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When do the symptoms of autonomic nervous system malfunction appear in patients with Parkinson's disease?

Kada se pojavljuju simptomi oštećenja autonomnog nervnog sistema kod obolelih od Parkinsonove bolesti?

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Abstract

Background/Aim. Dysautonomia appears in almost all patients with Parkinson's disease (PD) in a certain stage of their condition. The aim of our study was to detect the development and type of autonomic disorders, find out the factors affecting their manifestation by analyzing the potential association with demographic variables related to clinical presentation, as well as the symptoms of the disease in a PD patient cohort. **Methods.** The patients with PD treated at the Clinic of Neurology in Belgrade during a 2-year period, divided into 3 groups were studied: 25 *de novo* patients, 25 patients already treated and had no long-term levodopa therapy-related complications and 22 patients treated with levodopa who manifested levodopa-induced motor complications. Simultaneously, 35 healthy control subjects, matched by age and sex, were also analyzed. **Results.** Autonomic nervous system malfunction was defined by Ewing diagnostic criteria. The tests, indicators of sympathetic and parasympathetic nervous systems, were significantly different in the PD patients as compared with the controls, suggesting the failure of both systems. However, it was shown, in the selected groups of patients, that the malfunction of both systems was present in two treated groups of PD patients, while *de novo* group manifested only sympathetic dysfunction. For this reason, the complete autonomic neuropathy was diagnosed only in the treated PD patients, while *de novo* patients were defined as those with the isolated sympathetic dysfunction. The patients with the complete autonomic neuropathy differed from the subjects without such neuropathy in higher cumulative and motor unified Parkinson's disease rating score (UPDRS) ($p < 0.01$), activities of daily living scores ($p < 0.05$), Schwab-England scale ($p < 0.001$) and Hoehn-Yahr scale. There was no difference between the patients in other clinical-demographic characteristics (sex, age at the time of diagnosis, actual age, duration of disease, involved side of the body, pain and freezing), but mini mental status (MMS) score and Hamilton depression and anxiety rating scale were significantly lower ($p < 0.05$). **Conclusion.** Our results confirm a high prevalence of autonomic nervous system disturbances among PD patients from the near onset of disease, with a predominant sympathetic nervous system involvement. The patients who developed complete autonomic neuropathy (both sympathetic and parasympathetic) were individuals with considerable level of functional failure, more severe clinical presentation and the existing anxiety and depression.

Key words:
parkinson disease; autonomic nervous system.

Apstrakt

Uvod/Cilj. Poremećaji autonomnog nervnog sistema javljaju se kod gotovo svih obolelih od Parkinsonove bolesti (PB) u nekom stadijumu njihove bolesti. Cilj našeg istraživanja bio je da se utvrde pojava i tip autonomnih poremećaja, kao i faktori koji utiču na njihovu pojavu ispitivanjem potencijalne povezanosti sa demografskim varijablama vezanim za kliničku prezentaciju i simptome bolesti u grupi bolesnika sa PB. **Metode.** Ispitivali smo obolele od PB koji su lečeni u Klinici za neurologiju u Beogradu u dvogodišnjem periodu, podeljene u tri grupe: 25 *de novo* bolesnika, 25 obolelih koji su lečeni i nisu imali nikakve komplikacije vezane za dugotrajnu primenu levodope i 22 bolesnika na levodopi kod kojih su se pojavile motorne komplikacije izazvane levodopom. Istovremeno je analizirano 35 zdravih (kontrolnih) ispitanika, uparenih prema uzrastu i polu. **Rezultati.** Disfunkcija autonomnog nervnog sistema definisana je prema Ewing-ovim dijagnostičkim kriterijumima. Testovi, pokazatelji ispada simpatičkog i parasimpatičkog nervnog sistema, bili su statistički značajno različiti kod obolelih od PB u poredjenju sa kontrolom, što je sugerisalo poremećaj oba sistema. Kada su izdvojene pojedine

