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Comparison of motor and non-motor features between essential tremor and tremor dominant Parkinson's disease

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ABSTRACT

Background: Differential diagnosis of tremor disorders, including essential tremor (ET) and Parkinson's disease-tremor dominant type (PD-TDT), requires further investigation. Therefore, the current study aimed to compare non-motor and tremor features in order to differentiate between ET and PD-TDT.
Methods: Twenty-eight patients with classic ET and 24 patients with typical PD-TDT were retrospectively enrolled in a multi-stage investigation process. Tremor features including surface electromyogram (EMG) were analyzed in detail. For non-motor symptom analyses, the global cognition test, frontal function test, and non-motor symptoms scale (NMSS) were administered, in addition to collecting patient history data.
Results: Patients with PD-TDT presented with more asymmetric tremor, whereas patients with ET presented with more symmetric tremor. Leg tremor was observed only in patients with PD-TDT. Surface EMG analyses of arm tremor demonstrated considerable overlaps in tremor type, tremor frequency, and contractive patterns. However, patients with PD-TDT were significantly more likely to exhibit resting tremor, and experienced alternative contraction patterns only for kinetic tremor, which was in contrast to patients with ET. For non-motor symptom analyses, patients with PD-TDT had more non-motor symptoms compared to patients with ET (mean = 5.0 vs. 2.6; $P = 0.002$). Specifically, patients with PD-TDT exhibited higher frequencies of hyposmia, REM sleep behavior disorder (RBD)-like symptom, urinary frequency, and memory disturbance. Age- and gender- matched analyses for the severity of NMSS scores did not indicate significant differences. However, patients with PD-TDT displayed slightly lower scores of frontal function test compared to patients with ET.
Conclusions: Careful and detailed evaluations of both tremor features and non-motor symptoms are required in order to distinguish between ET and PD-TDT.

1. Introduction

Tremor is a complex and heterogeneous symptom. Accordingly, accurate diagnosis of a variety of tremor disorders, including essential tremor (ET) and Parkinson's disease (PD), is clinically important. ET is predominantly characterized by action or postural tremor [1], whereas most patients with PD exhibit resting tremor [2]. However, ET and PD may show overlapping features during clinical examinations. Firstly, more than 90% of patients with PD experience action tremor [3]. In contrast, 18% of patients with ET exhibit resting tremor [4]. Secondly, although asymmetry is a crucial characteristic of PD tremor, ET tremor can also be asymmetric [5,6]. Lastly, some patients with ET experience mild bradykinesia and/or rigidity [7]. Therefore, patients with other tremor disorders, including PD, are frequently misdiagnosed with ET, potentially affecting as many as 37–50% of patients [8,9].

ET has been regarded as a benign mono-symptomatic disorder characterized by an 8–12 Hz postural or kinetic tremor [10]. However, recent findings from clinical, neuroimaging, and pathophysiological studies of ET provide evidence for it being a slowly progressive neurodegenerative disorder accompanied by non-motor symptoms including mild cognitive deficits, depression, and anxiety [11]. In contrast, PD includes diverse non-motor features such as cognitive deficits, sleep abnormalities, depression, constipation, and hyposmia [12,13]. Although both ET and PD include non-motor symptoms, clinical studies comparing non-motor symptoms between these disorders are currently limited.

PD is classified as either PD-tremor dominant type (PD-TDT) or PD-akinetic rigid type (PD-ART), based on the predominant motor symptoms [14]. Since patients with PD-TDT not only exhibit tremor as their primary symptom, but also experience bradykinesia and/or rigidity to a lesser extent in a similar fashion to patients with ET, it is clinically

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important to distinguish between ET and PD-TDT. However, tremor characteristics and non-motor features that differentiate between ET and PD-TDT have not been fully elucidated. Therefore, in the current study, we compared motor and non-motor symptoms between these tremor-dominant disorders.

2. Subjects and methods

2.1. Subjects

This study was approved by the Institutional Review Board of the Korea University Guro Hospital (IRB #KUGH13263). We reviewed medical records of patients who first visited the movement disorder clinic at the Parkinson's Disease Centre of Korea University Guro Hospital between March 2012 and December 2013. All patients with PD or ET were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) Part III at the baseline medication-off examination. Since patients did not have functional neuroimaging including dopamine transporter scans, a multi-step process was required to recruit patients with PD-TDT or ET. A movement disorder specialist (S-B.K.) initially diagnosed 203 patients with PD, in accordance with the UK brain bank criteria [15,16]. Probable PD was indicated when a patient exhibited at least 3 of the following features: resting tremor, rigidity, bradykinesia, and asymmetric onset [17]. Then, we selected only patients with PD-TDT, based on UPDRS Part III scores at the baseline medication-off examination and on the findings of previously published findings [14]. Briefly, the PD-TDT was calculated and defined when the ratio of tremor score (sum of UPDRS Part III items 20 and 21, divided by 4) to akinetic-rigid score (sum of UPDRS Part III items 22–27 and 31, divided by 15) was higher than 1.0 point. Additionally, another movement disorder specialist (K-Y.K.) re-evaluated the videos showing tremor, including at rest, while attempting to maintain posture, and during action of patients with PD-TDT. This re-evaluation confirmed the diagnosis of PD-TDT, and excluded the possibility of ET comorbidity. Following this multi-step process, we enrolled 24 patients with PD-TDT, who exhibited classic resting tremor including pill-rolling tremor. Besides, a movement disorder specialist (S-B.K.) also diagnosed 61 patients with ET, and the detailed clinical characteristics of these patients, including UPDRS Part III scores, were evaluated by another movement disorder specialist (S-M.L.). A third movement disorder specialist (K-Y.K.) re-evaluated patients with typical ET, from the group of 61 patients with ET, by conducting a medical chart review according to the MDS consensus criteria [4]. Patients with ET who had relatively short durations of tremor (less than 3 years since onset) were excluded from the study in order to consolidate the diagnosis of ET. Since ET and PD may show overlapping features during clinical examination, patients diagnosed with ET who also met the criteria for PD were excluded from the ET group. We also excluded patients with more than 4 points on the akinetic-rigid indicators (i.e., sum of all bradykinesia and rigidity scores from the UPDRS Part III), in order to exclude the possibility of comorbid PD. We therefore enrolled 28 probable patients with ET in the current study.

