

Syncope and autonomic cardiovascular dysfunction in Parkinson disease

Zaburzenia unerwienia autonomicznego układu sercowo-naczyniowego a występowanie omdleń u osób z chorobą Parkinsona

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Abstract

Background and purpose: The aim of the study was to investigate the relationship between syncope or presyncope occurrence and dysfunction of the cardiovascular autonomic system in patients with Parkinson disease (PD).

Material and methods: Twenty-four PD patients were studied, including 10 subjects with syncope/presyncope and 14 controls without those symptoms. Ambulatory blood pressure monitoring (ABPM), Holter electrocardiographic monitoring, carotid sinus massage, tilt test, and cardiac scintigraphy with ¹²³I metaiodobenzylguanidine (MIBG) were performed.

Results: Differences between the two groups were found in myocardial scintigraphy and ABPM. The stepwise regression analyses suggest that the values of late phase reduced uptake of MIBG (95% CI: 0.0–0.77; $p < 0.05$) and daytime minimum systolic blood pressure (95% CI: 0.78–0.98; $p = 0.007$) may be related to the occurrence of syncope/presyncope.

Conclusions: The findings suggest an association between syncope/presyncope occurrence and dysfunction of the cardiovascular autonomic system in PD patients. Both ¹²³I MIBG myocardial scintigraphy and ABPM may help identify a group of patients with an elevated risk for syncopic episodes which, in turn, may affect the choice of treatment.

Key words: myocardial scintigraphy, Parkinson disease, syncope.

Streszczenie

Wstęp i cel pracy: Celem pracy była analiza wpływu uszkodzenia unerwienia układu sercowo-naczyniowego na występowanie omdleń i stanów przedomdleniowych w grupie osób z chorobą Parkinsona (ChP).

Materiał i metody: Do badania włączono 24 chorych, u których rozpoznano prawdopodobną ChP. Grupę badaną stanowiło 10 osób, które zgłaszały występowanie omdleń i stanów przedomdleniowych, a grupę kontrolną 14 pacjentów bez takich incydentów w wywiadzie. Protokół badawczy obejmował następujące czynności: masaż zatoki szyjnej, monitorowanie EKG i ciśnienia tętniczego metodą Holtera (ABPM), test pochyleniowy oraz badanie scyntygraficzne serca z zastosowaniem ¹²³I metaiodobenzylguanidyny (MIBG).

Wyniki: W analizie regresji logistycznej wykazano istnienie związku między występowaniem omdleń/stanów przedomdleniowych a wynikami ABPM – minimalnym ciśnieniem skurczowym w interwale dziennym (95% CI: 0,78–0,98; $p = 0,007$), a także wynikami fazy późnej badania scyntygraficznego serca z użyciem MIBG (95% CI: 0,0–0,77; $p < 0,05$).

Wnioski: Wyniki badań sugerują związek pomiędzy występowaniem omdleń i stanów przedomdleniowych a zaburzeniami unerwienia autonomicznego układu sercowo-naczyniowego u chorych na ChP. Scyntygrafia serca z użyciem ¹²³I MIBG oraz ABPM mogą być użyteczne przy ocenie

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Introduction

Non-motor symptoms of Parkinson disease (PD), according to Braak [1], are associated with neuropathological findings outside the substantia nigra. The cardiovascular autonomic nervous system is vulnerable to α -synuclein pathology. In early pathological Braak stages (stages 1-2), a decreased density of TH-immunoreactive nerve fibres in the epicardium was found. In later stages (2-3) of PD, α -synuclein-immunoreactive neurites in the epicardium were found [2]. Metaiodobenzylguanidine (MIBG) labelling with 123 Iodine permits the visualization of sympathetic innervation in vivo [3]; its uptake correlates with adrenergic function. MIBG is a physiological analogue of noradrenaline competing for active uptake into the postganglionic sympathetic nerve terminal [4]. The impaired cardiac uptake of 123 I-MIBG in PD patients is the result of involvement of postganglionic sympathetic cardiac neurons and is observed in nearly all patients [5-8]. The most common index used for imaging interpretation – the heart/mediastinum (H/M) ratio – is reduced in PD patients from the earliest stages of the disease and can be a sensitive tool for the detection of silent autonomic dysfunction in patients without clinical evidence of dysautonomia [9-11]. The sympathetic denervation in PD occurs concurrently with parasympathetic dysfunction and both can result in symptoms of autonomic failure, such as orthostatic hypotension [12,13] and falls [14]. The existence of correlations between the severity of parkinsonian clinical features and MIBG uptake remains controversial [4]. 123 I-MIBG scintigraphy has been reported to be useful for differentiating PD from other atypical parkinsonian syndromes, especially MSA, when central and pre-ganglionic neurons are involved [15]. The objective of the present study was to investigate the correlation between cardiovascular autonomic system dysfunction and cardiovascular symptoms, i.e. the occurrence of syncope and presyncope in PD patients.

