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Hyperhomocysteinemia and low vitamin B12 associated with autonomic dysfunction in Parkinson's disease: A time domain analysis of heart rate variability

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Abstract

Background: Parkinson's disease (PD) is associated with autonomic dysfunction as well as hyperhomocysteinemia and low serum vitamin B12 level. Heart rate variability (HRV) is an important tool for assessing autonomic function. **Objective:** To evaluate the association of hyperhomocysteinemia and low vitamin B12 with autonomic dysfunction by time domain measures of HRV in male patients with PD. **Methods:** This observational analytical cross sectional study was conducted on 30 newly diagnosed male PD patients of 50-60 years age attending Out Patient Department of the Department of Neurology, BSMMU, Dhaka. Thirty (30) age and BMI matched apparently healthy male subjects were included as control for comparison. Serum vitamin B12 and homocysteine were measured by chemiluminescent immunoassay method and HRV was measured by time domain method using a data acquisition device, Power lab 8/35, AD instruments. Independent sample t-test and Pearson's correlation coefficient test were used for statistical analysis by SPSS version 25 and p value < 0.05 was considered as statistical significance. **Results:** In this study, resting pulse rate and mean heart rate were found significantly higher ($p<0.001$) and mean RR interval, standard deviation of the RR intervals (SDRR), coefficient variation of RR interval (CVRR), standard deviation of the difference between

successive RR intervals (SDSD), square root of mean squared differences of successive RR intervals (RMSSD), proportion of RR interval with duration >50ms (pRR50%) were found significantly lower ($p<0.001$) in PD patients compared to control. In addition, serum vitamin B12 level was found significantly lower ($p<0.01$) and homocysteine level was found significantly higher ($p<0.001$) in PD patients than that of control. On correlation analysis, serum homocysteine was significantly negatively correlated with SDSD ($p<0.01$) and RMSSD ($p<0.01$). **Conclusion:** Hyperhomocysteinemia is associated with autonomic dysfunction in male patients with PD.

Keywords: Parkinson's disease, Heart rate variability, Vitamin B12, Homocysteine.

Introduction

Parkinson's disease (PD) is recognized as second most common neurodegenerative movement disorder in worldwide affecting more than 10 million people.[1-2] In Bangladesh prevalence of PD is increasing and death rate is 3.49 per 100000 of population.[3] It is more common in older adults with male predominance.[1] Pathologically PD is characterized by degeneration of dopamineregic neuron and deposition of neural inclusion in form of Lewy bodies (pathological hallmark) in basal ganglia and other areas of brain.[1-2] This pathology also involves autonomic nervous system (ANS) leading to autonomic dysfunction which is one of the most common non-motor features of PD.[4,5] Although impairment of both sympathetic and parasympathetic nervous system occurs in PD[5] but vagal impairment is more prominent in PD.[4,6] To assess functional status of ANS Heart rate variability (HRV) is considered one of the most valuable tools.[7] Reduced HRV is an indicator of cardiac autonomic dysfunction as well as adverse outcome whereas increased HRV is a marker of improved health profile.[7-9] Usually, time domain, frequency domain and nonlinear (poincare plot) methods are used for analysis of HRV.[7] Among them time domain method is the simplest method which reflects overall variability as well as cardiac vagal tone.[7] It can detect autonomic dysfunction from early stage[10] and ideal for long term analysis.[7] Common time domain measures include mean heart rate, mean RR interval (mean of all interval between adjacent QRS complex), standard deviation of the RR interval (SDRR), coefficient of variation of the RR interval (CVRR), standard deviation of the difference between successive RR intervals (SDSD), root of the mean squared differences of successive RR intervals (RMSSD) and pRR50% (proportion of RR interval with duration >50 ms).[7-8] SDRR reflects total variability whereas SDSD, RMSSD and pRR50% reflect parasympathetic activity.[7] Besides autonomic dysfunction PD is also associated with hyperhomocysteinemia with or without lower level of vitamin B12 which contribute further progression of disease itself also.[11-16] In several study association of hyperhomocysteinemia and low vitamin B12 with autonomic dysfunction were reported.[17-18] On the contrary, some researchers found no significant association of hyperhomocysteinemia and vitamin B12 with autonomic dysfunction.[19] Moreover, no published data is available to observe the association of these biochemical variables with HRV in PD. Therefore, the present study has been designed to assess the association of hyperhomocysteinemia and low serum vitamin B12 level with autonomic dysfunction by time domain measures of HRV in PD.

