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Cardiovascular dysautonomia and cognition in Parkinson's Disease — a possible relationship

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ABSTRACT

Dementia in advanced Parkinson's Disease (PD) is a fatal milestone resulting in reduced life expectancy and nursing home placement. Cognitive impairment and cardiovascular dysautonomia are common and debilitating non-motor symptoms that frequently coexist in PD since the early stages and progress in subsequent years.

In particular, blood pressure (BP) abnormalities, including orthostatic hypotension (OH), supine hypertension (SH) and the loss of nocturnal BP fall (non-dipping) in PD have been associated with cognitive deterioration. They usually have multifactorial aetiology, including neuronal (central and peripheral) mechanisms and concomitant intake of medications. BP abnormalities can influence cognition in many ways, including repeated cerebral hypoperfusion leading to cerebral ischaemic lesions, higher burden of white matter hyperintensities, and possible impact on neurodegenerative process in PD. They are often asymptomatic and remain unrecognised, hence 24-hour ambulatory BP monitoring is recommended in patients with clinical symptoms of dysautonomia. Management is challenging and should address the multifactorial nature of BP disturbances. The aim of this review was to present the state of current knowledge regarding the possible relationship between cardiovascular dysautonomia and cognition in PD, its diagnosis and treatment.

Key words: cognitive impairment, dementia, orthostatic hypotension, Parkinson's Disease, supine hypertension

Introduction

Parkinson's Disease (PD) is, after Alzheimer's Disease (AD), the most frequent neurodegenerative disorder. Bradykinesia, tremor, rigidity and postural instability are the most prominent motor features. PD pathophysiology includes the impairment of not only dopaminergic but also cholinergic, serotoninergic and noradrenergic systems. Therefore, cognitive decline, sleep and mood disorders, gastrointestinal, genitourinary or cardiovascular disturbances are common since early stages and deteriorate with disease progression [1]. Among cardiovascular abnormalities there have been noted orthostatic hypotension (OH), supine hypertension (SH) and the absence of a decrease of blood pressure (BP) during the night [2]. The aetiology of BP abnormalities in PD patients is multifactorial. It is neurogenic, regarding the pathophysiology of PD and both peripheral and central denervation, but also influenced by treatment, as almost all dopaminergic medications (levodopa, dopamine agonists) can decrease BP [3]. Dysautonomia and Parkinson's Disease-related dementia (PDD) are the most disabling non-motor symptoms resulting in short life expectancy and nursing home placement [4].

The pathogenesis of cognitive impairment in PD remains unclear [5]. Combination of Lewy- and Alzheimer-pathology have presumably an additive effect on cognition impairment [6]. Apolipoprotein E polymorphism (ε4 allele) was also considered as a risk factor for PDD, although results are inconsistent, with negative impacts [7, 8], not confirmed in

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other studies [9, 10]. Also genetic forms of PD (mutations in: α synuclein gene – SNCA, leucine-riche repeat serine/threonine protein kinase gene - *LRRK2*) or specific genes variants (*glucocerebrosidase – GBA*, *microtubule-associated protein tau – MAPT*, and *catechol-o-methyl transferase – COMT)* can influence cognition in PD [11, 12].

The relationship between cardiovascular risk factors and cognition in PD studies remains inconclusive [13–17].

White matter hyperintensities (WMH) — T2 hyperintense lesions seen on magnetic resonance imaging (MRI) scans, may result from cerebrovascular disease. Several studies have indicated a negative impact of WMH on cognition in PD [2, 14, 18, 19]. Increasing WMH volume leads to deteriorations in executive function, memory and language [20]. Correlation between WMH and progression from mild cognitive impairment (MCI) to PDD has been also described [21]. Higher scores of WMH rating scales have been observed in a group of PD patients with MCI and PDD than in a group with normal cognition [14, 20, 22], but these results were not confirmed in other studies [23, 24].

Autonomic dysfunction, especially BP fluctuations, are an early manifestation of the disease, more pronounced in advanced stages and may result (as part of the neurodegenerative process) in cognitive decline. Its aetiology might be multifactorial and likewise in AD, vascular risk factor potentially might be an important co-factor or even trigger the neurodegeneration.

The aim of this review was to present the current state of knowledge regarding the relationship between cardiovascular dysautonomia (with the particular role of OH, SH and non-dipping effect) and cognition in PD (Fig. 1).

