



The clinical significance of lower limb tremors

Rajasumi Rajalingam^a, David P. Breen^{b,c,d}, Robert Chen^{a,e,f}, Susan Fox^{a,e,f}, Lorraine V. Kalia^{a,e,f}, Renato P. Munhoz^{a,e,f}, Elizabeth Slow^{a,e}, Antonio P. Strafella^{a,e,f}, Anthony E. Lang^{a,e,f}, Alfonso Fasano^{a,e,f,*}

^a Edmond J. Safra Program in Parkinson's Disease and the Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, University Health Network, Toronto, Canada

^b Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, Scotland, UK

^c Anne Rowling Regenerative Neurology Clinic, University of Edinburgh, Edinburgh, Scotland, UK

^d Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, Scotland, UK

^e Division of Neurology, University of Toronto, Toronto, Canada

^f Krembil Brain Institute, Toronto, Ontario, Canada

ARTICLE INFO

Keywords:

Tremor
Lower limb tremor
Leg tremor
Essential tremor

ABSTRACT

Introduction: To explore the prevalence, clinical course and associated features of lower limb tremor in the most common tremor syndromes.

Methods: This retrospective chart review studied lower limb tremor patients as defined by a Tremor Rating Scale score ≥ 1 in either lower limb. We compared and correlated their characteristics, also comparing them with patients without lower limb tremor.

Results: Of the 283 patients with lower limb tremor (58.3% males, age: 65.0 ± 16.0 years, tremor duration: 25.6 ± 17.9 years), 255 patients within six tremor syndrome groups were included in the final analysis. Prevalence of patients with lower limb tremor (either rest, postural or kinetic) was lowest (28.6%) in the essential tremor (ET) group and highest (69%) in the parkinsonian tremor (PT) group. Lower limb tremor score was higher in patients classified as having intention tremor (IT) compared to ET and dystonic tremor (DT). Total tremor score was highest in IT and lowest in ET. We found a positive correlation between total lower limb tremor score and total tremor score in most groups. In addition, there was a positive correlation between lower limb tremor score and upper limb tremor score. Finally, compared to patients without lower limb tremor, all diagnostic groups with lower limb tremor, with the exception of functional tremor (FT), had worse total tremor score; and disease duration was longer in ET-plus, DT and PT patients with lower limb tremor compared to those without.

Conclusions: Lower limb tremor is less commonly observed in ET than other tremor syndromes, is a marker of symptom severity of the underlying disease condition in all tremor syndromes except FT, and reflects longer disease duration in ET-plus, DT and PT.

1. Introduction

Lower limb tremor is a well-established feature of orthostatic tremor but is also observed in other tremor syndromes [1,2]. Some studies have reported that lower limb tremor is an uncommon clinical feature in essential tremor (ET) [3,4]. However, relatively little is known about the clinical characteristics of lower limb tremor in other tremor groups.

In the absence of reliable biomarkers or diagnostic tests, clinicians continue to depend on history and examination when diagnosing tremor. Studying lower limb tremor characteristics using a standardized

tremor rating scale could therefore provide additional clinical clues to help distinguish between different tremor etiologies. One of the commonly used tremor rating scales in clinical practice is the Fahn-Tolosa-Marin Tremor Rating Scale (TRS), which includes a section to assess rest, postural and kinetic/intention tremor (with separate scores for lower and upper limbs) [5,6].

The objectives of this study were to explore the prevalence and associated demographic and clinical features of lower limb tremor in the most common tremor syndromes, as well as to contrast these characteristics with patients without lower limb tremor.

* Corresponding author. Professor of Neurology - University of Toronto, Clinician Investigator - Krembil Brain Institute, Movement Disorders Centre - Toronto Western Hospital, 399 Bathurst St, 7McL412, Toronto, ON, M5T 2S8, Canada.

E-mail address: alfonso.fasano@uhn.ca (A. Fasano).

<https://doi.org/10.1016/j.parkreldis.2019.06.007>

Received 19 February 2019; Received in revised form 6 June 2019; Accepted 7 June 2019

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2. Methods

2.1. Study design

This was a retrospective chart review of patients with lower limb tremor who were seen at the Movement Disorders Clinic in Toronto Western Hospital between January 2000 and August 2017.

2.2. Standard protocol approvals, registrations, and patient consents

The study was approved by the institution's research ethics board.

