

Autonomic dysfunction and peripheral nerve involvement in patients with Parkinson's disease

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Abstract

Introduction: Parkinson's disease (PD) is a chronic illness which damages central and peripheral nervous system. The presence of peripheral neuropathy (PN) in PD, it has been suggested to be the effect of treatment. The aim of this study was to investigate autonomic cardiac control in PD patients with normal serum levels of vitamin B12 by means of spectral analysis of short-term heart rate variability (HRV) and also to assess the prevalence of PN using electrophysiological examinations. **Methods:** 30 (18 male and 12 female) with PD were compared to 20 age- and sex-matched control subjects. Short-term ECG was used to calculate time domain and spectral parameters of HRV. The stimulodetection examination was realized in the motor fibers of median, peroneal and tibial nerves, and in the sensitive fibers of median and sural nerve according to the standard procedures. **Results:** Low and high frequency were lower in PD patients than in controls (LF: $332. \pm 288.4 \text{ ms}^2$ PD vs $723.9 \pm 348.2 \text{ ms}^2$ C; HF: $283.72 \pm 241.97 \text{ ms}^2$ PD vs $530.54 \pm 226.5 \text{ ms}^2$ C, $p < 0.01$). No differences between LF/HF ratio of PD and controls appeared. Sensory nerve action potential in sural nerve was reduced in PD patients. No differences between sensory and motor nerve conduction velocities of PD and controls appeared. **Conclusions:** PD causes dysfunction of autonomic cardiovascular regulation and peripheral nerve involvement.

Key words: *Parkinson's disease, heart rate variability, parasympathetic nervous system, low frequency, sensory nerve action potential, nerve conduction velocity,*

Introduction

Parkinson's disease (PD) is a chronic neurodegenerative movement disorder characterized by a progressive loss of the pigmented dopaminergic neurons of the substantia nigra pars compacta (SNpc) and by the presence of intra-neuronal aggregates called Lewy bodies (1). This degeneration affects not only the dopaminergic mesocorticolimbic system, but also the noradrenergic locus coeruleus (2), motor vagal nucleus, the serotonergic raphe nuclei (3) and many peptidergic brainstem nuclei containing substance P, somatostatin, and neuropeptide Y (4). Clinical manifestations of Parkinson's disease include motor dysfunction such as rigidity, resting tremor, bradykinesia, postural instability and gait dysfunction. PD is also associated with many non-motor features, including autonomic dysfunction, pain, mood disorders, sleep impairment, and dementia (5).

The pathogenesis of PD is largely unknown but mitochondrial dysfunction, oxidative stress, glutamate induced excitotoxicity, intracellular protein accumulation of Lewy Bodies containing α -synuclein protein, inflammation, loss of neurotrophic factors and apoptosis appear to have a key role in the development and progression of PD (6-8). Also the genetic factors, genes like parkin and α -synuclein has been involved in pathogenesis of PD (9).

It is well documented that PD may be associated with a dysfunction of the autonomic nervous system. Histological studies have proven the presence of Lewy's bodies in sympathetic and parasympathetic preganglionic neurons and also in central structures associated with the autonomic regulation (10).

Analysis of heart rate variability (HRV) from ambulatory ECG recordings has become an important method for assessment of cardiovascular autonomic regulation.

To characterize the cardiovascular autonomic regulation in PD, Ewing tests were used. These tests require an active participation of the patients, and the rigidity and tremor characteristic of PD make these tests difficult to assess. The measurement of autonomic parameters using power spectrum analysis of heart rate (HR) does not require the active participation of patients. Decrease of spectral power in PD patients was documented in 24-hour examination (11). The presence of peripheral neuropathy (PN) in PD is a relatively new clinical fact. PD patients may have sensory abnormalities which in some cases precede motor dysfunction. Alpha-synuclein was found in peripheral sensory neurons in PD patients (12). The presence of PN in PD, it has been suggested to be an iatrogenic effect of levodopa treatment, by deficiency of vitamin B12 after treatment (13). Toth et al. found that high levels of methylmalonic acid (MMA) are associated with levodopa-treatment and PN in PD patients (14).