Pathophysiology of dysautonomia in Parkinson's Disease

Structural — central and peripheral nervous system involvement

Autonomic dysfunction in PD has a complex aetiology, involving both central and peripheral mechanisms (Tab. 1) [25]. Neuronal loss and Lewy bodies (with neuronal cytoplasmatic inclusions of α-synuclein) are observed not only in the zona compacta of the substantia nigra, but also in regions responsible for the control of autonomic functions such as the hypothalamus, nucleus vagus dorsalis, intermediolateral column of spinal cord and sympathetic ganglia, myenertic and submucosal plexus of intestines [26].

In healthy subjects, baroreceptors response caused by standing results in noradrenaline release from sympathetic post-ganglionic nerves causing vasoconstriction. This mechanism maintains BP in a standing position [27]. Post-ganglionic sympathetic neuron degeneration is the main cause of cardiovascular dysautonomia in PD [27, 28]. Sympathetic denervation of the heart in PD has been shown in ^{123}I-meta-iodobenzylguanidine (MIBG, radioactive molecular analogue of noradrenaline) scintigraphy (low myocardial uptake) and in neuropathological studies (fibres loss) [29, 30]. The neuropathological hallmark of PD - Lewy bodies (LB) were found in cardiac plexus of patients with PD [31]. The function of extracardiac peripheral sympathetic nervous system is also impaired, affecting sympathetic innervation of blood vessels interfering with noradrenaline release and vasoconstriction in a standing position [28]. Mean resting

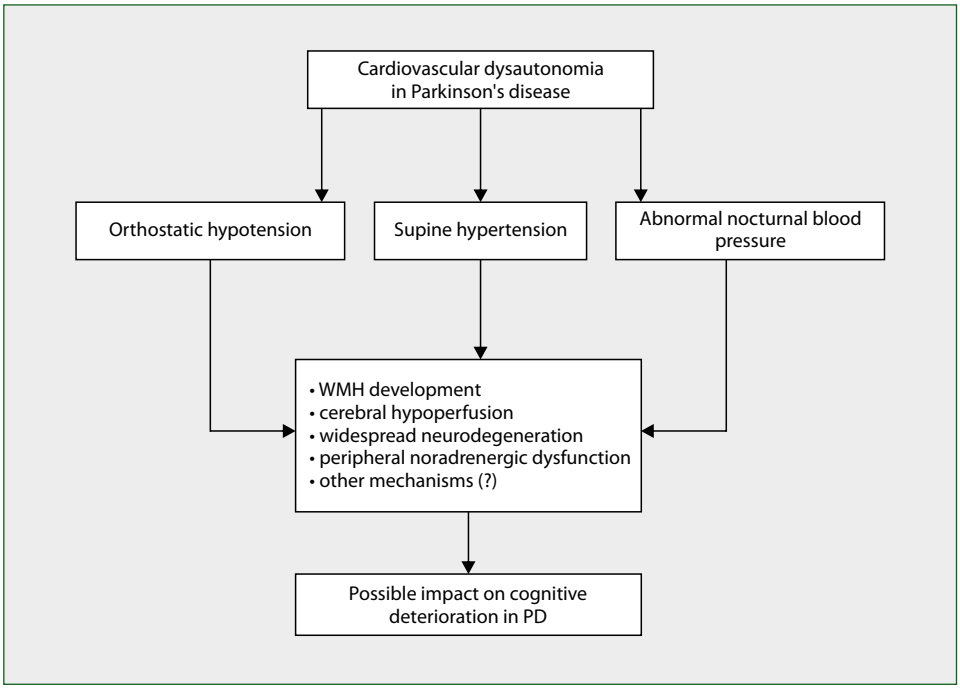

Figure 1. Cardiovascular dysautonomia in Parkinson's Disease: possible mechanisms linking it with cognitive impairment

Table 1. Central and peripheral autonomic structures affected in Parkinson's Disease (modified according to [25])