2.3. Search method and data collection

We searched our electronic medical records system using the keyword “tremor”. This electronic system is used to record demographic and clinical information from all patients during clinical consultations, as well as to document the results of any rating scales. After removal of non-relevant and duplicate results, a total of 2927 patients were identified. Patients with no TRS evaluation ($N = 2291$) and patients with a diagnosis of orthostatic tremor ($N = 43$) were excluded. Patients with TRS evaluation ($N = 593$) were identified for further chart review. Patients were defined as having lower limb tremor if they had TRS score ≥ 1 at any visit in either lower limb ($N = 283$). Patients were defined as ‘non-lower limb tremor’ cases if the lower limbs TRS was 0 ($N = 310$) (Fig. 1). Patients were classified according to the new International Parkinson and Movement Disorder Society tremor criteria [1]. Six tremor syndrome groups with the greatest sample sizes were chosen:

ET, ET-plus, parkinsonian tremor (PT), dystonic tremor (DT), intention tremor (IT) and functional tremor (FT). Patients who did not fall into one of the six groups were excluded from the final analysis on the basis of their small sample size, a potentially reversible etiology in some cases (e.g. drug-induced), or the presence of an indeterminate tremor with uncertain etiology. Classic parkinsonian tremor and classic parkinsonian tremor with antecedent ET were combined into a single ‘PT’ group, while patients with dystonic tremor and tremor associated with dystonia were combined into a single ‘DT’ group. IT syndromes are defined as those with intention tremor (amplitude of tremor increases during visually-guided movements toward a target at the termination of the movement) at < 5 Hz, with or without other localizing signs [1]. For this study, the IT frequency was based on a clinical estimate.

Data on demographics, clinical characteristics, and TRS scores (excluding disability sub-score) were extracted from the electronic medical records. For patients who had more than one TRS performed ($N = 179$), the assessment containing the worst lower limb tremor score was included in the analysis. This was done to enable differences in tremor phenotype across tremor groups to be more easily identified, and before the medications could have an effect.

2.4. Statistical analysis

We tested for normal distribution using a combination of Shapiro-Wilk tests, alongside visual inspection of Q-Q plots and skewness of histograms. All variables were non-normally distributed. Descriptive statistics are presented as mean \pm standard deviation (SD) for continuous variables, and as percentages for categorical variables. We

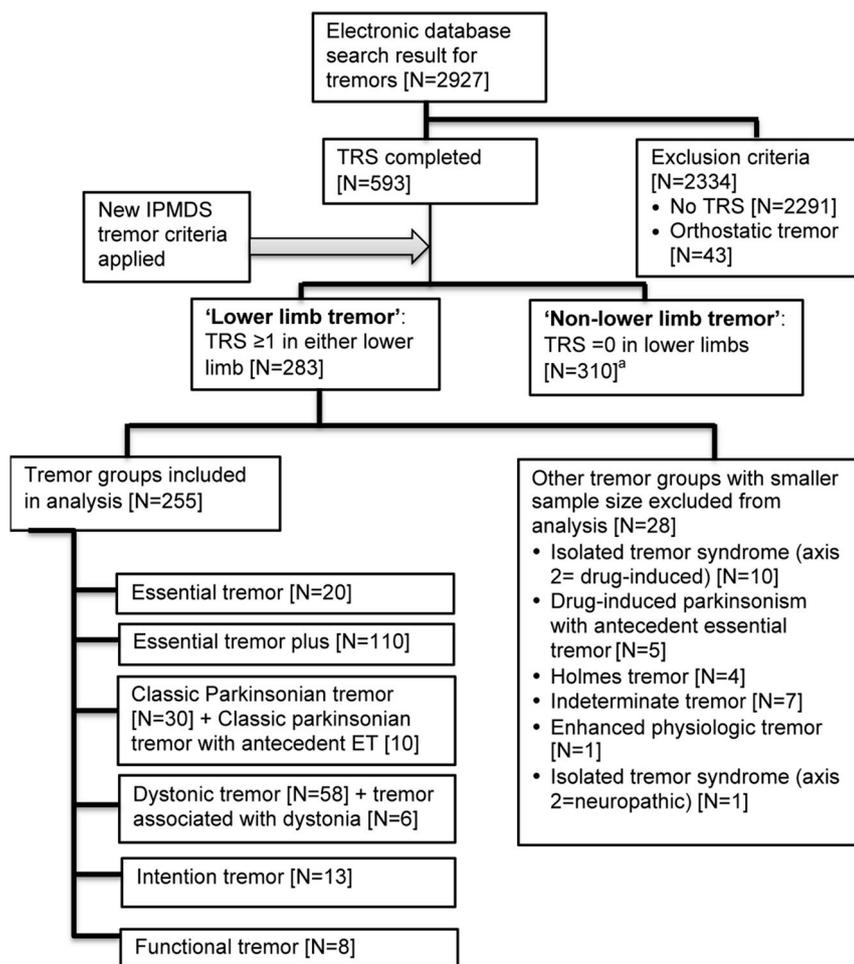


Fig. 1. Study flow chart. Abbreviations: ^a: Tremor groups with TRS < 1 in lower limbs (essential tremor-plus [$N = 105$]; essential tremor [$N = 52$]; dystonic tremor [$N = 49$]; tremor associated with dystonia [$N = 1$]; classic parkinsonian tremor [$N = 13$]; classic parkinsonian tremor with antecedent essential tremor [$N = 5$]; drug-induced parkinsonism with antecedent essential tremor [$N = 2$]; intention tremor [$N = 9$]; functional tremor [$N = 8$]; enhanced physiological tremor [$N = 12$]; Holmes tremor [$N = 7$]; indeterminate tremor syndrome [$N = 26$]; Isolated task-specific tremor [$N = 4$]; Isolated voice and head tremor [$N = 1$]; Isolated postural tremor syndrome [$N = 1$]; Isolated tremor syndrome [$N = 15$: axis 2 = drug-induced in 11; Wilson's disease in 1; Huntington's disease in 1; brain injury in 1; neuropathy in 1]).

