Published in final edited form as:

Neuroepidemiology. 2018 ; 50(1-2): 41–46. doi:10.1159/000486485.

Comparative Burden of Subclinical Tremor in a Cohort of Normal Individuals Stratified by Familial Risk for Essential Tremor

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Abstract

Background—The burden of mild (i.e., subclinical) tremor within essential tremor (ET) families is not fully understood. We assessed the burden of mild tremor in a cohort of 287 adults, none of whom reported tremor or had been diagnosed with ET.

Methods—We recruited adults in two groups based on familial risk for ET: 244 high-risk individuals (i.e., reporting one or more first-degree relative with ET) and 43 low-risk individuals (i.e., reporting no relatives with ET). Tremor was objectively assessed on four hand-drawn spirals (total spiral score = 0 – 12). Mild tremor was defined using three different cut points.

Results—The prevalence of mild tremor among high-risk individuals ranged from 41.4% to 98.4% and was highly dependent on the cut point. Above a certain threshold (i.e., a total spiral score ≥ 5), one-in-five (i.e., 19.7%) high-risk individuals exhibited mild tremor whereas no low-risk individuals did. High-risk individuals were 3.09 – 4.50 times more likely than low-risk individuals to exhibit mild tremor.

Conclusion—The burden of ET extends beyond the boundaries of the clinically-defined disease, and partially expressed forms of ET are abundant in ET families. This fact greatly complicates gene-finding studies and epidemiological studies whose goal is to detect disease-linked associations.

Keywords

Essential tremor; epidemiology; genetics; risk; penetrance; subclinical

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None of the authors has any conflicts of interest.

Introduction

Essential tremor (ET) is one of the most prevalent neurological disease [1-4]. The condition is often familial [5,6]. First-degree relatives of ET cases are five times more likely to develop ET than are members of the population [7]. Nonetheless, not all members of a family present in the same way; phenotypic expression of tremor varies considerably within families [5,8,9]. For example, some family members exhibit head tremor whereas others do not [8], and while some family members have *bona fide* ET others exhibit only mild (i.e., subclinical) tremor [10]. A current gap in knowledge is that we do not fully understand the burden of mild (i.e., subclinical) tremor within ET families. We know that within ET families are individuals who have tremor that is severe enough to qualify for a diagnosis of ET, but to what extent these families also include *forme frustes* of ET (i.e., mild tremor) is not known.

In this study, we assessed the prevalence of mild tremor in a large cohort of adults, none of whom reported tremor or had been diagnosed with ET. We stratified these individuals by familial risk for ET - some were high-risk because they were first-degree relatives of ET cases and the others were low-risk because they were not. Our four goals were to: (1) assess the prevalence of mild tremor among high-risk individuals, (2) compare the odds of mild tremor in high-risk vs. low risk individuals, (3) determine whether a greater odds pertained to certain characteristics of the tremor [11] in addition to its presence, and (4) determine whether the odds of mild tremor was greatest in high-risk individuals with a particularly strong family history of ET (i.e., individuals in families with a high genetic load).

Methods

Study Design

First-degree relatives of ET cases and the spouses of these first-degree relatives were screened for enrollment in an environmental epidemiological study of ET (May 2016 – present) [12].

ET cases had been ascertained from study advertisements to the membership of the International Essential Tremor Foundation, membership in current ET research studies at Yale University, and the clinical practice of the Yale Movement Disorders Group [12]. The goal of the study was to enroll only unaffected first-degree relatives of ET cases and their spouses.