Autonomic structures affected in PD			
Central		**Peripheral**	
Hypothalamus	+	Enteric nervous system	++
Periaqueductal grey	+	Postganglionic sympathetic neurons	++
Ventrolateral medulla	+	Cholinergic sudomotor	+
Medullary raphe	+	Noradrenergic cardiac	+++
Dorsal motor nucleus of vagus	+++	Noradrenergic vasomotor	+
Nucleus ambigus	+	Adrenal gland	+
Pontine micturion centre	–	Postganglionic parasympathetic neurons	++
Sacral perganglionic neurons	+	Submandibular gland	++
		Gonadal tissue	+
Onuf nucleus	+	Pelvic ganglia	+

PD — Parkinson's Disease

noradrenaline plasma levels in PD-OH patients is lower compared to patients without OH [32, 33]. Furthermore, during tilt test this level decreases in PD-OH group [33], whereas normally it should double after five minutes of standing [34]. Additionally, in this group of patients systolic BP increased after administration of low doses of adrenoreceptor agonists. This implies vascular adrenoreceptor supersensitivity resulting from noradrenaline deficiency [35]. It also proves extracardiac sympathetic denervation. Patients with neurogenic OH in phase II of Valsalva manoeuvre present a progressive BP decrease and lack of BP overshoot during phase IV, which suggests baroreflex sympathetic failure [28]. This may also lead to SH. Neurogenic OH may result in heart rate blunted response while changing from a supine/sitting position to standing [36]. Orthostatic hypotension with increase in heart rate ≤ 15 bpm [36] or baroreflex gain < 0.5 bpm/mmHg (change in heart rate/ falling systolic blood pressure (SBP)) [37] can help to distinguish neurogenic from non-neurogenic OH. Furthermore, cardiac responses to orthostatic stress deteriorate in PD patients who begin to fall [38]. Moreover, Tipre et al. [39] observed among PD-OH group a decreased renal sympathetic innervation, presumably leading to natriuresis and diuresis, thus increasing susceptibility to blood volume depletion.

Levodopa intake (the main medication used in PD treatment), even when combined with carbidopa or benserazide, increases plasma levels of dopamine and its metabolites. This results in vasodilatation (via dopamine receptors on smooth muscle cells) and increased natriuresis and diuresis, which leads to a reduction of blood volume and extracellular fluid [28]. In PD patients, both baroreflex and cardiovascular sympathetic innervations are impaired, and together these mechanisms may result in BP decrease [27, 28]. However, Noack et al. [40] suggested that hypotension response to levodopa may be caused by negative cardiac inotropism rather than vasodilatation.

The relationship between central autonomic structures involvement and dysautonomia manifestations in PD is poorly understood [25]. Affected structures are presented in Table 1. The suprachiasmatic nucleus (SCN) of the hypothalamus, as the central biological clock, regulates circadian rhythm of BP and heart rate [41]. The SCN stimulates autonomic nervous system not only through GABA-ergic neurons, but also by regulation of melatonin release [41]. De Pablo-Fernandez et al. in a neuropathological case control study found α-synuclein depositions in the SCN of PD patients [26], and another group observed blunted circadian rhythm of melatonin serum levels in PD compared to controls [42]. Nucleus coeruleus, a main source of noradrenaline in the brain, is affected in the early stage of the disease [43] and noradrenaline transporter density is decreased [44]. The number of catecholaminergic neurons of nucleus of the solitary tract is reduced, which could be connected with the baroreflex impairment [45].

In PD-OH patients, the increased density of Lewy Bodies in the insular cortex has been observed [46] along with a reduced functional connectivity between hypothalamus, thalamus and striatum [47].

Orthostatic hypotension

Orthostatic hypotension (OH) is a common nonmotor PD manifestation (30% of patients) [48] and increases with age, disease duration, its severity and LD equivalent dose (LEDD) [49]. It is defined as a reduction in SBP ≥ 20 mmHg or ≥ 10 mmHg in diastolic blood pressure (DBP) after 3 minutes of standing from a supine position. In some patients, testing should be prolonged, as they may suffer from a delayed OH [50]. Standards for such testing have not been provided yet. Delayed OH can evolve to classic OH after 10 years in up to 50% of cases [50]. Although age is one OH risk factor, it can also be observed in early stages of the disease and is one of the diagnostic markers of prodromal PD in the Movement Disorder Society's research criteria [51, 52], predicting motor decline in this group [53].