33 patients were excluded as indeterminate tremors (both lower limb tremor and non-lower limb tremor) due to these reasons: they did not meet the 3 years' cut-off for ET according to the new tremor criteria, not fit into an established tremor syndrome or further observation is needed to clarify the tremor syndrome.

77 non-lower limb tremor patients were excluded from the final analysis because they belonged to a tremor group with a very small sample size, a potentially reversible etiology (e.g. drug-induced), or an indeterminate tremor of uncertain etiology, as well as for not meeting the diagnostic criteria for the six tremor syndrome groups selected for comparison against the lower limb tremor patients.

compared the groups using the non-parametric Kruskal-Wallis test for continuous variables and chi-square test for categorical variables. Post-hoc Mann-Whitney *U* tests were performed for each significant Kruskal-Wallis. As for correlations, we carried out Spearman's Rho correlation analysis.

Initially, we determined the prevalence of lower limb tremor within each tremor group by calculating the percentage out of the total number of tremor patients of the same diagnostic group (i.e. including those with non-lower limb tremor). Subsequently, we compared the demographic and clinical characteristics of lower limb tremor patients across the six tremor groups. The latter included the severity of lower and upper limb tremor, upper/lower limb tremor ratio, distribution of tremor type (rest, postural and kinetic). In addition, we correlated tremor duration and lower limb tremor score with total tremor score. We also correlated lower limb tremor score with upper limb tremor score. Finally, we compared these characteristics in patients with and without lower limb tremor.

Statistical analyses were performed using SPSS version 22. All tests were two-tailed and *P* value < 0.05 was considered statistically significant. Bonferroni corrections for multiple comparisons were applied to all pair-wise comparisons (*p* < 0.0033 were deemed to be significant).

3. Results

3.1. Frequency of lower limb tremor

Out of the 283 patients with lower limb tremor (58.3% males, age: 65.0 ± 16.0 years, tremor duration: 25.6 ± 17.9 years), 255 patients within six tremor groups were included in the final analysis. 233 non-lower limb tremor patients from the same six tremor groups were also included in the final analyses.

The prevalence of lower limb tremor within each tremor group is shown in Fig. 2. Overall, there was a significant difference across the groups (*P* < 0.001). The lowest prevalence was seen in ET (28.6%), followed by ET-plus (51.4%), DT (56.1%), FT (57.1%) and IT (59.1%). The highest prevalence was seen in PT (69.0%).

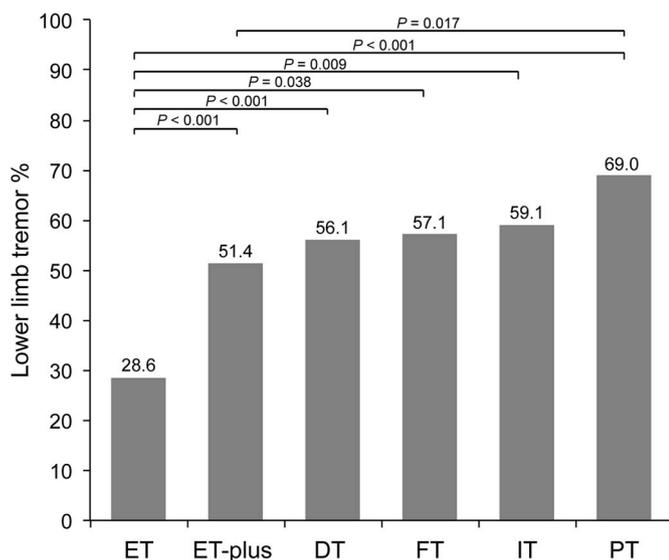


Fig. 2. Prevalence of lower limb tremor in the six tremor groups. Patients with incomplete data were excluded (2 ET, 1 ET-plus, 4 DT and 2 FT patients in the non-lower limb tremor cohort). Abbreviations: ET: essential tremor; FT: functional tremor; DT: dystonic tremor and tremor associated with dystonia; IT: intention tremor; PT: classic parkinsonian tremor and classic parkinsonian tremor with antecedent ET.

3.2. Demographic and clinical characteristics

The characteristics of the six tremor groups are presented in Table 1. Age at last visit, age at tremor onset, tremor duration, site of tremor onset, and family history of tremor were different across the groups. At the last visit, compared to the other groups, ET-plus and PT patients were older and had an older age of tremor onset. PT, FT and IT patients had the shortest tremor duration. DT patients were more likely than others to present with head tremor, whereas FT patients were the only group in whom a whole body distribution of tremor was present at onset. ET-plus patients had a positive family history of tremor more frequently than other groups (Table 1).

