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Loss of Autonomic Nervous System Control of Blood Pressure in Patients with Parkinson's Disease

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

Parkinson's disease (PD) manifests with motor symptoms of tremor, bradykinesia, muscle rigidity and postural instability. However, various nonmotor symptoms (NMS) have recently been recognized, among which autonomic dysfunction is observed long before the advent of motor symptoms and is aggravated through the course of the disease. Blood pressure (BP) abnormalities also result from autonomic dysfunction which induces orthostatic hypotension (OH), postprandial hypotension (PPH), nocturnal hypertension (NH) and, in particular, great fluctuation of BP over the range of 100 mmHg in a day that is often monitored by 24-hour ambulatory blood pressure monitoring (ABPM). A number of investigations on autonomic dysfunction in PD using ^{123}I-*meta*-iodobenzylguanidine (MIBG) myocardial scintigraphy, neuropathology and immunohistochemistry indicate the centripetal degeneration of the cardiac sympathetic nerves and other autonomic pathology in other organs. Since PD patients have lost neural control of BP, their BP should depend on humoral factors that cannot respond to changes in and out of the body as promptly as autonomic nerves. This may be one of the reasons for irregularly fluctuating and unpredictable BP. Hypertensive fluctuation is much riskier than OH and PPH for vascular events of cerebrovascular disease, cardiovascular disease and other organopathies. Non-medical and medical treatments such as calcium channel blocking may be effective to stabilize BP in patients.

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1. INTRODUCTION

Parkinson's disease (PD) is a common neurological disease developed in middle-aged persons, usually 60 years or older of age. Its main motor symptoms include a combination of slowness of movement (bradykinesia), resting tremor, muscle rigidity, postural instability and difficulty in gait [1,2]. However, not all these symptoms should appear in a patient and younger persons can also be affected in some cases.

In addition to these motor symptoms, various nonmotor symptoms (NMS) have recently been well recognized, which could begin long before the development of motor impairment and significantly deteriorate the patients' quality of life (QOL) in later stage [3]. These NMS comprise olfactory dysfunction, sleep disorders, rapid eye movement sleep behavior disorder (RBD), pain, psychosis, dementia, apathy, depression, and various autonomic dysfunction such as gastrointestinal symptoms, urinary disturbance, sudomotor dysfunction, cardiovascular symptoms and blood pressure fluctuation [4,5]. Although some of these NMS dominate early in the premotor stage, they are often overlooked or unnoticed. Later with disease progression, non-motor manifestations increase in frequency and severity and, in advanced stage along with levodopa-unresponsive axial motor symptoms such as postural instability and falls, NMS become major troubles that could bring the patients to institutionalization [3,6-9].

In postmortem examination, marked loss of neurons is noted in the substantia nigra [10], and Lewy bodies are found in the surviving neurons. Alpha-synuclein aggregates are the main constituent of Lewy bodies (LB) and these pathological α-synuclein deposits (synucleinopathy) are found in the neuronal soma (LB) as well as in the neurite (Lewy neurites; LN) [11]. Hitherto, however, α-synuclein aggregates have been diffusely demonstrated in the nervous system of PD to form LB and LN (LB/LN) not only in the central nervous system (CNS) but also in the peripheral nervous system (PNS), enteric nervous system [12-15] and parasympathetic and sympathetic pre- and postganglionic neurons [16].

Based on accumulated pathological data, Braak proposed six stages for the progression of α-synuclein deposition [11,12]. In stage 1, the olfactory bulb and/or the dorsal motor nucleus of the glossopharyngeal and vagal nerves are the sites where α-synuclein aggregates appear the earliest, and the α-synuclein aggregates spread therefrom in a spatially continuous manner to other nervous systems. In stage 2, they emerge in the medulla oblongata and the pontine tegmentum, and, in stage 3, in the amygdala and the substantia nigra. The motor symptoms of PD start to develop only after stage 3. In stage 4, α-synuclein aggregates progress into the temporal cortex and, in stages 5 and 6, into the neocortex. Thus, PD is not only a motor disorder resulting from destruction of the nigrostriatal system, but also a multisystem disorder that affects many different regions of the nervous system and induces diverse NMS [12]. Among NMS, blood pressure (BP) abnormalities, which are in part controlled by the autonomic nervous system, are discussed in this review.

2. AUTONOMIC DYSFUNCTION IN PD

The autonomic dysfunction manifested in PD patients is a constellation of gastrointestinal symptoms, urinary disturbance, sudomotor dysfunction, cardiac sympathetic denervation and BP abnormalities. Anatomically frontal and temporal cortex, anterior cingulate cortex, amygdala, basal ganglia, hypothalamus, brain stem, glossopharyngeal and vagal parasympathetic nerves, spinal sympathetic tract, and sympathetic pre- and postganglionic nerves are the responsible lesions [9,12,15,17,18].