narażenia na występowanie omdleń i stanów przedomdleniowych w tej grupie pacjentów, co powinno mieć wpływ na postępowanie terapeutyczne. Scyntygrafia serca z użyciem 123 I MIBG jest badaniem bezpiecznym. W przypadku metod jakościowych, takich jak test pochyleniowy czy masaż zatoki szyjnej, stwierdza się większy odsetek powikłań.

Słowa kluczowe: scyntygrafia serca, choroba Parkinsona, omdlenie.

Material and methods

Patients with probable PD, diagnosed according to Oertel and Quinn criteria [16], were assessed as potentially eligible for the study. The study was approved by the Ethics Committee of the Medical Centre for Postgraduate Education in Warsaw, Poland.

Patients were excluded on the basis of the presence of any disorder of the central or peripheral nervous system other than PD, diabetes mellitus, heart disease (ischaemic heart disease, cardiomyopathy), hypertension, or cancer. Patients receiving medications which interfere with MIBG uptake or affect the autonomic nervous system (e.g. beta-blockers) were also excluded.

Twenty-four patients with probable PD (10 females, 14 males; mean age, 62.3 years) were included in the study and were divided into two groups. Group I consisted of 10 patients with a history of syncope and/or presyncope episodes (3 females, 7 males; mean age: 63.9). Group II comprised 14 patients with no such history (7 females, 7 males; mean age: 61.1).

Syncope was defined as a transient, self-limited loss of consciousness and pre-syncope as a condition in which patients feel as if syncope was imminent. Symptoms associated with pre-syncope were similar to the premonitory phase of true syncope: light-headedness, nausea, sweating, weakness and visual disturbances or non-specific symptoms, e.g. 'dizziness' [17].

The average duration of PD was 8.6 years in group I and 7.3 years in group II ($p = 0.534$, t -test). The average Hoehn and Yahr stage (in 'on' state) in group I was 2.7 and in group II it was 2.57. The average daily levodopa-equivalent dose (mg) in group I was 570.0 and in group II it was 525.7. All patients from group II were on monotherapy. Patients from group I were also treated using other antiparkinsonian medications: amantadine (1 person), selegiline (3 persons), biperiden (1 person), pridinol (1 person) and entacapone (1 person).

All study patients underwent physical and neurological examinations. Historical features considering questions about circumstances just prior to the syncope, the onset and the end of the attack and the family background were taken. In group I, seven patients reported features typical for syncope due to orthostatic hypotension – it appeared after standing up and after prolonged standing in crowded, hot places. One patient associated syncope with head rotation, while another three reported that it appeared after exertion. Patients did not have vasovagal syncope in the history and cardiogenic causes (conduction blocks, other dysrhythmias) were quite unlikely as the primary causes of syncope. In group I only one patient experienced syncope before PD was diagnosed. For the rest, the average time from PD onset to the first syncope/presyncope experience was 5.8 years.

Echocardiogram, ambulatory blood pressure monitoring (ABPM), ambulatory electrocardiographic recording (Holter ECG), carotid sinus massage, tilt test, and myocardial scintigraphy with ^{123}I -MIBG were performed.

Echocardiogram (Philips Envisor C HD, MCMD 02 AA) was used to rule out heart diseases in which cardiac syncope occurs [17].

ABPM (Mobilograph) was used to determine the circadian rhythm of blood pressure (dipper or non-dipper profile), as well as daytime and nighttime values of minimum and maximum systolic blood pressure (minSBP, maxSBP), diastolic blood pressure (minDBP, maxDBP), and pulse pressure (PP).

