Mild Tremor in Relatives of Patients With Essential Tremor

What Does This Tell Us About the Penetrance of the Disease?

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Background: Mild tremor may occur in relatives of patients with essential tremor (ET). However, this phenomenon has not been studied quantitatively or with a comparison group. Such a study may provide information on the penetrance of ET.

Objective: To obtain data on the magnitude of tremor in case and control relatives who did not meet diagnostic criteria for ET.

Methods: Cases with ET and control subjects from the Washington Heights–Inwood community in northern Manhattan, NY, were enrolled in a family study. Their first- and second-degree relatives underwent a videotaped tremor examination. Two neurologists rated the severity of tremor, assigning a total tremor score (0-36 [maximum]). Data were analyzed on 201 case relatives and 212 control relatives who did not meet diagnostic criteria for ET.

Results: The mean total tremor score of first-degree case relatives was higher than that of first-degree control relatives (4.9 vs 3.9; \(P = .003\)). Total tremor scores for second-degree relatives did not differ (4.1 vs 4.2; \(P = .68\)). A larger percentage (35.2% vs 36.6%; \(P = .1\)) of first-degree case relatives had total tremor scores of 4 or more. Among first-degree relatives who were older than 60 years, 13 case relatives (59.1%) and 18 control relatives (45.0%) had total tremor scores of 4 or more.

Conclusions: A considerable number of seemingly normal case relatives may have a genetic predisposition for tremor. Even among older case relatives (\(\geq 60\) years of age), there was an increased prevalence of higher tremor scores, suggesting that in that age group, subclinical ET may be present and penetrance still may not be complete.

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SUBJECTS AND METHODS

SUBJECTS

As previously described, from 1992 to 1994, 98 subjects with ET were ascertained from the Washington Heights–Inwood community in northern Manhattan, NY. From 1995 to 1999, these 98 subjects were contacted to enroll them in the Washington Heights–Inwood Genetic Study of Essential Tremor, a family study of ET. Seventy-two (73%) of 98 subjects were enrolled. Each case was matched by age (5-year strata), sex, and ethnicity (white non-Hispanic, African American non-Hispanic, Hispanic) to a healthy control subject from the same community who had no neurologic symptoms or action tremor on neurologic examination. Subjects were informed that the aim of the Washington Heights–Inwood Genetic Study of Essential Tremor was to assess health conditions in northern Manhattan families.

EVALUATION OF PROBANDS (CASES WITH ET AND CONTROL SUBJECTS)

Cases with ET and control subjects underwent a semi-structured interview and a videotaped tremor examination, conducted in person by a study physician. During the 30-minute interview, clinical information on tremor, medical conditions, and medications was collected. The 10-minute videotaped tremor examination elicited tremor during 1 posture (sustained arm extension) and 5 actions (pouring water, drinking, using a spoon, finger-to-nose movements, and drawing spirals) performed with the dominant and nondominant arms (12 tests in total). The examination was videotaped with a manually operated video camera recorder (Sony CCD-TR700; Sony, Park Ridge, NJ); Hi-8 videotapes were used to increase the resolution of the recording.

All videotapes were independently reviewed by 2 of us (E.D.L. and either B.F. or S.F.), who rated the severity of the tremor. Ratings were as follows: 0 (no visible tremor), 1 (low-amplitude or intermittent tremor), 2 (tremor of moderate amplitude, clearly oscillatory [alternating between extremes with a definable period], and usually present), and 3 (large-amplitude tremor). A total tremor score (0-36 [maximum]) was calculated for each subject by the addition of the 12 scored items. The final total tremor score was the average of the 2 raters’ scores. Interrater agreement between E.D.L. and B.F. was substantial (weighted κ statistic, κw = 0.62-0.78). Agreement between E.D.L. and S.F. was similarly high (κw = 0.89).

Each neurologist independently assigned a diagnosis of ET or normal on the basis of review of the interview and videotaped examination. As previously described, diagnoses of ET required, at a minimum, a tremor rated as 2 or greater during at least 3 actions. In a previous study of 103 normal subjects, 8.7% had tremor rated as 2 or greater on 2 tasks, but none had tremor rated as 2 or greater on 3 tasks, suggesting that 3 ratings of 2 or greater is not within the range of normal.

Because there is no definitive diagnostic test for ET, clinical criteria are still somewhat arbitrarily defined. We used diagnostic criteria that were based on our previous experience evaluating ET cases and our review of the tremor literature. In previous studies, we found that diagnoses based on these criteria could be reliably assigned by independent raters, and in 94.4% of instances, these clinical diagnoses agreed with independent electrophysiological diagnoses based on quantitative computerized tremor analysis.

