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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

Table 2
Analysis of surface electromyogram in patients with essential tremor (ET) versus Parkinson's disease-tremor dominant type (PD-TDT).

	ET(n = 21)	PD-TDT(n = 21)	*P* value
Resting arm tremor			
Presence, n (%)	6 (28.6)	15 (71.4)	**0.005**
Frequency, Hz (mean ± SD, range)	5.5 ± 1.6	4.7 ± 0.8	0.281
Contraction pattern (total n = 17)	n = 6	n = 11	
Alternative, n (%)	3 (50)	9 (81.8)	0.280
Co-contractive, n (%)	3 (50)	2 (18.2)	
Postural arm tremor			
Presence, n (%)	12 (57.1)	14 (66.7)	0.525
Frequency, Hz (mean ± SD, range)	6.7 ± 1.7	6.0 ± 1.6	0.312
Contraction pattern (total n = 20)	n = 10	n = 10	
Alternative, n (%)	2 (20)	6 (60)	0.170
Co-contractive, n (%)	8 (80)	4 (40)	
Kinetic arm tremor			
Presence, n (%)	12 (57.1)	16 (76.2)	0.190
Frequency, Hz (mean ± SD, range)	7.3 ± 1.8	6.1 ± 1.6	0.064
Contraction pattern (total n = 21)	n = 10	n = 11	
Alternative, n (%)	1 (10)	7 (63.6)	**0.024**
Co-contractive, n (%)	9 (90)	4 (36.4)	

Assay value for 'uncertain' of contraction pattern in surface electromyogram is excluded.
Bold values indicate significance below 0.05.

3. Results

3.1. Demographic and clinical characteristics of patients with ET versus PD-TDT

Detailed demographics and clinical characteristics are described in Table 1. Patients with ET had younger ages of onset and longer disease durations, compared to patients with PD-TDT. Familial history of ET was frequent, with 68% incidence, whereas family history of PD-TDT did not occur in our study sample. Asymmetry was defined as having at least a 1.0 point difference on the UPDRS Part III between sides of the body; asymmetry of tremor was more common in patients with PD-TDT than in those with ET. As predicted, patients with ET exhibited a higher incidence of postural/kinetic tremor, and patients with PD-TDT exhibited higher rates of resting tremor. Although head tremor was observed in both disorders, predominant head tremor occurred only in patients with ET. Leg tremor was observed only in patients with PD-TDT.

3.2. Analysis of surface electromyogram in patients with ET versus PD-TDT

Table 2 shows our comparison of surface EMG findings for tremor features between ET and PD-TDT groups. Resting tremor occurred more frequently in patients with PD-TDT compared to patients with ET, while occurrence of postural or kinetic tremor was not significantly different between groups. No significant differences between groups occurred for tremor frequency in resting, postural, or kinetic conditions. The analysis of contractive patterns demonstrated that the patterns for resting and postural arm tremor were not significantly different between the ET and PD-TDT groups. However, kinetic tremor displayed a distinguishable feature; ET group recordings showed more co-contractive patterns, whereas PD-TDT group recordings showed more alternative patterns.

3.3. Comparison of total number and frequency of non-motor symptoms in ET versus PD-TDT

The medical chart reviews revealed that patients with PD-TDT (5.0 ± 2.6, mean ± SD) had significantly more non-motor symptoms compared to patients with ET (2.6 ± 2.1, mean ± SD) ($P = 0.002$), as shown in Fig. 1. Furthermore, frequencies of diverse non-motor symptoms are presented in detail in Table 3, including explanations regarding missing data. Hyposmia, RBD-like symptoms, urinary frequency, and memory disturbance were more common in patients with PD-TDT than in patients with ET.

3.4. Comparison of the severity of non-motor symptoms in ET versus PD-TDT

Data from the NMSS questionnaire were analyzed for 18 patients with ET and 23 patients with PD-TDT (see Table 4). No NMSS scores were significantly different between groups. In addition, the K-MMSE did not indicate differences between groups. In contrast, the K-FAB yielded lower scores for the PD-TDT group than for the ET group ($P = 0.042$ by ANCOVA; $P = 0.004$ by logistic regression). However, the MADRS scores were higher in the PD-TDT group (4.45 ± 2.76, mean ± SD) compared to the ET group (2.00 ± 2.32, mean ± SD) ($P = 0.044$ by ANCOVA; $P = 0.006$ by logistic regression), although the mean scores for both groups did not indicate diagnosis of depressive disorders. In general, scores of 0–6 points are within the normal (non-depressed) range when using the MADRS to assess depressive symptoms [18].