Blood pressure drop during an orthostatic test depends on the duration of rest before supine BP measurement, the way of obtaining upright position (active stand or passive tilt), and the duration of standing [54]. Orthostatic hypotension in PD occurs more frequently after tilting than on standing and is often delayed [54]. Symptomatic OH presents as light-headedness, dizziness, presyncope, syncope, visual disturbances, fatigue, and generalised weakness [36]. Both symptomatic and asymptomatic OH are associated with an increased prevalence of falls, hospital admissions and lower quality of life [55].

MCI may be present at the early stage of PD in 25% of patients and may develop into dementia in up to 78% after 12 years of follow up [56].

Several pathological mechanisms are considered to be responsible for the relationship between OH and cognition, such as cerebral hypoperfusion as a result of recurrent episodic hypotension, widespread neurodegeneration, or central and peripheral noradrenergic dysfunction [27, 57, 58].

In several cross-sectional studies, a positive correlation between OH and cognitive deterioration has been observed (Tab. 2). Attentional/executive and visuospatial functions were more impaired among patients with OH [58]. Age, male sex, baseline REM-sleep Behaviour Disorder (RBD), OH and MCI have been identified as predictors of PDD [59, 60]. In studies that included only a Mini Mental State Examination (MMSE) in the neuropsychological assessment, OH did not influence cognition [61–63]. MMSE is a screening tool dedicated to AD that may be not sensitive enough, and is not indicated as the only tool to diagnose cognitive decline in PD.

Cicero et al. [4] examined the correlation between cardiovascular autonomic function and MCI among 185 PD patients from two Movement Disorders centres. Orthostatic hypotension was recorded in 52 of them, significantly more frequently in patients with long disease duration, and was associated with amnestic MCI.

The relationship between OH and posture-related cognitive impairment in PD has been investigated, comparing cognition among PD patients with and without OH to controls. Groups were matched for age, sex, premorbid verbal IQ and PD groups also for disease stage/duration and LEDD. In supine position, both PD groups demonstrated fronto-striatal and visuospatial cognitive deficits, but a transient exacerbation of cognition in an upright-tilted position was observed only in PD-OH group [65]. Sforza et al. replicated these findings in a small cohort of 28 PD patients [66]. Additionally, asystolic drop was greater and attention more deteriorated among PDD than PD patients while standing [67].

Differences in cognitive impairment between symptomatic and asymptomatic PD-OH patients were compared in the Longardner et al. study. The first part was performed as a cross-sectional, retrospective study and included 226 PD patients of whom 62 had longitudinal follow-up (second part). Lower Montreal Cognitive Assessment (MoCA) scores and worse decline during follow-up period were observed among PD-OH group. Presence of OH symptoms did not influence cognitive deterioration [68].

It is still unclear whether the relationship between OH and cognitive dysfunction is causative or associative, because the results of some studies were not adjusted for important variables e.g. comorbidities, medications, or age [57].

Supine hypertension

In approximately 50% of PD-OH patients, orthostatic hypotension often coexists with supine hypertension (SH) [69, 70]. Patients with SH often have an abnormal nocturnal BP profile as well [2]. SH is defined as a SBP ≥ 140 mmHg or a DBP ≥ 90 mmHg after at least 5 min of rest in supine position [71]. This is often overlooked, because BP is usually measured in a seated position and it remains asymptomatic. The underlying mechanisms may result from baroreflex failure or vascular hypersensitivity, or both mechanisms combined [71]. SH is probably associated with milder peripheral sympathetic denervation than OH alone [72]. Older age, akinetic-rigid motor subtype (predisposing to cognitive decline), and pre-existing hypertension are independent risk factors [72]. SH alone can cause cognitive impairment and white matter hyperintensities (WMH), also in early PD [2]. The impairment is more severe when SH is combined with OH [2]. However, a few studies did not confirm this observation [68, 69, 73].

Palma et al. [74], in a prospective study of patients with α-synucleinopathies (35 with multiple system atrophy, 14 with PD, and eight with pure autonomic failure) and coexisting OH, observed that SH is associated with an increased risk of left ventricular hypertrophy, higher blood urea nitrogen levels, glomerular filtration rate decrease and WMH volume, and, in longitudinal observation, with cardiovascular adverse events and premature death. Both chronic SH and OH are associated with the development of WMH [75].

