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Subclinical Tremor in Normal Controls with vs. without a Family History of Essential Tremor: Data from the United States and Turkey

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Abstract

Background—Mild action tremor is very common in the population. One fundamental question is whether this tremor is related to the neurological disease essential tremor (ET), which occurs in a much smaller segment of the population? ET is often genetic and variable phenotypic expression is well-documented in the literature. We determined whether normal controls who report a family history of ET have greater action tremor than normal controls who do not report such a history.

Methods—Controls, enrolled in two epidemiological studies (New York and Turkey), were examined in detail and action tremor was rated using a valid and reliable clinical rating scale, resulting in a total tremor score (range 0 – 36).

Results—In New York, the total tremor score was higher in 44/406 (10.8%) controls who reported a family history of ET than in 362/406 controls with no such history (4.25 ± 2.51 vs. 3.78 ± 2.93, p = 0.02). Controls who reported a first-degree relative with ET had the highest total tremor scores. In Turkey, the total tremor score was higher in 7/89 (7.9%) controls with a family history than in 82/89 controls with no family history (3.43 ± 4.54 vs. 1.13 ± 2.54, p = 0.048). All affected relatives in Turkey were first-degree.

Conclusions—These data suggest that some of the normal tremor exhibited by people in the population is likely to be subclinical, partially-expressed ET and that the sphere of ET is wider than is apparent from a consideration of clinically-diagnosed cases.

Keywords

essential tremor; tremor; epidemiology; family history; genetics

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Introduction

Mild action tremor occurs in most “normal” control subjects [1]. Caffeine, nicotine, and other factors may exacerbate the tremor, while beta blockers may relieve it [2,3]. One fundamental question is whether this normal tremor, which is so widespread in the population, is related in some way to the neurological disease essential tremor (ET), which occurs in a smaller segment of the population [4]? ET is often genetic [5–7] and variable phenotypic expression is well-documented in the literature [8]. This raises the question as to whether any of the normal tremor, so commonly exhibited by people in the population, is subclinical, partially-expressed ET? If it were, it would suggest that the sphere of ET is wider than is apparent from a consideration of clinically-diagnosed cases. One way to address this question is to determine whether normal controls who have a family history of ET have greater action tremor than normal controls who do not report such a family history. We collected data on tremor severity from two very different sources: a group of approximately 400 normal controls recruited by random-digit telephone dialing for an epidemiological study of ET in the New York area [9] and a smaller group of controls recruited from a population-based prevalence study of ET in Mersin, Turkey [10]. In each study, controls were examined in-person and action tremor was rated by a neurologist specializing in movement disorders using the same examination and the same reliable [11] and valid [12] clinical rating scale. As the method used to quantify tremor was identical, data from the two sources were presented side by side in the same paper. Our aim was to determine whether the severity of action tremor was greater in controls with vs. without a family history of ET.

Methods

As detailed below, the same tremor examination and clinical rating scale were used in each study, which facilitated comparison across studies.

Epidemiological study of ET in New York

Individuals were enrolled in an ongoing (2000 – 2009) environmental epidemiological study of ET at the Neurological Institute of New York, Columbia University Medical Center (CUMC) [9], a tertiary referral center in northern Manhattan, New York. ET patients, age 18 and older, came from two primary sources: patients whose neurologist was on staff at the Institute or patients who were cared for by their local doctor in the tri-state region (New York, New Jersey, Connecticut) and, as members of the International Essential Tremor Foundation, had read advertisements for the study and volunteered. Controls were recruited using random-digit telephone dialing. They were ascertained from the same source population as the cases and were frequency-matched based on age, gender, and race [9]. Prior to enrollment, all cases and controls signed informed written consent as approved by the CUMC Institutional Review Board. Cases and controls were informed that the study was on lifestyle and work habits. Controls were furthermore informed that they were being selected because they, as a comparison group, did not have a neurological disorder. All cases and controls underwent demographic and medical histories in which data on names of medications and current medical conditions were collected. Data on caffeine consumed (number of cups of caffeinated coffee, tea, soda), ethanol consumed (number of drinks) and smoking (number of cigarettes) on the day of the evaluation were also collected. Each participant was asked whether anyone in his or her family (including first-, second-, and third-degree relatives) had ET or Parkinson’s disease (PD) and, if so, their relationship with the reportedly affected individual(s). A videotaped neurological examination was performed. This included one test for postural tremor and five for kinetic tremor (pouring water between

