Familial Aggregation of Cranial Tremor in Familial Essential Tremor

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Abstract
Background: Essential tremor (ET) is often familial and phenotypic features may be shared within families. Cranial (neck, voice, and jaw) tremor is an important feature of ET. We examined whether cranial tremor aggregates in ET families, after controlling for other factors (age, tremor severity, and duration).

Methods: Among ET probands and relatives enrolled in a genetic study at Columbia University (95 subjects in 28 families), we assessed the degree to which occurrence of cranial tremor in the proband predicted occurrence of cranial tremor in affected relatives.

Results: Forty-five (47.4%) subjects had cranial tremor on neurological examination (probands 66.7%, relatives 39.7%). Among 28 families, 23 (82.1%) contained individuals with and individuals without cranial tremor, indicating a high degree of within-family heterogeneity. In comparison to subjects without cranial tremor, those with cranial tremor had higher total tremor scores (p < 0.001), were older (p = 0.003), and had tremor of longer duration (p = 0.01). In logistic regression models, the odds of cranial tremor in a relative were not related to occurrence of cranial tremor in the proband (p > 0.24).

Conclusions: Cranial tremor did not aggregate in families with ET; the major predictor of this disease feature was tremor severity rather than presence of cranial tremor in another family member.

Introduction

Cranial tremor, including neck, voice, and jaw tremor, is an important feature of essential tremor (ET). Following upper limb tremor, it stands out as the most common site of tremor in this disease [1–3]. It also has several important clinical correlates; for example, it has been found to be associated with greater gait and balance difficulty [4–6] and may be more resistant to treatment than other tremor types [7–9]. Head and jaw tremor are also visually quite apparent and of particular cosmetic concern for patients.

ET is often familial [10]. In the ongoing search for susceptibility genotypes [11], the study of its manifestations within families is currently an area of considerable research focus.

Until recently, the familial aggregation of the phenotypic features of ET has received little attention. We re-
recently found that age of onset and rate of progression aggregate in ET families [12, 13]. Despite the high prevalence of cranial tremor, there are no readily available data on the concordance for such tremor within ET patients and their families. This is an issue that has research as well as clinical ramifications. ET patients whose relatives (e.g. parents) have/had head tremor often ask whether they, too, are likely to develop a similar feature. Data to guide clinicians on how to answer this question are lacking.

In the current investigation, our goal was to study the familial aggregation of cranial tremor in families containing multiple individuals with ET, enrolled in a genetic study of ET at Columbia University Medical Center (CUMC) [14]. We also considered whether several other factors (age, tremor severity, and duration) predicted occurrence of cranial tremor. Our hypothesis was that the presence of cranial tremor in one or more family members would strongly predict the presence of such tremor in their relatives, after controlling for other factors. Given the higher prevalence of cranial tremor among women with ET [15], we also expected that female gender would predict presence of cranial tremor.

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 [14]. The study 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 was ≤40 years (this was later changed to ≤50 years to be more inclusive), and (3) ≥2 living relatives in the United States with ET also diagnosed by a doctor and who were not reported to have dystonia or Parkinson’s disease (PD). The exclusion criterion for probands was a prior diagnosis of dystonia or PD. The rationale for enrolling probands whose tremor onset was ≤40 years was to increase the likelihood of enrolling probands with underlying susceptibility genotypes of ET. ET patients with younger age of tremor onset often have the familial form of the disease. Indeed, we previously reported that a large proportion of the young-onset cases had the familial form of ET [16].

Potential ET probands contacted the FASET study coordinator. Prior to final selection for enrollment, a set of four Archimedean spirals (two right, two left) was 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 [17].

Ascertainment of Relatives
Based upon a telephone interview with the proband, relatives with ET were identified [14]. 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, relatives submitted four Archimedean spirals. These spirals were rated (E.D.L.), and relatives were included if one or more of the spirals had a rating ≥2 [17].