Abnormal nocturnal blood pressure

Physiologically, BP follows a circadian rhythm characterised by a decrease of >10% BP at night (dipping) [76]. An abnormal nocturnal BP profile is another frequent manifestation of autonomic dysfunction in PD. Most PD patients present as either non-dippers or reverse dippers (also called risers) i.e. with loss of nocturnal BP fall or even an increase of BP values during the night, respectively [76, 77] (Fig. 2). These disturbances of circadian BP pattern have been associated with coronary heart disease, stroke and increased mortality [77]. Furthermore, they have been linked with target organ damage, impairment of cognition in the elderly, and increased burden of WMH [77, 78].

The literature on the disturbances of the circadian BP rhythm in PD is scarce and only a few studies have explored this topic. Tanaka et al. [77] assessed 137 PD patients with 24-hour ambulatory BP monitoring, MMSE, the Hasegawa dementia scale-revised (HDS-R), Hoehn and Yahr scale (H&Y) and MRI. Twenty-seven patients met the diagnostic criteria

Table 2. Studies on association between orthostatic hypotension and cognitive decline (modified according to [58], with supplement of later studies)

Study	Design	Subjects	Cognitive outcome
Allcock et al. (2004) [62]	Cross-sectional	PD-OH, n = 42, mean age 72.6 PD without OH, n = 45, mean age 68.2	No difference in MMSE score between two groups
Allcock et al. (2006) [63]	Cross-sectional	PD-OH, n = 80, mean age 72.1, median UPDRS 19, median PD duration 3 years PD without OH, N = 79, mean age 69.1, median UPDRS 17, median PD duration 5 years	No difference in MMSE score between two groups
Allcock et al. (2006) [96]	Cross-sectional	PD-OH, n = 87, mean age 72.4, median UPDRS 18.5, median PD duration 3.5 years PD without OH, n = 88, mean age 69.2, median UPDRS 17, median PD duration 5 years	PD-OH group performed worse on digit vigilance and picture recognition tasks. No difference in MMSE score between two groups
Peralta et al. (2007) [67]	Cross-sectional	PD, n = 10, mean age 74.1, mean disease duration 6.4 years, mean H&Y 2.1 PDD, n = 8, mean age 77.3, mean disease duration 7.8, mean H&Y 2.9	OH in 5 PDD, 2 PD. Decrease in attention scores in PDD in tilt position. Significant correlation between orthostatic changes and attention scores in PDD and no influence on word fluency tasks observed. Results not adjusted for dopaminergic medication
Idiaquez et al. (2007) [61]	Cross-sectional	PD, n = 29, mean age 66.2, mean PD duration 9.9 years, mean H&Y 2.6 PDD, n = 11, mean age 76.4, mean PD duration 10.5 years, mean H&Y 3.4	No correlation between PD, OH, cognitive impairment (MMSE, FAB). In PDD, cardiovascular symptoms more prominent
Hohler et al. (2012) [97]	Cross-sectional	PD-OH, n = 17 PD without OH, n = 27	PD-OH patients had lower cognitive FIM score and lower MMSE, worse motor, walking and balance compared to PD without OH. Results not adjusted for dopaminergic medication or age
Kim et al. (2012) [2]	Cross-sectional	PD with normal cognition, n = 25, mean age 63.4, mean PD duration 1.8 years, mean H&Y 1.4 PD-MCI, n = 48, mean age 70, mean PD duration 1.9, mean H&Y 1,7 PDD, n = 14, mean age 66.2, mean PD duration 1.6 years, H&Y 2.1	Drug-naive patients, early stage disease. OH was correlated with verbal immediate and delayed memory and CHIPS scale. Patients with coexisting OH and SH had more severe cognitive impairment and higher CHIPS scores. Mean CHIPS score was higher in PDD than in others
Pilleri et al. (2013) [73]	Cross-sectional	PD-OH, n = 23, mean age 64.96, mean PD duration 11.48 years, mean H&Y 2.76 PD without OH, n = 25, mean age 65.6, mean PD duration 11.6 years, mean H&Y 2.76	Among PD-OH patients, impairment of attention, visuospatial working memory, verbal delayed recall compared to PD without OH were observed. No differences in WMH between groups. LEDD were similar
Bae et al. (2014) [98]	Cross-sectional	PD-OH, n = 18, mean age 61.3, mean PD duration 13.8 months, mean H&Y 2 PD without OH, n = 27, mean age 65.5, mean PD duration 16.1 months, mean H&Y 2	Drug-naive patients. Verbal memory recognition performance worse in PD-OH patients
Anang et al. (2014) [99]	Prospective – followed up mean 4.4 years	PDD, n = 27, mean age 70.5, mean PD duration 6.02 years, mean H&Y 2,8 PD without dementia, n = 53, mean age 63.5, mean PD duration 5.4 years, mean H&Y 2.3	Strong association between OH and risk of dementia. SBP drop of >10 mmHg increased odds of developing dementia by 84%. Risk factors for developing dementia: baseline MCI, RBD, higher baseline BP, abnormal colour vision, proportion of gait involvement, falls and freezing. Not adjusted for dopaminergic medication or age
Centi et al. (2016) [65]	Cross-sectional	PD-OH, n = 18, mean age 64.3, mean PD duration 6.7 years, mean H&Y 2 PD without OH, n = 19, mean age 65.6, mean PD duration 5.7 years, mean H&Y 2 Controls, n = 18, mean age 62.9	In both PD groups, in supine position deficits in sustained attention, response inhibition, semantic fluency, verbal memory observed. In upright posture, they exacerbated and broadened (phonemic fluency, psychomotor speed, auditory working memory) only in PD-OH group
Sforza et al. (2018) [66]	Cross-sectional	PD-OH, n = 14, mean age 73.5, mean PD duration 9 years, mean H&Y 2.54 PD without OH, n = 14, mean age 72.5, mean PD duration 8 years, mean H&Y 2.39	In supine position, no differences in cognition between two groups observed. In upright position, PD-OH patients were worse at Stroop's test word reading time, interference time, number of errors at interference section than patients without OH