The gastrointestinal symptoms are due to gastrointestinal dysmotility causing constipation, excessive drooling, oesophageal dysmotility and delayed gastric emptying [19]. The enteric nervous system including Auerbach's and Meissner's plexuses where LB/LN are found is involved from the earliest stage of the disease progression [13-15], later affecting the glossopharyngeal and vagal nuclei in the medulla [11].

The manifestations of urinary disturbance include for the most part frequent micturition desire (urgency and frequency), urge incontinence and nocturia [20]. On the contrary to detrusor overactivity, difficulty in urination turns to be the main complaint in some patients, though not frequently [21]. These symptoms are considered

to result from the dysfunction of the sympathetic and parasympathetic nerves, pontine micturition center and storage center and possibly more central parts of the brain.

There are three types of sudomotor functions: thermal sweating, mental sweating and gustatory sweating. They are different from each other in terms of physiological functions and corresponding neural networks. Thermal sweating appears on the whole body in response to heat and regulates body temperature. It has been reported that PD patients usually show hypohidorosis or anhidrosis [22-24], but in other parts of the body such as face and neck, compensatory hyperhidrosis may be observed [25,26]. The regulatory center of thermal sweating is hypothalamus, and from there through the spinal cord to the pre- and postganglionic sympathetic nerves is the neural tract extending to the eccrine glands. Anhydrosis in PD is presumed to be caused by postganglionic sympathetic nerve degeneration.

Mental sweating appears on palms and soles (palmo-pedal sweating) independently from thermal sweating in response to mental stress or emotional excitement. The effector organs are eccrine glands innervated by sympathetic nerves [27]. In the study of mental sweating in PD, palmar sweating was significantly reduced in the elderly controls as compared to the young controls and further reduced in the PD patients as compared to the elderly controls, though the PD patients were younger than the elderly controls. These findings indicate that the sympathetic nervous system involved in mental sweating declines in function according to age; however, in PD, it is pathologically impaired and the postganglionic sympathetic nerves are speculated to be the responsible lesions which are consistent with the postganglionic sympathetic nerve degeneration in the thermal sweating [28].

Although cardiac autonomic nerve dysfunction includes both sympathetic and parasympathetic nerve abnormalities, parasympathetic dysfunction in PD has not yet been fully elucidated. There have been conducted, however, a few studies that indicate parasympathetic nerve abnormality in PD [29-33].

Meanwhile, ^{123}I-*meta*-iodobenzylguanidine (MIBG) myocardial scintigraphy has been examined in detail to evaluate postganglionic cardiac sympathetic innervation in PD and other neurodegenerative disorders [34,35]. Decreased cardiac MIBG uptake has been demonstrated in the early stage of PD and dementia with Lewy bodies (DLB), but not in multiple system atrophy (MSA), progressive supranuclear palsy (PSP) or corticobasal degeneration (CBD), which manifests parkinsonian symptoms, nor in parkin-associated PD and Alzheimer disease (AD) [36-38]. Histologically, LBs/LNs are found in the cardiac sympathetic nerves, and immunohistochemically staining of tyrosine hydroxylase and phosphorylated neurofilament with antibodies demonstrated prominent decrease in immunoreactive axons of the epicardial nerve fascicles [39,40]. These findings indicate degeneration or loss of cardiac sympathetic nerve even in the early stage of PD, which is closely related to the presence of LB/LN in the nerve [40,41]. Clinically, however, low Heart/Mediastinum (H/M) of MIBG myocardial scintigraphy does not appear to bring about ischemic heart disease, heart failure or arrhythmia, but MIBG myocardial scintigraphy is proven to be useful (helpful) for differential diagnosis of PD and DLB from MSA, PSP, CBD, or AD. Another important point obtained by the MIBG myocardial scintigraphy findings is that one of the initiation sites of the disease progression might be the cardiac sympathetic postganglionic nerves. In fact, Orimo et al. [42] elucidated that accumulation of α-synuclein aggregates in the distal axons of the cardiac sympathetic nervous system precedes that in the neuronal somata or neurites in the paravertebral sympathetic ganglia, which suggests centripetal degeneration of the cardiac sympathetic nerve in PD.

