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Essential Tremor 10, 20, 30, 40: Clinical Snapshots of the Disease by Decade of Duration

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Abstract

Background—Essential tremor (ET) is a chronic, progressive neurological disorder in which disease burden may slowly accrue. There are few long-term studies, and the clinical and functional status of patients, with each decade of disease duration, has not been documented in detail. We used cross-sectional data on 335 ET patients (disease duration 1–81 years) to produce clinical snapshots of the disease at each 10-year milestone (i.e., <10, 10, 20, 30 and 40 years). We hope these data will be of value in clinical-prognostic settings both to patients and their treating physicians.

Methods—In this cross-sectional, clinical-epidemiological study at Columbia-University Medical Center, each patient underwent a single evaluation, including self-reported measures of tremor-related disability, performance-based measures of function, and neurologist-assessments of tremor type, location, and severity.

Results—A variety of metrics of tremor severity increased across the 10-year time intervals. By 40 years duration, one-third of patients had tremor in at least two cranial locations (neck, voice, jaw), and the proportion with high amplitude tremor reached 20.3% (while drawing spirals), 33.8% (spilling while drinking), and 60.8% (spilling while using a spoon). Yet even in the longest tremor duration group, very few (<10%) were incapacitated (i.e., completely unable to perform the above-mentioned tasks), and one-third continued to exhibit no cranial tremor.

Conclusions—These data paint a picture of progressive decade-by-decade decline in ET. Yet patients with long disease duration did not relentlessly converge at the same end-stage of severe, functionally-incapacitating, diffuse tremor. In this respect, long-duration ET patients presented a heterogeneous picture.

Keywords

essential tremor; clinical; prognosis

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Introduction

Essential tremor (ET) is a chronic neurological disease [1] that may be accompanied by functional disabilities [2] and reduced health-related quality of life [3–6]. The main motor feature of ET, kinetic tremor of the arms, tends to increase in severity over time [1]; several studies have provided estimates of the annual rate of change [7, 8]. Additional forms of tremor (rest tremor [9], intention tremor [10], head tremor) have the tendency to accumulate, as do other motor features (e.g., gait and balance difficulty) [11]. Thus, disease burden may slowly accrue, resulting in diminishing functional capability and health status with time.

Despite this picture, there are few prospective, longitudinal studies of ET, in which patients were followed for either modest time periods (e.g., 5 years) or longer (> 10 years). Furthermore, there are no long-term studies of ET patients with longer disease duration (i.e., patients with disease of 30 or 40 years duration). The clinical and functional status of patients who are reaching each decade of disease duration (e.g., 10 years, 20 years, 30 years, etc) has not been described in the neurological literature.

Given the paucity of such information, the current analyses utilized cross-sectional data on 335 ET patients, who ranged widely in disease duration (1 – 81 years), to produce clinical snapshots of the disease at each 10-year milestone (i.e., <10, 10, 20, 30 and > 40 years). The data were clinically-motivated; indeed, in treatment settings, patients often ask the question “how bad will my tremor be in 10 or 20 years?” Our aim is that the presented data will be of value in clinical-prognostic settings to ET patients and their treating physicians.

Methods

ET patients were enrolled in a clinical-epidemiological research study at the Center for Parkinson’s Disease and Other Movement Disorders at Columbia-University Medical Center (CUMC) [12, 13]. Recruitment began in 2000 and ended in 2009. By design, ET patients were identified from several sources; the major ones were a computerized billing database of patients at the Center, and the International Essential Tremor Foundation, whose members were mailed advertisements. All patients lived within two-hour driving distance of CUMC, in the New York Metropolitan area, and had received a diagnosis of ET from their treating neurologist, who considered other causes of tremor (e.g., medications, thyroid disease) when assigning the diagnosis. When clinically suspected, patients underwent phlebotomy to exclude other disorders (hyperthyroidism, Wilson’s disease). Additionally, all diagnoses were reconfirmed based on chart review and videotaped neurological examination by a senior movement disorder neurologist (E.D.L.) who used published diagnostic criteria for ET (moderate or greater amplitude kinetic tremor during three activities or a head tremor in the absence of Parkinson’s disease [PD], dystonia, or another known cause [e.g., thyroid disease, medications, Wilson’s disease]) [9, 10]. ET diagnoses were also consistent with the Consensus Statement of the Movement Disorders Society regarding classic ET [14].

