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Does Rate of Progression Run in Essential Tremor Families? Slower vs. Faster Progressors

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Abstract

Background—Essential tremor (ET) is a progressive disorder, worsening gradually with time in most patients. Yet there are few data on the factors that influence rate of progression. ET is a highly familial disorder, and physicians often care for patients who have other affected family members. Do ET families differ from one another with respect to rate of progression? Are some families slower progressors and other families faster progressors? We are unaware of published data.

Methods—ET probands and relatives were enrolled in a cross-sectional genetic study at Columbia University. Rate of progression was calculated as total tremor score ÷ log disease duration.

Results—There were 100 enrollees (28 probands, 72 relatives). Data from 78 enrollees (23 probands, 55 relatives) were selected for final analysis. The mean familial rate of progression ranged from as little as 8.4 to as much as 34.3, a >4-fold difference. In an analysis of variance, we found significant evidence of heterogeneity in the log rate of progression across families (p

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<0.001), with more than one-half (i.e., 55.4%) of the total variance in the log rate of progression explained by the family grouping.

Conclusions—Familial factors seem to affect rate of tremor progression in ET. There was a 4-fold difference across families in observed mean rate of progression; thus, some families seemed to be more rapid progressors than others. We hope these data may be used by clinicians to provide basic prognostic and family guidance information to their patients and families with ET.

Keywords

essential tremor; genetics; familial; clinical; rate of progression

Introduction

Essential tremor (ET) is a progressive disorder, worsening gradually over time in most patients [1]. Despite previous attempts to identify factors that influence rate of progression [2,3], there are few published data.

ET is generally considered to be a highly familial disorder [4]. Treating physicians often care for patients who have multiple affected family members (e.g., siblings) as well as other at risk family members (esp., children and grandchildren). Surprisingly, it is not known whether the basic clinical features of the ET in one family member can be used to predict the course the disease will take in other family members. More specifically, the extent to which rate of progression runs in ET families is not known: are some families slower progressors and some families faster progressors? There are no published data to guide treating clinicians.

ET cases (probands) and their relatives were enrolled in a genetic study of ET at Columbia University Medical Center (CUMC); 100 subjects have been enrolled to date. We asked whether families differed with respect to rate of progression and whether some families were slower progressors and other families faster progressors. We hope these data will be useful to clinicians in providing a basic prognostic framework and family guidance information to their patients and families with ET.

Methods

Ascertainment of Probands

ET cases (probands) and their reportedly affected first- and second-degree relatives were enrolled in a genetic study of ET, the Family Study of Essential Tremor (FASET) at CUMC. The study was cross-sectional, and was advertised on two ET society websites. The three initial inclusion criteria for probands were: (1) a diagnosis of ET had been assigned by a doctor, (2) age of tremor onset ≥ 40 years (later changed to ≥ 50 to be more inclusive), (3) ≥ 2 living relatives in the United States who have ET that was diagnosed by a doctor; these relatives were not reported to have dystonia or Parkinson's disease (PD). The exclusion criterion for probands was a prior diagnosis of dystonia or PD. Potential ET probands contacted the FASET study coordinator. Prior to final selection for enrollment, a set of four Archimedes spirals (two right, two left) were submitted by probands, and rated by a senior neurologist specializing in movement disorders (E.D.L.). Probands were included if one or more of the spirals had a Washington Heights Inwood Genetic Study of Essential Tremor rating of 2 (moderate tremor) or higher [5].

Ascertainment of Relatives

Based upon a telephone interview with the proband, relatives with ET were identified. With the proband's permission, these relatives were then contacted by telephone, and were pre-enrolled if they reported the presence of tremor in the absence of a prior diagnosis of dystonia or PD. Prior to final selection for enrollment, four Archimedes spirals were submitted by relatives and rated. Relatives were included if one or more of the spirals had a rating ≥ 2 [5].

In-person Evaluation

An in-person evaluation was then conducted in the enrollees' homes; this included a series of questionnaires and a videotaped neurological examination, which included a detailed assessment of postural, kinetic, intention and rest tremors, as well as dystonia and other movement disorders [6]. Data on age of onset of tremor were collected; prior studies have shown that this is reliably reported [7]. A senior movement disorders neurologist reviewed all videotaped examinations, and the severity of postural and kinetic arm tremors were rated on 12 examination items using a reliable 0–3 rating scale [8], resulting in a total tremor score (range = 0–36 [maximum]) [6]. The study was approved by the CUMC Institutional Review Board and all participants signed written informed consent.

