Ethnic Differences in Essential Tremor

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Background: Ethnic differences in the clinical characteristics (severity and distribution) of essential tremor (ET) have not been studied. The presence of these differences suggests that ET is not a homogeneous disease and that there is variability in disease expression under different circumstances. As part of a community-based study, we evaluated a multiethnic group of cases.

Objective: To assess whether there are ethnic differences in the clinical characteristics of ET.

Methods: Elderly residents of Washington Heights–Inwood, New York, were enrolled in a community-based health study (N = 2117). Participants underwent a medical interview and a neurological examination conducted by a neurologist, and subjects with ET were identified. These subjects with ET were then enrolled in a community-based study of ET and underwent a tremor interview, a videotaped tremor examination, and in some cases, a performance-based test of function and quantitative computerized tremor analysis. A total tremor score (range, 0-36, with 0 indicating no tremor and 36 indicating maximum tremor) was assigned to each subject based on 2 neurologists’ ratings of the tremor examination.

Results: Among 62 subjects with ET (white [n = 16], African American [n = 18], and Hispanic [n = 28]), there were ethnic differences in the total tremor score (F = 3.68, P = .03). In a multiple regression model adjusting for age, white subjects had a mean total tremor score that was 5.3 points lower than that of nonwhite subjects (P = .008). We divided the nonwhite group into African American and Hispanic subgroups. In a regression model adjusting for age and duration, the white group had a mean total tremor score that was 6.1 points lower than that of the Hispanic group (P = .07) and 7.2 points lower than that of the African American group (P = .05). The mean performance-based test score was 1.7 times higher in the African American group and 2.1 times higher in the Hispanic group compared with the white group (P = .38). No subjects in the African American group had head tremor, while 4 subjects in the white group (25%) and 8 subjects in the Hispanic group (29%) did have head tremor (\( \chi^2 = 6.17, P = .05 \)).

Conclusions: There are ethnic differences in the expression of ET, suggesting that ET is not a homogeneous disorder. These differences may reflect phenotypic variability caused by genotypic differences or differences in exposure to environmental factors that influence tremor.

Arch Neurol. 2000;57:723-727

Despite the observation that essential tremor (ET) is one of the most prevalent neurological disorders, little is known about its etiology or pathogenesis. While there has been some study of ethnic differences in the prevalence of this disorder, there have been no studies of ethnic differences in the clinical characteristics (e.g., severity, distribution) of the tremor itself. Such differences, if present, might represent phenotypic variability in the setting of genotypic differences or differences in exposures to environmental factors that influence the expression of tremor. Such ethnic differences would also suggest that ET is not a homogeneous disease, but rather that there is variability in disease expression under different circumstances.

As part a community-based study of ET, we examined a multiethnic group of subjects with ET who were not identified through clinics, physicians’ offices, or hospital rosters. They were not selected because of health-seeking behavior or severity of symptoms (i.e., factors that might confound analyses of the association between ethnicity and tremor severity). The aim of this study was to assess whether there are ethnic differences in the clinical characteristics (severity and distribution) of tremor in ET.

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SUBJECTS AND METHODS

SUBJECTS AND SETTING

Two thousand one hundred seventeen subjects aged 65 years and older who were residents of the Washington Heights–Inwood community in northern Manhattan, New York, were enrolled in a longitudinal, community-based study of health issues in the elderly, the Northern Manhattan Aging Project.13 At each evaluation, subjects underwent a 90-minute medical interview and a standardized medical and neurological examination conducted by a neurologist. Eighty-three subjects with ET were initially identified, and 15 additional subjects were identified later (total n = 98).12,14

One to 3 years later, an effort was made to recontact these 98 subjects with ET to enroll them in a second study, the Washington Heights–Inwood Genetic Study of Essential Tremor (WHIGET), a community-based study of ET aiming to estimate the extent of familial aggregation of ET.12,13 Seventy-two (74%) of 98 subjects were enrolled in WHIGET; diagnoses were confirmed in 62 (63%). Of the 26 who were not enrolled, 14 (54%) were deceased, 10 (38%) declined participation or could not be located, and 2 (8%) were too cognitively impaired to be able to follow the evaluation instructions.