Methods

Study design & setting

This observational analytical cross sectional study was carried out in 2023 in Department of Physiology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka.

Study participants & sampling

For this study, 30 newly diagnosed male patients with PD (50-60 years & BMI:18-24.9kg/m^2) upto stage III (Hoehn & Yahr scale) attending Out Patient Department of the Department of Neurology, BSMMU were enrolled purposively according to selection criteria. Thirty age and BMI matched apparently healthy male subjects were enrolled as control for comparison.

Exclusion criteria

Patients with history of cardiovascular disorders, respiratory disorders, renal insufficiency, liver disease, arthritis, neurological disorders (migraine, epilepsy, stroke), thyroid disorders, psychiatric disorders, malignancy, gastric surgery, vegan diet, medications for cardiac, respiratory or other reasons which may interfere with autonomic nervous system balance or current use of vitamin supplementation, current smokers and consumption of alcohol or any substance abuse were excluded from this study.

Data collection procedure

After taking history and informed written consent baseline characteristics of participants were recorded. Then 04 ml of venous blood was collected for estimation of random blood glucose, serum creatinine and serum TSH as screening purpose. The finally selected subjects were instructed properly to prepare for recording of HRV. For this, they were instructed to take their meal by 9:00 pm and to have a sound sleep in the previous night as well as to avoid any physical or mental stress, sedatives, hypnotics medication. They were also requested to take light breakfast in the morning without tea or coffee and then attend to the Noorzahan Begum Neurophysiology Laboratory, Department of Physiology, BSMMU between 8-9 a.m. After taking rest for 15-20 minutes time domain measures of HRV were recorded in a noise free and comfortable laboratory environment in supine position by a data acquisition device, powerlab 8/35, AD instruments, Australia. During the procedure, any talking, eating or drinking as well as performing physical or mental activity even sleep were strictly prohibited. Finally 02 ml of venous blood was collected and immediately sent to the laboratory of the Department of Biochemistry and Molecular Biology, BSMMU for the estimation of serum vitamin B12 and homocysteine levels.

Statistical analysis

All quantitative data were expressed as mean ± SD. For statistical analysis independent sample t-test, Chi-square test and Pearson's correlation coefficient test were done by using SPSS version 25 and p value <0.05 was considered as statistical significance.

Results

General characteristics of the subjects were presented in Table I in which both groups were found age and BMI matched ($p>0.05$) but the mean value of resting pulse rate was found significantly higher ($p<0.01$) in PD patients than that of control. In this study, mean heart rate was found significantly higher ($p<0.001$) and mean RR interval, SDRR, CVRR, SDSD, RMSSD, pRR50% were found significantly lower ($p<0.001$) in PD patients compared to control (Table II). In addition, serum homocysteine level was found significantly higher ($p<0.001$) serum vitamin B12 level was found significantly lower ($p<0.01$) and in PD patients than that of control (Table III). Comparison of time domain measures of HRV between PD patients with normal and low levels of serum vitamin B12 showed non significant difference ($p>0.05$) (Table IV) whereas SDSD and RMSSD were found significantly lower ($p<0.05$) in PD patients with high homocysteine level than that of PD patients with normal homocysteine level (Table V). On correlation analysis, only serum homocysteine was significantly negatively correlated with SDSD and RMSSD ($p<0.01$) (Figure 1 and 2 respectively) but no association was observed between low serum vitamin B12 with time domain measures of HRV.

Table I : Age, BMI, resting pulse rate and blood pressure in two groups (N=60)

Variables	PD (n=30)	Control (n=30)	p value
Age (Years)	55.37±3.24	54.30±3.12	0.199
	(50-60)	(50-60)	
BMI (Kg/m^2)	22.52±1.21	22.92±0.79	0.131
	(20.48-24.62)	(21.45-24.56)	
Pulse rate (beats/min)	81.27±3.95	78.67±5.64	0.001
	(70-90)	(68-88)	
SBP (mm Hg)	128.17±5.17	128.33±5.14	0.901
	(120-135)	(120-135)	
DBP (mmHg)	78.83±4.29	79.00±3.57	0.871
	(70-85)	(70-85)	

Data were expressed as mean ± SD. Values in parentheses indicate ranges. Statistical analysis was done by Independent sample t-test. BMI- Body Mass Index; SBP-systolic blood pressure; DBP- diastolic blood pressure; PD-Parkinson's disease; Control-Apparently healthy subjects; N- Total number of subjects; n- Number of subjects in each group.