The aim of this study was to investigate autonomic cardiac control in PD patients in early stages of the disease, with normal serum levels of vitamin B12 (cobalamin) and methylmalonic acid, by means of spectral analysis of short-term HRV and also to assess the prevalence of PN using electrophysiological examinations.

Methods

Participant recruitment and inclusion criteria

30 patients (18 male and 12 female) with PD were compared to 20 age- and sex-matched control subjects. Parkinson's disease was diagnosed according to the United Kingdom Parkinson Disease Society Brain Bank criteria (15). PD severity was determined using the Hoehn and Yahr scale (H&Y) (16). The patients included into the study also meet the criteria of normal serum levels of vitamin B12 (cobalamin) and methylmalonic acid.

Patients with stroke, epilepsy, coronary artery disease, arrhythmias, atrioventricular block or bundle branch block were excluded from the study. Inclusion criteria for the controls were the absence of any history of PD and with two normal consecutive ECG in the course of one month. Patients who had medication known to influence autonomic system (anticholinergic and monoamine oxidase inhibitor) were excluded. The study was carried out in accordance with the Helsinki Declaration. All subjects participated voluntarily after being given a detailed explanation of the purpose of the study.

Clinical and paraclinical assessment

All the subjects underwent detailed history taking and neurological examination. A standardized autonomic questionnaire was used to detect autonomic complaints.

Score of Unified Parkinson's Disease Rating Scale (UPDRS) part III (Motor section) was recorded when patients were at "on" state (17). The motor examination of UPDRS is the most used measure to assess motor symptoms such as rest and action tremor, rigidity, bradykinesia, gait and posture, facial masking. Each items are scored on a 0 (no impairment) to 4 (severe impairment), the total motor UPDRS exam score ranges from 0 to 108 (17).

For each person in the study we measured: body mass index (BMI) (calculated as weight divided by height squared-Kg/m²), fasting blood glucose, serum total cholesterol, high density lipoprotein cholesterol-HDL, low density lipoprotein cholesterol-LDL, triglycerides; systolic and diastolic arterial blood pressures in standard examination conditions.

Measurement of heart rate variability

Using BIOPAC Acquisition System, we monitored the HRV in basal condition (18-20). HRV was analyzed following the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (21). Short time ECG data were digitized and stored on computer for subsequent off-line analysis. The ectopic bits or artifacts were manually edited.

Time-domain parameters used were Mean-R-R, Standard deviation of all NN intervals (SDNN), square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), percentage of differences between adjacent NN intervals differing more than 50 msec (pNN50 %). pNN50% has been proven to be a valid index of vagal tone. Frequency Domain HRV measured were: very low frequency (VLF) from 0.0033–0.04 Hz, low frequency (LF) from 0.04–0.15 Hz and high frequency (HF) 0.15–0.4 Hz. The HF fluctuation of RR intervals mainly reflects the cardio-vagal modulation and the inspiratory inhibition of vagal tone (21). We analyzed LF and HF power, ratio of LF/HF (considered an index of cardiac sympathetic/parasympathetic tone balance). All HRV tests were made always in the morning hours between 9 and 11 a.m.

Table 1. Recording and stimulation site for nerve conduction studies

<i>Nerve</i>	<i>Recording (surface electrodes)</i>	<i>Distal stimulation</i>	<i>Proximal stimulation</i>
<i>mNCV Median nerve</i>	<i>Abductor Pollicis Brevis Muscle</i>	<i>3 cm above the wrist</i>	<i>Elbow</i>
<i>mNCV Peroneal nerve</i>	<i>Extensor Digitorum Brevis Muscle</i>	<i>Ankle (between the extensor digitorum longus and extensor hallucis longus tendons)</i>	<i>behind the fibular head</i>
<i>mNCV Tibial nerve</i>	<i>Abductor Hallucis Muscle</i>	<i>behind the medial malleolus</i>	<i>popliteal fossa</i>
<i>sNCV Median nerve ortodromic stimulation</i>	<i>3 cm above the wrist</i>	<i>Finger II</i>	
<i>sNCV Sural nerve antidromic stimulation</i>	<i>behind the Lateral Malleolus</i>	<i>distal to the lower border of the bellies of the gastrocnemius, at the junction of the middle and lower thirds of the leg, just lateral to the midline.</i>	

