have enough evidence to demonstrate that other dysautonomic phenotypes diagnosed in spite of ^{123}I-MIBG scintigraphy can be used to support PD diagnosis in clinical practice. Future studies may be required to examine the possibility that other dysautonomic phenotypes, such as constipation, OH, erectile dysfunction, and urinary dysfunction, could be supporting diagnostic criteria for PD.

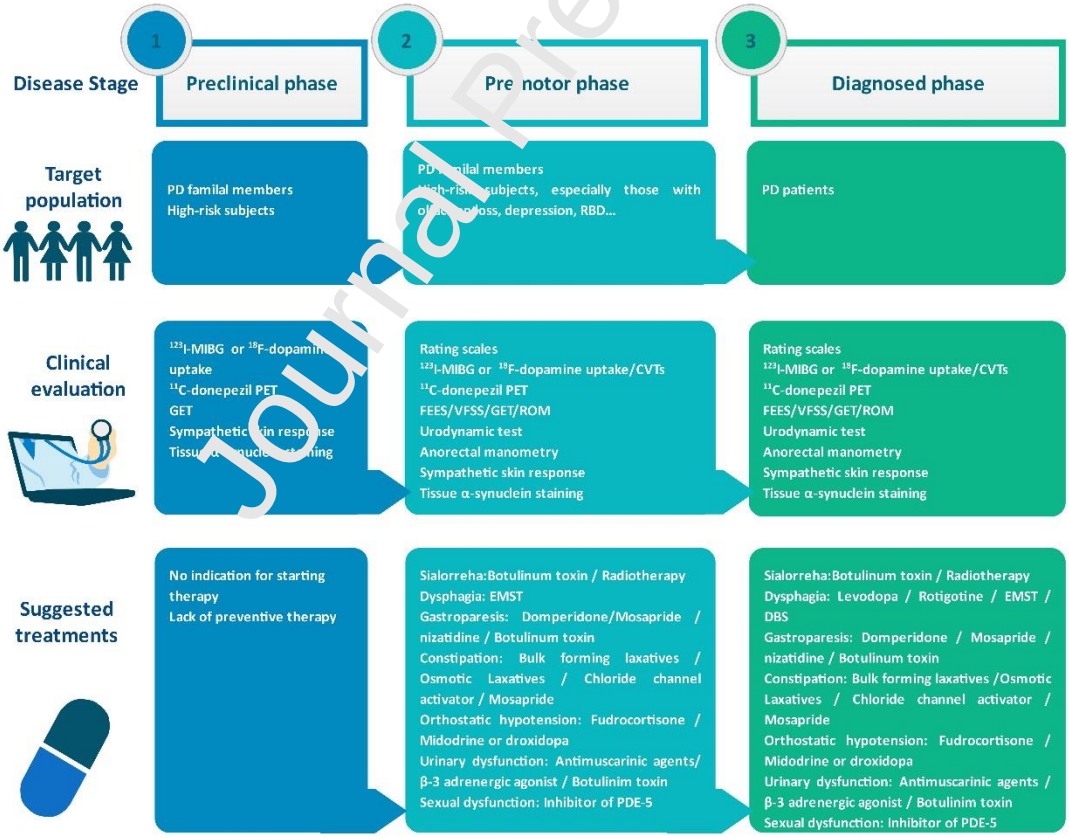

Figure 3. An algorithm for the evaluation and management of autonomic dysfunction in PD.

The figure shows the target population and the evaluation of and potential therapies for autonomic dysfunction in PD from the preclinical stage to the diagnosed stage. In the preclinical stage, it should be suggested that PD familial members and other high-risk subjects should be screened for potential dysfunction of the autonomic nervous system using objective examinations as this would help to identify those with early α-synuclein pathology or autonomic function abnormalities and the development and design of preventive therapies for them. In the premotor phase, the prodromal PD had non-motor symptoms and a high risk of converting to PD. Patients with both autonomic dysfunction and other non-motor phenotypes, such as subjects with hyposmia, iRBD, and depression, should be targeted. In this stage, autonomic symptoms should be treated, and therapies for prevention and conversion may be explored. In diagnosed PD patients, good management of dysautonomic symptoms, including urinary dysfunction and sexual dysfunction, should be achieved. Abbreviations: CVTs: Cardiovascular functional tests; DBS: Deep brain stimulation; EMSS: Expiratory muscle strength training; FESS: Fibreoptic endoscopic evaluation of swallowing; GET: Gastrin emptying time; PET: Positron emission tomography; RBD: REM sleep behaviour disorder; ROM: Radio-opaque marker; VFSS: Video-fluoroscopic swallowing study.

