Clinical Subtypes of Essential Tremor

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Background: There is clinical variability in essential tremor (ET), but it is not clear whether this variability is because of the existence of distinct clinical subtypes of ET (ie, forms of ET that may differ in their etiology, rate of progression, or response to treatment).

Objectives: To examine in a group of ET cases the age of onset, anatomic distribution, and rate of progression of tremor, and to look for associations between these factors.

Methods: Cases of ET were ascertained from a community (n=60) and a tertiary referral clinic (n=55) in northern Manhattan, New York, NY. All subjects underwent an interview and videotaped tremor examination. Rate of progression was estimated based on the tremor severity and reported disease duration at the time of evaluation.

Results: Age of onset was bimodally distributed in clinic cases. There were differences in the anatomic distribution of the tremor (arm tremor only vs head and arm tremor vs isolated head tremor). Rate of progression was distributed exponentially; there was a large cluster of subjects with slower rates of progression, and a smaller number who had faster rates. There was an association between age of onset and rate of progression ($r = 0.46-0.50, P < .002$); cases with older age of onset (>60 years) progressed more rapidly ($P < .001$). In addition, upper limb tremor progressed more slowly among those with concomitant head tremor ($P = .03$).

Conclusions: Essential tremor is not a homogeneous condition. There are differences in age of onset, anatomic distribution of tremor, and rate of progression. The ET in several groups of patients in this study (those with age of onset >60 years and those without head tremor) progressed more rapidly, suggesting that these ET cases may define distinct clinical subtypes. These subtypes should be further assessed for etiologic and genetic heterogeneity as well as differences in responsiveness to therapeutic agents.

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SUBJECTS AND METHODS

Subjects with ET came from 2 geographic locations: a community in northern Manhattan, New York, NY, and a tertiary referral center for patients with involuntary movements.

SUBJECTS ASCERTAINED FROM THE WASHINGTON HEIGHTS–INWOOD COMMUNITY

Residents aged 65 years or older (N=2117) of the Washington Heights–Inwood community in northern Manhattan were enrolled in a longitudinal, community-based study of health issues in the elderly, the Northern Manhattan Aging Project. All subjects underwent a 90-minute medical interview and a standardized examination conducted by a neurologist, and individuals with ET were identified and enrolled in a second study, the Washington Heights–Inwood Genetic Study of Essential Tremor (WHIGET), a community-based family study of ET.

SUBJECTS ASCERTAINED FROM THE CLINIC

The Center for Parkinson’s Disease and Other Movement Disorders at Columbia-Presbyterian Medical Center, New York, is a large referral center for patients with involuntary movement disorders. All patients have been examined by attending neurologists who specialize in movement disorders. A computerized database provides demographic and clinical information on all patients evaluated since 1983. A search for the diagnosis “essential tremor” yielded 794 names. These were selected at random and their clinical records reviewed to ensure that there was no accompanying dystonia or Parkinson disease. They were then contacted for enrollment in a study of the functional correlates of ET. Fifty-five (63.2%) of 87 patients participated; 16 (18.4%) could not be located; 15 (17.2%) refused; and 1 patient (1.2%) died.

THE CADET AND WHIGET PROTOCOL (TREMOR INTERVIEW AND EXAMINATION)

All participants in the Columbia University Assessment of Disability in Essential Tremor (CADET) and WHIGET underwent a 30-minute semistructured tremor interview and a 10-minute videotaped tremor examination. The 84-item, 30-minute tremor interview was conducted in person. The interviewer collected information on the distribution and severity of tremor, use of different tremor medications, and presence (≥1 first- or second-degree relative reported to have ET) or absence of a family history of ET. The subject was also asked “how old were you when you first noticed tremor?” Before recording a response, the interviewer was instructed to ask each of the following additional questions to increase the likelihood that the subject’s response was accurate: (1) “Did you have tremor when you were a child?” (2) “Did you have tremor when you were an adolescent?” (3) “Did you have tremor as a young adult?” (4) and “Did you have tremor in middle age?” Patients were consistent about their reported age of onset; test-retest reliability over a 1-year follow-up period was excellent (r>0.90).

The 26-item, 10-minute videotaped tremor examination was designed to elicit tremor during 6 tasks (sustained arm extension, pouring water, drinking water, using a spoon, finger-to-nose movements, and drawing spirals). Each task was performed with the dominant arm and nondominant arm.

TREMOR RATING AND ASSIGNMENT OF DIAGNOSES

In WHIGET, 2 neurologists specializing in movement disorders (E.D.L. and B.F.) independently reviewed the material from each subject’s tremor interview and videotaped tremor examination. In CADET, 1 neurologist (E.D.L.) reviewed this material. The reviewers rated the severity of tremor that occurred during different tasks. Ratings were 0, no visible tremor; 1, low-amplitude tremor or intermittent tremor; 2, tremor of moderate amplitude, clearly oscillatory, and usually present; and 3, high-amplitude tremor resulting in difficulty completing the task. A total tremor score (range, 0-36 [maximum tremor]) was calculated for each subject by the addition of the 6 task-specific scores on each side. Head tremor was rated as either present or absent.

Each reviewer 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. Diagnoses of definite ET required (1) postural tremor rated as 2; (2) kinetic tremor rated as 2 during 4 tasks; and (3) tremor that by history interfered with at least 1 activity of daily living. The diagnosis of probable ET required a kinetic tremor rated as 2 during 4 tasks or a head tremor. The diagnosis of possible ET required a kinetic tremor rated as 2 during 3 tasks.

This diagnostic protocol has proven reliable. Two neurologists assigning diagnoses to 226 subjects (52 patients with ET and 174 control subjects) demonstrated excellent interrater reliability (weighted k statistic, 0.84, indicating nearly perfect agreement).