For ethnic group classification, we used the categories African American, white (non-Hispanic white), Hispanic, and other.13 The ethnic group assigned to each subject was based on the subject’s own report of ethnicity rather than an interviewer’s classification.14

WHIGET PROTOCOL

All participants in WHIGET underwent a 30-minute semi-structured tremor interview and a 10-minute videotaped tremor examination.12,13,16 The 84-item tremor interview was conducted in person by a study physician and included 12 questions to screen for ET.17 The interviewer also collected information on the distribution and severity of tremor and the use of different tremor medications. The subject was also asked “how old were you when you first noticed tremor?” and “does anyone in your family have tremor?”12,13,16,18 Of 62 subjects with ET, 38 (61%) recognized their tremor prior to our evaluation, and estimates of disease duration were limited to these 38 subjects.

The 26-item videotaped tremor examination was designed to elicit tremor during 6 different tasks (sustained arm extension, pouring between 2 cups, drinking, using a spoon, finger-to-nose movements, and drawing spirals).12,13,16 Each task was performed with the dominant arm and the nondominant arm.

Two neurologists specializing in movement disorders (E.D.L. and B.F.) independently reviewed each subject’s tremor interview responses and videotaped tremor examination.12,13,16 They rated the severity of tremor as observed during different tasks. Ratings were as follows: 0 (no visible tremor), 1 (low-amplitude tremor or intermittent tremor), 2 (tremor of moderate amplitude, clearly oscillatory, and usually present), or 3 (large-amplitude tremor or jerky tremor resulting in difficulty completing the task). A total tremor score (range, 0–36, with 0 indicating no tremor and 36 indicating maximum tremor) was calculated for each subject by adding the 6 task-specific scores for the right and left sides.12,13,16 Head tremor and voice tremor were each rated as either present or absent.

Each reviewer independently assigned a diagnosis of ET (definite, probable, or possible) or normal based on information collected during the tremor interview and review of the videotaped tremor examination.12,13,16 Diagnoses of definite ET required the following: (1) postural tremor rated as 2 or higher, (2) kinetic tremor rated as 2 or higher during 4 tasks, and (3) tremor that by history interfered with 1 or more activities of daily living. The diagnosis of probable ET required a kinetic tremor rated as 2 or higher during 4 tasks or a head tremor, but there was no stipulation that the tremor interfered with activities of daily living. The diagnosis of possible ET required a kinetic tremor rated as 2 or higher during 3 tasks.12,13,16

This diagnostic protocol was reliable. Two neurologists, using this protocol to assign diagnoses to 226 subjects (ET [n = 52] and control [n = 174] subjects), demonstrated excellent interrater reliability (weighted κ...
hours after enrollment in WHIGET, an effort was made to enroll the 62 subjects with ET in another study, the Columbia University Assessment of Disability in Essential Tremor (CADET), which aims to determine the functional disabilities associated with tremor. Forty (64%) of 62 subjects were enrolled in CADET; 22 (33%) were not enrolled for the following reasons: 15 had dementia and were unable to follow the study protocol, 6 were deceased, and 1 declined participation.

**CADET PROTOCOL**

A performance-based test was administered. This 15-item, 10-minute test was validated using quantitative computerized accelerometry results. The test included the performance of activities that might be impaired by action tremor (eg, carrying a cup and saucer, carrying a tray, copying sentences, signing one’s name, inserting coins into slots, placing paper money in a wallet, and threading a needle). Each item was scored as 0 to 4 (0, no difficulty; 4, unable to perform) by a trained rater, and the total score was converted to a percentage (with 100% indicating that the subject was maximally impaired).

Subjects also underwent quantitative computerized tremor analyses in the Motor Neurophysiology Laboratory at Columbia-Presbyterian Medical Center that were conducted by 2 authors (S.L.P. and Q.Y.).

The tremor analysis involved the use of ultralight piezoresistive miniature accelerometers (±25g, 0.3 gm) with linear sensitivities of approximately 4.5 mV/g in the physiologic range that were attached to a proximal (the distal humerus) and distal (the dorsum of each hand at the distal end of the middle metacarpal bone) position on each arm. Silver/silver chloride electromyogram surface electrodes were used to record the activity of the flexor carpi radialis muscle and extensor carpi radialis muscle along with the accelerometry. As previously described, accelerometeric and electromyogram signals were digitized at 500 Hz using a 15-microsecond 16-bit analog-to-digital system and stored in eight 4-second trials during different conditions: with the arms at rest, with arms extended, during finger-to-nose movements, while pouring water, and while drawing spirals. Tremor was sampled over a 1-hour period to record variation over time. Tremor amplitudes were derived offline by the double integration of wrist accelerometric data after filtering out low-frequency drift (less than 2 Hz) and averaging them. Tremor frequencies were calculated using a fast Fourier transform algorithm to generate autocorrelation spectra. Electromyograms were full-wave rectified, integrated, and processed with the accelerometric data.