6. Treatments

Autonomic dysfunction is frequent and can occur in every stage of PD. When recognized, patients with autonomic dysfunction can be targeted, evaluated, and treated. In this section, we propose an algorithm to assist in the future recognition, evaluation, and treatment of dysautonomia in patients in different stages of PD (Figure 3). As we show in this figure, identifying the population with a higher risk of PD is the priority of this algorithm. In different stages of the disease, various approaches can be used to evaluate early alterations in autonomic functions. After populations with early autonomic dysfunction are screened, preventive therapies can be explored for both dysautonomia and PD in clinical trials. This would be invaluable to translational studies of prodromal PD. The initial consideration for the management of autonomic dysfunction in prodromal PD or PD is to identify whether the observed autonomic dysfunction is due to disease development or other environmental or medical conditions. If autonomic

dysfunction is not primary, it is secondary to causative/aggravating drugs or other non-PD diseases. The discontinuation of related causative/aggravating drugs and treatment of other diseases should be considered first. Clinical trials designed to treat autonomic dysfunction in PD are challenging to perform. Currently, only a few therapeutic options are supported by large, randomized, placebo-controlled trials (RCTs). According to previous clinical studies, patient education, nonpharmacological approaches, and drug therapy have been demonstrated to be effective for the improvement of autonomic dysfunction in PD. Here, in the last section, we summarize the options for the treatment of autonomic dysfunction in PD patients, including nonpharmacological and pharmacological therapeutic strategies, with the hope that this review will provide a practical algorithm for the management of autonomic dysfunction in PD.

6.1. Gastrointestinal dysfunction

6.1.1. Weight loss

Wight loss occurs in many medical conditions. In PD patients, the regular assessment of weight is needed to maintain energy homeostasis. If clinical weight loss is identified, specific approaches are required to prevent further weight loss. Diet adjustment is the most useful approach to maintaining body weight. A balanced diet with healthy nutritional factors is recommended for PD patients (Muraki et al., 2019). If gastrointestinal symptoms, including dysphagia, gastroparesis, or intestinal dysmotility, affect food intake in a PD patient, these symptoms should be managed. Currently, few clinical trials are evaluating the effects of drug therapies on weight loss in PD patients. Exenatide is a drug used for the treatment of diabetes in clinical practice. Aviles-Olmos et al. (2013) reported that exenatide did not significantly improve weight loss in PD patients (Aviles-Olmos et al., 2013). Considering that weight loss is not always bad (e.g., in overweight PD patients), future clinical trials are needed to treat weight loss with a focus on patients with dramatic weight loss, which can produce significant medical benefits.

6.1.2. Sialorrhea

Botulinum neurotoxin has been shown to be effective in treating sialorrhea or drooling in clinical trials. A systematic review published by Egevad et al. (2014) concluded that botulinum

neurotoxin was effective for the treatment of sialorrhea in PD based on data obtained from 12 studies (Egevad et al., 2014). Ruiz-Roca et al. (2019) reported a new systematic review of 21 studies demonstrating that botulinum toxin is an effective therapeutic strategy or option for the treatment of sialorrhea in PD patients (Ruiz-Roca et al., 2019). In a systematic review reported in 2018, researchers found that among previously published pharmaceutical interventions for sialorrhea used in PD, only botulinum toxin was associated with significant therapeutic effects (Sridharan and Sivaramakrishnan, 2018). Radiotherapy has been used for the treatment of sialorrhea in patients with amyotrophic lateral sclerosis (ALS). A series of studies have shown that salivary gland radiotherapy effectively improved sialorrhea in ALS patients (Slade and Stanic, 2015). For patients with parkinsonism, only one study has evaluated the efficacy of salivary gland radiotherapy for sialorrhea treatment. Postma et al. (2007) reported that applying radiotherapy to the major salivary glands was an effective and safe long-term treatment for sialorrhea patients with parkinsonism (Postma et al., 2007). Thus, radiotherapy may actually have some potential to assist the treatment of sialorrhea in PD patients.