Holter ECG recording (3-channel, Rozzin Holter Recorder 151) was conducted to diagnose intermittent arrhythmias. The rate-corrected QT (QTc), the standard deviation of NN intervals (SDNN), the average heart rate (avrHR), the maximum heart rate (maxHR), supraventricular ectopy (SVE), and ventricular ectopy (VE) were analysed.

The carotid sinus reflex was tested during the carotid sinus massage. The inclusion criterion for the massage was the absence of atherosclerotic plaque in the carotid artery (duplex Doppler ultrasonography). Massage was performed in the supine position. ECG monitoring was employed. After baseline measurements, the right carotid artery was massaged for 5 seconds and, after a 2-minute-break, the left one. The test was considered positive if, during or immediately after the massage, an asystole longer than 3 seconds or a fall in systolic blood pressure of 50 mm Hg or more were present.

In the tilt test, the supine pre-tilt phase lasted 5 minutes and the passive phase, at an angle of 70° , lasted

45 minutes. Drug provocation was not used. The end point of the test was the induction of syncope (test positive) or completion of the planned duration of the tilt.

Myocardial scintigraphy with ^{123}I -MIBG was performed to detect alterations in myocardial sympathetic activity [18]. Before intravenous administration of approximately 111 MBq of ^{123}I -MIBG, the thyroid was blocked by oral administration of 500 mg of potassium perchlorate. Planar scintigraphic images of the heart were acquired 20 minutes and 4 hours (early and late phase) later. The H/M ratio was calculated for both phases to quantify the cardiac MIBG uptake as a fraction of the mean counts per pixel in the heart divided by those in the upper mediastinum with a value of >1.8 considered normal on the basis of previous studies [18].

Group comparisons were performed using *t*-tests, Fisher exact tests, and logistic regression analyses. The strength of association between measures was evaluated by Pearson correlations for normally distributed random variables (avrHR, maxHR, QTc, SDNN) and by Kendall tau-b rank correlation for non-normally distributed random variables (SVE, VE).

Results

Group I showed significantly lower daytime values of minSBP ($p = 0.006$), minDBP ($p = 0.013$), and PP ($p = 0.027$) and lower nighttime values of minSBP ($p = 0.023$) and PP ($p = 0.022$) than group II (Table 1).

The Holter ECG monitoring chosen for analysis did not show any significant differences between the two study groups.

Carotid sinus massage was done in 6 patients from group I and 10 from group II. The others were excluded, based on Doppler ultrasonography. Hypotension during carotid massage was observed only in one patient from group I.

The tilt test was performed with 8 patients from group I and 13 from group II. Three patients refused to continue the test immediately after the pre-tilt phase. Two patients from group I and one patient from group II exhibited syncope during the tilt phase. Orthostatic hypotension was identified in all 3 patients with positive test results.

The H/M ratio was reduced in all patients in group I and II, both in early and late phases of myocardial scintigraphy. The decrease in the H/M ratio was more pronounced in group I, with the differences being sta-

Table 1. Results and mean values for qualitative and quantitative methods for the assessment of the autonomic cardiovascular function in Parkinson's disease patients with and without syncope/presyncope occurrence

Method	Patients with syncope/presyncope n = 10	Patients without syncope/presyncope n = 14	P-value (t-test or *Fisher exact test)
ABPM – daytime			
minSBP, mean [mm Hg]	83.0	95.7	0.006
maxSBP, mean [mm Hg]	149.0	162.8	0.07
minDBP, mean [mm Hg]	45.0	53.6	0.013
maxDBP, mean [mm Hg]	94.5	100.4	0.27
pulse pressure, mean [mm Hg]	40.73	48.6	0.027
ABPM – nighttime			
minSBP, mean [mm Hg]	84.5	95.1	0.023
maxSBP, mean [mm Hg]	142.2	144.9	0.72
minDBP, mean [mm Hg]	50.4	53.4	0.44
maxDBP, mean [mm Hg]	91.9	88.6	0.46
pulse pressure, mean [mm Hg]	38.7	44.3	0.022
Holter EKG			
QTc, mean [ms]	422.0	418.0	0.72
SDNN, mean [ms]	132.7	118.7	0.24
average heart rate, mean [1/s]	71.6	75.2	0.24
maximal heart rate, mean [1/s]	112.0	116.9	0.38
supraventricular ectopy, mean [n]	30.3	46.6	0.46
ventricular ectopy, mean [n]	41.6	8.7	0.23
Carotid sinus massage			
normal	5	10	0.37*
abnormal	1	0	
Tilt test			
normal	6	12	0.24*
abnormal	2	1	
Myocardial scintigraphy (heart/mediastinum ratio)			
early phase, mean	1.37	1.49	0.06
late phase, mean	1.24	1.39	0.028

ABPM – arterial blood pressure monitoring, ECG – electrocardiogram, SBP – systolic blood pressure, DBP – diastolic blood pressure, PP – pulse pressure, QTc – rate-corrected QT, SDNN – deviation of NN intervals

tistically significant in the late phase ($p < 0.03$; *t*-test) (Fig. 1).