4. Discussion

Tremor features of ET and PD-TDT often overlap and can therefore result in misdiagnosis. Clinical differentiation between ET and PD-TDT is important for treatment, as well as for determining patient prognosis. However, both tremor disorders may occur in the same patient, with findings indicating that this may occur in as many as 5.8% of patients during a 3.3 year long follow up period [19]. Therefore, in the current study, we tried to eliminate the possibility of co-occurrence for both ET and PD-TDT, using multi-step inclusion criteria. To our knowledge, the current study is the first report of clinical characteristics for both tremor and non-motor symptoms in patients with ET and PD-TDT.

Table 1 presents several features for differentiating between ET and PD-TDT, which were indicated at the baseline neurological examination. Firstly, asymmetry of tremor was significantly more common in patients with PD-TDT compared to those with ET. However, about 40% of patients with ET had asymmetric arm tremors, consistent with previous studies [5,6]. Secondly, dominant head tremor suggested ET in the current study, although head tremor does not differentiate between ET and PD-TDT, as previously reported in the literature [7]. In contrast, the existence or dominance of leg tremor indicated PD-TDT. The findings regarding tremor dominancy provide crucial information to enable differential diagnosis. Thirdly, regarding frequency of tremor subtype, the presence of resting tremor in the arm/leg was more common in

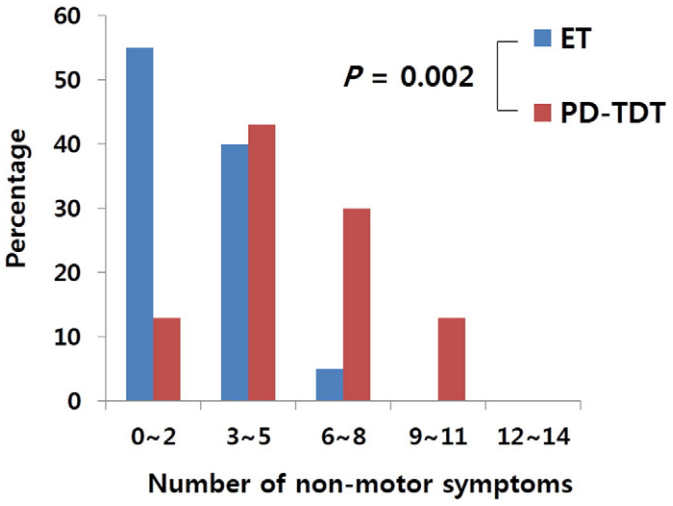

Fig. 1. Total number of non-motor symptoms between ET and PD-TDT. ET = essential tremor; PD-TDT = Parkinson's disease- tremor dominant type.

Table 3
Frequency of non-motor symptoms in patients with essential tremor (ET) versus Parkinson's disease-tremor dominant type (PD-TDT).

Non-motor items (n, ET vs PD-TDT)	ET, n (%)	PD-TDT, n (%)	*P* value
Hyposmia (n = 21 vs 22)	0 (0)	6 (27.3)	**0.021**
Vivid dream (n = 20 vs 23)	7 (35)	14 (60.9)	0.091
Insomnia (n = 19 vs 22)	7 (36.8)	8 (36.4)	0.975
RBD-like Symptom (n = 20 vs 23)	3 (15)	11 (47.8)	**0.027**
Constipation (n = 21 vs 23)	3 (14.3)	8 (34.8)	0.169
Depression (n = 28 vs 23)	15 (53.6)	10 (43.5)	0.473
Anxiety (n = 26 vs 19)	8 (30.8)	5 (26.3)	0.745
Agitation (n = 26 vs 19)	1 (3.8)	1 (5.3)	1.000
Urinary frequency (n = 27 vs 23)	6 (22.2)	13 (56.5)	**0.013**
Nocturia (n = 27 vs 23)	8 (29.6)	8 (34.8)	0.697
Orthostatic dizziness(n = 20 vs 23)	6 (30)	7 (30.4)	0.975
Visual hallucination (n = 28 vs 23)	0 (0)	1 (4.3)	0.451
Restless leg syndrome (n = 19 vs 23)	0 (0)	4 (17.4)	0.114
Fatigue (n = 12 vs 22)	5 (41.7)	12 (54.5)	0.473
Memory disturbance (n = 19 vs 23)	2 (10.5)	10 (43.5)	**0.037**

*RBD; REM sleep behavior disorder.
Bold values indicate significance below 0.05.