Diagnoses

All ET diagnoses were reconfirmed based on review of questionnaires and videotaped neurological examination data. Diagnoses of ET were assigned based on published diagnostic criteria (moderate or greater amplitude kinetic tremor during three or more activities or a head tremor in the absence of PD or another known cause) [5,8].

Statistical Analyses

Analyses were performed in SPSS (Version 19.0). Duration of disease was the current age – age of onset. In prior publications, rate of progression was calculated as the total tremor score $\div$ duration of disease [2,9,10]. To diminish the effect of the wide range of reported durations (2–90 years), we log-transformed duration of disease; hence, rate of progression was total tremor score $\div$ log (duration of disease). Rate of progression was not normally distributed (Kolmogorov-Smirnov $z = 1.71$, $p = 0.006$); the log-transformed variable (log rate of progression) was normally distributed (Kolmogorov-Smirnov $z = 0.99$, $p = 0.28$). In an analysis of variance, we tested for heterogeneity across families in log rate of progression.

Results

There were 100 enrollees, including 28 probands and 72 relatives (58 first-degree, 11 second-degree, and 3 third-degree) (Table 1). We excluded 10 enrollees who did not recall their age of onset, one with incomplete data, three others because they were probands with no enrolled family members, 4 with dystonia rather than ET, and 4 who were normal. The final sample comprised 78 enrollees (23 probands and 55 relatives); these were similar to the base sample of 100 (Table 1).

In the 78 enrollees, the mean $\pm$ SD rate of progression was 15.4 ± 6.5 (range = 5.4–43.2), median = 14.4 (Figure 1a). As expected, rate of progression was associated with total tremor score (Spearman's $r = 0.53$, $p < 0.001$) and disease duration (Spearman's $r = -0.41$, $p < 0.001$). Rate of progression was also associated with age of onset (Spearman's $r = 0.45$, $p < 0.001$), but not age at evaluation (Spearman's $r = 0.02$, $p = 0.88$). Rate of progression was not associated with gender ($p = 0.68$), white race ($p = 0.44$), daily use of ET medication ($p =$

0.92), presence vs. absence of head tremor ($p = 0.36$) or subject type (i.e., proband vs. relative, $p = 0.68$).

Each family's mean rate of progression is plotted (Figure 1b) as are individual data points within and across families (Figure 1a). The mean familial rate of progression ranged from as little as 8.4 (Family 1) to as much as 34.3 (Family 23, Figure 1b), a >4-fold difference.

In an analysis of variance, we found significant evidence of heterogeneity in the log rate of progression across families (ANOVA $F = 3.11$, $p < 0.001$), with more than one-half (i.e., 55.4%) of the total variance in the log rate of progression explained by the family grouping. Adjusting for age of onset, which was associated with rate of progression, did not change the results ($p < 0.001$). While rate of progression was not identical in different members of the same family, members of the same family seemed to follow a similar pattern (Figure 1a).

The use of ET medications could reduce observed tremor severity. To assess the impact of medication usage on our results, we excluded 33 participants who were taking ET medications. The results did not change: the mean familial rate of progression ranged from as little as 8.4 to as much as 34.3. As the diagnosis of ET in some individuals was based primarily on the presence of head tremor, which would not have been reflected in the total tremor scores, we also performed an analysis in which we excluded 22 individuals with head tremor. The results did not change: the mean familial rate of progression ranged from as little as 8.4 to as much as 34.3.

Because disease duration was the denominator in the index that was used to assess rate of progression, a very short duration could magnify the rate of progression. We therefore performed an analysis in which we excluded 12 cases with short disease duration (< 10 years). The results were similar: the mean familial rate of progression ranged from as little as 8.4 to as much as 29.8. We also performed an analysis in which we stratified the sample based on median age of onset (27.5 years) into two groups (younger vs. older age of onset). The results were similar in the two strata.

Discussion

In terms of rate of progression in ET, family matters. In this family study of ET, there was a 4-fold difference across families in observed mean rate of progression; some ET families seemed to be more rapid progressors than others. Family membership explained more than one-half of the total variance in the rate of progression. Furthermore, while rate of progression was not identical in different members of the same family, family members seemed to follow a similar pattern.