2.2. Tremor analyses by surface electromyogram to compare ET and PD-TDT

All surface electromyography (EMG) data during rest, posture, and kinetic tremor were re-investigated in detail by a neurologist (M.K.) who was blinded to the clinical diagnosis. Surface EMG electrodes were positioned on appropriate arm muscles, including the extensor carpi radialis (ECR) and flexor carpi radialis (FCR), on the side with more pronounced arm tremor. Two channel surface EMGs were recorded under 3 conditions: 1) resting in a comfortable position (i.e., arms fully flexed at 90° against gravity), 2) postural state with outstretching, and 3) action position when writing, spooning, and/or cup-holding. Since it was very difficult to obtain the tremor amplitude under our conditions, EMG analysis for tremor was limited to tremor frequency and the contraction pattern of agonist–antagonist muscles.

2.3. Comparison of non-motor symptoms between ET and PD-TDT

Non-motor symptoms were assessed with a questionnaire to determine their presence or absence at the time of initial visit (see Table 3). REM sleep behavior disorder (RBD)-like symptom was queried by asking the patient's spouse or caregiver if the patient 'acted out' his/her dreams while sleeping. Furthermore, the non-motor symptoms scale (NMSS) was administered to all patients on the same day, by a research nurse at the Parkinson's Disease Centre. In addition, the Korean version of the mini-mental status examination (K-MMSE), the Korean version of the frontal assessment battery (K-FAB), and the Montgomery-Åsberg Depression Rating Scale (MADRS) were administered.

2.4. Statistical analyses

For distributions and frequencies, group comparisons for ET versus PD-TDT were conducted using Fisher's exact test or the linear-by-linear association test. For ordinal scale data, group comparisons for ET versus PD-TDT were conducted using the Mann–Whitney U test. In addition, ANCOVA was used for the multivariate analyses, and logistic regression was applied for the binary comparisons. The statistical significance was determined using a P-value < 0.05. Statistical analyses were conducted using SPSS version 20.0 (IBM, Chicago, IL, USA).

Table 1
Clinical demographics and tremor characteristics in patients with essential tremor (ET) versus Parkinson's disease-tremor dominant type (PD-TDT).

	ET (n = 28)	PD-TDT (n = 24)	P value
Female, n (%)	17 (60.8)	15 (62.5)	0.895
Age at onset, years(mean ± SD, range)	38.5 ± 16.8 (9–67)	59.1 ± 10.1 (41–78)	<0.001
Age at exam, years(mean ± SD, range)	49.6 ± 16.9 (19–73)	61.4 ± 9.1 (46–80)	0.003
Duration of tremor, years (mean ± SD, range)	11.5 ± 7.5 (3.1–30.8)	2.9 ± 3.4 (0.4–14.1)	<0.001
Education, years (mean ± SD, range)	11.3 ± 4.4 (3–16)	8.8 ± 4.2 (0–16)	0.049
Family history, n (%)	19 (68.9)	0 (0)	<0.001
Asymmetry of tremor, n (%)	11 (39.3)	23 (95.8)	<0.001
Dominant site of tremor, n (%)			
Head tremor	6 (21.4)	0 (0)	0.025
Arm tremor	20 (71.4)	15 (62.5)	0.494
Leg tremor	0 (0)	7 (29.2)	0.003
In arm tremor, n (%)			
Dominant resting tremor	0 (0)	17 (70.8)	<0.001
Dominant postural/kinetic tremor	22 (78.6)	2 (8.3)	<0.001
Presence of specific tremor, n (%)			
Head tremor	11 (39.3)	4 (16.7)	0.124
Resting arm tremor	11 (39.3)	21 (87.5)	0.001
Resting leg tremor	0 (0)	19 (79.2)	<0.001
Postural/kinetic arm tremor	27 (96.4)	16 (66.7)	0.008
UPDRS part 3, (mean ± SD, range)			
Total motor score	4.6 ± 2.0 (2–10)	20.8 ± 9.3 (8–37)	<0.001
Tremor score	3.9 ± 1.5 (2–7)	7.3 ± 3.5 (2–14)	<0.001
Head tremor subscore	0.6 ± 0.6 (0–3)	0.3 ± 0.6 (0–2)	0.278
Resting arm tremor subscore	0.8 ± 1.0 (0–3)	3.0 ± 1.9 (0–6)	<0.001
Resting leg tremor subscore	0 ± 0 (0–0)	2.5 ± 1.7 (0–5)	<0.001
Postural/kinetic arm tremor subscore	2.6 ± 1.1 (0–4)	1.3 ± 1.2 (0–4)	<0.001
Akinetic rigid score	0.4 ± 0.8 (0–3)	10.9 ± 5.7 (2–24)	<0.001
Hoehn and Yahr stage (mean ± SD, range)	NA	1.9 ± 0.5 (1–2.5)	NA