Anticholinergic agents have been hypothesized to be effective for sialorrhea in PD patients; however, systematic treatment of anticholinergic drugs may produce central side effects, especially cognitive impairment. Thomsen et al. (2007) reported on the effects of sublingual application of an ipratropium bromide spray for sialorrhea therapy and found that it did not significantly reduce the saliva weight of PD patients (Thomsen et al., 2007).

6.1.3. Dysphagia

Drug therapy has been used for dysphagia treatment in PD. Levodopa is primarily targeted to motor impairment in PD patients; however, it has also been shown to improve swallowing capacity in PD (Warnecke et al., 2016). Conversely, according to a previous systematic review of 7 studies, levodopa intake did not improve swallowing dysfunction in PD patients (Menezes and Melo, 2009). More studies are required to confirm the efficacy of levodopa for the treatment of dysphagia in PD. In a pilot study, a rotigotine transdermal patch was shown to improve swallowing in PD patients (Hirano et al., 2015).

Expiratory muscle strength training (EMST) has been shown to improve swallowing and

cough functions in patients with dysphagia. It was also reported to improve cough and swallowing functions in PD patients (Pitts et al., 2009). However, that study found that the beneficial effects of EMST on swallowing were not continued after training; thus, a maintenance program aimed at sustaining function after EMST is required. Video-assisted swallowing therapy is another approach to treat swallowing disturbances. Manor et al. (2013) showed that video-assisted swallowing therapy was associated with improved swallowing-related quality of life and fewer food residues in the pharynx (Manor et al., 2013).

DBS has been shown to improve dysphagia, gastric emptying, constipation, and difficulty with defecation in PD patients by modulating the neural system that controls gastrointestinal functions (Arai et al., 2012; Krygowska-Wajs et al., 2016). However, some studies produced uncertain results regarding the efficacy of DBS as a dysphagia treatment. Interestingly, high-frequency repetitive transcranial magnetic stimulation has been shown to improve dysphagia in PD (Khedr et al., 2019). In addition, electrical stimulation is shown to increase hyoid bone movement and reduced aspiration in PD (Park et al., 2018).

Vocal fold augmentation with injection laryngoplasty (IL) is well-established as a treatment for glottal insufficiency. IL can improve dysphagia symptoms in PD with glottal insufficiency (Howell et al., 2019). Skill training on swallowing may also help to rehabilitate swallowing abilities in PD. Athukorala et al. (2014) showed that a skill-based training approach significantly improved swallowing-related quality of life (Athukorala et al., 2014).

6.1.4. Gastroparesis

In the PD literature, there is still a lack of well-designed RCTs aimed at the study of the treatment of gastroparesis in PD. Domperidone is a peripheral dopamine blocker that can enhance upper gastrointestinal motility and gastric emptying in PD patients (Soykan et al., 1997). Mosapride citrate is a selective 5-HT4 receptor agonist that has been shown to subjectively improve bowel frequency (Liu et al., 2005). Nizatidine is a selective histamine H2-receptor antagonist and a cholinomimetic. Nizatidine can shorten gastric emptying time in PD patients (Doi et al., 2014). Botulinum toxin type A was shown to improve gastroparesis symptoms in two cases of PD (Gil et al., 2011), and in a pilot study, it was also found to improve gastroparesis for

up to several months (Triadafilopoulos et al., 2017).

6.1.5. SIBOs

Before the treatment of SIBO is considered, the clinicians should confirm whether the SIBO is caused by secondary factors as the correction of secondary causes is the initial option for the treatment of SIBO. Reducing the intestinal bacterial content and gas production are two objectives of SIBO treatment. The traditional therapeutic for SIBO is antibiotics; however, antibiotics have not previously been used to treat SIBO in PD. Future studies should consider the use of antibiotics for the therapy of SIBO in PD patients. Probiotics are also a potential choice for the treatment of SIBO (Zhong et al., 2017). Probiotics can improve SIBO and constipation symptoms in the general population, but the value of probiotics for SIBO treatment in PD has not been assessed. Future studies are required to determine whether probiotics can improve SIBO in PD patients. At present, the treatment of SIBO is very demanding because of the lack of well-designed clinical trials in the previous literature.