As for tremor characteristics, there were significant differences across the groups for total tremor score, severity of lower and upper limb tremor, and distribution of tremor types (Table 1). The lower limb tremor score was higher in IT compared to ET and DT. Rest tremor in the lower limbs was higher in PT compared to ET-plus and DT. Kinetic tremor of the lower limbs was more common in IT compared to ET, PT and DT (details on the pair-wise comparisons are presented in Table 1). Interestingly, compared to other tremor groups, the lowest upper/lower limb TRS ratio (i.e. more homogenous tremor severity in upper and lower limbs) was found in FT but the comparison did not survive Bonferroni correction.

3.3. Correlation analyses

We found a correlation between total lower limb tremor score and total TRS tremor score in ET ($\rho = .557$, *P* = 0.011), ET-plus ($\rho = .580$, *P* < 0.001), DT ($\rho = .593$, *P* < 0.001), PT ($\rho = .729$, *P* < 0.001) and FT ($\rho = .976$, *P* < 0.001). Furthermore, there was a correlation between tremor duration and total TRS for tremor score in ET ($\rho = .503$, *P* = 0.024), ET-plus ($\rho = .293$, *P* = 0.002) and DT ($\rho = .301$, *P* = 0.017).

In addition, we found a correlation between lower limb tremor score and upper limb tremor score for the whole sample of patients ($\rho = .349$, *P* < 0.001). Among the individual tremor groups, there was a correlation between lower limb tremor score and upper limb tremor score in ET-plus ($\rho = .296$, *P* = 0.002), PT ($\rho = .425$, *P* = 0.006), DT ($\rho = .300$, *P* = 0.016), and FT ($\rho = .864$, *P* = 0.006).

3.4. Lower limb tremor vs. non-lower limb tremor

Comparison of baseline characteristics and TRS tremor scores in patients from each diagnostic group with and without lower limb tremor is shown in Table 2. ET-plus, DT and PT patients with lower limb tremor had a longer tremor duration compared to those without lower limb tremor. In addition, the total TRS tremor score was significantly higher for each group with lower limb tremor compared to those without any lower limb tremor in all tremor groups, with the exception of FT (details on the post-hoc analyses are presented in Table 2).

4. Discussion

In this study, we described the prevalence and associated features of lower limb tremor in the most common tremor syndromes. We also compared the clinical characteristics in patients with and without lower limb tremor.

The prevalence of patients with lower limb tremor was lowest (28.6%) in the ET group compared to the other groups. This is in keeping with previous studies reporting that ET less commonly affects the lower limbs compared to the upper limbs [3]. One study reported leg tremor in 13.8% of ET cases in rural Sweden [7], with another study observing leg tremor in 13.7% of 350 ET cases [8]. However, these studies did not report on the tremor severity or describe the lower limb tremor characteristics. Poston et al. compared leg tremor in ET patients with age-matched controls and found that nearly half (28/63, 44.4%) of

Table 1

Comparison of baseline characteristics and TRS scores of the six tremor groups only including patients with lower limb tremor.