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grupe obolelih, međutim, pokazano je da disfunkcija oba sistema postoji kod dve grupe lečenih od PB, dok je kod *de novo*, nelečenih bolesnika, uočen samo poremećaj simpatičkog nervnog sistema. Zbog toga je kompletna autonomna neuropatija dijagnostikovana samo kod lečenih od PB, dok su *de novo* oboleli definisani kao oboleli sa izolovanom simpatičkom disfunkcijom. Osobe sa kompletnom autonomnom neuropatijom razlikovale su se od osoba bez autonomne neuropatije po višem kumulativnom i motornom unifikovanom skoru za Parkinsonovu bolest ($p < 0,01$), skoru aktivnosti svakodnevnog života ($p < 0,05$), Schwab-England skali ($p < 0,001$) i procenjenoj težini bolesti prema Hoehn-Yahr-u. Bolesnici se nisu razlikovali prema drugim kliničkodemografskim karakteristikama (pol, uzrast u vreme postavljanja dijagnoze, aktuelnom uzrastu, trajanju bolesti, zahvaćenoj strani, bolu i „*freezing*-u"), ali su imali statistički značajno niži mini mentalni skor (MMS), kao i skor na Hamiltonovoj skali depresivnosti i anksioznosti ($p < 0,05$). **Zaključak.** Rezultati ove studije potvrđuju visoku prevalenciju poremećaja autonomnog nervnog sistema u ranoj fazi bolesti kod obolelih od Parkinsonove bolesti, sa predominantnom disfunkcijom simpatikusa. Bolesnici kod kojih se razvila kompletna autonomna neuropatija (simpatička i parasimpatička) imali su izraženu funkcionalnu slabost, teže kliničke simptome, uz prisustvo anksioznosti i depresije.

Ključne reči:
parkinsonova bolest; nervni sistem, autonomni.

Introduction

Autonomic nervous system dysfunctions have long been the "cornerstone" of Parkinson's disease (PD) and multiple systemic atrophy (MSA), and even currently accepted criteria of diagnosis and recognition of PD have exactly emphasized, as an exclusion symptom, the presence of severe autonomic neuropathy [1]. Nevertheless, autonomic dysfunction is being recorded in almost all PD patients in a certain stage of their disease [2–4], and a Sydney study has shown that 71% of patients develop, after 15 years of their condition, autonomic disorders, such as sphincter control dysfunction [5]. On the other hand, the presence of multiple autonomic disorders has been verified even before development of motor failures, when they have been accepted as non-motor manifestations of already existing disease [6], and perennial duration of individual non-motor signs has made them possible prodromal symptom of the disease [7].

Autonomic symptoms are consistent with the results of neuropathological studies and the presence of changes in hypothalamus, brainstem, intermediolateral cell column, autonomic ganglia, and myenteric plexus; the theory of Braak et al. [8] justifies and explains their appearance early in the course of disease, given the assumption of the ascending spread of disease in which the involvement of dorsal nuclei of the vagus nerve is one of the earliest stages of disease [8].

The aim of our study was to detect the occurrence and type of autonomic nervous system symptoms, to find out factors influencing their presence, by assessing the relation with demographic, disease-related and clinical variables in cohort of PD patients.

Methods

The patients with PD, diagnosed according to the Brain Bank Criteria [1], treated at the Institute of Neurology, Clinical Center of Serbia in the period from 2004 to 2006, and age-matched controls without PD, were evaluated. Three groups of PD patients were tested: 25 *de novo* patients (group I), 25 levodopa treated patients without levodopa-induced motor complications (group II), and 22 levodopa treated patients with levodopa-induced motor complications (group III), as well as 35 age-matched controls (group IV). Among the PD patients, as well as among the control group, neither diabetes mellitus nor other vascular risk factors were detected (hypertension, hypercholesterolemia, heart disease and peripheral nerve diseases).