3. BLOOD PRESSURE ABNORMALITIES IN PD

There are recognized three major manifestations of BP abnormalities in PD: (1) orthostatic hypotension (OH) [43-45]; (2) postprandial hypotension (PPH) [46]; and (3) nocturnal hypertension (NH) [46-50]. OH is a most typical symptom relating to BP in PD. The typical symptoms of OH include syncope, blurred vision, faintness, dizziness, easy fatigability, chest distress, shoulder pain (hanger coat syndrome), falling and so on. OH can be diagnosed by a head-up tilt test or Schellong test. In the head-up tilt test, when OH is present, a decrease in the BP of over 20 mmHg is observed within 3 minutes after a heading up action by an angle over 60 degrees from a supine position [51]. The occurrence of OH in PD increases with disease

progression to about one fourth of the patients at a later stage [27].

When a patient shows a 20 mmHg or more depression of systolic BP within 2 hours after a meal, he/she is presumed to have PPH. Many PD patients exhibit PPH with symptoms similar to those of OH such as dizziness, syncope, falling, hanger coat pain and sleepiness, often accompanying OH. However, PPH precedes OH and occurs more frequently than OH or coincidentally with OH. The pathophysiology of PHH is described by many clinical studies [46,52]. Ingestion is believed to cause secretion of insulin and gastrointestinal peptides such as neurotensin that induce visceral and peripheral vascular dilatation, leading to persistent hypotension. In ordinary person, however, sympathetic nervous activity prevents hypotension and maintains blood pressure.

4. BP FLUCTUATION IN PD

In addition to the above-mentioned BP abnormalities, extreme rise and fall of BP in PD patients in a day, which cannot be classified into OH or PPH, are noticed by nurses or caregivers at hospitals, nursing homes, or visiting nursing, or adult day-care centers. To determine how the BPs of PD patients fluctuate, in the previous report [5], we monitored their BPs every 30 minutes by 24-h ambulatory blood pressure monitoring (ABPM) and compared the monitoring results with those of age-matched other disease controls (OD) (37 PD patients and 44 OD patients). No significant difference was found in the average BP between the two groups, but the highest systolic BP was higher in the PD patients (average ± standard deviation = 194±23 mmHg) than in the OD patients (177±24 mmHg) and the lowest systolic BP was lower in the PD patients (89±14 mmHg) than in the OD patients (97±15 mmHg) (P<0.05). A range of BP fluctuation over 100 mmHg was observed in 67.6% of the PD patients, but only in 13.6% of the OD patients (P<0.001). A BP of over 200 mmHg was observed in a period of 1 day in 35.1% of the PD patients and 13.6% of the OD patients (P<0.001). Thus, the PD patients experience much greater BP fluctuations with the BP often exceeding 200 mmHg.

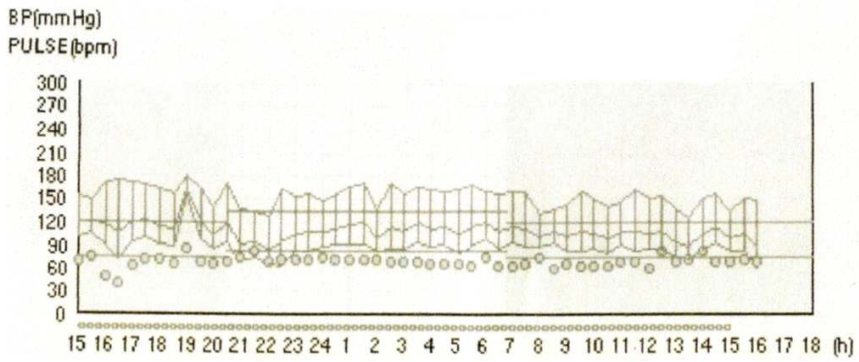
Here, I summarize some cases to demonstrate how the BP fluctuates in a day (Fig. 1A-D).

Case 1 is an 85-year-old man with left femoral neck fracture who showed an average systolic BP of 156 mmHg and a difference of 51 mmHg between the highest and the lowest systolic BP, without nocturnal hypertension (Fig. 1A). This individual was one of the OD patients and observed as a control subject.

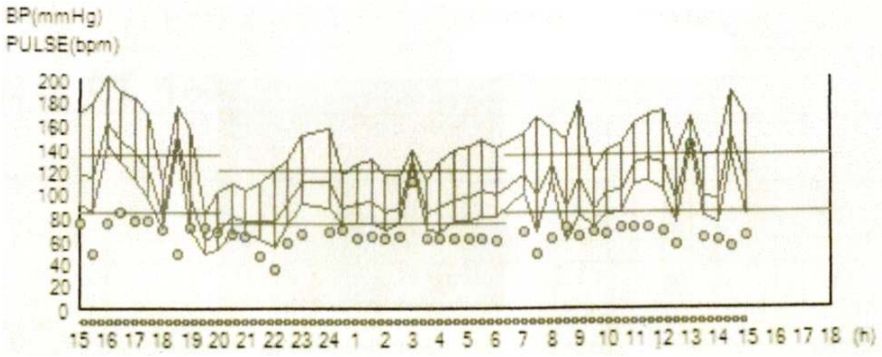
Case 2 is a 72-year-old female PD patient with 23 years duration of the disease and at the Hoehn-Yahr stage 5, whose BP fluctuated between 83 and 202 mmHg without nocturnal hypertension (Fig. 1B).