Nerve conduction studies

For electrophysiological investigations the electromyograph Neuro-MEP Micro was used. The stimulodetection examination was realized in the motor fibers of median, peroneal and tibial nerves, and in the sensitive fibers of median and sural nerve according to the standard procedures (22). The surface electrodes were used to obtain muscular response according to the principle "belly-tendon" (the active electrode was placed on the muscle belly and the reference electrode on its tendon). The ground was placed between distal stimulation and the recording electrodes. Stimulation and collection points are shown in Table 1. The investigations were carried out in a warm room, the temperature of the patient's skin being at least 35°C. For data acquisition specific settings were used: sensitivity (500 µV - 2 mV for motor and 2-5 µV for sensory nerve conduction velocity- NCV); frequency range (20 Hz - 5 kHz motor NCV and 20 Hz - 7 kHz sensory NCV); sweep (5 ms/division motor and 2 ms/division sensory NCV). Stimulation used single stimuli with duration of 0.1 ms and variable intensity to obtain maximum response (maximum 100 mA). For each motor nerve the following electro-physiological indices were studied: motor distal latency (MDL - ms), compound motor action potential (CMAP - mV), motor nerve conduction velocity (mNCV - m/s). At the examination of sensitive nerves the following parameters were measured: sensitive latency (SL - ms), sensory nerve action potential (SNAP - microV), sensory nerve conduction velocity (sNCV - m/s).

Statistical Analysis

The statistical analysis of the results was performed using the software package STATISTICA 6.0 (StatSoft Inc., USA). The values are presented as mean values and standard deviation. Test t- Student or variance analysis (ANOVA) was used to determine the differences between the groups. The Pearson correlation coefficient *r* was used for determining relationship between parameters. The values *p*<0.05 were considered statistically significant.

Results

We studied 30 patients (18 males and 12 females) with PD in 1-2 H&Y stage (mean age 63.2±3.47 years, body mass index 24.44±1.74kg/m²). These were compared to 20 normal patients (10 males/10 females, age 61.84±3.54 years, BMI 25.63±1.56 kg/m²) without history of PD and cardiovascular event.

Characteristic of study groups, time and frequency domain parameters of HRV are summarized in Table.2. UPDRS motor was 19.2±5.2 in PD, orthostatic hypotension was found in 13 PD patients (43.3%) and in 5 controls (25%) patients with *p*<0.01. Mean systolic and diastolic blood pressure did not differ when compared to the control group, but heart rate was found increased in PD patients with *p*<0.05. Mean RR showed statistically significant reduction in PD patients (822 ±115 ms in PD vs 983.2±116.8 ms in controls, *p*<0.05). The SDNN (38.7±16.7 ms PD vs 51.36±21.65ms C, *p*<0.01), rMSSD (36.9±14.7 ms PD vs 43.1±8.6 ms C, *p*<0.05) were reduced in PD patients when compared to the control group.

Both LF and HF were lower in PD patients than in

controls (LF: 332.±288.4 ms² PD vs 723.9±348.2 ms² C; HF: 283.72±241.97 ms² PD vs 530.54±226.5 ms² C, p<0.01). No differences between LF/HF ratio of PD and controls appeared.

Table 2. Characteristic of study groups, according to morphometric and comparison of time domain and spectral parameters of HRV

Parameter	Control n=20	PD n=30
Age (years)	61.84±3.54	63.2±3.47
BMI (Kg/m ²)	25.63±1.56	24.44±1.74*
UPDRS motor	-	19.5±5.2
Fasting blood sugar (mg/dl)	91.1±22.12	95.3±17.34
Total cholesterol (mg/dl)	196.6±29.6	185.4±21.33
HDL-cholesterol (mg/dl)	47.2±3.1	41.34±3.53*
Triglyceride (mg/dl)	158.2±14.96	162.5±32.32
Vitamin B12 (pg/ml)	581.9±108.4	597.75±149.5
Acid folic (ng/ml)	9.27±2.19	9.34±2.31
Mean SBP (mmHg)	131.86±20.5	129.6±14.87
Mean DBP (mmHg)	69.21±8.01	71.17±9.17
HR (b/min)	68.81±8.96	73.31±9.82*
Mean RR (ms)	983.2±116.8	822 ±115*
SDNN (ms)	51.36±21.65	38.7±16.7**
rMSSD (ms)	43.1±8.6	36.9±14.7*
pNN50 (%)	16.09±4.6	12.41±4.8*
LF (ms ²)	723.9±348.2	332.±288.4**
HF (ms ²)	530.54±226.5	283.72±241.97*
LF/HF	1.59±0.37	1.79±0.97