	ET (N = 20)	ET-plus (N = 110)	PT (N = 40)	DT (N = 64)	IT (N = 13)	FT (N = 8)	P-value
Gender (% male)	14(70.0)	69(62.7)	27(67.5)	29(45.3)	6(46.2)	6(75.0)	0.090
Age at last clinic visit (y)	52.3 ± 17.6 ^{a,b}	70.8 ± 13.0^{a,c,d,e}	74.9 ± 10.9^{b,f,g,h}	58.9 ± 15.1 ^{c,f}	50.8 ± 16.4 ^{d,g}	55.4 ± 14.9 ^{e,h}	< 0.001
Age at tremor onset* (y)	26.2 ± 19.8 ^{a,b}	38.1 ± 20.9^{a,c,d,e,i}	54.1 ± 18.5^{b,f,g,i}	31.1 ± 20.8 ^{c,f}	38.4 ± 11.1 ^{d,g}	42.8 ± 16.2 ^e	< 0.001
Tremor duration* (y)	26.1 ± 16.2 ^j	32.8 ± 18.4 ^{d,e,i}	20.9 ± 16.0^{g,i}	27.7 ± 15.0 ^k	9.5 ± 9.7^{d,g,j,k}	12.6 ± 12.8^e	< 0.001
Site of tremor onset:							< 0.001
Hand (%)	18(90.0)	98(89.1)	34(85.0)	39(60.9)	7(53.8)	2(25.0)	
Arm (%)	1(5.0)	6(5.5)	2(5.0)	7(10.9)	5(38.5)	0	
Head/Neck (%)	0	5(4.5)	2(5.0)	16(25.0)	1(7.7)	0	
Leg (%)	1(5.0)	1(0.9)	2(5.0)	1(1.6)	0	1(12.5)	
Foot (%)	0	0	0	1(1.6)	0	1(12.5)	
Whole body (%)	0	0	0	0	0	4(50.0)	
Asymmetry at onset* (%)	8(100.0)	50(90.9)	32(80.0)	31(100.0)	6(85.7)	4(100.0)	0.341
Family history of tremor* (%)	13(65.0)	83(79.0)	23(43.4)	38(60.3)	4(33.3)	1(12.5)	< 0.001
<i>TRS score analysis</i>							
Total TRS score	11.4 ± 3.2^{a,b,j}	17.0 ± 7.4 ^{a,d}	16.8 ± 7.5 ^b	15.4 ± 7.5 ^k	25.4 ± 11.2^{d,j,k}	20.8 ± 16.9	< 0.001
Upper limb TRS score	6.5 ± 2.2^{a,j}	9.5 ± 3.7 ^a	9.2 ± 4.1	8.0 ± 3.5 ^k	12.4 ± 4.8^{j,k}	9.3 ± 7.3	< 0.001
Lower limb TRS score	3.4 ± 1.4 ^l	4.2 ± 3.1	4.1 ± 2.3	3.4 ± 2.2 ^k	7.3 ± 4.3^{j,k}	7.4 ± 5.9	0.004
Upper/lower limb TRS ratio	2.3 ± 1.3	3.4 ± 2.8	2.9 ± 2.5	3.2 ± 2.3	3.2 ± 4.9	1.4 ± 1.0	0.019
Asymmetry of lower limb tremor (%)	5(25.0)	39(35.5)	18(45.0)	29(45.3)	5(38.5)	3(37.5)	0.561
Lower limb rest TRS score	–	0.6 ± 1.2 ⁱ	1.3 ± 1.6^{fi}	0.5 ± 1.1 ^f	0.7 ± 1.5	2.3 ± 2.7	< 0.001
Lower limb rest tremor: degree of asymmetry	–	0.1 ± 0.4	0.3 ± 0.6	0.2 ± 0.4	0.1 ± 0.3	0.5 ± 0.8	0.013
Lower limb postural TRS score	2.0 ± 1.3	2.1 ± 1.4	1.7 ± 1.4	1.6 ± 1.3	3.1 ± 1.9	2.9 ± 1.8	0.007
Lower limb postural tremor: degree of asymmetry	0.2 ± 0.4	0.2 ± 0.4	0.5 ± 0.7	0.3 ± 0.5	0.3 ± 0.5	0.4 ± 0.7	0.491
Lower limb kinetic TRS score	1.4 ± 1.0 ^l	1.5 ± 1.6	1.2 ± 1.2 ^g	1.2 ± 1.1 ^k	3.5 ± 1.9^{g,j,k}	2.3 ± 2.5	0.003
Lower limb kinetic tremor: degree of asymmetry	0.2 ± 0.4	0.1 ± 0.4	0.3 ± 0.4	0.2 ± 0.4	0.2 ± 0.6	–	0.302

Data are presented as mean ± SD if not otherwise specified, significant differences after Bonferroni correction for multiple comparisons ($p < 0.0033$) are highlighted in bold.

Abbreviations: *: age of tremor onset unknown in 1 ET-plus, 1 DT, and 1 IT patients; symmetrical vs. asymmetrical side of tremor onset unknown in 12 ET, 55 ET-plus, 7 PT, 33 DT, 6 IT, and 4 FT patients; family history of tremor unknown in 5 ET-plus, 1 PT, 1 DT, and 1 IT patients; The following post-hoc comparisons are significant at $p < 0.0033$: ^a: ET vs. ET-Plus ^b: ET vs. PT ^c: ET-plus vs. DT ^d: ET-plus vs. IT ^e: ET-plus vs. FT ^f: PT vs. DT ^g: PT vs. IT ^h: PT vs. FT ⁱ: ET-plus vs. PT ^j: ET vs. IT ^k: DT vs. IT; ET: essential tremor; PT: classic parkinsonian tremor and classic parkinsonian tremor with antecedent ET; DT: dystonic tremor and tremor associated with dystonia; IT: intention tremor; FT: functional tremor; TRS: Fahn-Tolosa-Marin Tremor Rating Scale.

ET patients had a mild or greater kinetic leg tremor in either leg (rated ≥ 1) versus 9/63 (14.3%) controls [4]. The same study, however, found that of these patients, 9/63 ET cases (14.3%) had moderate kinetic tremor in either leg (rated ≥ 1.5) versus only one (1.6%) control [4].

We observed the highest total and lower limb tremor score in IT, in keeping with the notion that outflow cerebellar tremor is associated with disability resulting from lack of adequate treatment response [9,10]. Furthermore, except for FT, the total TRS tremor score was higher in all groups with lower limb tremor compared to patients without lower limb tremor, indicating that lower limb tremor may be regarded as a marker of overall tremor severity. This was further confirmed by the positive correlation between total lower limb tremor score and total TRS tremor score. We also found a positive correlation between lower limb tremor score and upper limb tremor score indicating that lower limb tremor is associated with more severe upper limb tremor. A higher kinetic tremor score in the IT group and a higher rest tremor score of the lower limbs in the PT group also reflects the greater symptom burden resulting from more advanced underlying disease.