Evaluation
An in-person evaluation was then conducted in the enrollees’ homes; this included a series of questionnaires and a videotaped neurological examination [14]. Age of tremor onset was by self-report and was the age at which the individual first noted tremor. Prior studies have indicated that it is reliably reported by ET patients [18]. Tremor duration was the difference between current age and age of tremor onset. The videotaped neurological examination included a detailed assessment of postural, kinetic, intention, and rest tremors in the limbs, as well as dystonia and other movement disorders [19]. Voice tremor was assessed during sustained phona-
tion, conversational speech, and while reading a prepared passage. Neck (i.e. head) tremor was assessed while seated comfortably and facing the camera. Jaw tremor was assessed while the mouth was stationary (closed), while the patient was asked to hold their mouth slightly open, during sustained phonation, and during speech [3]. The neurologist (E.D.L.) reviewed all videotaped examinations and rated the severity of postural and kinetic arm tremors (0–3), resulting in a total tremor score [range 0–36 (maximum)] [19]. The study was approved by the CUMC Institutional Review Board and all participants gave written informed consent.

Diagnoses
All ET diagnoses were reconfirmed based on review of questionnaires and videotaped neurological examinations [14]. 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) [17, 20].

Final Sample
There were 145 enrollees (38 probands and 107 relatives). For the current analyses, we excluded 47 enrollees for the following reasons: 26 families did not contain ≥1 relatives with ET, 22 had dystonia (mainly torticollis), and 2 had incomplete data. Hence, the final sample consisted of 27 probands and 68 relatives (95 ET total). These 95 included 1 family (family 23) in which there were 4 relatives, but the proband had dystonia, so only the data on the 4 relatives are presented here. The final sample of 95 (table 1) was similar to the initial sample of 145 in terms of age (56.3 ± 18.5 vs. 58.5 ± 18.0 years, t = 0.92, p = 0.36), gender [49 (51.6%) vs. 86 (59.3%) female, μ = 1.39, p = 0.24], tremor duration (28.3 ± 18.9 vs. 29.6 ± 20.0 years, t = 0.50, p = 0.62), total tremor score (18.5 ± 6.3 vs. 17.5 ± 7.0, t = 1.13, p = 0.26), and proportion with cranial tremor [45 (47.4%) vs. 58 (50.0%), μ = 1.27, p = 0.26].

Statistical Analyses
Analyses were performed in SPSS (version 19.0). Subject characteristics were compared using Student’s t tests and χ2 tests. Correlations between continuous variables were assessed with Pearson’s correlation coefficients. Bivariate and then multivariate logistic regression models assessed the predictors of cranial tremor in relatives. We used these models to assess the predictors of cranial tremor in relatives, using the presence versus absence of cra-
nial tremor in the proband as a primary predictor of interest. Other predictors that we considered included relative’s age, total tremor score, tremor duration, and gender. Because of the non-independence of proband-relative pairs within each family, we used generalized estimating equations (GEEs) to compute odds ratios (ORs) and 95% confidence intervals (CIs).

**Results**

**Prevalence and Correlates of Cranial Tremor**

The 68 relatives included 28 (41.2%) children, 16 (23.5%) siblings, and 6 (8.8%) parents, with the remainder comprising other types of relatives (e.g. aunts/uncles).

Forty-five subjects (18 probands and 27 relatives) had cranial tremor on neurological examination (Table 1). Compared with the 50 subjects without cranial tremor, the 45 with cranial tremor had higher total tremor scores (20.9 ± 6.5 vs. 16.3 ± 5.3, t = 3.72, p < 0.001), were older (62.5 ± 18.2 vs. 50.7 ± 17.1 years, t = 3.25, p = 0.003), and had tremor of longer duration (33.3 ± 17.7 vs. 23.8 ± 18.9 years, t = 2.51, p = 0.01). Cranial tremor was more prevalent in women than men [20 (40.8%) vs. 11 (23.9%), χ² = 3.08, p = 0.079]. Total tremor score, age, and duration were collinear (all pairwise Pearson’s r > 0.51, p < 0.001). The association between total tremor score and presence of cranial tremor is shown by family; in most families, the individuals with cranial tremor were those with the highest tremor scores (fig. 1). Similar relationships were seen when age and duration were plotted by presence of cranial tremor within families (data not shown).

**Familial Aggregation of Cranial Tremor**

Twenty-three (82.1%) of 28 families included both individuals with and without cranial tremor, indicating a high degree of within-family heterogeneity. Three families (Nos. 20, 24, 28) were completely concordant for presence of cranial tremor (i.e. each family contained 2 affected family members both of whom had cranial tremor). Two families (Nos. 21 and 23) were concordant for absence of cranial tremor. Eighteen (66.7%) of 27 probands versus 27 (39.7%) of 68 relatives had cranial tremor (χ² = 5.63, p = 0.018). With regard to presence versus absence of cranial tremor, 25 (36.8%) relatives were discordant with their proband, 38 (55.9%) relatives were discordant with their proband, and 5 relatives (family 23) did not have a proband with ET.