Case 4 is a 73-year-old female PD patient with 16 years duration of the disease and at the Hoehn-Yahr stage 3, who showed a highest systolic BP of 232 mmHg and a lowest BP of 106 mmHg (Fig. 1C).

Case 5 is a 77-year-old male PD patient with 17 years duration of the disease and at the Hoehn-Yahr stage 5, whose BP fluctuated in a rage of 148 mmHg. Surprisingly, this patient was bedridden and an extreme high BP (227 mmHg) was observed in the midnight (Fig. 1D).



A



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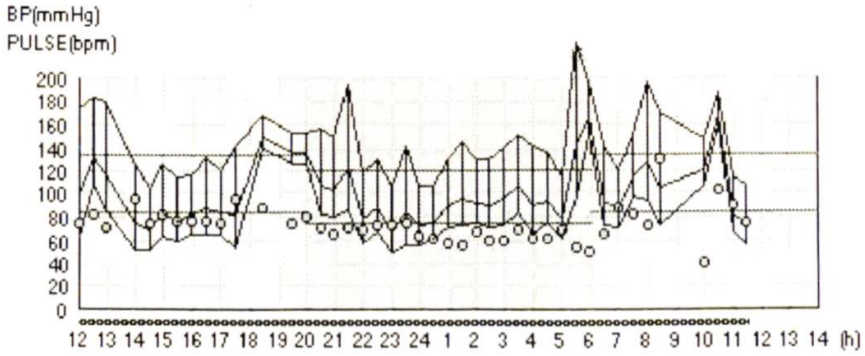
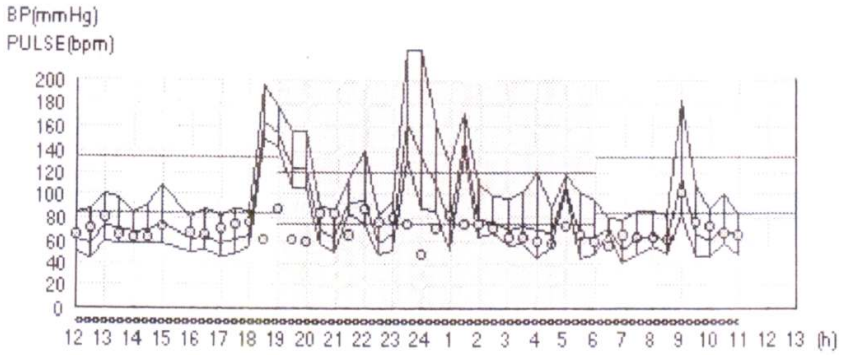


C



D

Fig. 1. 24-h ABPM recordings of a control patient and three PD patients
A. An 85-year-old man with left femoral neck fracture who showed an average systolic BP of 156 mmHg and a difference of 51 mmHg between the highest and the lowest systolic BP without nocturnal hypertension. This individual was one of the other disease control patients.
B. A 72-year-old female PD patient with 23 years duration of the disease and at the Hoehn-Yahr stage 5, whose BP fluctuated between 83 and 202 mmHg without nocturnal hypertension.
C. A 73-year-old female PD patient with 16 years duration of the disease and at the Hoehn-Yahr stage 3, who showed a highest systolic BP of 232 mmHg and a lowest BP of 106 mmHg.
D. A 77-year-old male PD patient with 17 years duration of the disease and at the Hoehn-Yahr stage 5, whose BP fluctuated in a rage of 148 mmHg. Surprisingly, this patient was bedridden and the extreme high BP (227 mmHg) was observed in the midnight

Although 64.9% of the PD patients showed BP fluctuations ranging not less than 100 mmHg, none of the patients complained of syncope, dizziness or headache during the ABPM. The types of those BP fluctuations were different among the patients and could not be categorized into OH, PPH or NH [5].