the PD-TDT group than it was in the ET group, whereas postural/kinetic arm tremor displayed the opposite. Tables 1 and 2 present data on the proportion of co-occurrence for resting and postural/kinetic tremors in ET and PD-TDT. Consistent with our results, in a clinical setting, the prevalence of resting tremor in patients with ET ranged from 19 to 30% [7], and postural/kinetic tremor in patients with PD were commonly observed. Moreover, as previously described, the presence of head tremor could not differentiate between the 2 tremor disorders. Taken together, our findings suggest that tremor subtype cannot be used to discriminate between ET and PD-TDT, with the exception of resting leg tremor. Lastly, regarding arm tremor dominancy, the ET group demonstrated dominant kinetic tremor, whereas the PD-TDT group exhibited dominant resting tremor, as predicted. We observed dominant kinetic arm tremor in 2 patients with PD-TDT. The 2 patients had leg tremor dominancy rather than arm tremor; the tremors were scored as follows: no resting arm tremor (0 points), and minimal postural arm tremor (1 point). However, postural arm tremors may have been influenced by severe resting leg tremors.

Table 2 presents surface EMG data for arm tremors, comparing tremor frequency and contractive pattern between the ET and PD-TDT groups. Since leg tremor was specific to the PD-TDT group, only arm tremor data were analyzed. Our results were consistent with the current knowledge that resting tremor in PD occurs at 4–7 Hz, whereas action tremor in ET occurs at 5–12 Hz [20,21]. However, there was no significant difference in tremor frequency between the ET and PD-TDT groups, including specific analyses for tremor during resting (mean Hz 5.5 vs. 4.7; ET vs. PD-TDT, $P = 0.281$), posturing (mean Hz 6.7 vs. 6.0; ET vs. PD-TDT. $P = 0.321$), and action (mean Hz 7.3 vs. 6.1; ET vs. PD-TDT. $P = 0.064$). We also observed tremor frequency phenomena common to both disorders. These phenomena include resting tremor with a relatively low frequency (5.5 Hz in ET and 4.7 Hz in PD-TDT), postural tremor with a relatively mid-range frequency (6.7 Hz in ET and 6.0 Hz in PD-TDT), and kinetic tremor with a relatively high frequency (7.3 Hz in ET and 6.1 Hz in PD-TDT). Regarding contractive patterns, we found that kinetic arm tremor differed between the disorders, observing that patients with ET exhibited more co-contractive kinetic tremor patterns compared to patients with PD-TDT, who exhibited more alternative contraction. However, resting and postural arm tremor overlapped considerably between groups regarding contractive patterns. Therefore, our surface EMG results for arm tremor suggest that only contractive patterns of kinetic arm tremor can be used to differentiate between ET and PD-TDT.

Compared with ET, PD is characterized by a higher prevalence of several non-motor symptoms, including hyposmia, orthostatic dizziness, RBD-like symptom, vivid dreams, and hallucinations [22]. However, it is unclear whether such differences in non-motor symptoms between ET and PD-TDT are consistently observed, as these findings are from a single study. In the current study, we elucidated detailed features of non-motor symptoms in patients with ET and PD-TDT. The data in Fig. 1 presents our finding that patients with PD-TDT exhibited more frequent non-motor symptoms than patients with ET. In contrast, a previous study reported that the total number of non-motor symptoms was not different between patients with PD and those with ET [22]. Moreover, patients with PD-TDT typically exhibit fewer non-motor symptoms than patients with other types of PD [22,23]. The discrepancy between the previous study and our current findings may be explained by the following methodological differences: 1) our study included predominantly women, whereas the previous study participants were predominantly men; 2) the patients with ET in the current study were younger than the patients with PD-TDT; and 3) we included only patients with PD-TDT and excluded patients with other subtypes of PD. However, in the current study, the duration of time since diagnosis with PD-TDT was shorter than the duration of time since diagnosis with ET, indicating that PD-TDT may reflect an earlier stage of disease than ET. Therefore, our data suggest that PD-TDT may include more non-motor symptoms than ET even at very early stages. More detailed and comprehensive studies will be required in order to make strong conclusions. Olfactory dysfunction, RBD-like symptoms, visual symptoms, and cognitive loss have been regarded as crucial non-motor features of PD, and have relatively high diagnostic accuracy [24,25]. We

Table 4
Comparison between essential tremor (ET) and Parkinson's disease-tremor dominant type (PD-TDT) for various non-motor scales.