**INDEPENDENCE OF TESTS**

A total tremor score was assigned independently by each of 2 neurologists (E.D.L. and B.F.) based on their review of the WHIGET videotaped tremor examination. The performance-based test was administered and rated by another trained rater (L.F.B.) as part of CADET. The quantitative computerized tremor analysis was performed by 1 of 2 investigators (Q.Y. or S.L.P.).

**STATISTICAL ANALYSES**

A total tremor score was assigned by each of 2 neurologists, and the mean was used for these analyses; χ² was used to test associations between categorical variables, and 2-tailed t test and analysis of variance were used for continuous variables. Multiple linear regression models were used. In these models, the variable tremor-inducing medication was coded as present if the patient was currently taking any of the following medications: lithium, thyroxine, oral hypoglycemic agent, valproate, theophylline, or steroids. In these models, the variable tremor-suppressing medication was coded as present if the patient was currently taking any of the following medications: β-blocker, calcium channel blocker, primidone, phenobarbital, or benzodiazepines. In the multiple linear regression models, when comparing white and nonwhite subjects (2 groups), we did not adjust for disease duration because duration was virtually identical in the 2 groups. When comparing white, African American, and Hispanic subjects (3 groups), we adjusted for duration because of the 5.2-year difference in mean duration of tremor between African American and Hispanic subjects (Table).

points lower than that of nonwhite subjects (P = .009). After subdividing the nonwhite group into African American and Hispanic groups, we performed a multiple regression model that adjusted for the 2 medication variables, age, and disease duration, which revealed that the white group had a mean total tremor score that was 5.9 points lower than that of the Hispanic group (P = .08) and 7.2 points lower than that of the African American group (P = .06).

When family history of ET (present vs absent) and age were included in a multiple linear regression model, the white group had a mean total tremor score that was 5.2 points lower than that of the nonwhite group (P = .01). After subdividing the nonwhite group into African American and Hispanic groups, a multiple regression model that adjusted for family history of ET, age, and disease duration demonstrated that the white group had a mean total tremor score that was 6.2 points lower than that of the Hispanic group (P = .07) and 7.4 points lower than that of the African American group (P = .05).

One subject was diagnosed with ET because of head tremor, despite having minimal hand tremor and a low total tremor score. This subject was white. When we excluded this subject in a multiple regression model that adjusted for age, the white group had a mean total tremor score that was 5.2 points lower than that of the nonwhite group (P = .01).

When we restricted our analyses to the 46 subjects with probable or definite ET (ie, excluding 16 [26% of 62] subjects with possible ET), a multiple regression model that adjusted for age showed that the difference in total tremor score between the white and nonwhite groups remained similar (4.6 points), although there was a loss of statistical power (P = .08).

There was a nonsignificant difference among ethnic groups in terms of the proportion of subjects who re-
called the age of tremor onset: white subjects (43.8%), Hispanic subjects (64.3%), and African American subjects (72.2%) ($\chi^2 = 1.9, P = .40$). Hypothetically, one might expect that subjects with severe ET would have given more thought to their age of onset than those with mild ET; the 38 subjects who were able to recall their age of onset had more severe tremor than did the 24 subjects who were unable to recall their age of onset (total tremor score, 20.7 vs 17.9), although this difference did not reach significant levels ($t = 1.7, P = .11$). The relative inability of white subjects to recall their age of onset, if anything, strengthens the argument that their disease was milder.

**PERFORMANCE-BASED TEST SCORE AND QUANTITATIVE COMPUTERIZED TREMOR ANALYSES**

When compared with white subjects, the mean performance-based test score was 1.7 times higher in African American subjects and 2.1 times higher in Hispanic subjects, but this did not reach statistical significance (n = 40, $P = .38$) (Table). White subjects were compared with nonwhite subjects in a multiple regression model that adjusted for age, and white subjects had a mean performance-based test score that was 8.3 points (8%) lower than that of nonwhite subjects ($P = .13$). After subdividing the nonwhite group into African Americans and Hispanic groups, a multiple regression model that adjusted for age and disease duration demonstrated that the white group had a mean performance-based test score that was 10.3 points (10%) lower than that of the Hispanic group ($P = .28$) and 12.5 points (12%) lower than that of the African American group ($P = .18$).