5. BP CONTROL OF PD

Blood pressure is regulated by complex multiple mechanisms, mainly by neural factors and humoral or chemical factors as well as interaction therebetween [53-59]. In PD as mentioned above, there are many evidences that suggest autonomic dysfunction, especially sympathetic postganglionic denervation, from the early stage of the disease [36-38]. If autonomic nerves involved in BP control are degenerated and dysfunctional, the BP should depend on the control of humoral factors, mainly on the renin-angiotensin-aldosterone system [56]. In terms of reaction time for BP regulation, rapid regulation in several seconds to minutes is dominated by the autonomic nervous system, and intermediate and longer regulation is dominated by humoral factors and neural factors. Therefore, irregularly fluctuating BP in PD may be derived from impairment of such rapid regulation of BP by the autonomic nervous system and may in most part be regulated by humoral factors. Once the BP is elevated, elevated BP cannot be lowered immediately and may be sustained for a long time. On the contrary, a lowered BP cannot be recovered at once due to sympathetic nerve dysfunction. Since PD patients have lost neural control of BP in the above-described manner, they can offer a good model for investigating the BP control without neural factors.

6. TREATMENT FOR BP ABNORMALITIES IN PD

Several management methods are suggested for prevention and treatment of OH. First, as a non-medical method, it is recommended not to stand up rapidly, but to sit down or lie down for a while when dizziness or lightheadedness occurs, to avoid hot environment such as hot and long bathing and to wear elastic bands on the lower extremities. Second, several medicines are available for hypotension [60-62]. However, as they potentially induce supine hypertension, such medicines should be carefully used except for those cases where the systolic BP on standing up is measured to be less than 75 mmHg [62]. For PPH, caffeine, fludrocortisone, octreotide, midodrine administered with denopamine, and voglibose have been reported to be effective [63-65]. Taking water adequately before eating may be helpful as a non-medical treatment. However, there are not enough reports to recommend the use of these agents.

The BPs of PD patients are not simply regarded as certain time-restricted changes, but they rise and drop irregularly over a wide range and cannot be predicted beforehand, as we demonstrated using 24-h ABPM [5]. For example, a PD patient showed BP of over 200 mmHg at one time and a BP of lower than 80 mmHg at other time. We face the dilemma of abnormally high and low BPs in a patient in a day. It should, however, be emphasized that rather hypertension with BP fluctuation over a wide range is more important and life-threatening than hypotension because it brings about cerebrovascular events, cardiovascular diseases and other organopathies [66-71], while hypotension appears to be only transient and usually asymptomatic and thus does not present a serious issue [62]. Among antihypertensive drugs calcium channel blockers such as amlodipine besilate may be a choice for hypertension in PD, because they work on the vascular smooth muscle to relax vascular tension and are effective for reducing in the range of BP fluctuation [72,73]. These drugs may reduce to some extent the direct influence of autonomic nerves or chemical factors on vessels and stabilize the vascular strain.

7. DEEP BRAIN STIMULATION

Deep brain stimulation (DBS) has been developed for treating motor symptoms of PD [74-76], especially when the motor symptoms are unresponsive to anti-PD drugs [77]. Stimulating electrodes are bilaterally introduced usually to the subthalamic nucleus sometimes to the thalamus, to globus pallidus or to periaqueductal gray (PAG) [76,78,79]. The effects of DBS in the treatment of motor symptoms have widely been accepted, but some reports demonstrated that it is also effective for NMS [80] and autonomic dysfunction [81,82] such as urinary disturbance [83], sudomotor dysfunction [84], and orthostatic hypotension [85]. It is also reported that vasodilatation or sustained reduction of hypertension could be induced by DBS [79,86]. Considering that the autonomic nervous system of PD is known to be impaired in the early stage and the sympathetic postganglionic nerves must have been degenerated and that DBS is usually

performed after drug therapy for a while, it is controversial [87,88] and interesting whether or not DBS is effective for autonomic dysfunction. Other different network or humoral factor migrating to effective organs may exist besides the known autonomic nervous system.

8. CONCLUSION

NMS, together with several motor symptoms of classic PD, are disabling matters for PD patients from the beginning to the final stage of the disease. Among NMS, autonomic dysfunction represents a large part of NMS. BP abnormalities are caused by autonomic dysfunction, especially by sympathetic nerve degeneration. Although OH, PPH and NH are well-recognized abnormalities of BP, 24-h ABPM revealed that the BP of a PD patient fluctuates greatly in a day. It should be stressed that the extensive BP fluctuation with hypertension frequently reaching over 200 mmHg is more important than those OH, PPH or NH, because hypertensive fluctuation is much riskier for vascular events such as cerebrovascular disease, cardiovascular disease and other organopathies. Medical treatments such as the use of a calcium channel blocker are required for stabilizing BP against the dilemma between high and low BP in a patient.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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