ET cases signed informed written consent approved by the CUMC Institutional Review Board, and were evaluated in person by a trained tester who collected demographic and clinical data.

The study was initially cross-sectional; each patient had a single in-person evaluation. Demographic and clinical information, including family history information, were collected using semi-structured questionnaires. Among other questions, patients were also asked, “Does your tremor often embarrass you?” [15]. Medical co-morbidity was assessed using the Cumulative Illness Rating Scale, in which the severity of medical problems (0 [none] – 3 [severe]) was rated in 14 body systems (e.g., cardiac, respiratory, renal) and a Cumulative

Illness Rating Scale score was assigned (range = 0 – 42 [maximal co-morbidity]) to each patient [16].

Tremor-related motor disability was evaluated with a brief 10-item version of a 36-item, validated tremor disability questionnaire [17]; self-reported ability to perform a range of motor activities was assessed (signing name, carrying a cup, dialing a telephone, using a key), with the possible score range from 0 – 100 (maximum disability).

Each ET patient underwent a videotaped neurological examination, which included a detailed assessment of postural tremor and five tests of kinetic tremor (e.g., drinking from a cup, drawing spirals) [12, 13]. E.D.L. reviewed all videotaped examinations, and the severity of postural and kinetic arm tremors were rated (0–3), resulting in a total tremor score (range = 0–36 [maximum]), a measure of the severity of action tremor. Ratings of 2 indicated moderate amplitude tremor; ratings of 3 were applied when the tremor was severe (e.g., spilling when handling liquids, and see example in Figure 5 of Louis et al. [18]). Voice tremor was assessed during sustained phonation, during conversational speech, and while reading a prepared passage, and was noted as present or absent. Neck (i.e., head) and jaw tremors were assessed while seated comfortably and facing the camera. As in prior analyses, the cranial tremor score (0–3) was the number of locations (neck, jaw, voice) in which tremor was present [19]. Rest tremor in either arm, noted as present or absent, was assessed in three positions: resting in the lap, relaxed at sides while standing, and while walking. Intention tremor of each arm was rated on the finger-to-nose task (0 [no visible tremor], 1 [mild and intermittent], and 2 [moderate amplitude and usually present]), resulting in an intention arm tremor score (0 – 4 [maximum]) [10]. The videotaped examination also included the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS) [20], with the diagnosis of PD requiring bradykinesia and rest tremor in the absence of unusual features or identifiable secondary causes; this videotape-based method has previously been shown to be a valid means of assessing and diagnosing PD (sensitivity=91.3% and specificity=98.8%) [21].

A 15-item performance-based test of function included the performance of activities that might be impaired by action tremor (e.g., pouring, carrying a cup and saucer, signing one's name, inserting a key in a lock)(score range = 0–100 [maximally impaired]) [22].

A follow-up phase to the study is currently ongoing, with the follow-up evaluation including a core set of questionnaires and a videotaped tremor examination on ET cases.

Statistical analyses were carried out using SPSS (version 19; Chicago, Illinois). Patients were divided into five groups based on years of tremor duration (0 – 9, 10 – 19, 20 – 29, 30 – 39, 40 years). Parametric tests were used, including chi-square tests, analysis of variance, and Pearson's correlation coefficients. To test for trend, a linear regression analysis was performed in which the variable of interest (e.g., age, total tremor score) was the dependent variable and the tremor duration group was the independent variable.

Results

There were 335 ET patients (Table 1). The mean tremor duration was 23.9 ± 18.8 years, but ranged from 1 – 81 years (Table 1). There were five tremor duration groups (Tables 1, 2)

Age did not increase across the five tremor duration groups ($p = 0.52$, test for trend), and the groups were similar with respect to other demographic features (gender, race, education, Table 2). The cumulative illness rating scale scores were similar across groups (Table 2). As expected, tremor duration was longer and age of onset was younger in each successive

tremor duration group (Table 2). The proportion with a family history of ET or tremor increased across groups (Table 2).

Clinical metrics are presented for each 10-year tremor duration group (Table 2, Figure 1). Many of the metrics increased with each 10-year time interval; therefore, these metrics paint a picture of progressive decade-by-decade decline (Figure 1, Table 2). The results were similar after stratifying patients by source (i.e., Center for Parkinson's Disease vs. International Essential Tremor Foundation).