BMI – body mass index, UPDRS- Unified Parkinson's Disease Rating Scale, MMSE- Mini-Mental Status Examination, BDI- Beck depression inventory
SBP - systolic blood pressure, DBP - diastolic blood pressure, MAP-mean arterial pressure, PP- pulse pressure, HR- heart rate

Mean RR, SDNN, rMSSD, pNN50, LF, HF, LF/HF: explanation in method section.

Data: expressed as means±standard deviation;

*- P< 0.05; ** - P< 0.01 for difference between controls and PD

The results of Pearson correlation test, for a confidence interval of 95% indicate a significant inverse correlation between the age and LF values (r= - 0.41, p<0.02) and triglycerides with HF (r=-0.36, p<0.05). Also HF was correlated with BDI score (r=0.43, p<0.001).

Sensory nerve action potential in median nerve was reduced in PD patients: 9.81±5.2µV vs 11.53±5.5µV in controls, but we didn't find any statistical significance (Table 3). For median motor nerve parameters didn't show any differences between the study groups. The results of sural nerve exploration

show that the sensitive potential amplitude was 8.16±2.36 µV vs 10.95±2.73 µV for the control group, difference with high statistical significance (p<0.01). No differences in sNCV of sural nerve, mNCV of tibial or peroneal nerves between PD patients and controls appeared. Also we found differences between CMAP of tibial nerve in PD 3.72±1.73 µV and controls 5.34±1.71µV with p<0.01.

Table 3. Results of neuroelectrophysiological examination on controls and PD patients

Parameter	Control n=20	PD n=30
Median		
CMAP(µV)	7.23±2.2	6.8±2.6
mNCV (m/s)	48.3±3.2	48 ±3.23
MDL (ms)	2.92±1.5	2.82±1.5
SNAP (µV)	11.53±5.5	9.81±5.2
SL (ms)	1.84±0.01	1.9±0.01
sNCV (m/s)	50.3±6.4	48.73±6.5
Sural		
SNAP (µV)	10.95±2.73	8.16±2.36**
SL (ms)	3.4±0.1	3.5±0.1
sNCV (m/s)	46.28±6.29	45.8±6.5
Tibial		
CMAP(µV)	5.34±1.71	3.72±1.73**
mNCV (m/s)	43.71±4.15	43.78±4.6
MDL (ms)	4.32±1.2	5.4±1.21*
Peroneal		
CMAP(µV)	4.15±1.2	3.9±1.6
mNCV (m/s)	48.41±2.28	46.15±5.21
MDL (ms)	2.93±1.21	3.36±1.33

SL-sensitive latency, SNAP-sensory nerve action potential, sNCV - sensory nerve conduction velocity, MDL- motor distal latency, CMAP- compound motor action potential, mNCV - motor nerve conduction velocity.

*- P< 0.05; ** - P< 0.01 for difference between controls and PD

The results of Pearson correlation test, for a confidence interval of 95% indicate a significant inverse correlation between age and the sensory nerve conduction velocity value of the sural nerve (r= -0.47, p<0.05).

Discussion

PD is a neurodegenerative disorder, with an average age at onset of about 60 years and with the aging of the population it is anticipated that the prevalence of PD will increase dramatically in the coming decades. Recent studies suggest that PD may start in the gastrointestinal tract. According to the 'Braak's' hypothesis, protein aggregation in enteric neurons

spreads to the brain through the dorsal motor nucleus of the vagus (10). Pre-symptomatic PD patients had protein aggregation in the peripheral nervous system but not in the central nervous system (1). Protein aggregation ascended into the central nervous system and correlated with the development of motor dysfunction. Braak had postulated that the early Stages 1 to 3 of disease develop in patients who have not yet been diagnosed with classical motor symptoms of disease. Motor symptoms start to develop in Stage 3, when pathology has spread to the substantia nigra. Cognitive problems and dementia would occur when the neocortex becomes affected in Stages 5 and 6.