Thus, at least in the context of familial ET, family membership seems to be an important contributor/predictor of rate of progression. There are few other data on factors that contribute to rate of progression in ET. We have previously demonstrated in both a community-based and clinic-based sample of ET cases that older age of onset was associated with faster rate of progression [2,10]. Here too, in the context of familial ET, we showed that the rate of progression was also associated with age of onset (Spearman's $r = 0.45$, $p < 0.001$). The faster rate of tremor progression in older onset ET is similar to that reported in patients with several neurodegenerative disorders. As discussed elsewhere [10], in PD patients, age at disease onset was the main predictor of motor decline, indicating a faster and less restricted pathologic disease process in patients with older onset PD. Postmortem studies in PD also support the notion that in advanced age, brain pathology advances more rapidly. Similar findings have been reported in patients with multiple system atrophy and motor neuron disease [10]. In complex diseases, rate of progression is probably determined by both genetic and environmental factors. Good examples of this can be found

in the PD literature. For example, *parkin* mutation carriers have an earlier age of onset than other PD [11]. LRRK2-linked PD displays high variability in age at onset [12].

This study had limitations. We utilized data on reported age of onset. Prior studies have shown that these data are reliably reported [7], yet the validity of reported age of onset is not fully known. Second, rate of progression was assessed with a cross-sectional measure (tremor severity $\div$ log duration) rather than a longitudinal measure (change in tremor severity across two or more time points), and future studies could improve on our methods by using such an approach. Third, the mix of families that we studied may not be representative of all ET families, so that studies with larger sample sizes would be valuable. Finally, the study did not attempt to assess specific patterns in the disease progression (e.g., the hand tremor followed by head tremor vs. the converse).

With these new data, what can we counsel ET patients? First, we can identify some factors that influence rate of tremor progression. More specifically, familial factors do seem to affect rate of tremor progression. Thus, ET families differ with regards to rate of tremor progression; some families are slower progressors and some families are faster progressors. Indeed, we observed a four-fold difference in rate of tremor progression across families. Second, while rate of progression is not identical in different members of the same family, family members seem to follow a similar pattern. Future study of these familial factors and how they may translate into biologically-meaningful factors of mechanistic importance would be important.

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Figure 1.

Figure 1a. Rate of progression by family number. Each family was assigned a unique family number (1, 2, 3, 4...n) based on increasing value of rate of progression. Thus, the family with the smallest value (i.e., slowest rate of progression) was assigned the family number of 1. Each data point represents one individual. Vertical grid lines run through the data points in each family. Rate of progression was calculated as the total tremor score $\div$ log (duration of disease).

Figure 1b. Rate of progression by family number. Each family was assigned a unique family number (1, 2, 3, 4...n) based on increasing value of rate of progression. Thus, the family with the smallest value (i.e., slowest rate of progression) was assigned the family number of 1. Circles represent the mean (all family members within than family) and bars represent ± 1 standard error. Rate of progression was calculated as the total tremor score $\div$ log (duration of disease).

Table 1

Demographic and Clinical Characteristics of Enrollees

	All Enrollees (N = 100)	Enrollees in Final Sample (N = 78)
Age (years)	59.0 ± 17.4, 19–95	59.2 ± 17.6, 19–95
Female Gender	55 (55.0)	41 (52.6)
White Race	88 (88.0)	68 (87.2)
Ashkenazi Jewish Ancestry	12 (12.0)	10 (12.8)
Relationship to Proband		
Self	28 (28.0)	23 (29.5)
Child	27 (27.0)	20 (25.6)
Sibling	24 (24.0)	17 (21.8)
Parent	7 (7.0)	7 (9.0)
Grandchild	1 (1.0)	1 (1.3)
Aunt/Uncle	3 (3.0)	3 (3.8)
Nephew/Niece	7 (7.0)	5 (6.4)
Other (Third-degree)	3 (3.0)	2 (2.6)
Total tremor score on neurological examination	17.6 ± 6.5	19.4 ± 5.5
Voice tremor on neurological examination	16 (16.0)	16 (20.5)
Head (neck) tremor on neurological examination	24 (24.0)	22 (28.2)
Currently takes daily medication for ET	39 (39.0)	33 (42.3)
Age of tremor onset (years), median	28.1 ± 18.3, 22	28.6 ± 18.3, 27.5
Duration of tremor (years), median	30.8 ± 19.4, 29.5	30.6 ± 19.3, 29

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