A low positive correlation was found between the H/M ratio in the early phase of myocardial scintigraphy and avrHR ($r = 0.48$; $p < 0.02$). A weak negative correlation was found between the H/M ratio in the late

phase of myocardial scintigraphy and VE ($r = -0.36$; $p < 0.02$). Both the early phase ($r = -0.49$, $p = 0.015$) and the late phase ($r = -0.44$, $p = 0.031$) H/M ratios correlated negatively with nighttime minDBP values.

The stepwise regression analyses suggest that the values of late phase reduced uptake of MIBG (95% CI:

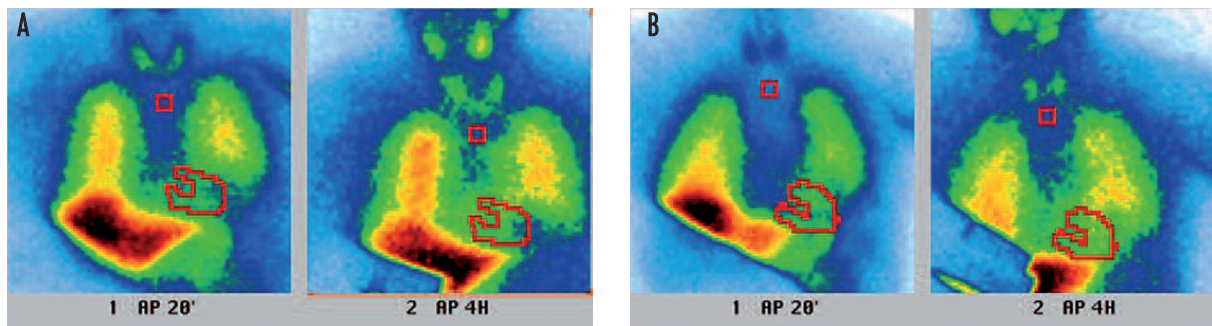


Fig. 1. A) Patient with Parkinson disease and syncope/presyncope occurrence. Results of ^{123}I -MIBG cardiac scintigraphy: early phase (heart/mediastinum ratio = 1.33) and late phase (heart/mediastinum ratio = 1.19). B) Patient with Parkinson disease without syncope and presyncope occurrence. Results of ^{123}I -MIBG cardiac scintigraphy: early phase (heart/mediastinum ratio = 1.63) and late phase (heart/mediastinum ratio = 1.50)

0.0-0.77; $p < 0.05$) and daytime minSBP (95% CI: 0.78-0.98; $p = 0.007$) may be related to the occurrence of syncope/presyncope.

Discussion

To the best of our knowledge, this is the first study with PD patients in which it has been shown that the impaired cardiac uptake of ^{123}I -MIBG specifying the dysfunction of the sympathetic cardiac nervous system might be considered a risk factor for syncope/presyncope occurrence. The resulting research design, dividing patients into those with and without syncope/presyncope on the basis of clinical interviews, allowed for a fresh, assumption-free look at the possible causes and correlates of syncopic incidents in PD.

Traditional, qualitative clinical methods are limited in their ability to identify the cause of syncopic episodes [17]. This was also shown in our study, where such a cause was identified in only 3 of the 10 patients in group I. Similarly, the fact that orthostatic hypotension was identified during the non-pharmacological tilt test in only 2 of the 10 patients in group I (8 patients exhibiting no such symptoms) may suggest that any study which limits the research group to PD patients with orthostatic hypotension may possibly miss other causes of syncopic episodes by looking at a research group pre-selected with a limited screening device.