The group with the largest disease burden was the longest duration group (Table 2). Thus, the proportion who reported that their ET was embarrassing reached nearly three-quarters in the longest duration group (Figure 1, Table 2). The proportion with severe tremor while drawing a spiral, while drinking, or while using a spoon, rose to 20.3%, 33.8%, and 60.8%, respectively, in the longest duration group (Figure 1, Table 2). Tremor-related motor disability, performance-based test scores and total tremor scores also increased across groups (Table 2, all p values <0.006). With each passing decade, the proportion who complained of head tremor increased, reaching a maximum of 51.4% among patients with disease of 40 or more years (Figure 1, Table 2). The proportion with rest tremor on examination rose to 21.6% and the intention tremor score tripled across groups (Table 2). Nearly one-half had voice tremor by the fifth decade, and the cranial tremor score rose as well, such that one in three cases had cranial tremor in two or more locations (neck, voice, jaw) by the fifth decade (Table 2). The cranial tremor score exhibited a mild significant association with disease duration in years (Pearson's correlation coefficient = 0.14, $p = 0.01$).

In the longest tremor duration group, only 7/74 (9.5%) were unable to attempt to pour water with their dominant hand due to the presence of an extremely large amplitude tremor. Similarly, the proportions in that group who were unable to write, drink or use a spoon were all $<10\%$.

Interestingly, the proportion who were taking daily medication for tremor remained at approximately 50% in each tremor duration group, and the proportion who had stopped such prescribed medications remained similar; the proportion who had had tremor surgery gradually rose to 6.8% in the longest tremor duration group ($p = 0.03$, Figure 1, Table 2).

A follow-up phase to the study is currently ongoing; to date, 96 ET cases have been re-evaluated (mean baseline age = 70.3 ± 12.5 years) at a mean follow-up interval of 64.9 months (median = 61 months). Three (3.13%) of 96 ET (i.e., 0.63%/year) had developed new onset PD.

Discussion

ET is a chronic and generally progressive disorder, yet there are surprisingly few long-term studies, and the clinical and functional status of patients who are reaching each decade of disease duration (e.g., 10 years, 20 years, etc) has not been depicted in detail in the neurological literature.

We used cross-sectional data on 335 ET patients to produce clinical snapshots of the disease at each 10-year milestone (i.e., <10 , 10, 20, 30 and 40 years). These data show that the tendency was for many clinical metrics to worsen with time in ET. This included self-reported measures of tremor-related motor disability, performance-based measures of function, neurologist-assigned ratings of tremor severity, and increase in different types of tremor and locations of tremor. Among patients with tremor of 40 or more years duration, three-quarters reported embarrassment, one-half had voice tremor, one-third had cranial

tremor in at least two locations (neck, voice, jaw), nearly two-thirds had severe tremor (spilling) while using a spoon and one-fifth had severe tremor while drawing spirals.

On the one hand, many clinical metrics worsened with increasing duration, and in the longest tremor duration group, 9.5% were unable to attempt to handle liquid (pour water) with their dominant hand due to the presence of an extremely large amplitude tremor. Yet the converse of this is that even at this late stage, greater than 90% were able to perform this activity, albeit in a modified manner. Therefore, unlike PD and Huntington's disease, in which all patients with long duration disease end up at a functionally-incapacitating end-stage, all ET patients did not end up with diffuse body tremor and complete inability to function. That is, ET does not relentlessly progress in all cases to end-stage disease.

Rajput et al. [23] followed 20 ET patients for variable lengths of time; these patients came to autopsy over a 31 year period. Functional disability and psychological distress were common in this small clinical cohort. Elble et al.[24] measured wrist tremor and forearm using electromyography in 18 ET patients on two occasions separated by 4 to 8 years, noting a decrease in frequency over time. We are unaware of any other longitudinal data.

We reported that 6.8% of patients in the longest duration group had had tremor surgery, suggesting that fewer than one in ten ET patients reach this point and/or are willing to undergo surgery.

The proportion with familial ET increased across tremor duration groups. There are several possible explanations. First, age of onset decreased in these groups; younger age of onset cases are more likely to be familial [25]. Second, with longer disease duration in the proband, the cumulative incidence of ET is expected to increase in their family members [26].