two cups, using a spoon, drinking from a cup, finger-nose-finger, drawing spirals) performed with each arm (12 tests total). A neurologist specializing in movement disorders (E.D.L.) used a reliable [11] and validated [12] clinical rating scale, the Washington Heights-Inwood Genetic Study of ET (WHIGET) tremor rating scale, to rate tremor during each of twelve tests: 0 (none), 1 (mild), 2 (moderate), 3 (severe). These ratings resulted in a total tremor score (range = 0 – 36) [9]. There are 406 control subjects, none of whom qualified for a diagnosis of ET based on published diagnostic criteria (kinetic tremor rated ≥ 2 during at least 3 tests or head tremor, in the absence of PD or dystonia) [9] and none of whom had PD or dystonia. Data on these 406 control subjects were used for the present analyses.

Population-based prevalence study of ET in Turkey

A population-based study of the prevalence of ET was conducted in Mersin, Turkey [10]. As described previously [10], the target study population consisted of 2,500 adults who represented 0.65% of the Mersin population ≥ 40 years old. The epidemiological survey used door-to-door interviews and examinations; there were 2,253 participants. Four study neurologists performed the evaluations; each evaluation was performed by two of the four. The neurologists visited the 2,253 residents in their homes between July and December 2002 [10,13]. The study protocol was approved by the Turkish Health Ministry's board prior to the start of the study and all study subjects signed a consent form. Demographic and medical histories were obtained in which data on names of medications were collected and each participant was asked whether anyone in their family (including first- and second-degree relatives) had ET or PD. Data on ethanol consumption (yes vs. no) and smoking (yes vs. no) were also collected. A neurological examination was performed. As in New York, the examination included one test for postural tremor and five tests for kinetic tremor (pouring water between two cups, using a spoon, drinking from a cup, finger-nose-finger, drawing spirals) performed with each hand (12 tests total). The neurologists used the WHIGET tremor rating scale to rate the severity of the tremor during the examination and assigned a total tremor score (range = 0 – 36). They had been trained to use the rating scale by viewing a training videotape that included educational and self-assessment sections [14]. There were 89 prevalent ET cases [10], diagnosed using the same criteria as were used in the New York study and 2164 individuals without ET who were available as potential controls. The 2164 potential controls were stratified by gender, geographic ward within Mersin, and age. One control from the same ward was matched to each case of the same gender based on the proximity of their birthdays. Three of the 89 (3.4%) selected controls declined participation and were replaced by three other controls of the same gender and similar birthday. There were 89 controls, none of whom had ET, PD, or dystonia. Data on these 89 control subjects were used for the present analyses.

Analyses

The total tremor score was not normally distributed and there were many zero values; therefore, the value $\log_{10}$ (total tremor score + 0.5) was used in for the purposes of statistical testing. Log-transformed total tremor scores were compared using the Student's t test. In a linear regression model, we examined the association between family history of tremor (independent variable) and log-transformed total tremor score (dependent variable) in an unadjusted model and then, in a model that adjusted for age, gender, use of beta-blocker medications, caffeine, ethanol and smoking, each of which may be associated with tremor severity in normal controls [2,3,15]. In Turkey, the model adjusted for age, gender, use of beta-blocker medications, ethanol and smoking but it did not adjust for caffeine intake.

Results

Epidemiological study in New York

There were 406 controls (mean age = 67.8 ± 12.5 years, 59.1% women, Table 1). Forty-four (10.8%) controls reported having a relative with ET (Table 1). The total tremor score was higher in the 44 controls who reported a family history of ET than in the 362 controls who did not report a family history of ET (Table 2). The 30 controls who reported having a first-degree relative with ET had the highest total tremor scores, whereas the 14 controls who reported having second- or third-degree relatives with ET had total tremor scores that were similar to those of controls with no reported family history of ET (Table 2). Controls who reported a family history of ET did not differ by age or gender from controls who did not report a family history of ET (data not shown). Eighteen (4.4%) controls reported having a relative with PD; the total tremor score in these 18 was similar to that of the 388 controls who did not report a family history of PD (Table 2).

