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Heart rate variability to differentiate essential tremor from early-stage tremor-dominant Parkinson's disease

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ABSTRACT

Background: Essential tremor (ET) and Parkinson's disease (PD) are the most common movement disorders in the elderly, but it is difficult to differentiate ET from early-stage tremor-dominant Parkinson's disease (TDPD).
Methods: We investigated heart rate variability (HRV) in 23 patients with ET, 27 patients with TDPD, and 23 healthy controls. HRV was determined using the RR intervals of a 5-min electrocardiogram recording. Measurements of beat-to-beat RR variability, including time domains [(standard deviation of the normal-to-normal RR interval (SDNN), and the root mean square difference of successive RR intervals (RMSSD)] and frequency domains [low-frequency (LF) and high-frequency (HF) components and total spectral power (TP)], were assessed retrospectively.x
Results: In the TDPD group, SDNN, LF, HF, and TP were significantly lower than those in the ET group. In a receiver operating characteristic area under the curve (AUC) analysis, LF was the best potential diagnostic marker (AUC = 0.87).
Conclusion: Non-invasive and routine electrocardiography may be helpful in differentiating ET from TDPD during the early disease stage.

1. Introduction

Essential tremor (ET) and Parkinson's disease (PD) are the most common movement disorders in the elderly. Both ET patients and the elderly can display subtle parkinsonian signs [1,2]. Furthermore, a recent study demonstrated that one in five patients with ET have tremor at rest [3]. In patients with PD, postural tremor occurs as frequently as tremor at rest and may be the presenting symptom. Accordingly, differentiating between ET and TDPD is often challenging [4,5].

To improve the early diagnosis of ET and TDPD, positron emission tomography (PET), cardiac meta-iodobenzylguanidine (MIBG) scan, and olfaction studies have been proposed [4,6–8], but simple markers are also needed to allow the accurate identification of TDPD during its early stages.

Cardiac autonomic dysfunction occurs early in Lewy body disorders (LBD), including PD, dementia with Lewy bodies (DLB), and REM sleep behavior disorder (RBD), reflecting the early accumulation of LB in cardiac sympathetic postganglionic nerves [9]. Heart rate variability (HRV), as determined by electrocardiography (ECG), is a simple and non-invasive method used to investigate cardiac autonomic abnormalities [10]. HRV is reduced in PD, DLB or RBD [11–16], and predictive of PD development in elderly [17,18], suggesting the utility of HRV as an early diagnostic tool in LBD. However, HRV has not been compared between ET and TDPD. Therefore, in this study, we investigated HRV in elderly patients with ET and early TDPD, focusing on the clinical application of HRV in the early differentiation between these conditions.

2. Patients and methods

2.1. Patients

We prospectively enrolled 27 patients with TDPD, 23 with drug-naïve ET, and 23 healthy controls. PD was diagnosed according to the U.K. Parkinson's Disease Society Brain Bank Clinical Diagnosis Criteria. The PD patients enrolled in this study had drug-naïve early stage disease (symptom duration <2 years). The mean tremor score was calculated as the mean of the following nine items in the Unified Parkinson's Disease Rating Scale, assessed by the investigator's examination: right and left arm tremor as determined by history, tremor at rest of either the face, lips, chin, or all four limbs, and action or postural tremor in both arms. The mean postural instability and gait difficulty scores were calculated as the mean of the following five items: falling, freezing, history of walking difficulty, and gait and postural instabilities assessed by

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examination. The patients were diagnosed with TDPD if the ratio of the mean tremor score to the mean postural instability and gait difficulty scores was ≥1.50. All patients with ET met the published diagnostic criteria.

All patients underwent laboratory tests for physiological functions that could affect tremors, such as thyroid function, hepatic function, and renal function. Patients with laboratory abnormalities were excluded from the study. Additionally, we excluded patients (1) with diabetic mellitus or neuropathy (2) with a previous relevant cardiac diseases, or any abnormalities on routine chest radiography or ECG, and (3) who were taking medications known to influence autonomic functions, such as beta-blockers, dopaminergic medication (levodopa or dopamine agonist) or thyroxine [19].

2.2. Measurement of HRV

Both the patients and the controls were instructed to avoid alcohol or caffeinated beverages after 10 p.m. (22:00) on the night before the HRV determination and to refrain from smoking 1 h before the measurements. To control for diurnal variation, HRV was measured between 8 a.m. (08:00) and 12 a.m. (12:00) using the SA-2000E model (Medicore, Seoul, Korea) [20,21]. Each patient or control was seated in a comfortable reclining chair, after which electrodes for measuring HRV were placed on his or her wrists and left foot. During the 5-min measurement, the subject was told to breathe at his or her usual rate. The HRV parameters measured by frequency domain spectral analysis were total spectral power (TP) and the LF/HF ratio. TP is the variance of the normal-to-normal interval (NN) over a temporal segment. The LF/HF ratio reflects sympatho-vagal balance or sympathetic modulation. The standard deviation of the normal-to-normal interval (SDNN), used to estimate the long-term components of the HRV, was calculated by statistical time domain measurements. The root mean square difference of successive RR intervals (RMSSD) was also calculated based on statistical time domain measurements. Power distribution across frequencies in the RR interval signal is obtained using power spectral density. Frequency domain analysis of HRV was performed with nonparametric fast Fourier transforms technique, a commonly used mathematical approach for transforming time-dependent signals (e.g., RR intervals) to the frequency domain. Powers in the three frequency bands of HRV, very low frequency (VLF: 0–0.04 Hz), low frequency (LF: 0.04–0.15 Hz), high frequency (HF: 0.15–0.4 Hz), and total spectral power were obtained. Ethical approval was given by the local ethics committee, and written informed consent was obtained from each patient.