After obtaining the informed consent and the approval of the Ethics Committee of the Faculty of Medicine, University of Belgrade (No. 440/XII-2), all the patients were tested in Neurocardiology Unit, Clinical Center "Bežanijska kosa", Belgrade. All the tests were performed under standardized conditions, in climate-controlled rooms (temperature 23°C), in the morning, after a period of relaxation. Tobacco, alcohol, caffeine, and medications were not allowed before the test. Autonomic nervous system dysfunction was diagnosed by means of cardiovascular reflex tests according to Ewing [9], and was considered to exist if, at least, two tests were positive. Vagal dysfunction was diagnosed using 3 tests: Valsalva maneuver, deep breathing test and heart rate response to standing. Sympathetic dysfunction was assessed with 2 tests: blood pressure response to standing, and handgrip test. A patient is diagnosed as one with autonomic neuropathy (AN) after having two pathological tests (two sympathetic or two parasympathetic tests) and as complete autonomic neuropathy (CAN) in case of confirmed both parasympathetic and sympathetic denervation.

The results of each test were expressed as normal (0), borderline (1) or abnormal (2), as in reference values according to Ewing [9]. Maximal possible cumulative score was 10 (i.e. if all five tests had pathological findings). A cumulative score of 0 or 1 was considered normal, while the score of 2 or 3 was interpreted as mild autonomic dysfunction. The patients with scores between 4 and 6 were diagnosed with moderate dysfunction and those who scored 7 or higher were considered to have severe autonomic dysfunction.

The Mini Mental State Examination (MMSE) [10], the 21-item Hamilton Depression Rating Scale (HDRS) [11], as well as Hamilton Anxiety Rating Scale (HARS) [12] were conducted by the same trained interviewer (MS).

When data collection was completed, the differences between arithmetic means were assessed by Student's *t*-test and between proportions by $\chi 2$ test.

Results

A total of 72 patients as well as 35 age-matched controls agreed to participate in the study by signing the informed consent.

Clinical and demographic data of our PD patients and the control subjects are shown in Table 1.

Autonomic function tests

Tests for the sympathetic nervous system (SNS) evaluation were significantly different [hand grip – $p < 0.0001$; orthostatic hypotension (OH) – $p < 0.0001$) in comparison to the controls, suggesting the sympathetic failure in parkinsonian patients ($p < 0.0001$). The same was proved for the parasympathetic nervous system functions (Valsalva maneuver – $p < 0.0001$; deep breathing – $p < 0.05$; standing test – $p < 0.001$) (Table 2).

However, when the SNS and parasympathetic nervous system (PNS) were compared in *de novo* patients and the control group, the significance was found in both tests for SNS (hand grip – $p < 0.0001$; orthostatic hypotension – $p < 0.01$), while the significance was irrelevant for PNS (Valsalva maneuver – $p < 0.05$; deep breathing – NS; standing – non significant). The patients with good therapeutical response, as well as those with developed complications of levodopa treatment differed from the controls in both SNS ($p < 0.0001$) and PNS dysfunction ($p < 0.0001$).

Autonomic neuropathy was established in 44% of the *de novo* patients, 88% of the patients with good response to the therapy and in all the patients with complications of levodopa treatment (on average, 76% of the PD patients). Complete autonomic neuropathy was not established in the group I, while 36% and 50% in the groups II and III, respectively, had the dysfunction of both SNS and PNS (on average, 28% of the PD patients) (Figure 1). The presence of autonomic neuropathy ($p < 0.0001$) as well as CAN ($p < 0.0001$) differed significantly between the groups.