The present study shows statistically significant differences in some ABPM measures and in the H/M ratio of late phase myocardial scintigraphy between the syncope and control group. Group I showed generally lower values of daytime blood pressure and pulse pressure, which may cause reduced cerebral blood flow and the ensuing syncopic episodes. Regression analysis, showing daytime minSBP as the best predictor of syn-

cope/presyncope, provides confirmation of this interpretation. Lower H/M ratio values in group I suggest a greater extent of cardiac sympathetic nervous system impairment in these patients. Additionally, those ABPM and H/M ratio values which differentiated group I from group II did not correlate with each other. One exception was the nighttime minDBP. This pattern suggests that the dysfunction of postganglionic sympathetic cardiac neurons and sympathetic control of blood vessels occur independently. It also suggests that minSBP may be the most important predictor, bearing in mind the pathogenesis of syncope, especially neurally-mediated as well as that associated with orthostatic hypotension. The decreasing arterial blood pressure could be the effect of vasodilatation. In PD patients, syncope, like orthostatic hypotension, seems to be the result of generalized sympathetic cardiovascular denervation [13]. This is also a group of older persons and other mechanisms should be taken into consideration, for example heart function (appropriate atrial contraction, heart rate). In the present study heart dysfunction was an exclusion criterion.

PD patients lose the nocturnal blood pressure dip with a 24-hour blood pressure profile [19]. The negative correlation between nighttime minDBP and both early and late phase H/M ratios may suggest an association between the level of dysfunction of the sympathetic cardiac nervous system and non-dipper profile of ABPM. Taking into consideration the pathophysiology, the impaired cardiac uptake of ^{123}I -MIBG should be perceived only as a determinant of the sympathetic and parasympathetic denervation level of the cardiovascular system.

The low correlations found between the H/M ratio in the early phase of myocardial scintigraphy and avrHR as well as between the H/M ratio in the late phase of

myocardial scintigraphy and VE may suggest an association between alterations in myocardial sympathetic activity and changes in baseline cardiac rhythm [20,21]. However, their low strength only underscores the limited utility of the qualitative assessments.

The present study suggests that a decreased H/M ratio could correlate with syncope/presyncope occurrence. The demonstrated correlation between the H/M ratio in the late phase of myocardial scintigraphy and VE might suggest the existence of arrhythmias. However, a lack of correlation between VE and syncope/presyncope precludes a suggestion that arrhythmias could contribute to syncopic episodes. Decreased myocardial MIBG uptake can predict major cardiac events. Its prognostic value has been reported mainly in heart failure patients [22]. In the present study major cardiac events were not noted, because heart disease was one of the exclusion criteria.

The importance of medical history cannot be replaced with modern technology in the case of syncope. In group I seven patients reported features typical of syncope due to orthostatic hypotension – it appeared after standing up or after prolonged standing in crowded, hot places. One patient associated syncope with head rotation, while another three reported that it appeared after exertion. Only in two cases did patients reporting features typical for syncope due to orthostatic hypotension exhibit syncope during the tilt phase of the tilt test. The limitation of the study in this case is that, according to the protocol, only a non-pharmacological test was performed.

Both ¹²³I MIBG myocardial scintigraphy and ABPM may help identify a group of patients with an elevated risk for syncopic episodes which, in turn, may affect the choice of antiparkinsonian treatment: type of medication and its dosage. MIBG cardiac scintigraphy is a very safe method with no serious adverse effects [7,23]. Unification of the technical standards (acquisition protocols and positions of H/M ratio calculation regions of interest) is necessary [4]. Traditional methods, particularly carotid sinus massage, have a higher rate of complications. On the other hand, they are less expensive, easier to arrange, can lead to the proper diagnosis of syncope type, initiation of its treatment and to the conclusion that there is sympathetic dysfunction in a given patient. In the present study positive results of sinus carotid massage and tilt test were obtained in only a few patients. It allowed for modification of their treatment and a start to education regarding avoidance of triggering events, recognition of premonitory symptoms, etc.

The low number of studied patients limits the power of statistical inferences and suggests the need for greater caution in generalizing the results. Further studies are needed to confirm our preliminary findings.

Conclusions

1. The findings suggest an association between syncope/presyncope occurrence and dysfunction of the cardiovascular autonomic system in PD patients.
2. Both ¹²³I MIBG myocardial scintigraphy and ABPM may help identify a group of patients with an elevated risk for syncopic episodes which, in turn, may affect the choice of treatment.

Disclosure

The authors report no conflict of interest.

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