EVALUATION OF RELATIVES

Each case and control was asked to name all living or dead first- and second-degree relatives. Relatives who were 18 years of age and older, for whom contact information (telephone number and address) was available, and who lived within 2 hours of the medical center were contacted and asked to participate in a study of health in families. Those who agreed to participate (234 case relatives [82.7%] and 226 control relatives [79.6%]) were given the same evaluation as the probands. Videotapes were rated by 2 neurologists (E.D.L. and either B.F. or S.F.), blinded to the subjects’ status as case, control, or relative, and diagnoses were assigned.

RE-EVALUATION OF CASE PROBANDS

As previously described, 40 probands with ET underwent an annual evaluation. Final assignment of a diagnosis of ET required that both study neurologists had diagnosed ET at baseline and, when available, at all of the follow-up assessments. Fifty-nine (82%) of the 72 cases and 13 did not.

FINAL SUBJECT SELECTION

We did not exclude the 13 enrolled control subjects whose matched case had been excluded, as this would have resulted in loss of valuable data on their relatives. Despite this, the 59 cases with ET and 72 control subjects did not differ by age, sex, or ethnicity (Table).

STATISTICAL ANALYSES

Data were analyzed by χ² tests (categorical variables) and Pearson correlation coefficients. Total tremor score was not normally distributed; it also correlated with age. When differences were assessed between total tremor scores, data were logarithmically transformed, and a 1-factor analysis of covariance (ANCOVA) with age as the covariate was used. In addition, in multiple linear regression analyses (enter method), the logarithm of the total tremor score, which was normally distributed, was used as the outcome variable.
The mean total tremor score among first-degree case relatives (4.9; median, 4.5; range, 0-13) was higher than that of first-degree control relatives (3.9; median, 3.0; range, 0-12; ANCOVA F=8.80, \(P=0.003\)), whereas among second-degree relatives, the mean total tremor scores were similar (mean, 4.1 vs 4.2; ANCOVA F=0.18, \(P=0.68\)). It is important to emphasize that these individuals had very mild tremor that was well within the range of normal. A given subject could be assigned a total tremor score of 4 if he or she had a rating of 1 on only 4 items and absolutely no tremor on the remaining 8 of 12 scored items. To further place these total tremor scores in perspective, our 59 control subjects had a mean total tremor score of 6.6 (range, 0-16.5) and our probands with ET (excluding those with isolated head tremor) had a mean total tremor score that was considerably higher (19.4; range, 10.5-34.5).

Across age, first-degree relatives of cases had higher total tremor scores than did first-degree relatives of control subjects (Figure 1), and multiple regression analyses (see below) demonstrated that this difference was significant. For second-degree relatives, the regression lines were approximately superimposed (Figure 2).

The mean total tremor score was higher in men than in women. This was observed both in case relatives (4.9 vs 3.5; ANCOVA F=24.53, \(P<.001\)) and control relatives (6.1 vs 3.7; ANCOVA F=9.83, \(P=.002\)). There were no differences between sexes in use of a medication that could enhance physiologic tremor (including lithium carbonate, theophylline, levothyroxine sodium, prednisone, valproate sodium, oral hypoglycemic
Relatives with mild tremor represent a difficult diagnostic challenge in genetic studies of ET. To our knowledge, these individuals have not been studied systematically, nor have they been compared with relatives of normal control subjects.

We plotted the distribution of total tremor scores in the 2 groups of relatives, excluding individuals who had been diagnosed as having ET, and found that total tremor scores of 4 or greater were approximately 20% more prevalent among first-degree relatives of cases than among first-degree relatives of control subjects. A total tremor score of 4 is well within the range of normal. In fact, the mean total tremor score of our 59 control subjects (6.6) was higher than this (because the control subjects were significantly older [mean age, 79.2 years] and there was a correlation between age and total tremor score). While the existence of mild, partially expressed forms of ET among relatives of cases has been reported previously, most references to these individuals allude to relatives whose tremor was considered borderline abnormal rather than clearly within the range of normal. Our data draw attention to the latter.