Disease duration was significantly longer in ET-plus, DT and PT when a lower limb tremor was present compared to patients with only upper limb involvement. There was also a positive correlation between tremor duration and total TRS for tremor score in ET, ET-plus and DT. Therefore, lower limb tremor may be a marker of longer tremor duration in certain tremor disorders. Most of the patients in our lower limb tremor cohort had tremor onset in the upper limbs. This again points to the likelihood that tremor progresses to involve other body parts as the disease progresses.

In contrast, FT group had a relatively short tremor duration and were likely to present with whole body distribution at tremor onset. FT has well-known clinical features such as variability and inconsistency

[11]. Therefore, our data indicate that a lower limb tremor with whole body distribution of tremor at onset or any inconsistent characteristics combined with shorter tremor duration, are possible clues to the diagnosis of FT. It is worth mentioning that none of the patients with FT had additional ‘organic’ tremor in our tremor cohort.

In the PT group, only 2 (5%) patients had tremor onset in the legs. The disease onset in these individuals were at an older age. No genetic testing was performed on either of these two patients. It has been shown in a previous study of young onset PD patients that tremor starting in, or restricted to, the lower limbs can be a feature of *Parkin* gene mutations [12].

There are some limitations to our study. First, this is a retrospective study from a single, tertiary centre. It is possible that the patients recruited either had severely expressed tremor or less typical tremor syndromes. The severity of lower limb tremor maybe be inflated by our decision to choose worst lower limb tremor score to compare across disease groups. However, we felt that this was a more robust way to explore the differences in tremor phenotype. Second, our study only included lower limb tremor patients evaluated with TRS. Therefore, classic parkinsonian tremor patients are underrepresented because very few PD patients were assessed with TRS. In fact, in our movement disorder clinic PD patients are routinely assessed with UPDRS. However, tremor-dominant PD patients are also assessed with TRS regardless of the occurrence of lower limb tremor. Although this is certainly a small proportion, this subgroup of patients can be seen as a proxy of all PD patients with tremor. Likewise, patients with IT in the context of cerebellar ataxia may be assessed with other scales (such as the Scale for the Assessment and Rating of Ataxia), however in our center TRS is used in all tremor patients other than PD regardless of the tremor type and its cause. Third, the TRS assessments were performed by multiple different clinicians, which may be relevant since it has been

Table 2
Comparison of baseline characteristics and TRS scores of patients with lower limb tremor compared to those without lower limb tremor for each of the six tremor groups.