Table 1

Clinical and demographic characteristics of Parkinson's disease patients

Parameters	Group I	Group II	Group III	*p*
Sex (F:M)	9/16	13/12	9/13	NS
Age at onset (years)	56.9 ± 7.6	57.2 ± 8.2	55.3 ± 6.9	NS
Actual age (years)	57.1 ± 7.2	60.6 ± 8.8	63.0 ± 5.0	NS
Disease duration (months)	4.6 ± 9.7	41.6 ± 39.5	102.2 ± 60.3	< 0.0001
Schwab-England scale	84.4 ± 6.5	70.0 ± 11.2	58.6 ± 11.7	< 0.0001
Hoehn&Yahr scale	1.5	2	3	< 0.0001
UPDRS	26.3 ± 12.8	40.3 ± 17.2	53.2 ± 17.5	< 0.0001
MMS	27.7 ± 1.6	26.5 ± 2.6	25.6 ± 3.4	NS
Hamilton A	5.5 ± 3.3	6.9 ± 3.4	10.1 ± 4.3	< 0.0001
Hamilton D	6.4 ± 3.7	8.4 ± 4.1	10.9 ± 4.4	< 0.0001

Note: results are given as n or $\bar{x}$ ± SD; UPRDS – Unified Parkinson's Disease Rating Score; MMS – mini mental state; NS – non significant; F – female; M – male; group I – *de novo* patients; group II – levodopa treated patients with no levodopa-induced motor complications; group III – levodopa treated patients with levodopa-induced motor complications.

Table 2

The tests for evaluation of the sympathetic (SNS) and parasympathetic nervous system (PNS) symptoms in the Parkinson's disease (PD) and control groups

Parameters	Points	PD (n)	Control (n)	*p*
SNS				
hand grip	0	3	12	< 0.0001
	1	5	15	
	2	64	8	
orthostatic hypertension	0	34	34	< 0.0001
	1	11	1	
	2	27	0	
DS	0	7	27	< 0.0001
	1	65	8	
PNS				
Valsalva maneuver	0	16	15	< 0.0001
	1	25	18	
	2	31	2	
deep breathing	0	41	28	< 0.05
	1	15	6	
	2	16	1	
standing	0	19	21	< 0.001
	1	15	7	
	2	38	7	
DPS	0	17	25	< 0.0001
	1	55	10	

0 – normal; 1 – borderline; 2 – pathological; DS – denervation of the sympathetic nervous system; DPS – denervation of the parasympathetic nervous system.

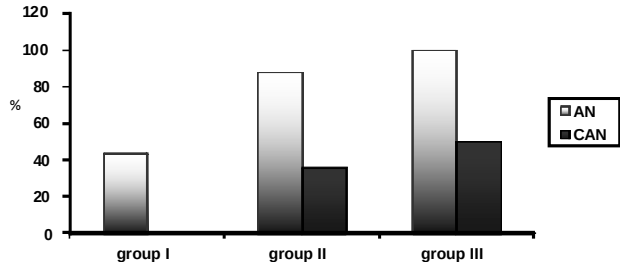

Fig. 1 – The percentage of patients with autonomic neuropathy (AN) and complete autonomic neuropathy (CAN).

group I – *de novo* patients; group II – levodopa treated patients with no levodopa-induced motor complications; group III – levodopa treated patients with levodopa-induced motor complications.

Patients with and without complete autonomic neuropathy

The patients with determined complete autonomic neuropathy (CAN) significantly differed from those without CAN, according to Schwab-England ($p < 0.001$) and Hoehn-Yahr scale ($p < 0.01$), while there was no difference in other examined clinical characteristics (sex, age at diagnosis, actual age, duration of disease, affected side, pain and "freezing"). A statistical difference was found in cumulative and motor UPDRS ($p < 0.01$), as well as in daily activities score ($p < 0.05$), when compared the patients with and without CAN. All the performed mental tests (MMSE, HDRS and HARS) showed a statistical difference ($p < 0.05$) between the patients who developed CAN and those who did not (Table 3).

saliva is continually draining from the mouth….") [13]. The conflicting conclusions were reported in the following decades. Many researchers stated that there was no direct connection between the autonomic failure and PD [14], contrary to others who estimated that 80–90% of all parkinsonian patients suffered from one or another type of dysautonomia [15]. Besides conflicting conclusions regarding the presence and frequency, an important issue was the onset of autonomic symptoms.