The screening process for reportedly unaffected relatives was as follows. First, ET cases informed the investigator of all reportedly unaffected living first-degree relatives age ≥ 40. With permission, these family members were contacted by telephone. During this telephone call, they were consented (using a protocol approved by the Yale University Institutional Review Board) and interviewed. During the interview, a 12-item tremor screening questionnaire [13] was administered and they were asked about a prior diagnosis of ET. They also completed and mailed four hand-drawn spirals (two right, two left), which were rated by a senior movement disorder neurologist (E.D.L.) using the following scale: 0, 0.5, 1, 1.5, 2, 3 (see definitions and examples in Louis et al) [14]. Each of the four ratings

resulted in a 0 – 3 score (i.e., spiral score R1, spiral score R2, spiral score L1, spiral score L2) and a total spiral score (i.e., the arithmetic sum of the four scores, range = 0 - 12). We previously reported that on spiral drawing, the wave forms of ET cases often align along a single predominant axis rather than several axes [11,15]. Therefore, each of the four spirals was assessed for the presence of a single identifiable tremor orientation axis, and a spiral axis score (range = 0 - 4) [4 = a single axis on all 4 spirals] was assigned to each individual [11].

During the telephone call, information was collected on medications, and caffeine and cigarettes use on the day the spirals were drawn. The number of reportedly affected first-degree relatives was defined as the genetic load.

Relatives were initially categorized as unaffected if they met each of the following criteria: (1) they did not report tremor during the 12-item telephone-administered tremor screening questionnaire [13], (2) they had never been assigned an ET diagnosis by a treating physician, and (3) their two right and two left-hand-drawn screening spirals were assigned tremor scores <2.0. They were included in these analyses if they were categorized as unaffected.

As a comparison, the spouses of these unaffected first-degree relatives were also screened, if available. Each then underwent the same screening process as described above and they were included in these analyses if they were categorized as unaffected and if they reported no family history of ET.

Final Sample

Of 292 individuals screened, 287 were included in this analysis. The remaining 5 (all high-risk) had spiral ratings ≥ 2 and were excluded for this reason.

Statistical Analyses

For continuous variables, normality was assessed (Kolmogorov Smirnov test); when the distribution was not normal ($p < 0.05$), non-parametric tests were used (e.g., Mann-Whitney test, Spearman's r). We first compared high-risk to low-risk individuals in terms of demographic and clinical features (Table 1) using Mann Whitney tests, chi-square tests and Fisher's exact tests. Spiral score data were ordinal rather than continuous; hence, we used Mann Whitney tests and Spearman's r when assessing these variables.

We compared high-risk to low-risk individuals in terms of the proportion with mild tremor. Since there is no precedent for defining "mild tremor", for the purposes of these analyses we used three progressively more stringent cut points based on the scores >0 , 0.5 and 1: (1) the presence of any tremor (i.e., total spiral score >0), (2) the presence, on average, of tremor ratings of 0.5 or higher (i.e., total spiral score ≥ 2), (3) the presence, on average, of tremor ratings of 1 or higher (i.e., total spiral score ≥ 4).

We estimated the odds of mild tremor, comparing high-risk to low-risk individuals, using each of the above-mentioned definitions and report odds ratios (OR) and 95% confidence intervals (95% CI). To determine whether the odds of mild tremor was greatest in high-risk individuals who had a particularly strong family history of ET (i.e., a high genetic load), we

stratified the high-risk individuals into those with ≥ 2 affected relatives vs. those with only one affected relative, and then compared the proportion with mild tremor according to our three definitions (chi-square tests). Finally, we determined whether the number of cigarettes or cups of coffee on the day the spirals were drawn, or number of prescription medications could have influenced the total spiral score (Spearman's r).

Results

There were 287 individuals (244 high-risk individuals, 43 low-risk individuals) who belonged to 230 and 43 families, respectively. Fourteen high-risk individuals were from the same 7 families. Hence, in large measure, individuals were not from the same families.

High-risk and low-risk individuals were similar in age and most other demographic factors; however, they differed by gender (Table 1). As expected, the genetic load was higher in the high-risk group (Table 1). Each of the four spiral scores as well as the total spiral score was greater in high-risk than low-risk individuals (all $p < 0.002$, Table 1).

The mean of each of the four spiral scores indicated that, when present, tremor was mild (i.e., on average a rating < 1 , Table 1). Indeed, there were 1,148 spiral ratings (i.e., $287 \text{ individuals} \times 4 \text{ spiral ratings each}$), all of which received ratings < 2 .