Three ET cases (i.e., 0.63%/year [95% confidence interval = 0.01 – 0.09%/year] had developed new onset PD. None had had rest tremor or bradykinesia at baseline. Similarly, in a prior population-based study in Spain (mean baseline age 73 – 74 years), we reported that 6/201 ET patients developed PD during a 3.3 year median follow-up (0.90%/year)[27]. In that same study in Spain, only 24/3574 controls (0.21%/year) developed PD [27]. This is similar to the 0.1%/yr – 0.15%/yr that is reported for controls in epidemiological studies [28].

This study had limitations. First, the main data were cross-sectional rather than longitudinal; hence the tremor duration groups represent different individuals rather than a cohort of the same individuals who were sampled over time. Second, the group with tremor duration of 30 – 39 years had a sample size that was approximately one-half of the other groups, and some estimated proportions in this subgroup may have been unstable. This study had a number of strengths. First, the large sample size of more than 300 ET patients provided enough power for a broad range of analyses. Second, the sample included patients with a wide range in disease duration; in some instances this was >80 years, and in others, it was as short as 1 year. Third, the same set of scales was applied to all patients, in a uniform manner, and included a range of assessment tools including disability questionnaires, performance-based tests, and neurological examination items.

These data paint a picture of progressive decade-by-decade decline in ET. Yet patients with long disease duration did not relentlessly converge at the same end-stage of severe, functionally- incapacitating, diffuse tremor. Long-duration ET patients presented a heterogeneous picture in this regard.

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Figure 1. Clinical metrics are presented for each 10-year tremor duration group

Patients were divided into five groups based on decade of tremor duration: 0 – 9 years, 10 – 19 years, 20 – 29 years, 30 – 39 years, 40 years. Writing = percentage of patients with severe tremor on examination (rating 3) while drawing a spiral in dominant hand. Drinking = percentage of patients with severe tremor on examination (rating = 3) while drinking with the dominant hand. Using spoon = percentage of patients with severe tremor on examination (rating = 3) while using a spoon with the dominant hand. Head shakes, embarrassment, ET medication, ET surgery = percentage of patients who report head tremor, embarrassment, the use of daily ET medication, or ET surgery, respectively.

Table 1**Demographic and Clinical Characteristics of 335 ET Patients**

Age (years)	68.4 ± 14.5, 18 – 95
Female gender	175 (52.2)
White race	316 (94.3)
Education (years)	14.9 ± 3.9
Currently takes medication to treat ET	174 (51.9)
Age of tremor onset (years)	44.5 ± 22.7
Tremor duration (years)	23.9 ± 18.8, 1 – 81
Tremor duration group	
0 – 9 years	N = 96
10 – 19 years	N = 69
20 – 29 years	N = 62
30 – 39 years	N = 34
40 years	N = 74
Total tremor score on neurological examination	19.6 ± 6.9

All values are mean ± standard deviation, range or number (%), unless otherwise specified.

Table 2
Demographic and Clinical Characteristics of Patients by Tremor Duration Group