We performed several secondary analyses. First, we removed all controls who complained of tremor. This lessened the likelihood of reporting bias (controls with more tremor themselves might be more conscious of their own tremor and hence more likely to report having an affected relative). Eleven controls were thus removed, including 3 (27.3%) with a first-degree relative reported to have ET; the total tremor score remained higher in the 41 remaining controls who reported a family history of ET than in the 354 controls with no family history of ET (log-transformed total tremor scores = 0.59 ± 0.27 vs. 0.50 ± 0.38, t = 2.07, p = 0.04). Second, we performed linear regression analyses to control for the effects of potential confounders on the association between family history of tremor (independent variable) and log-transformed total tremor score (dependent variable). These analyses showed an association both in an unadjusted model (beta = 0.11, p = 0.07) and in a model that adjusted for age, gender, use of beta-blocker medications, caffeine and ethanol consumption on the day of the evaluation, and smoking on the day of evaluation (beta = 0.13, p = 0.025), indicating that the association was not the result of confounding.

Population-based study in Turkey

Among 89 controls (mean age = 57.2 ± 11.6 years, 47.3% women, Table 1), seven (7.9%) reported having a relative with ET (Table 1) and 0 (0.0%), a relative with PD. The total tremor score was higher in seven controls who reported a family history of ET than in 82 controls who did not report a family history of ET; all of the reportedly affected relatives were first-degree relatives (Table 2). Controls who reported a family history of ET did not differ by age or gender from controls who did not report a family history of ET (data not shown). We removed five controls who complained of tremor (including one [20.0%] with a relative reported to have ET); the total tremor score remained higher in the six controls with a family history of ET than in 78 controls with no family history of ET (log-transformed total tremor scores = 0.39 ± 0.59 vs. −0.07 ± 0.41, t = 2.53, p = 0.01). We also performed linear regression analyses to control for the effects of potential confounders on the association between family history of tremor (independent variable) and log-transformed total tremor score (dependent variable). These analyses showed an association both in an unadjusted model (beta = 0.34, p = 0.048) and in a model that adjusted for age, gender, use of beta-blocker medications, ethanol (yes vs. no) and smoking (yes vs. no) (beta = 0.39, p = 0.028), indicating that the association was not the result of confounding.

Discussion

We collected data on tremor severity from two very different sources in Turkey and New York. The methods used to both evaluate and then quantify tremor, however, were identical

and the results from the two studies were very similar. We found that the severity of action tremor was greater in controls with vs. without a reported family history of ET. Controls who reported a family history of PD and controls who had no family history of PD had similar total tremor scores.

The controls who reported a first-degree relative with ET had the highest total tremor score whereas those who reported second- or third-degree relatives with ET had total tremor scores that were similar to those of controls with no reported family history of ET. These data are consistent with the hypothesis that the increased tremor in controls with a family history of ET is due to a shared genetic predisposition for the disease.

We previously demonstrated that relatives of ET cases had more tremor than relatives of controls [16], a finding that parallels that in the current study in suggesting a shared genetic susceptibility to mild tremor and ET. Our previous study was carried out in a different sample and used a different study design: sampling of 59 elderly community-dwelling ET cases and 72 elderly controls residing in Washington Heights-Inwood, northern Manhattan, and ascertaining tremor in their relatives [16]. The previous results had not been validated elsewhere until the current study. Here we have validated the finding using two new samples and a different ascertainment strategy and study design. In addition, we were able to adjust for a number of important confounding factors (caffeine intake, ethanol intake, cigarette smoking and use of beta-blockers), which we were not able to adjust for previously [16].

Controls with more tremor themselves might be more conscious of their own tremor and, hence more likely to report having an affected relative. This bias could create a situation in which persons with family histories of tremor had higher total tremor scores. However, we do not think this was the case. First, all of our study participants were normal controls. Their tremor (mean total tremor score = 3.84 in New York and 1.32 in Turkey) was well within the range of normal (e.g., mean total tremor score in normal controls = 4.8 in previous studies in New York)[1] and considerably lower than that seen in ET (mean = 17.8 in Turkey [13] and 18.9 in New York [9]). Indeed, few (2.7% in New York and 5.6% in Turkey) controls even reported having tremor. In an analysis that excluded controls who noticed their own tremor, the results remained similar (controls with a family history of ET had higher tremor scores than controls without a family history).