We defined "mild tremor" using three different cut points. First, we defined it as the presence of any tremor (i.e., total spiral score > 0). The total spiral score was > 0 in 240 (98.4%) of 244 high-risk individuals and 40 (93.0%) of 43 low-risk individuals (Fisher's exact test $p = 0.071$, Table 2). Second, we defined mild tremor as the presence, on average, of tremor ratings of 0.5 or higher (i.e., total spiral score ≥ 2); this was present in 223 (91.4%) high-risk individuals and 32 (74.4%) low-risk individuals (Fisher's exact test $p = 0.003$, Table 2). Third, we defined mild tremor as the presence, on average, of tremor ratings of 1 or higher (i.e., total spiral score ≥ 4); this was present in 101 (41.4%) high-risk individuals and 8 (18.6%) low-risk individuals (chi-square = 8.06, $p = 0.005$, Table 2). Of note was that 48 (19.7%) high-risk individuals and 0 (0.0%) low-risk individuals had a total spiral score that was ≥ 5 (chi-square = 10.16, $p = 0.001$, Table 2).

When we compared high-risk to low-risk individuals, the odds of mild tremor was as follows: OR = 4.50, 95% CI = 0.97 – 20.86, $p = 0.055$ (definition 1), OR = 3.65, 95% CI = 1.61 – 8.27, $p = 0.002$ (definition 2), and OR = 3.09, 95% CI = 1.38 – 6.94, $p = 0.006$ (definition 3). Including current age or gender in these models did not change the results (data not shown).

On average, the spiral axis score was six-times higher in high-risk than low-risk individuals (Table 1, $p = 0.002$). A spiral axis score of 1 or higher was found in 30.8% of high-risk individuals vs. 9.3% of low-risk individuals (chi-square = 8.47, $p = 0.004$, Table 3). A spiral axis score of 2 or higher was found in 18.3% of high-risk individuals vs. 0.0% of low-risk individuals (chi-square = 9.34, $p = 0.002$, Table 3).

To determine whether the odds of mild tremor was greatest in high-risk individuals who had a particularly strong family history of ET (i.e., a high genetic load), we stratified high-risk

individuals into those with two or more affected relatives vs. those with one affected relative, and compared the proportion with mild tremor according to our three definitions. For definition 3, 42 (50.6%) individuals with two or more affected relatives vs. 56 (36.1%) individuals with one affected relative had mild tremor (chi-square = 4.68, $p = 0.03$). For the other definitions, these values were 97.6% vs. 98.7% (definition 1) (chi-square = 0.41, $p = 0.52$) and 94.0% vs. 89.7% (definition 2) (chi-square = 1.24, $p = 0.27$).

Cigarettes smoked or intake of coffee on the day the spirals were drawn did not influence the total spiral score (Spearman's $r = -0.04$, $p = 0.57$ [for cigarettes and total spiral score] and Spearman's $r = 0.002$, $p = 0.97$ [for coffee and total spiral score]). There was no correlation between the number of prescription medications and the total spiral score (Spearman's $r = 0.09$, $p = 0.15$). Similarly, high-risk and low-risk individuals did not differ with respect to cigarettes smoked on the day the spirals were drawn, coffee intake on that same day, or number of prescription medications (respective p values = 0.50, 0.56 and 0.80 in Mann Whitney tests).

Discussion

We assessed the burden of tremor in a large cohort of approximately 300 adults, none of whom self-reported tremor on a screening questionnaire or had been diagnosed with ET. On examination of hand-drawn spirals, the amount of tremor was less than that which is present in patients with ET [16].

We stratified these individuals by familial risk for ET (i.e., high-risk individuals had a first-degree relative with ET and low-risk individuals had no family history of ET). The goal of these analyses was to address a gap in knowledge; at present, we do not fully understand the burden of mild (i.e., subclinical) tremor within ET families. We found that the prevalence of mild tremor in ET families was dependent upon the definition of mild tremor, and ranged from 41.4% to 98.4%. Regardless of the definition, more high-risk individuals than low-risk individuals exhibited tremor. Above a certain threshold (i.e., a total spiral score ≥ 5), one-in-five (i.e., 19.7%) high-risk individuals had mild tremor whereas no low-risk individuals did. Aside from confirming the high burden of mild tremor within ET families, these data begin to identify a certain threshold of tremor that is not likely to be normal and which is more likely than not to be a *forme fruste* of ET.