<table>
<thead>
<tr>
<th>Table 1. Demographic and clinical characteristics of enrollees</th>
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<tr>
<td><strong>All enrollees (n = 95)</strong></td>
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<td>Currently takes medication to treat ET</td>
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<td>Age of tremor onset, years</td>
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<td>Duration of tremor, years</td>
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All values are means ± standard deviation, range or number (%), unless otherwise specified.
Predictors of Cranial Tremor in Relatives: Regression Modeling

Presence of cranial tremor in the relative (outcome variable) was associated with the relative’s age (OR = 1.03, 95% CI = 1.003–1.06, p = 0.03) and tremor duration (OR = 1.03, 95% CI = 1.00–1.06, p = 0.047). The strongest predictor of cranial tremor in the relative was the relative’s total tremor score (OR = 1.1, 95% CI = 1.01–1.22, p = 0.035).

Presence of cranial tremor in relatives was not associated with presence of cranial tremor in the proband (OR = 0.7, 95% CI = 0.36–1.40, p = 0.32). This result was not substantially changed after adjusting for the relative’s total tremor score (OR = 0.8, 95% CI = 0.37–1.58, p = 0.47), relative’s tremor duration (OR = 0.9, 95% CI = 0.45–1.88, p = 0.82), or relative’s age (OR = 0.6, 95% CI = 0.26–1.40, p = 0.24) in multivariate models. The relative’s gender was not a confounder either. Total tremor score, age, and duration could not be included in the same model because they were collinear.

Additional Analyses

The large majority of individuals with cranial tremor had neck tremor. In a parallel set of analyses, we examined the predictors of neck tremor, and results were similar. Presence of neck tremor in relatives was not associated with presence of neck tremor in the proband (OR = 0.6, 95% CI = 0.23–1.63, p = 0.33). Adjusting for potential confounders (relative’s total tremor score, relative’s tremor duration, and relative’s age) did not change the results. There was no confounding by gender.

Discussion

Head tremor is highly prevalent in ET, occurring in 30–50% of cases [15, 21]. In addition to its reported clinical correlates [4–6], imaging studies have suggested that ET patients with head tremor may form a distinct subgroup, with reductions in cerebellar volume relative to those without head tremor [22, 23]. The presence/absence of cranial tremors is also often used as a stratification point in genetic studies of ET [24, 25]. Yet, there are no readily available data on the concordance for such tremors in ET patients and their affected family members.

A large population-based family study in Sweden in the late 1950s included phenotype information on approximately 200 ET cases descended from a small number of ancestral families, and cranial tremors were reportedly present in some members of some families but not others, suggesting, as observed in our families, a high degree of within-family heterogeneity with respect to cranial tremor in ET, although the investigators did not consider the contributions of subject age, gender, duration, and other factors in their analyses [26]. Aside from that
study, we are not aware of any prior published data on the concordance for cranial tremors in ET families.

ET patients whose relatives (e.g. parents) have/had head tremor often ask whether they, too, are likely to develop a similar head bobble. In the absence of published data, it has not been clear how to counsel these patients. The current data suggest that the development of head tremor is not strongly linked with family history, but rather, it seems to be more dependent on the extent of tremor severity and disease progression.

Eighteen (66.7%) of 27 probands versus 27 (39.7%) of 68 relatives had cranial tremor. Probands in this study may have self-selected based on the severity of their disorder, resulting in a high proportion with cranial tremor.

This study had limitations. Sample size was limited due to our restriction of the study to individuals who received in-person examination rather than including individuals with self-reported or proband-reported ET [27]. Despite the modest sample size, we were able to detect several important associations. Our restrictive inclusion criteria may also be viewed as a study strength, because they probably increased the validity of our diagnoses. Further strengths included the presence of multi-case families and a broad range of phenotypic features.

In summary, the familial aggregation of cranial tremor was low in ET. The major predictor of this disease feature was tremor severity rather than the presence of cranial tremor in another family member.

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Disclosure Statement

The authors declare that there are no conflicts of interest and no competing financial interests.

References

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