Table II: Time domain measures of HRV in two groups (N=60)

Variables	PD (n=30)	Control (n=30)	p value
Mean heart rate (beats/min)	83.94±7.27	75.79±6.60	0.000
	(69.93-99.42)	(62.63-89.50)	
Mean R-R Interval (ms)	721.00±62.60	799.41±69.30	0.000
	(604-858.6)	(672.1-959)	
SDRR (ms)	25.24±6.34	39.84±5.92	0.000
	(14.36-40.87)	(29.76-51.45)	
CVRR	0.04±0.01	0.05±0.01	0.000
	(0.02-0.06)	(0.03-0.07)	
SDSD (ms)	15.18±4.69	35.13±9.44	0.000
	(7.24-26.8)	(26.76-51.45)	
RMSSD (ms)	15.07±4.61	35.09±9.42	0.000
	(7.24-26.7)	(21.41-52.21)	
pRR50	0.64±0.10	12.25±9.54	0.000
	(0-4.5)	(1.02-31.71)	

Data were expressed as mean ± SD. Values in parentheses indicate ranges. Statistical analysis was done by Independent sample t-test. SDRR- Standard deviation of all RR interval; CVRR- coefficient variation of RR interval, SDSD- Standard deviation of successive RR interval differences between adjacent RR intervals; RMSSD- Square root of mean of squared differences of successive RR interval; pRR50%- Proportion of RR interval with duration > 50ms; PD- Parkinson's disease; Control-Apparently healthy subjects; N- Total number of subjects; n- Number of subjects in each group.

Table III : Serum homocysteine and vitamin B 12 level in two groups (N=60)

Variables	PD (n=30)	Control (n=30)	p value
Homocysteine (µmol/L)	16.76±3.98 (9.85-24.94)	7.43±1.69 (3.77-9.85)	0.000
Vitamin B12 (pg/ml)	423.10±201.97 (109-830)	548.13±181.70 (217-931)	0.014

Data were expressed as mean ± SD. Values in parentheses indicate ranges. Statistical analysis was done by Independent sample t-test. PD-Parkinson's disease; Control-Apparently healthy subjects; N=number of subjects; n=Number of subjects in each group.

Table IV : Time domain measures of HRV in PD on basis of vitamin B12 (N=30)

Variables	Low B12 (n= 05)	Normal B12 (n= 25)	p value
Mean heart rate (beats/min)	85.57±6.18 (78.29-93.60)	83.61±7.54 (69.93-99.42)	0.592
Mean R-R Interval (ms)	705.08±50.65 (642.20-766.90)	724.18±65.15 (604-858.6)	0.543
SDRR (ms)	24.72±6.84 (17.8-35.0)	25.34±6.38 (14.36-40.87)	0.847
CVRR	0.04±0.01 (0.03-0.05)	0.04±0.01 (0.02-0.06)	0.954
SDSD (ms)	12.01±2.72 (8.21-15.26)	15.82±4.70 (7.25-26.76)	0.098
RMSSD (ms)	12.01±2.72 (8.2-15.26)	15.68±4.70 (7.24-26.73)	0.104
pRR50 (%)	0.21±0.37 (0-0.85)	0.72±1.06 (0-4.5)	0.302

Data were expressed as mean ± SD. Values in parentheses indicate ranges. Statistical analysis was done by Independent sample t-test. SDRR- Standard deviation of all RR interval; CVRR- coefficient variation of RR interval, SDSD- Standard deviation of successive RR interval differences between adjacent RR intervals; RMSSD- Square root of mean of squared differences of successive RR interval; pRR50%- Proportion of RR interval with duration > 50ms; N- Total number of subjects; n- Number of subjects in each group.

Table V : Time domain measures of HRV in PD on basis of homocysteine (N=30)

Variables	High homocysteine (n=18)	Normal homocysteine (n=12)	p value
Mean heart rate (beats/min)	85.63±7.29 (72.90-99.42)	81.39±6.73 (69.93-91.72)	0.119
Mean R-R Interval (ms)	706.43±59.97 (604-824.1)	742.85±62.49 (654.90-858.6)	0.120
SDRR (ms)	24.89±6.90 (14.36-40.87)	25.76±5.65 (16.2-35.0)	0.718
CVRR	0.04±0.01 (0.02-0.06)	0.04±0.01 (0.02-0.05)	0.976
SDSD (ms)	13.54±4.74 (7.25-26.76)	17.64±3.50 (11.22-23.10)	0.016
RMSSD (ms)	13.53±4.74 (7.24-26.73)	17.37±3.42 (11.2-23.08)	0.023
pRR50 (%)	0.55±0.78 (0-2.78)	0.78±1.28 (0-4.5)	0.539

Data were expressed as mean ± SD. Values in parentheses indicate ranges. Statistical analysis was done by Independent sample t-test. SDRR- Standard deviation of all RR interval; CVRR- coefficient variation of RR interval, SDSD- Standard deviation of successive RR interval differences between adjacent RR intervals; RMSSD- Square root of mean of squared differences of successive RR interval; pRR50%- Proportion of RR interval with duration > 50ms; N- Total number of subjects; n- Number of subjects in each group.