Alpha synuclein deposits have been found in the autonomic nervous system, in sensory and motor peripheral nerves (12, 23). Existing reports indicate that autonomic nervous system dysfunction occurs in the very early stages of PD. Evidence shows that both parasympathetic and sympathetic functions are impaired in PD (24).

123I-MIBG myocardial scintigraphy (Metaiodobenzylguanidine—a physiological analogue of noradrenaline) is clinically used to evaluate myocardial sympathetic nerve damage in PD. Reduced uptake of 123I-MIBG is considered to reflect cardiac sympathetic denervation, which precedes the neuronal loss of the paravertebral sympathetic ganglia, suggesting distal-dominant degeneration (25).

Patients with PD have shown suppressed heart rate responses to deep breathing indicating parasympathetic dysfunction (26). PD patients have low supine blood pressure levels and orthostatic hypotension is frequent because degeneration of sympathetic neurons is found (27). That can increase susceptibility to falls in PD patients.

HRV is widely accepted non-invasive, providing information on sympathetic and parasympathetic modulation of the sinus node. HF is regarded as a marker of cardiac vagal activity. LF represents the sympathetic activity with vagal modulation. Goldstein et al, 2011, suggests that LF power should be seen as an index of baroreflex function rather than cardiac sympathetic tone (28). SDNN, pNN50%, time domain indicator of the HRV, represents the activity of the vagal nerve.

In our study the analysis of HRV demonstrated that both parasympathetic and sympathetic nerve functions were impaired in PD patients because the

measures of SDNN, pNN50%, HF and LH were significantly lower than in controls. No differences between LF/HF ratio of PD and controls appeared. Our results agree with other studies demonstrating that both branches of autonomic nervous system are affected early in the course of PD.

In PD recent clinical and pathological studies point to defects in function of the peripheral nervous system in patients with early onset PD due to *parkin* mutation (29). The occurrence of peripheral neuropathy in a genetic type of PD suggests that a link may be present between central and peripheral neuronal degeneration. Reichling and Levine, 2011, suggest that in PD we can see a combination of peripheral afferent abnormalities with central pathological changes resulting in neuropathic pain. They suggest that it is the result of the same neurodegenerative processes, but occurring in the peripheral nervous system (30, 31).

In a longitudinal study of PD patients Toth et al., 2008, found that over half of the patients tested had peripheral neuropathy (14). The severity of the PN correlated with increased exposure to L-DOPA. Blood testing showed that the PD patients with PN had increased serum levels of methylmalonic acid (14). They also suggested that treatment with cobalamin will prevent the formation of methylmalonic acid, and thus could help protect against PN during long term L-DOPA therapy (14).

Abnormalities in SNAP or CMAP amplitude and a conservation of the nervous conduction velocity reflect axonal loss or degeneration (22). The signs of demyelination are decrease of the nervous conduction velocities, decrease of the action potentials, and an extension of the distal latencies (22). In our study we found reduced SNAP of sural nerve in PD patients. Therefore we concluded that the neuropathy in PD patients was mostly of a sensory axonal-predominant type. Our PD patients had normal levels of cobalamin suggesting that the presence of PN in early stages may be intrinsic to PD. PN may contribute to distal limb weakness, pain and risk of falling. A possible limitation of our study is the presence of a small number of subjects this decreases the statistical power to detect differences between the groups. Therefore, more research and longer observation of a larger group of patients are needed, including the most advanced form of Parkinson's disease.

Conclusions

PD causes dysfunction of autonomic cardiovascular regulation and peripheral nerve involvement especially axonal neuropathy even in early stage of the disease. The neurodegeneration process occurs both in the central and peripheral nervous systems so we can consider that PD is a multi-systemic disorder. Future work will seek to clarify pathophysiological mechanisms inducing the peripheral nerve damage seen in idiopathic Parkinson's disease.

Conflict of Interest Statement: The Authors declare that they have no conflict of interests.

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