	Tremor Duration = 0–9 years	Tremor Duration = 10–19 years	Tremor Duration = 20–29 years	Tremor Duration = 30–39 years	Tremor Duration = 40 years	Significance
N	96	69	62	34	74	
Age (years)	70.0 ± 13.3, 18 – 95	66.1 ± 17.0, 22 – 90	65.4 ± 18.1, 27 – 91	67.5 ± 12.2, 36 – 84	71.4 ± 9.8, 48 – 89	0.06 <i>a</i> 0.52 <i>b</i>
Female gender	52 (54.2)	345 (49.3)	29 (46.8)	20 (58.8)	40 (54.1)	0.77 <i>c</i>
White race	88 (91.7)	66 (95.7)	59 (95.2)	31 (91.2)	72 (97.3)	0.49 <i>c</i>
Education	14.8 ± 4.0	15.5 ± 3.5	14.1 ± 3.6	14.9 ± 3.7	15.2 ± 4.3	0.33 <i>a</i>
Cumulative Illness Rating Scale Score	5.4 ± 3.5	5.4 ± 3.5	5.95 ± 4.5	5.5 ± 3.5	5.8 ± 3.3	0.82 <i>a</i> 0.38 <i>b</i>
Duration of tremor (years)	5.1 ± 2.3, 1 – 9	13.6 ± 2.9, 10 – 19	23.9 ± 3.1, 20 – 29	32.8 ± 2.7, 30 – 39	53.8 ± 9.4, 40 – 81	<0.001 <i>a</i> <0.001 <i>b</i>
Age of tremor onset (years)	64.9 ± 13.8, 11 – 90	52.6 ± 17.4, 6 – 80	41.5 ± 18.3, 5 – 70	34.7 ± 11.8, 6 – 53	17.7 ± 9.4, 3 – 45	<0.001 <i>a</i> <0.001 <i>b</i>
Family history of ET or tremor	19 (19.8)	23 (33.3)	24 (38.7)	8 (23.5)	33 (44.6)	0.006 <i>c</i>
Currently takes daily medication to treat ET	45 (46.9)	38 (55.1)	37 (59.7)	14 (41.2)	40 (54.1)	0.35 <i>c</i>
Had been prescribed ET medication but had stopped it	23 (24.0)	14 (20.3)	15 (24.2)	11 (32.4)	20 (27.0)	0.73 <i>c</i>
Had surgery for ET	0 (0.0)	0 (0.0)	4 (4.8)	2 (5.9)	5 (6.8)	0.03 <i>c</i>
Complaints of head tremor	25 (26.0)	27 (39.1)	22 (35.5)	14 (41.2)	38 (51.4)	0.019 <i>c</i>
Tremor is embarrassing	45 (46.9)	41 (59.4)	41 (66.1)	16 (47.1)	53 (71.6)	0.008 <i>c</i>

	Tremor Duration = 0–9 years	Tremor Duration = 10–19 years	Tremor Duration = 20–29 years	Tremor Duration = 30–39 years	Tremor Duration = 40 years	Significance
Severe tremor (spilling) on examination while drinking with dominant hand	8 (8.3)	10 (14.5)	14 (22.6)	10 (29.4)	25 (33.8)	<0.001 ^c
Severe tremor (spilling) on examination while using a spoon with dominant hand	28 (29.2)	21 (30.4)	28 (45.2)	15 (44.1)	45 (60.8)	<0.001 ^c
Severe tremor in dominant hand while drawing spiral	7 (7.3)	5 (7.2)	6 (9.7)	3 (8.8)	15 (20.3)	0.05 ^c
Tremor-related motor disability score	45.6 ± 31.7	49.6 ± 29.8	58.2 ± 25.7	57.8 ± 27.5	60.6 ± 27.5	0.005 ^a <0.001 ^b
Performance-based test of function [*]	27.6 ± 17.2	32.2 ± 24.2	32.2 ± 19.2	35.9 ± 23.7	39.9 ± 23.0	0.09 ^a 0.006 ^b
Total tremor score on neurological examination	16.8 ± 6.2	18.6 ± 6.5	20.8 ± 6.0	21.1 ± 7.3	22.5 ± 7.3	<0.001 ^a <0.001 ^b
Rest tremor on neurological examination	13 (13.5)	10 (14.5)	7 (11.3)	7 (20.6)	16 (21.6)	0.42 ^c
Intention tremor score [*]	0.38 ± 0.57	0.46 ± 0.56	0.93 ± 0.67	0.71 ± 0.75	0.95 ± 0.78	0.003 ^a <0.001 ^b
Voice tremor on neurological examination	30 (31.3)	21 (30.4)	19 (30.6)	7 (20.6)	36 (48.6)	0.028 ^c
Neck tremor on examination	39 (40.6)	26 (37.7)	24 (38.7)	17 (50.0)	34 (45.9)	0.69 ^c
Cranial tremor score						0.29 ^a 0.049 ^b
0	40 (41.7)	30 (44.8)	39 (49.2)	14 (41.2)	25 (34.2)	
1	36 (37.5)	27 (40.3)	16 (26.2)	13 (38.2)	23 (31.5)	
2	18 (18.8)	6 (9.0)	19 (16.4)	5 (14.7)	19 (26.0)	
3	2 (2.1)	4 (6.0)	5 (8.2)	2 (5.9)	6 (8.2)	

All values are mean ± standard deviation, range or number (%), unless otherwise specified.

^a Analysis of variance.

^b test for trend (linear regression analysis).

^c chi-square test.

* n < 200 because test was added after study was initiated.