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Table 2 cont. Studies on association between orthostatic hypotension and cognitive decline (modified according to [58], with supplement of later studies)

Study	Design	Subjects	Cognitive outcome
Cicero et al. (2019) [4]	Cross-sectional	PD with normal cognition, n = 106, mean age 63.6, mean PD duration 4.9 years, mean H&Y 2.2 PD-MCI, n = 79, mean age 66, mean PD duration 6.5 years, mean H&Y 2.3	OH significantly more frequent in patients with long disease duration and associated only with amnestic MCI subgroup
Longardner et al. (2020) [68]	First part cross-sectional, second part longitudinal observation (mean follow-up 5.3 years)	First part: PD-OH, n = 69, mean age 71.0, mean PD duration 6.9 years, mean H&Y 2.4 PD without OH, n = 157, mean age 64.8, mean PD duration 4.5 years, mean H&Y 2.1 Second part: PD-OH, n = 28, baseline mean age 62.7, baseline PD duration 3.2 years, follow-up interval 5.5 years, baseline mean H&Y 1.8, follow-up mean H&Y 2.3 PD without OH, n = 14, baseline mean age 58.3, baseline PD duration 2.4 years, follow-up interval 5.0 years, baseline mean H&Y 1.6, follow-up mean H&Y 2.4	PD-OH patients had lower MoCA scores than patients without OH. After adjusting for age and disease duration, this difference was observed at trend level. Furthermore, MoCA score declined more for PD-OH group during follow-up period. Cognitive deterioration did not differ between symptomatic and asymptomatic PD-OH patients, either in cross-sectional or in longitudinal analyses

CHIPS scale — cholinergic pathways hyperintensities scale, a measure of WMH; FAB — frontal assessment battery; FIM — functional independence measure; MoCA — Montreal Cognitive Assessment