Our results support the view that dysfunction of autonomic nervous system represents important clinical feature of PD, even in its early phase. It is intriguing that not all parts of autonomic system were involved equally. In *de novo* patients, the tests for sympathetic evaluation showed significant difference, while the results for PNS were not statistically different among the groups, thus defining *de novo* patients as those manifesting only sympathetic dysfunction.

Shibata et al. [16] and Buob et al. [17] also found considerable dysfunction of the SNS, even at the initial phase of the disease, which was confirmed by recent results obtained by Gaenslen et al. [6]. They demonstrated dysregulation of the heart sympathetic noradrenergic innervation (PET scan using 6-[^{18}F] fluorodopamine) even before clinical diagnosis of Parkinson's disease. Post-mortem studies of the accidental Lewy bodies in patients without the clinical features of Parkinson's disease showed a decrease in tyrosine hydroxylase immunoreactivity in the epicardial nervous tissue, which also pointed to early noradrenergic denervation of the heart [18]. Okada et al. [19] showed the existence of Lewy body formation in the sinoatrial ganglion in 33% of patients with idiopathic PD.

Table 3

Clinical and demographic characteristics and (complete) autonomic neuropathy

Scores and demographic characteristics	Autonomic neuropathy	Complete autonomic neuropathy	*p*
UPDRS (cumulative)	39.7 ± 21.6	53.7 ± 24.1	< 0.01
UPDRS (mental)	3.5 ± 2.2	4.0 ± 2.3	
UPDRS (daily activities)	13.2 ± 7.5	17.7 ± 7.5	< 0.05
UPDRS (motor)	22.9 ± 13.8	32.0 ± 15.6	< 0.01
UPDRS (complications)	4.1 ± 3.6	5.5 ± 3.9	
Schwab-England	71.4 ± 15.8	58.9 ± 16.9	< 0.001
Hoehn-Yahr	2	3	< 0.01
MMS	26.9 ± 2.5	25.5 ± 3.2	< 0.05
HARS	7.3 ± 4.0	9.7 ± 5.1	< 0.05
HDRS	8.4 ± 4.4	11.0 ± 5.9	< 0.05
Sex (M/F)	39/19	15/14	
Age at onset	59.1 ± 8.1	62.4 ± 8.7	
Duration of disease (months)	42.4 ± 53.6	59.8 ± 58.8	
Affected side (left/right/both)	2/39/17	7/19/3	
Pain (yes/no)	25/33	14/15	
Freezing (yes/no)	18/39	14/14	

Note: results are given as n or $\bar{x}$ ± SD; UPDRS – Unified Parkinson's Disease Rating Score; MMS – mini mental state; HARS – Hamilton Anxiety Rating Scale; HDRS – Hamilton Depression Rating Scale; M – male; F – female.

Discussion

In 1817 James Parkinson described that other than classical symptomatology, the disease includes dysautonomia as well ("… the bowels demand stimulating medicines of very considerable power, … the urine passed involuntarily, … the

In attempt to stress an early manifestation of the autonomic dysfunction, Barbic et al. [20] compared a control group and PD individuals with and without orthostatic hypotension (OH), revealing certain autonomic impairment in non-OH patients, therefore suggesting that parkinsonian patients without dysautonomia were somewhere between healthy in-

dividuals and PD subjects with developed OH. Mihci et al. [21] reached similar conclusions, emphasizing the need for autonomic assessment, even in the absence of autonomic symptoms. Nowadays, it is a possibile to early detect postganglionic sympathetic dysfunction using I-125-MIBG-SPECT [22].

There are assumptions that the autonomic disturbances may be prodromal signs of Parkinson's disease [23]. It is also considered that constipation is an early manifestation of Parkinson's disease and that even men who reported having less than one bowel movement daily had a risk of developing PD 2.7 times higher than men who had bowel movements on regular daily basis [24]. It is even believed that the presence of constipation with the abnormal sense of smell and REM sleep behavior disorder already represent a defined type of PD [25].