6.1.6. Constipation

Constipation is one of most common non-motor symptoms in PD. The priority for constipation treatment in PD is lifestyle modification. Increasing fiber and water intake and physical activity are usually recommended for PD patients in clinical practice; however, whether these lifestyle modifications are effective for constipation treatment in PD patients is unknown. Before constipation in PD can be treated, any secondary causes that could induce constipation, such as gastrointestinal tumour and inflammatory bowel disease, should be treated. In previous years, multiple strategies, such as bisacodyl, milk of magnesia, lactulose and senna products, have been tried to treat constipation in PD. Bulk-forming laxatives are the most common prescription for the treatment of constipation in the general population. Bulk-forming laxatives contain psyllium, polycarbophil, wheat dextrin, methylcellulose, and soluble dietary fiber. All of these ingredients can promote intestinal motility and increase intestinal transit time. Psyllium has been shown to be effective in treating constipation in PD (Ashraf et al., 1997). Osmotic laxatives are another type of constipation treatment option. Osmotic laxatives can increase water

retention in the stool and thus enhance stool frequency. Polyethylene glycol (PEG) is an osmotic laxative agent used for constipation treatment. PEG improved constipation symptoms in PD patients in an RCT (Zangaglia et al., 2007). Chloride channel activators can stimulate chloride channels in the intestinal lumen and thereby increase intestinal fluid secretion and gut motility. Ondo et al. (2012) reported that lubiprostone appeared to be effective for the short-term treatment of constipation in PD (Ondo et al., 2012). Mosapride is a 5-HT4 receptor agonist that has been demonstrated to be beneficial for the improvement of constipation in PD patients (Liu et al., 2005). In addition, probiotics have been shown to improve stool consistency and bowel habits in PD patients (Cassani et al., 2011). Botulinum toxin is beneficial for gastroparesis and dysphagia, and a study also showed that it may relieve constipation symptoms in PD patients (Albanese et al., 1997). Furthermore, levodopa has been found to attenuate constipation symptoms of PD patients (Tateno et al., 2011). Finally, functional magnetic stimulation has been reported to reduce colonic transit time and improve colonic motility in PD patients (Chiu et al., 2009).

6.1.7. Defecatory dysfunction

Endoscopic botulinum neurotoxin injection is the only therapeutic that has been examined for the treatment of defecatory dysfunction in PD (Triadafilopoulos et al., 2017). The injection of botulinum neurotoxin into the canal is safe and well-tolerated and produces significant symptomatic improvement for up to several months (Triadafilopoulos et al., 2017). Future studies may be required to confirm this result, and well-designed RCTs are required to examine the therapeutic value of other approaches for defecatory dysfunction in PD.

6.2. Cardiovascular dysfunction

6.2.1. OH

Guidelines are available for the treatment of OH in PD patients. The primary goal for treating OH in PD is to reduce symptom burden, improve life quality, and decrease associated morbidity and mortality. Currently, the treatments available for OH include correcting aggravating factors, implementing nonpharmacological measures, and drug therapies. Drugs that may aggregate OH

include diuretics, sildenafil, nitrates, α-blockers, centrally acting α2-agonists, and tricyclic antidepressants (Palma and Kaufmann, 2018). All of these drugs should be avoided when treating OH (Palma and Kaufmann, 2018). Increasing water and salt intake may be useful for the treatment of OH in PD (Palma and Kaufmann, 2018). L-dopa or dopamine agonists may also exacerbate OH, and thus, a dose adjustment of levodopa and dopamine agonists may be considered in patients with OH (Palma and Kaufmann, 2018). For PD patients with OH, gradual position changes and briefly sitting before standing are recommended. Fudrocortisone can increase intervascular volume and has been demonstrated to be an effective pharmaceutical treatment for OH in PD (Schoffer et al., 2007). Midodrine and droxidopa can increase peripheral vascular resistance and have been successfully used for the treatment of OH in PD (Hauser et al., 2015). According to a systematic review, droxidopa was found to be a safe and effective drug for the short-term management of OH symptoms. However, the efficacy of droxidopa for long-term use has not been demonstrated (Elgebaly et al., 2016). Pyridostigmine bromide is a cholinesterase inhibitor that can enhance cholinergic neurotransmission in both sympathetic and parasympathetic terminals. It has been shown to improve OH symptoms in PD patients (Schreglmann et al., 2017).