	ET (N = 70)			ET-plus (N = 214)			PT (N = 58)		
	With lower limb tremor (N = 20)	Without lower limb tremor (N = 50) ^a	P value	With lower limb tremor (N = 110)	Without lower limb tremor (N = 104) ^b	P value	With lower limb tremor (N = 40)	Without lower limb tremor (N = 18)	P value
Gender (% male)	14(70.0)	36(72.0)	0.867	69(62.7)	55(52.9)	0.145	27(67.5)	16(88.9)	0.085
Age at last clinic visit (y)	52.3 ± 17.6	62.3 ± 15.9	0.024	70.8 ± 13.0	71.4 ± 10.5	0.781	74.9 ± 10.9	74.7 ± 9.4	0.814
Age at tremor onset ^b (y)	26.2 ± 19.8	37.0 ± 24.0	0.082	38.1 ± 20.9	46.8 ± 20.4	0.001	54.1 ± 18.5	61.8 ± 15.0	0.106
Tremor duration ^b (y)	26.1 ± 16.2	26.0 ± 20.1	0.706	32.8 ± 18.4	32.8 ± 18.6	< 0.001	20.9 ± 16.0	12.8 ± 11.2	0.043
Site of tremor onset:									
Hand (%)	18(90.0)	48(98.0)	0.226	98(89.1)	98(94.2)	0.238	34(85.0)	17(94.4)	0.586
Arm (%)	1(5.0)	1(2.0)		6(5.5)	1(1.0)		2(5.0)	1(5.5)	
Face (%)	0	0		0	0		0	0	
Voice (%)	0	0		0	1(1.0)		0	0	
Head/									
Neck (%)	0	0		5(4.5)	4(3.8)		2(5.0)	0	
Leg (%)	1(5.0)	0		1(0.9)	0		2(5.0)	0	
Foot (%)	0	0		0	0		0	0	
Whole									
body (%)	0	0		0	0		0	0	
Asymmetry at onset ^b (%)	8(100.0)	22(84.6)	0.238	50(90.9)	58(87.9)	0.592	32(97.0)	14(100.0)	0.510
Family history of tremor ^b (%)	13(65.0)	32(68.1)	0.806	83(79.0)	70(72.9)	0.309	18(46.2)	6(35.3)	0.450
Total TRS score	11.4 ± 3.2	7.2 ± 2.5	< 0.001	17.0 ± 7.4	10.3 ± 4.6	< 0.001	16.8 ± 7.5	7.9 ± 4.3	< 0.001
DT (N = 110)									
	With lower limb tremor (N = 64)	Without lower limb tremor (N = 46) ^a	P value	With lower limb tremor (N = 13)	Without lower limb tremor (N = 9)	P value	With lower limb tremor (N = 8)	Without lower limb tremor (N = 6) ^a	P value
Gender (% male)	29(45.3)	23(50.0)	0.627	6(46.2)	3(33.3)	0.548	6(75.0)	4(66.7)	0.733
Age at last clinic visit (y)	58.9 ± 15.1	64.3 ± 14.3	0.059	50.8 ± 16.4	50.8 ± 9.7	0.896	55.4 ± 14.9	46.5 ± 18.7	0.662
Age at tremor onset ^b (y)	31.1 ± 20.8	43.5 ± 19.8	0.002	38.4 ± 11.1	40.3 ± 9.6	0.808	42.8 ± 16.2	34.8 ± 25.3	0.662
Tremor duration ^b (y)	27.7 ± 15.0	21.7 ± 15.2	0.021	9.5 ± 9.7	11.0 ± 8.1	0.508	12.6 ± 12.8	12.1 ± 8.8	0.943
Site of tremor onset:									
Hand (%)	39(60.9)	26(56.5)	0.405	7(53.8)	7(77.8)	0.367	2(25.0)	5(83.3)	0.086
Arm (%)	7(10.9)	4(8.7)		5(38.5)	1(11.1)		0	1(16.7)	
Face (%)	0	2(4.3)		0	0		0	0	
Voice (%)	0	0		0	0		0	0	
Head/									
Neck (%)	16(25.0)	12(26.1)		1(7.7)	1(11.1)		0	0	
Leg (%)	1(1.6)	0		0	0		1(12.5)	0	
Foot (%)	1(1.6)	0		0	0		1(12.5)	0	
Whole									
body (%)	0	0		0	0		4(50.0)	0	
Asymmetry at onset ^b (%)	31(100.0)	17(94.4)	0.185	6(85.7)	3(60.0)	0.310	4(100.0)	4(100.0)	–
Family history of tremor ^b (%)	38(60.3)	25(56.8)	0.717	4(33.3)	1(20.0)	0.582	1(12.5)	3(50.0)	0.124
Total TRS score	15.4 ± 7.5	9.3 ± 4.1	< 0.001	25.4 ± 11.2	15.6 ± 8.0	0.032	20.8 ± 16.9	7.0 ± 4.9	0.115

Data are presented as mean ± SD if not otherwise specified, significant differences are highlighted in bold. Abbreviations: ^a, Patients with incomplete data excluded from this analysis (2ET, 1 ET-plus, 4 DT and 2 FT patients); ^b, age of tremor onset unknown in 1 ET patient with lower limb tremor and 2ET, 4ET-plus, 2 DT, and 1 FT without lower limb tremor; site of tremor onset data unknown in 1 ET patient without lower limb tremor; symmetrical vs. asymmetrical side of tremor onset is unknown in 12ET, 55ET-plus, 7PT, 33DT, 6IT, and 4 FT patients with lower limb tremor and 24ET, 38ET-plus, 4PT, 28DT, 4IT, and 2 FT patients without lower limb tremor; family history of tremor unknown in 5ET-plus, 1PT, 1DT, and 1IT patients with lower limb tremor and 3ET, 8ET-plus, 1PT, 2DT, and 4 IT patients without lower limb tremor; ET: essential tremor; PT: classic parkinsonian tremor and classic parkinsonian tremor with antecedent ET; DT: dystonic tremor and tremor associated with dystonia; IT: intention tremor; FT: functional tremor; TRS: Fahn-Tolosa-Marin Tremor Rating Scale.

shown that inter-rater reliability can vary according to the rater's background [6]. Fourth, in PD patients with antecedent ET, we lacked precision in terms of the onset of lower limb tremor to know whether the tremor was due to PD or ET. It has been suggested that a pathophysiological relationship exists between the two or this might be pure coincidence. At this point, we cannot make any conclusion about whether a relationship exists between ET and PD, and this has been covered comprehensively elsewhere [13]. In this study, we only identified 10 PD patients with antecedent ET after applying the new tremor criteria as strictly as possible, while taking into account the time of onset of ET symptoms before developing parkinsonism. Further research involving longitudinal cohorts is needed to determine if an association exists between ET and PD or the co-occurrence of these two disorders is by chance alone. Fifth, the results of the IT and FT groups have to be interpreted with caution because of their relatively small sample sizes. Sixth, orthostatic tremor is not included in our study since there have been numerous studies on the characteristics of lower limb tremor in orthostatic tremor patients and not many in other common tremor syndromes. Therefore, our study excluded orthostatic tremor patients in order to focus on lower limb tremor characteristics in these other tremor syndromes. Seventh, the tremors were classified according to the recently published tremor criteria [1], which presented a few challenges in the application of the ET-plus criteria as discussed in a separate paper [14]. Lastly, ET was retrospectively divided into a 'pure' ET subtype and 'ET-plus' subtype on the basis of the new tremor criteria, even though there is currently no evidence that they differ on a genetic or biological basis and further studies are needed to understand if these differences exist.