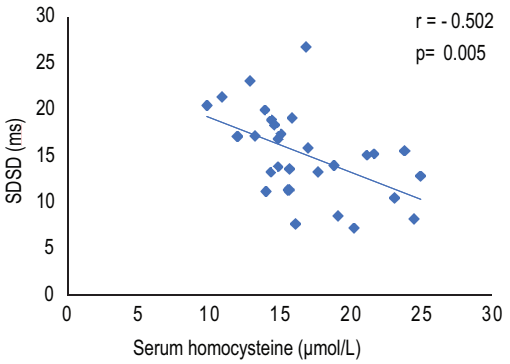

Figure 1: Correlation of SDSD (ms) with serum homocysteine level (µmol/L) in PD patients (N=30)

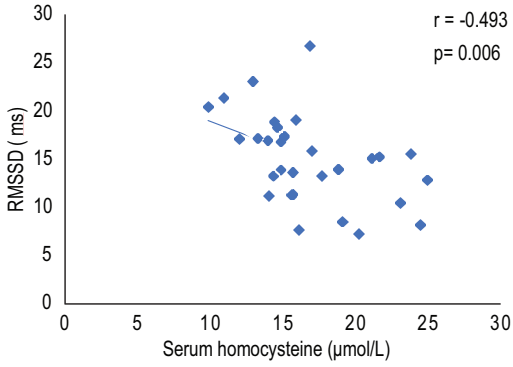

Figure 2: Correlation of RMSSD(ms) with serum homocysteine level (µmol/L) in PD patients (N=30)

Discussion

The present study investigated the association of hyperhomocysteinemia and low vitamin B12 with autonomic dysfunction by time domain measures of HRV in 50-60 years of male PD patients. Almost similar age range and sex in PD patients were reported by different researchers.[1] In this study, significantly higher values of resting pulse rate, mean HR and lower values of mean RR interval, SDRR, CVRR, SDSD, RMSSD,

pRR50% in PD patients suggested reduced overall variability and parasympathetic hypoactivity which is consistent with the findings of other researchers.[4-6,20-22] In addition, significantly higher value of serum homocysteine and lower value of serum vitamin B12 level in PD patients suggested association of these biochemical variables with PD and also reported by the results of different studies.[11-16] Besides, time domain measures of HRV were also compared between PD patients with normal and altered levels of serum vitamin B12 and homocysteine and lower values of SDSD and RMSSD were observed in PD patients with high homocysteine level than that of PD patients with normal homocysteine level suggesting association of high homocysteine with reduced heart rate variability as well as autonomic dysfunction. On correlation analysis of time domain HRV measures with serum vitamin B12 and homocysteine, SDSD and RMSSD were found negatively correlated with homocysteine which was statistically significant suggesting that hyperhomocysteinemia is associated with parasympathetic hypoactivity in PD. Previous evidence also reported such association of hyperhomocysteinemia with PD. This high homocysteine in PD is converted into highly reactive homocysteine-thiolactone which triggers abnormal aggregation of alpha synuclein protein in different areas of brain[11]. Abnormal aggregation of alpha synuclein protein in dorsal motor nucleus of vagus nerve may result in parasympathetic hypoactivity as well as autonomic dysfunction.[4,21] So, hyperhomocysteinemia could be a potent risk factor for autonomic dysfunction in PD patients.

Conclusion

According to the results of this study, it may be concluded that PD patients had impaired parasympathetic activity and hyperhomocysteinemia is associated with autonomic dysfunction in male patients with Parkinson's disease. But vitamin B12 deficiency was associated with PD though low vitamin B12 had no role on autonomic dysfunction of PD.

Ethical issue

The study protocol was first approved by the departmental ethical and academic committee and then further reviewed and approved by Institutional Review Board (IRB) of BSMMU.

Conflict of interest None

Acknowledgments

Department of Neurology, BSMMU and Department of Biochemistry and Molecular Biology, BSMMU.

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