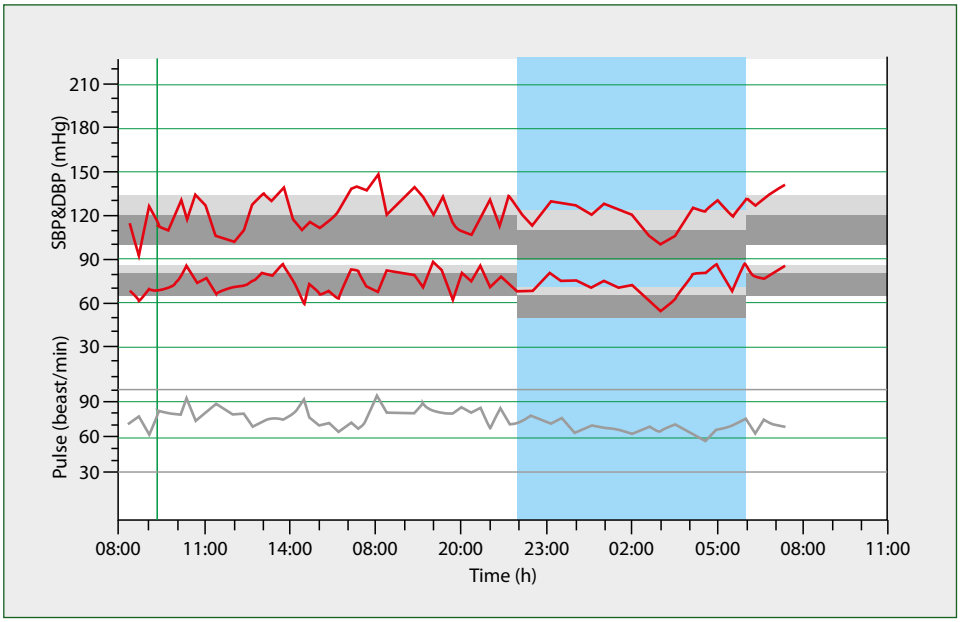

Figure 2. Non-dipping pattern at 24h ambulatory blood pressure monitoring in patient with Parkinson's Disease

of the Movement Disorder Society Task Force for Parkinson's Disease with dementia (PDD). The authors found statistically significant correlations between non-dipping pattern (negative) and riser pattern (positive) and dementia [77]. The correlation between abnormal nocturnal BP and dementia was independent of age, gender, H&Y score, diabetes, history of stroke and WMH [77]. Moreover, non-dipping pattern was significantly associated with an increased burden of periventricular hyperintensities [77]. Kim et al. [2] assessed 87 patients with early, not treated (medication-naïve) PD at average H&Y score of 1.7 ± 0.7 with 24-hour BP recording, 3.0-Tesla MRI of the brain and neuropsychological tests. They found MCI and PDD in 48 and 14 patients, respectively. The non-dipping pattern was present in the majority of patients (79.3%) and was associated with higher burden of WMH and lower scores in the neuropsychological tests, although the differences were not statistically significant [2].

As in other neurodegenerative diseases, cognitive deterioration in PD most probably develops as a result of multiple underlying processes [79]. In addition to alpha-synuclein

Table 3. Medications used to treat orthostatic hypotension in Parkinson's Disease (modified according to [27])

Medication	Recommended dosing	Mechanism of action	Adverse event
Midodrine	2.5—5 mg three times a day (last dose 3–4 hours before bedtime)	Direct α_1 — adrenergic receptor agonist	SH, piloerection, scalp tingling, urinary retention; use carefully in congestive heart failure and chronic renal failure
Droxidopa*	100–600 mg three times a day (last dose 3–4 hours before bedtime) or according to patient's needs	Synthetic noradrenaline precursor	SH, headache, dizziness, nausea; use carefully in congestive heart failure and chronic renal failure
Fludrocortisone	0.05–0.2 mg daily	Synthetic mineralocorticoid — increase of sodium and water reabsorption	SH, low potassium level, renal failure, myocardial fibrosis, oedema; use carefully in congestive heart failure
Pyridostygmine	30–60 mg twice or three times a day	Acetyl-cholinesterase inhibitor. Marginal efficacy in nOH	Abdominal pain, diarrhoea, sialorrhea, excessive sweating, muscle twitches; does not cause SH
Atomoxetine	10–18mg twice a day	Noradrenaline transporter (NET) blocker	SH, insomnia, irritability, decreased appetite

nOH — neurogenic orthostatic hypotension; SH — supine hypertension; *The only one licensed for this indication

aggregations spread into limbic and neocortical regions, there are also accompanying Alzheimer's type and vascular pathologies [79]. In previous studies, patients with cognitive decline due to AD exhibited a non-dipping or a reverse dipping pattern significantly more often than healthy controls [80]. Additionally, abnormal nocturnal BP was linked with greater β-amyloid deposition in the brain [81]. Abnormal nocturnal BP was found to be also associated with cognitive deterioration related to cerebrovascular lesions [77, 82]. An absence of dipping significantly correlated with vascular cognitive impairment and dementia (VCI) and WMH burden [82]. Moreover, there was a statistically relevant association between periventricular WMH and VCI [82]. The relationship between the extent of WMH and abnormal nocturnal BP was also demonstrated in PD and it was most pronounced in the reverse dipping pattern [78]. Furthermore, the burden of WMH significantly correlated with risk of dementia in PD [21].