	ET (mean ± SD)	PD-TDT (mean ± SD)	P^1 value	Logistic regression	
				OR (95% CI)	P^2 value
K-MMSE (n = 17 vs 18)	28.19 ± 1.72	27.22 ± 2.78	0.171	0.818 (0.616–1.086)	0.164
K-FAB (n = 17 vs 20)	16.62 ± 0.98	14.15 ± 3.00	**0.042**	0.489 (0302–0.792)	**0.004**
MADRS (n = 17 vs 20)	2.00 ± 2.32	4.45 ± 2.76	**0.044**	1.446(1.113–1.880)	**0.006**
NMSS score (n = 18 vs 23)					
Cardiovascular	0.52 ± 0.80	0.41 ± 0.50	0.858	0.747 (0.316–1.767)	0.507
Sleep/fatigue	4.26 ± 3.62	4.50 ± 4.10	0.444	1.028 (0.887–1.192)	0.715
Mood	9.04 ± 7.87	8.05 ± 5.91	0.627	0.976 (0.900–1.058)	0.553
Perceptual	0.04 ± 0.19	0.00 ± 0.00	0.978	0.000 (0.000–N.A.)	1.000
Attention/memory	2.19 ± 1.80	2.91 ± 2.33	0.093	1.202 (0.899–1.606)	0.215
Gastrointestinal	0.78 ± 1.50	1.32 ± 2.08	0.922	1.174 (0.842–1.638)	0.344
Urinary	2.04 ± 2.59	2.09 ± 2.20	0.716	1.009 (0.797–1.278)	0.940
Sexual function	1.56 ± 2.24	1.18 ± 1.71	0.175	0.895 (0.670–1.195)	0.452
Miscellaneous	1.04 ± 1.82	1.09 ± 1.54	0.684	1.002 (0.714–1.407)	0.992
Total NMSS	21.41 ± 15.16	20.61 ± 15.32	0.709	0.996 (0.960–1.033)	0.822

P^1 values were adjusted for age, education, and disease duration (ANCOVA); P^2 values were obtained from binary logistic regression analysis.
K-MMSE, Korean version of mini-mental status examination; K-FAB, Korean version of frontal assessment battery; MADRS, Montgomery–Åsberg Depression Rating Scale; NMSS, Nonmotor symptoms scale.
Bold values indicate significance below 0.05.

found that patients with PD-TDT experienced more frequent hyposmia, RBD-like symptoms, urinary frequency, and memory disturbance, compared to patients with ET (see Table 3). In addition, only some patients with PD-TDT reported visual hallucinations and restless leg syndrome, despite these symptoms being associated with PD [26,27]. Collectively, our findings suggest that the existence of hyposmia, RBD-like symptom, memory disturbance, visual hallucination, or restless leg syndrome might be important for distinguishing PD-TDT from ET.

We compared the severity of non-motor symptoms between the groups (see Table 4). Assessment of global cognition using the MMSE did not reveal any difference between the groups. However, patients with PD-TDT had mild frontal lobe dysfunction compared to patients with ET, according to the FAB assessment. Prominent frontal executive dysfunction has reported in the early stages of PD [28,29], so these findings suggest that frontal lobe function assessments may be useful in distinguishing PD-TDT from ET, even at early stages. Depression, as assessed by the MADRS, was not significantly different in patients with ET versus patients with PD-TDT, although the depressive scores for the PD-TDT groups were higher than for the ET group, as previously described. There were also no differences between groups for analyses of each scale item, or for total scores on the NMSS. Our results suggest that the NMSS is not useful for investigating the severity of non-motor symptoms when attempting to differentiate between ET and PD-TDT.

Our study has several weaknesses. Firstly, all patients were diagnosed according to clinical criteria only, and functional neuroimaging, such as dopamine transporter scans were not conducted. Although we used a multi-step approach to classify patients into groups, and feel confident that patients with typical ET (28 of 63 ET cases) or PD-TDT (24 of 203 PD cases) were included, it is possible that some patients were misdiagnosed. Additionally, the duration of PD-TDT was very short (2.9 ± 3.4 years). However, atypical Parkinsonism including multiple system atrophy is rarely classified as typical PD-TDT. Secondly, since kinematic assessment was not performed in conjunction with surface EMG, detailed analyses including tremor amplitude could not be investigated. Thirdly, non-motor symptoms, which were assessed through patient interviews, may be somewhat subjective and therefore, potentially inaccurate. Lastly, we studied a relatively small number of patients, using a retrospective analysis. Therefore, a larger well-designed study is required.

In conclusion, we found that motor and non-motor symptoms could overlap between patients with ET and patients with PD-TDT. However, specific features may allow for differentiation between these tremor-dominant disorders. Symptoms suggestive of ET included kinetic/postural tremor dominancy, head tremor dominancy, co-contractive pattern for kinetic arm posture, and a relatively small number of non-motor symptoms. In contrast, several features are suggestive of PD-TDT, including resting tremor dominancy, presence of leg tremor, and alternative contractive pattern for kinetic arm posture, as well as non-motor features including hyposmia, RBD-like symptom, visual hallucinations, restless leg syndrome, and impairment of frontal lobe function. Comprehensive evaluations of both non-motor and motor symptoms are therefore necessary in patients with tremor disorders.

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None.

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