6.2.2. Supine hypertension

The guidelines for the treatment of supine hypertension associated with neurogenic OH have been recently published (Jordan et al., 2019). The goal for the treatment of supine hypertension in PD patients is to reduce end organ damage without exacerbating OH. Antihypertensives, including captopril, nebivolol, clonidine, hydralazine, losartan, and nitroglycerine patches, can be prescribed for the treatment of supine hypertension in PD patients (Palma and Kaufmann, 2018). However, patients should be instructed about the risk of hypotension and falls when taking these antihypertensives.

6.3. Urogenital dysfunction

6.3.1. Urinary symptoms

Regarding the treatment of bladder overactivity, few large RCTs have been conducted in this

field. In a recent systematic review, the authors concluded that at present, there is little or no evidence showing that current therapeutics improve urinary outcomes in PD patients (Takahashi et al., 2014). It is widely recognized that dopaminergic drugs can improve or worsen urinary symptoms in PD patients (Sakakibara et al., 2016). For example, rotigotine, a dopaminergic agonist, was found to be effective for the treatment of urinary symptoms (Brusa et al., 2017). While antimuscarinic agents have been used for the treatment of urinary symptoms, it should be warned when the patients had cognitive impairment. Antimuscarinic agents include darifenacin, trospium, solifenacin, oxybutynin, tolterodine, and fesoterodine. In a pilot trial, solifenacin was found to improve urinary incontinence in PD (Zesiewicz et al., 2015), and was thought to be performed with lower risk bias (Peyronnet et al., 2018). β-3 Adrenergic agonists are another potential treatment option for detrusor overactivity in PD patients because they have no central cognitive effects. Mirabegron is the only β-3 adrenergic agonist examined in PD that has been demonstrated to effectively relieve urgency symptoms in elderly OAB patients with PD or other neurological diseases (Peyronnet et al., 2018).

Botulinum toxin A has been demonstrated to be effective for the treatment of urinary symptoms (Kulaksizoglu and Parman, 2010). Due to the involvement of the nigrostriatal pathway in urinary dysfunction in PD, the application of DBS in the subthalamus nuclei has been shown to improve bladder dysfunction and urinary symptoms, and this effect was related to the facilitated processing of afferent bladder information (Herzog et al., 2008).

6.3.2. Sexual dysfunction

Few treatment options have been examined for the therapy of erectile dysfunction in male PD patients. Sildenafil is a potent inhibitor of phosphodiesterase type 5 (PDE-5) and has been approved for sexual dysfunction treatment by the FDA. In 2002, it was demonstrated to be effective for the treatment of erectile dysfunction in PD (Raffaele et al., 2002). Pergolide mesylate is a dopamine agonist that has been shown to substantially improve sexual dysfunction in PD patients (Pohanka et al., 2005). Because sildenafil usually meets the contraindications for PD subjects, pergolide mesylate is thought to be a better choice for the treatment of erectile dysfunction (Pohanka et al., 2005). Whether other therapeutic options, such as intracavernosal

injection therapy, vacuum pump devices, and intraurethral prostaglandin suppositories, are also effective for the treatment of erectile dysfunction in PD remains unknown (Bronner and Vodusek, 2011; Palma and Kaufmann, 2018). Therapeutics for sexual dysfunction in female patients are also limited, and the use of vaginal lubrication, hormonal therapy, and psychotherapy may be validated in future RCTs.

7. Conclusion

Autonomic dysfunction is a common non-motor symptom in PD. It significantly impairs the quality of life of patients, exacerbates motor dysfunction, and increases the economic burden of PD patients. The pathophysiological mechanisms underlying autonomic dysfunction are largely unknown and deserve to be explored in future studies. The objective evaluation of autonomic dysfunction in PD is essential for disease evaluation, prediction, diagnosis, and management. As an important prodromal marker of PD, the value of autonomic dysfunction in PD prediction and diagnosis deserves further investigation. The management of autonomic dysfunction in PD is very challenging and limited, well-designed RCTs should be performed in future studies.

Conflict of interest

None of the authors have any conflicts of interest to disclose.

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