This study had limitations. We asked controls whether they had affected relatives but did not examine their relatives. Since people routinely under-report tremor in their affected relatives, we probably under-estimated the number of controls with affected relatives [17]. Hence, our group of controls with no reported family history of ET is likely to have included some controls with a true yet unreported family history of ET. Therefore, it is possible that the total tremor scores of controls with no reported family history of ET are even lower than we report here and that the results we report underestimate the difference between controls with vs. without a family history of ET. Second, the Turkish study was designed as a prevalence survey so that data on caffeine use were not collected. Despite this, we adjusted for a variety of other confounders and there is no reason to assume that caffeine consumption differed with regards to family history of ET, making this an unlikely source of residual confounding.

These data suggest that some of the normal tremor exhibited by people in the population is likely to be subclinical, partially-expressed ET and that the sphere of ET is wider than is apparent from a consideration of clinically-diagnosed cases.

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Table 1

Demographic and clinical characteristics of control subjects

	Study in New York	Study in Turkey
N	406	89
Age in years	67.8 ± 12.5 (18 – 94)	57.2 ± 11.6 (40 – 83)
Female gender	240 (59.1%)	42 (47.3%)
Total tremor score (range = 0 – 36)	3.84 ± 2.89 (0 – 15)	1.32 ± 2.78 (0 – 12)
Answered yes to the question: "Do you often have shaking that you can't control?"	11 (2.7%)	5 (5.6%)
Does anyone in your family have ET?		
No	362 (89.2%)	82 (92.1%)
Yes, First-Degree	30 (7.4%)	7 (7.9%)
Yes, Second-Degree	13 (3.2%)	0 (0.0%)
Yes, Third-Degree	1 (0.2%)	0 (0.0%)
Does anyone in your family have PD?		
No	388 (95.6%)	89 (100%)
Yes, First-Degree	10 (2.5%)	0 (0%)
Yes, Second-Degree	7 (1.7%)	0 (0%)
Yes, Third-Degree	1 (0.2%)	0 (0%)

All values are mean ± SD (range) or numbers (%).

Table 2

Total tremor score by family history

	N	Study in New York	N	Study in Turkey
Total tremor score (log total tremor score)	406	3.84 ± 2.89 (0.51 ± 0.37)	89	1.32 ± 2.78 (-0.02 ± 0.43)
Total tremor score (log total tremor score)				
Family history of ET	44	4.25 ± 2.51 (0.61 ± 0.27)	7	3.43 ± 4.54 (0.29 ± 0.59)
No reported family history of ET	362	3.78 ± 2.93 (0.50 ± 0.38)	82	1.13 ± 2.54 (−0.05 ± 0.41)
		t = 2.36, p = 0.02		t = 2.01, p = 0.048
Total tremor score (log total tremor score)				
First-degree relative with ET	30	4.60 ± 2.74 (0.63 ± 0.30)		3.43 ± 4.54 (0.29 ± 0.59)
Second- or third-degree relative with ET	14	3.50 ± 1.79 (0.56 ± 0.19)		No relatives
No reported family history of ET	362	3.78 ± 2.93 (0.50 ± 0.38)		1.13 ± 2.54 (−0.05 ± 0.41)
		t = 2.22, p = 0.03 (first-degree vs. no family history)		t = 2.01, p = 0.048 (first-degree vs. no family history)
Total tremor score (log total tremor score)				
Family history of PD	18	3.83 ± 3.49 (0.54 ± 0.28)		No relatives
No reported family history of PD	388	3.84 ± 2.87 (0.51 ± 0.37)		1.32 ± 2.78 (−0.02 ± 0.43)
		t = 0.46, p = 0.65		
Total tremor score (log total tremor score)				
First-degree relative with PD	10	3.30 ± 2.41 (0.51 ± 0.25)		No relatives
Second- or third-degree relative with PD	8	4.50 ± 4.60 (0.58 ± 0.32)		No relatives
No reported family history of PD	388	3.84 ± 2.87 (0.51 ± 0.37)		1.32 ± 2.78 (−0.02 ± 0.43)
		t = 0.01, p = 0.99 (first-degree vs. no family history)		
		t = 0.54, p = 0.59 (second or third-degree vs. no family history)		

All values are mean ± SD. Log-transformed total tremor scores (shown in parentheses) were compared using the Student's t test.