Thus, disturbances of circadian BP rhythm may contribute to cognitive decline in PD through many different and independent mechanisms.

Treatment options

Before starting the treatment, 24h ambulatory BP monitoring should be performed. This can provide information about the frequency of OH episodes as well as the severity and duration of SH or abnormal nocturnal BP.

The first step in OH treatment should be a revision of concomitant medications and non-pharmacological interventions. Many PD patients previously treated with antihypertensive medications (also those for benign prostate hyperplasia as alfa-1 receptor antagonists) present OH when dopaminergic therapy (levodopa, dopamine agonists as ropinirole, pramipexole or rotigotine) is started, due to a cumulative effect. Therefore, doses should be adjusted, or even some medications withdrawn, if possible [83]. When it is safe for the PD patient, there should be avoided substances causing intravascular volume reduction, vasodilatation and affecting noradrenaline release or its activity - mainly antihypertensive and tricyclic antidepressants [27]. Antiparkinsonian medications such as monoamine oxidase B inhibitors (MAO-B, like selegiline), and N-Methyl-D-aspartate receptor antagonist (amantadine) may also exacerbate OH [84].

Fluid and salt intake are recommended, to 2–2.5 L/day and by adding 1–2 teaspoons of salt daily respectively [27, 36]. Fast but short-lasting increase of BP can be achieved by quickly drinking 500 mL of water [85]. Consumption of caffeine and alcohol needs to be restricted, due to their diuretic effect [27]. Postprandial hypotension can be improved by eating more, but smaller, meals, with a limited amount of carbohydrates [86]. Other recommended methods are: physical counterpressure manoeuvres, abdominal binders, and high waist compression stockings [87]. Physical exercises in a lying or sitting position may also be helpful [27]. Some patients, despite properly performed non-pharmacological methods, require pharmacological treatment to relieve OH symptoms. If OH is symptomatic and results in syncope with falls, the use of specific medications is recommended: acting via increasing intravascular volume (fludrocortisone) or increasing peripheral vascular resistance (midodrine, droxidopa, noradrenaline transporter inhibitors). Droxidopa is the only licensed medication for OH treatment; others are included in experts' recommendations (Tab. 3). Most of them (particularly fludrocortisone and midodrine) cause SH as a side effect. Therefore, 24h BP monitoring is crucial to avoid long-acting medication effects and in cases of nocturnal non-dipping. After midodrine, supine position is not recommended [88]. Short-acting drugs taken before bedtime, such as captopril, clonidine, hydralazine, losartan or a nitroglycerin patch are recommended in non-dippers [36, 88]. α-blockers, β-blockers and short-acting calcium channel blockers should be used with caution.

Moreover, patients should be aware of drugs used for different indications which can raise BP (e.g. ibuprofen, indomethacin, atomoxetine) [88]. Sleeping with a head-up tilt can be helpful for both OH and SH. This reduces night

time natriuresis and thus improves morning orthostatic tolerance [89]. Patients suffering from SH should also avoid lying down during the day and limit water intake near bedtime [88].

Conclusions

Our literature review suggests a possible association between cardiovascular dysautonomia, OH in particular, and cognitive impairment not only among PD patients, but also in the general population [90–94]. The observed differences between the studies may result from small groups of patients, short follow-ups, no controls, or different methods used to assess OH. Cognitive screening tests such as MMSE or MoCA are inappropriate for a full assessment of cognition in α-synucleinopathies [95]. Active screening for OH, SH and abnormal nocturnal BP profile should be provided among PD patients, since these treatable abnormalities are commonly unrecognised and undertreated [49].

A few questions still need to be answered, such as the safe level of SH among patients treated for OH, or the way of treating OH with pre-existing hypertension [70]. The relationship between dysautonomia and the possible prevention of cognitive decline needs more thorough studies.

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