2.3. Statistics

The data are expressed as means ± SD. Differences in demographic characteristics between groups were assessed using Mann-Whitney and Fisher exact tests for categorical and continuous variables, respectively. Comparisons of HRV data were performed using the general linear model including age, sex as covariates. Statistical significance was defined as a p value <0.05. The sensitivity and specificity for differentiating TDPD from ET were assessed using a receiver operating characteristic (ROC) analysis. Statistical analysis was performed using IBM SPSS V.19 (IBM Corp, New York, NY, USA).

3. Results

The demographic data and clinical characteristics of the control, ET, and TDPD groups are summarized in Table 1. There were no differences among the three groups with respect to age, sex, or past medical history.

A comparison of the HRV data of patients between groups is presented in Table 2. After adjusting for age and sex, the TDPD group showed significant and severe reductions in all time and frequency domain parameters than the ET group, except RMSSD and the LF/HF ratio. The differences were especially evident in the SDNN and TP, LF components (Table 2). By contrast, there were no significant differences between the ET and control groups. In none of the groups did the HRV parameters correlate with age or disease duration.

Table 1
Basic demographics.

Group	TDPD (n = 27)	ET (n = 23)	Controls (n = 23)	P
Age	64.1 (5.1)	64.7 (3.1)	63.2 (7.1)	NS
Sex (number of men, %)	15 (55%)	13 (56%)	12 (52%)	NS
Disease duration (months)	19.1 (5.7)	68.2 (23.6)	N/A	0.03
Body mass index (kg/m2)	22.8 (1.9)	23.5 (2.1)	23.8 (2.1)	NS
Motor UPDRS	10.9 (2.2)	N/A	N/A	N/A
Hypertension, n (%)	5 (14%)	3 (13%)	4 (17%)	NS
Dyslipidemia, n (%)	4 (14%)	3 (13%)	2 (8%)	NS
Diabetes mellitus	0 (0%)	0 (0%)	0 (0%)	NS
Current or ex-smoker	3 (11%)	4 (17%)	2 (8%)	NS
Heart rate (beats/min)	65.2 (10.2)	68.3 (11.3)	66.2 (8.9)	NS
Systolic blood pressure (mmHg)	128.1 (12.2)	126.3 (13.2)	125.3 (11.4)	NS
Diastolic blood pressure (mmHg)	76.3 (12.4)	73.5 (8.7)	76.3 (7.5)	NS
Total cholesterol (mg/dL)	180.2 (30.4)	183.4(29.4)	181.3(29.4)	NS
Triglyceride (mg/dl)	121.2 (29.4)	119.4 (32.4)	123.2 (28.4)	NS
High-density lipoprotein (mg/dL)	51.9 (11.1)	49.9 (12.8)	50.2 (11.6)	NS
Low-density lipoprotein (mg/dL)	105.3 (25.4)	110 (23.3)	107.4 (25.5)	NS
Glucose (mg/dL)	91.1 (9.4)	89.8 (10.1)	92.2 (10.2)	NS
HbA1c (%)	4.1 (0.7)	4.2 (1.1)	4.0 (0.8)	NS
Blood pressure mediation, n (%)	4 (15%)	5 (21%)	4 (17%)	NS
CCB	2 (7%)	2 (8%)	1 (4%)	NS
ARB	2 (7%)	3 (13%)	3 (13%)	NS
Psychotropic medication, n (%)	1 (3%)	1 (4%)	0 (0%)	NS
TCA	0 (0%)	0 (0%)	0 (0%)	NS
SSRI	1 (3%)	1 (4%)	0 (0%)	NS

Values are mean (SD). UPDRS, Unified Parkinson's Disease Rating Scale; CCBs: Calcium channel blocker, ARBs: angiotensin II receptor blockers; TCA: tricyclic antidepressant; SSRIs: selective serotonin reuptake inhibitors.

The comparative receiver operating characteristic (ROC) curves for HRV parameters in differentiating the TDP group from the ET group are presented in Fig. 1.

ROC area under the curve (AUC) analysis revealed that LF was the best potential diagnostic marker (AUC = 0.87) compared with TP (0.85), SDNN (0.78), HF (0.75), LF/HF ratio (0.72), RMSSD (0.65).

4. Discussion

This is the first study to assess whether HRV can be used to distinguish TDPD from ET. The results showed that almost all parameters of HRV were significantly lower in patients with TDPD than in those with ET, whereas differences between the ET and control groups were not significant. These data suggest that HRV may be helpful to differentiate TDPD from ET at the early stage of PD.

Although TDPD and ET differ in their pathogenesis, their clinical features are similar. Patients with tremor-dominant PD (TDPD) usually respond poorly to levodopa treatment, and their prognosis is favorable. In addition, some patients with definite signs of PD have normal 18F-dopamine (Dopa) PET scans, and those with isolated resting or action tremors have consistently abnormal striatal dopamine transporter (DAT) uptake [22]. Thus, early TDPD is commonly misdiagnosed as ET, emphasizing the need for an additional, simple diagnostic tool capable of distinguishing between the two conditions. The distinction is important in determining the prognosis, treatment planning, and identifying patients eligible for clinical studies [4]. However, the relationship between ET and PD remains controversial. Several previous studies have shown the increased risk of PD in ET [28–30]. Further large and longitudinal studies examining this relationship are warranted.

There is ample evidence that cardiac autonomic dysfunction is an early finding in patients with LBD such as PD and DLB [15]. Several recent studies have found that HRV is more profound in patients with PD than in controls [15,16]; however, most of the PD patients enrolled