There are several possible explanations for the observed difference in distribution of tremor among case and control relatives. First, there may be subclinical forms of ET among relatives of ET cases. We demonstrated that the mean total tremor score was higher among first-degree relatives of cases than among first-degree relatives of control subjects, but this difference was not present when we examined more distantly related (second-degree) relatives. This suggests that a genetic predisposition for tremor, and possibly ET, may have contributed to the observed difference in tremor scores. While the relatives may have a predisposition to develop tremor, since they did not have ET, a disposition for this particular type of tremor cannot be assumed. Longitudinal follow-up data would be important to see whether the case relatives with more tremor actually developed ET at a later date. An alternative explanation is that there may be more enhanced physiologic tremor in relatives of cases. We realize that we cannot fully exclude this possibility, but we explored it by examining the proportion...
of case and control relatives who were taking tremor-inducing medications or who had medical conditions (eg, hyperthyroidism) that might result in enhanced physiologic tremor. We did not find a difference. It is also not apparent to us why relatives of cases would be prone to developing more enhanced physiologic tremor than relatives of controls, unless one were to hypothesize an etiologic link between ET and enhanced physiologic tremor. Loading the limb and measuring a change in tremor frequency may sometimes allow one to differentiate ET from enhanced physiologic tremor, although the role of this technique in classifying extremely mild tremors as early ET vs enhanced physiologic tremor is still unclear. In addition, this method is not practical in epidemiologic or genetic field studies because the equipment is not portable. A third possibility is that our diagnostic criteria for ET were too stringent, and that some of the case relatives who did not meet our diagnostic criteria for ET actually had ET. This was probably not the case. The prevalence of ET among relatives of our control subjects (6.2%) was actually higher than most published prevalence estimates for ET (0.4%-3.9%), suggesting that our diagnostic criteria were not overly stringent.

We also demonstrated more tremor among older (mean age, 71.5 years) first-degree case than among first-degree control relatives. These case and control relatives had similar ages. These findings have important implications because they suggest that subclinical ET may still exist in as many as 15% of relatives who have reached this advanced age. In other words, the penetrance of ET may not be complete. The penetrance of ET is generally considered to be complete by age 65 to 70 years, although there are very few data. One study in Sweden suggested that the penetrance was complete at age 70 years because the highest registered age at onset in their cohort was 70 years, although it is apparent from their data that there were many unaffected relatives who were older than 70 years, and it is not known how many of these carried a genetic predisposition for ET. The most thorough study of penetrance suggested that the penetrance was complete by age 65 years because 46% (ie, nearly half) of the children of cases with familial ET had developed tremor by that age. Assuming an autosomal dominant model and complete penetrance, 50% of first-degree relatives of familial cases should develop the disease. However, these calculations do not account for nongenetic causes of ET among relatives. We reported that 11.1% of control subjects' relatives had developed ET by age 60 years and 22.2% by age 80 years. Nongenetic causes of ET should be similar in relatives of cases and relatives of controls. Therefore, assuming an autosomal dominant model with complete penetrance and the occurrence of nongenetic forms of ET, as many as 72.2% (rather than 50%) of first-degree relatives of familial cases should develop the disease by age 80 years. One additional argument against complete penetrance by age 70 years is that the incidence of the disease continues to rise, even after the age of 80 years. If penetrance were complete by age 70 years, then one would have to hypothesize that 100% of the cases that arose after the age of 70 years were sporadic.

We reported that men had higher total tremor scores than women. We are not certain of the cause. One possibility is that men may have had more exposure to work-related tremorogenic toxins (eg, mercury, lead, and pesticides), or may have engaged in more behaviors (smoking and caffeine consumption) that were likely to enhance tremor. A hormonal or other biological difference should be considered as well. Interestingly, the sex difference in total tremor scores persisted even in older (≥60 years) subjects (6.4 in men vs 4.2 in women; ANCOVA F = 4.31, P = .04), suggesting that postmenopausal women have lower total tremor scores than do men of similar age.

Strengths of our study included the use of a standardized clinical assessment of tremor severity by 2 independent neurologists with a high level of agreement.

The total tremor score is a clinical measure of tremor severity that correlates with physiologic measures of tremor severity, including a modified Klove Matthews Motor Steadiness Test Battery and quantitative computerized tremor analysis results (eg, correlation [r] of 0.46 between total tremor score and tremor amplitude of dominant arm tremor while writing; P < .001; n = 60). Our study had limitations. We did not systematically assess smoking or use of caffeine, both behaviors that might increase tremor. While it is conceivable that relatives of cases might have engaged in these behaviors to a greater extent than relatives of controls, it is unlikely that these behaviors would have been more prevalent among first-degree relatives of cases than among first-degree relatives of controls but not among the respective second-degree relatives. Also, independent objective measurements of tremor severity by methods such as electromyography or accelerometry were not routinely performed; these would have helped to more precisely quantify the observed difference in tremor severity between case and control relatives. Despite this, clinical diagnoses and tremor scores were assigned by 2 neurologists independently and blinded to knowledge of whether they were studying a relative of a case or of a control, so that any systematic errors in diagnosis or assignment of tremor scores would not have been differential across relative type (ie, case vs control relative).

In summary, a considerable number of seemingly normal case relatives may have a genetic predisposition for tremor and, possibly, ET. Even among older case relatives (≥60 years of age), there was an increased prevalence of higher tremor scores, suggesting that, in that age group, subclinical ET may be present and penetrance may not be complete. These data should be of interest to individuals who are performing genetic linkage studies, which hold the clues to the pathophysiology of ET and its treatment.

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