When comparing high-risk to low-risk individuals, the odds of mild tremor depended somewhat on the definition of mild tremor. Nonetheless, across these definitions, the ORs were fairly constant at 3.09 – 4.50. It is interesting that these odds are quite similar to the increased risk of ET in first-degree relatives of ET cases vs. first-degree relatives of controls, namely, 4.67 [7]. This suggests that the two values are measuring the same entity, that is, the burden of ET in ET families (in the previously published study, full-fledged ET and in the current analyses, a *forme fruste* of ET). The implication is that these fragments of ET we are now observing should in some way be aligned with ET in family studies of ET. This observation confounds the results of gene-finding studies.

We previously reported that on spiral drawing, the wave forms of ET cases generally aligned along a single predominant axis rather than several axes [11,15]. In the current study, we observed that greater tremor burden in high risk individuals extended beyond the mere presence of tremor and also included a greater burden of typical characteristics of ET tremor [11]. Thus, on average, spiral axis score was nearly six-times higher in high-risk than low-risk individuals, and spiral axis scores of 1 and 2 were significantly higher in high-risk than low-risk individuals.

To determine whether the odds of mild tremor was greatest in high-risk individuals who had a particularly strong family history of ET (i.e., a high genetic load), we stratified high-risk individuals into those with two or more affected relatives vs. one affected relative, and compared the proportion with mild tremor according to our three definitions. Overall, the differences were not significant.

We previously conducted studies with different designs assessing mild tremor in ET families. ET cases and controls were enrolled in a family study [10]. Their first- and second-degree relatives underwent a videotaped tremor examination. Data were analyzed on 201 case relatives and 212 control relatives who did not meet diagnostic criteria for ET [10]. The mean total tremor score of first-degree case relatives was higher than that of first-degree control relatives ($p < 0.003$) and a larger percentage (55.2% vs 36.6%; $p = 0.01$) of first-degree case relatives had total tremor scores of 4 or more [10]. That study differed from the present study because we did not attempt to estimate the increased odds of mild tremor in relatives of ET cases. Also, we did not assess the role of genetic load as we did in the current study. In another study, we noted that controls who reported a family history of ET had more tremor than controls who did not report a family history of ET ($p < 0.05$ in several analyses) [17]. That study differed from the present because we only sampled controls.

The goal of the study was to enroll only unaffected first-degree relatives of ET cases and their spouses. Relatives were initially categorized as unaffected if they met each of three criteria. Thus, by history, they did not report tremor during the 12-item telephone-administered tremor screening questionnaire and had never been assigned an ET diagnosis by a treating physician. Objectively, their two right and two left-hand-drawn screening spirals were assigned tremor scores < 2.0 . One issue is whether some of these individuals might still have had mild ET. As these individuals did not undergo a detailed neurological examination, we acknowledge this as a possibility. However, in a prior study of 429 reportedly unaffected individuals who similarly had spiral ratings < 2.0 in both arms, all 429 also underwent detailed neurological examinations and none (0.0%) were diagnosed with ET [18]. Hence, it is highly likely that few of our unaffecteds would have met criteria for ET.

This study should be interpreted within the context of certain limitations. The sample size for low-risk individuals was small. Despite this, we detected a number of significant associations. Nonetheless, future studies with expanded samples would be valuable. In addition, computerized tremor analysis was not performed to assist with the evaluation and documentation of the extent of enhanced physiological tremor in our study sample.

In summary, we show here that the burden of ET extends beyond the boundaries of the clinically-defined disease, and partially expressed forms of ET are abundant in ET families. This fact greatly complicates gene-finding studies as well as clinical and epidemiological studies whose goal it is to detect disease-linked associations in ET families.

Acknowledgments

Funding:

This study was supported by the National Institutes of Health, R01 NS094607.