In conclusion, lower limb tremor may be observed in ET, however, less commonly and with reduced severity in comparison to other tremor syndromes. Lower limb tremor may be a marker of longer disease duration and overall symptom severity of the underlying disease condition for most tremor subtypes, with the notable exception of FT. Future studies involving electrophysiological studies, in addition to clinical ratings, in a cohort with more evenly distributed sample sizes across tremor groups is needed to confirm our findings.

Conflicts of interest

None.

Authors' contributions

Rajasumi Rajalingam: study design, acquisition of data, analysis and interpretation of the data, drafting of the manuscript.

David P. Breen: analysis and interpretation of the data, critical revision of manuscript for intellectual content.

Robert Chen: critical revision of manuscript for intellectual content.

Susan Fox: critical revision of manuscript for intellectual content.

Lorraine V. Kalia: critical revision of manuscript for intellectual content.

Renato P. Munhoz: critical revision of manuscript for intellectual content.

Elizabeth Slow: critical revision of manuscript for intellectual content.

Antonio P. Strafella: critical revision of manuscript for intellectual content.

Anthony E. Lang: critical revision of manuscript for intellectual content.

Alfonso Fasano: study concept and design, interpretation of the data, critical revision of manuscript for intellectual content, study supervision.

Study funding

None.

Full financial disclosures

Rajasumi Rajalingam: Reports no disclosures.

David P. Breen: Reports employment with University of Edinburgh and NHS Lothian; grants from Wellcome Clinical Research Career Development scheme.

Robert Chen: Received consultancies from Allergan and Merz; grants from CIHR, NINDS, Weston Brain Institute, CFI, and Dystonia Medical Research Foundation.

Susan Fox: Reports employment with UHN Dept of Medicine Practice Plan; contracts with Biotie, Cynapsus, and Eisia for site PI. Provided expert testimony for CPSO. Received consultancies from Merz, Kyowa, Palidan, Sunovion, Teva, and Zambon; honoraria from International Parkinson and Movement Disorder Society and American Academy of Neurology; royalties from Oxford University Press; grants from Michael J Fox Foundation for Parkinson Research, NIH (Dystonia Coalition), CIHR and Parkinson Canada. She serves on the advisory board for CHDI, Acadia, Palidan, and Sunovion.

Lorraine V. Kalia: Reports contract with Apopharma for site PI. Received honoraria from National Institutes of Health, and University of California Irvine; grants from Allergan, Canadian Institutes of Health Research, J. P. Bickell Foundation, Krembil Research Institute, Michael J. Fox Foundation for Parkinson's Research, Natural Sciences and Engineering Research Council of Canada, and Parkinson Canada.

Renato P. Munhoz: Received honoraria from Medtronic; grants from University of Toronto.

Elizabeth Slow: Reports no disclosures.

Antonio P. Strafella: Received consultancies from GE; grants from CIHR, Brain Canada, National Parkinson Foundation, Parkinson Canada, and PSI. He serves on the advisory board for CIHR.

Anthony E. Lang: Reports employment with University Health Network; University of Toronto. Received consultancies from Abbvie, Acorda, Biogen, Bristol Myers Squibb, Janssen, Sun Pharma, Kallyope, Merck, Paladin, Theravance, and Corticobasal Degeneration Solutions; honoraria from Sun Pharma, Medichem, Medtronic, AbbVie and Sunovion; grants from Brain Canada, Canadian Institutes of Health Research, Corticobasal Degeneration Solutions, Edmond J Safra Philanthropic Foundation, Michael J. Fox Foundation, the Ontario Brain Institute, National Parkinson Foundation, Parkinson Society Canada, and W. Garfield Weston Foundation; royalties from Elsevier, Saunders, Wiley-Blackwell, Johns Hopkins Press, and Cambridge University Press.

Alfonso Fasano: Received consultancies from Abbvie, Medtronic, Boston Scientific, Sunovion, Chiesi farmaceutici, UCB, and Ipsen; honoraria from Abbvie, Medtronic, Boston Scientific, Sunovion, Chiesi farmaceutici, UCB, and Ipsen; grants from University of Toronto, Weston foundation, Abbvie, Medtronic and Boston Scientific. He serves on the advisory board for Abbvie, Boston Scientific and Ipsen.

Acknowledgements

The authors thank Dr. Connie Marras from the Edmond J. Safra Program in Parkinson's Disease and the Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, University Health Network, Toronto, Canada, for her invaluable critical revision of the manuscript.

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