Interestingly, however, there are people with PD who have a normal finding of the heart suggesting that the autonomic disturbances (loss of cardiac uptake of 123-I-MIBG) and nigrostriatal degeneration can exist independently in patients with PD [26].

Contrary to previous findings, some researchers [13, 16] suggest a simultaneous deficit of both divisions of ANS, while Siddiqui et al. [27], as well as Buob et al. [17], claim that the initial dysfunction is of parasympathetic nature, whereas both SNS and PNS become involved with the disease evolution.

If we accept the theory of Braak et al. [8], then a huge percentage of patients with the autonomic disturbances in *de novo* group can be explained by their hypothesis. According to their proposition of six stages of pathological process, after the initial degeneration in *bulbus olfactorius* and anterior olfactory nucleus, this degeneration, in the next stage, spreads to the brain stem, the region that supposedly represents the key role in mediating autonomic phenomena.

An early appearance of autonomic disorders is the reason why sometimes it is not possible to differentiate, on the basis of positive tests, the multiple system atrophy and Parkinson's disease [28].

The issue of risk factors associated with CAN is also interesting, because an association between the presence of autonomic nervous system and disease severity, age at onset and drug intake is not clear [29].

The Schwab-England and Hoehn-Yahr scales differ significantly parkinsonian patients with complete autonomic neuropathy from those without it. This characterizes individuals with developed CAN as patients with higher degree of functional impairment and severe clinical status. CAN patients vary according to the number of UPDRS motor scale items especially according to postural instability and bradykinesia. This is consistent with the finding that autonomic disorders are more common problem in people with PIGD form of the disease [3]. Interestingly, albeit negative correlation between parkinsonian symptoms and autonomic failure indicates that patients with more prominent disorders of gait and stability have more severe dysautonomia, this connection is lost among our patients when daily levodopa therapy is taken into consideration.

CAN patients also vary from non-CAN group by the presence of anxiety and depression. Other clinical and demographic characteristics did not vary between these two groups of patients. Verbaan et al. [30] found that the severity of the autonomic phenomena was higher in people with the severe motor disorders, depressive symptoms, cognitive impoverishment, psychiatric complications, sleep disorders and excessive day sleepiness.

It was found that the most frequent symptoms in patients with the autonomic dysfunction are the orthostatic hypotension, bladder dysfunction, constipation and erectile disturbances [31].

In our study, the patients with CAN were not different from the patients without CAN by age. Although aging changes the function of the autonomic nervous system, according to many studies, an autonomic failure becomes apparent just after the age of 75 years [32]. In addition, our patients did not differ by the application and length of dopaminomimetic treatment (data not shown), though it has been described that levodopa aggravates the impairment of the autonomic control of BP and HR [29]. In our group of patients, impaired cardiovascular autonomic control was detected early in the course of PD, when patients were drug naïve. Contrary, in some reports, the use of levodopa agonists produced lessening of detrusor hyperreflexia, whereas in others it provided improvement of voiding difficulty [31]. A large study of Sakakibara and coworkers [33] showed that patients taking levodopa and dopamine agonists had voiding phase disorder more frequently than those taking levodopa only. Lucetti et al. [34] offered an interesting concept after 5-year follow-up of PD patients with and without autonomic dysfunction. The patients with dysautonomia required earlier introduction of dopaminergic therapy, which indirectly suggested their rapid deterioration.

Conclusion

Our results confirm a high prevalence of autonomic nervous system disturbances among Parkinson's disease patients from the near onset of disease, with a predominant sympathetic nervous system involvement. The patients who developed complete autonomic neuropathy (both sympathetic and parasympathetic) were individuals with considerable level of functional failure, more severe clinical presentation and the existing anxiety and depression.

Conflict of interest

The authors had no conflict of interest regarding the material and information presented in the article.

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