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Table 1

Demographic and clinical features of 244 high-risk vs. 43 low-risk individuals

	High-risk individuals n = 244	Low-risk individuals n = 43	Significance
Current age in years	59.3 ± 10.1 [58] Range = 39 – 89	58.3 ± 10.4 [60] Range = 40 – 86	0.78 ^a
Female gender	174 (71.3)	14 (32.6)	<0.001 ^b
Education in years	16.6 ± 2.6 [16.0]	16.7 ± 2.6 [16.0]	0.97 ^a
White race	234 (95.9)	42 (97.7)	1.00 ^c
English language	239 (98.0)	41 (95.3)	0.28 ^c
Current cigarette smoker	5 (2.0)	0 (0.0)	1.00 ^c
Genetic load ¹	1.5 ± 0.9 [1.0]	0.0 ± 0.0 [0.0]	<0.001 ^a
Spiral score R1	0.73 ± 0.38 [0.50]	0.52 ± 0.31 [0.50]	0.001 ^a
Spiral score R2	0.71 ± 0.40 [0.50]	0.51 ± 0.35 [0.50]	0.002 ^a
Spiral score L1	0.93 ± 0.42 [1.00]	0.70 ± 0.35 [0.50]	0.001 ^a
Spiral score L2	0.96 ± 0.43 [1.00]	0.69 ± 0.38 [0.50]	<0.001 ^a
Total spiral score ²	3.33 ± 1.41 [3.00]	2.42 ± 1.18 [2.00]	<0.001 ^a
Spiral axis score ³	0.57 ± 0.98 [0.00]	0.09 ± 0.29 [0.00]	0.002 ^a

Values are mean ± standard deviation [median] or number (percent).

^aMann Whitney test.

^bChi-square test.

^cFisher's exact test.

¹The genetic load was the number of reported affected relatives.

²The total spiral score was the arithmetic sum of spiral score R1 + spiral score R2 + spiral score L1 + spiral score L2. The potential range was 0 – 12.

³On spiral drawing, the wave forms of ET cases generally align along a single predominant axis rather than several axes. Therefore, each of the four spirals was assessed for the presence of a single identifiable tremor orientation axis, and a spiral axis score (range = 0-4) [4= a single axis on all 4 spirals] was assigned to each individual.

Table 2

Total spiral scores of 244 high-risk vs. 43 low-risk individuals

Total spiral score ^I	High-risk individuals n = 244	Low-risk individuals n = 43
0	4 (1.6)	3 (7.0)
0.5	6 (2.5)	0 (0.0)
1.0	4 (1.6)	3 (7.0)
1.5	7 (2.9)	5 (11.6)
2	51 (20.9)	12 (27.9)
2.5	13 (5.3)	2 (4.7)
3	38 (15.6)	6 (14.0)
3.5	20 (8.2)	4 (9.3)
4	39 (16.0)	7 (16.3)
4.5	14 (5.7)	1 (2.3)
5	23 (9.4)	0 (0.0)
5.5	15 (6.1)	0 (0.0)
6	10 (4.1)	0 (0.0)
>6	0 (0.0)	0 (0.0)

Values are number (percent).

^IThe total spiral score was the arithmetic sum of spiral score R1 + spiral score R2 + spiral score L1 + spiral score L2. The potential range was 0 – 12.

Table 3

Spiral axis scores of high-risk vs. low-risk individuals

Spiral axis score ¹	High-risk individuals	Low-risk individuals
0	166 (69.2)	39 (90.7)
1	30 (12.5)	4 (9.3)
2	29 (12.1)	0 (0.0)
3	11 (4.6)	0 (0.0)
4	4 (1.7)	0 (0.0)

Values are number (percent). Values are missing in 4 high-risk individuals.

¹ On spiral drawing, the wave forms of ET cases generally align along a single predominant axis rather than several axes. Therefore, each of the four spirals was assessed for the presence of a single identifiable tremor orientation axis, and a spiral axis score (range = 0-4) [4= a single axis on all 4 spirals] was assigned to each individual.