Twenty-seven subjects underwent quantitative computerized tremor analysis. The mean tremor amplitude was 1.3 to 2.4 times higher among Hispanic subjects than white subjects in 3 of the 4 tests and 1.3 to 1.5 times higher among African American subjects than white subjects in all 4 of the tests, although these differences did not reach significance (n = 27) (Table).

**OTHER CHARACTERISTICS OF TREMOR**

Subjects were classified as having head tremor if both neurologists agreed that tremor was present. There were ethnic differences. No African American subjects had head tremor compared with 4 (25%) of 16 white and 8 (29%) of 28 Hispanic subjects ($\chi^2 = 6.17, P = .05$). The proportion of subjects with voice tremor according to both neurologists did not differ (white subjects, 2 [12%] of 16; African American subjects, 1 [6%] of 16; and Hispanic subjects, 3 [11%] of 28; $\chi^2 = 0.53, P = .77$).

These data suggest that there are ethnic differences in the clinical characteristics (severity and distribution) of tremor in ET. White subjects exhibited the mildest form of tremor. In contrast, head tremor was least prevalent among African American subjects. Tremor was studied with a variety of assessment tools, including a clinical rating scale, a performance-based test, and a quantitative computerized tremor analysis. The differences in the severity of tremor were not the result of differences in age, disease duration, medications, or family history of ET.

Ethnic differences in the clinical characteristics of ET could reflect variable phenotypic expression in the setting of underlying ethnically related genotypic differences. Alternatively, ethnic differences in the characteristics of tremor could reflect varying levels of exposure to environmental factors that may influence the expression of tremor. The identity of these environmental factors is not clear, although exposure to mercury, lead, or pesticides may result in action tremor.22-27 One interpretation of the ethnic differences in tremor severity, despite adjustments for differences in age or disease duration, is that the disease itself may progress more rapidly among African American and Hispanic people than it does among white people. This hypothesis needs to be tested using a prospective follow-up study design. Finally, the presence of ethnic differences in the clinical character-
istics of ET suggests that ET is not a homogeneous disease, but rather that there is variability in disease expression under different circumstances.

There are no studies in the literature focusing on ethnic differences in the clinical characteristics of ET, although Hornabrook reported on a group of individuals with prominent head tremor (“head nodders”) living in the Okapa Subdistrict in New Guinea, and a large proportion of the ET cases reported by Larsson and Sjögren in northern Sweden exhibited tongue tremor, suggesting that there may be regional variability in the expression of tremor and that ET is not completely homogeneous. Hubble et al noted that head or voice tremor was significantly more frequent and severe among female patients with ET, while men with ET had more severe postural hand tremor. In addition, certain electrophysiologically defined forms of ET respond clinically to β-blockers, whereas others do not.

This study had limitations. First, a smaller number of subjects underwent performance-based testing and quantitative computerized tremor analysis than videotaped tremor examination. While the performance-based test and tremor analysis data suggested that tremor was less severe among white subjects, the results did not reach the level of statistical significance that characterized the videotaped tremor examination results. Second, it is hypothetically possible that white subjects who were not enrolled had more severe tremor than nonwhite subjects who were not enrolled, although the reason for such selection bias is not apparent. Conversely, one could argue that white subjects who were enrolled were older than their nonwhite counterparts, that white subjects who were not enrolled were younger than their nonwhite counterparts and because of this may have had milder tremor. Third, one might question whether our diagnostic protocol was ethnically biased. It is hypothetically possible that white subjects whose tremor was of borderline severity were more often diagnosed as having ET, while nonwhite subjects were more often diagnosed as normal, resulting in a larger proportion of false positives among white subjects with ET. If this were the situation, one would expect that white control subjects would have had lower total tremor scores than nonwhite control subjects because more of the white subjects with tremor of borderline severity would have been diagnosed as having ET. This was not the case. Among 59 control subjects participating in WHIGET, the total tremor score was similar across ethnic groups: white group, 6.4; African American group, 5.6; and Hispanic group, 7.4 (P = .36).

In summary, there may be ethnic differences in the expression of tremor in ET, and these differences suggest that the disease is not homogeneous. Explanations for this variability in tremor expression include variability in underlying genotypes or variability in exposure to environmental risk factors. It is important to confirm the presence of these ethnic differences in ET, since these differences suggest the existence of genetic or environmental factors that could modify the expression of this condition.

Accepted for publication October 12, 1999.

This study was supported in part by grants NS01863 and P30 ES09089 from the National Institutes of Health.

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