STATISTICAL ANALYSES

When a total tremor score was assigned by 2 neurologists in WHIGET, the mean was used. Head tremor was considered present only if both raters agreed it was present. A measure of the rate of progression of tremor was estimated. Rate of progression was calculated by dividing the total tremor score by disease duration in years as reported by the patient. An older age of onset did not necessarily imply a more rapid rate of progression. Among individuals with an older age of onset, a slower rate of progression could occur in the context of a low total tremor score or an older current age. Correlation between continuous variables was assessed using Pearson’s correlation coefficients (r). Multiple linear regression models were used, with a stepwise approach.
Among subjects with ET from the community group, 10 (16.7%) of 60 had head tremor. Among these 10, the mean (SD) total tremor score was 19.7 (11.2) (range, 5-36). Because a tremor rating of 1 is present for 1 or more tasks in 96% of normal subjects, we analyzed our data on tremor ratings of 2 and 3 (tremor of at least moderate amplitude). The distribution of subjects according to the number of tasks that received tremor ratings higher than 1 was as follows: 0 tasks, 2 subjects; 1 task, 1 subject; 3 tasks, 1 subject; 6 tasks, 2 subjects; and 12 tasks, 4 subjects. Two (3.3%) of 60 subjects had isolated head tremor (ie, tremor ratings of 2 on 0 tasks); 8 (13.3%) had head and arm tremor; and 50 (83.3%) had arm tremor without head tremor.

**ANATOMIC DISTRIBUTION OF TREMOR**

Among clinic cases, 14 (25.5%) of 55 had head tremor. Among these 14, the mean (SD) total tremor score was 24.2 (8.7) (range, 7-34). The distribution of subjects according to the number of tasks that received tremor ratings higher than 1 was as follows: 1 task, 2 subjects; 3 tasks, 1 subject; 7 tasks, 2 subjects; 11 tasks, 4 subjects; 12 tasks, 5 subjects. None of the subjects had isolated head tremor.

**RATE OF PROGRESSION**

Among 36 subjects from the community group who recalled their age of onset, the mean (SD) rate of progression was 4.4 (4.4) tremor score points per year (median, 3; range, 0.1-20). Among 54 clinic cases, the rate of progression was 1.7 (1.7) tremor score points per year (median, 1.4; range, 0.2-10). Data were exponentially distributed for both community and clinic cases.

The apparent difference between community and clinic cases in rate of progression was due to the older age of onset of ET in community cases. When rate of progression was the outcome variable in a multiple linear regression model with independent variables including age of onset, disease duration, current age, ethnicity, family history of ET (present vs absent), currently taking a medication to treat tremor (yes vs no), and source of ascertainment (clinic vs community), only age of onset (P<.001) was associated with rate of progression.

**ASSOCIATION BETWEEN AGE OF ONSET AND RATE OF PROGRESSION**

Age of onset was correlated with rate of progression in community cases (r=0.50; P=.002) and in clinic cases.
(r=0.46; P=.001), suggesting that the older the age of onset, the more rapid the progression (Figure 4). In separate multiple linear regression models, age of onset was correlated with rate of progression in community cases (P=.001) and in clinic cases (P<.001), independent of current age. In general, subjects with age of onset older than 60 years had a faster rate of progression than did subjects who were younger than 60 years at age of onset (Figure 4), with respective rates of progression being 4.6 vs 1.2 tremor score points per year (t=5.6; P<.001).

Few of our subjects were older than 90 years. It is possible that we systematically excluded subjects whose tremor began in their 70s or 80s and progressed slowly. These subjects might not yet have come to medical attention because of their slower rate of progress and milder tremor. However, when we examined our data from the community (ie, from subjects with ET who were not selected based on whether they came to medical attention), subjects whose tremor began at or after age 70 years did not have milder tremor than those whose tremor began at an earlier age (total tremor scores, 22.2 vs 20.8, respectively; t=0.61, P=.55), suggesting that we did not systematically exclude subjects with slow progression and older ages of onset.

ASSOCIATION BETWEEN RATE OF PROGRESSION AND ANATOMIC DISTRIBUTION OF TREMOR

Among subjects in the community group, those with head tremor (with or without arm tremor) experienced slower progression in the severity of their arm tremor than did those without head tremor (rate of progression, 2.34 [2.16] vs 5.14 [3.01] tremor points per year; t=2.39; P=.03). A similar relationship occurred among clinic cases (1.58 [0.97] vs 2.16 [3.01] tremor points per year; t=1.08; P=.49), although this was not significant.

ASSOCIATION BETWEEN AGE OF ONSET AND ANATOMIC DISTRIBUTION OF TREMOR

Among clinic cases, the mean [SD] age of onset was similar in those with and without arm tremor (46.79 [24.32] vs 42.3 [20.89] years; t=0.62; P=.55). A similar relationship occurred in community cases (61.67 [19.07] vs 66.81 [22.01] years; t=0.67; P=.52).

COMMENT

We studied the clinical features of 2 groups of subjects with ET. In clinic cases, age of onset was bimodally distributed. Bain et al,1 in a study of hereditary ET, and Lou and Jankovic12 similarly reported a bimodal distribution in age of onset with peaks in the second and sixth decades of life. In these studies, the perceived decline in the number of subjects in whom age of onset occurred after the sixth decade may be an artifact of the sampling frame, with a relatively small proportion of subjects who were in their seventh decade of life and older. In our community cases, with a mean age of 80 years, the older age of onset peak continued into the eighth and ninth decades (Figure 1).

In our cohort, subjects could be divided into those with isolated arm tremor, those with head and arm tremor, and those with isolated head tremor. Most had isolated arm tremor; less than one quarter had arm and head tremor; and only a small proportion had isolated head tremor. In other series, the proportions of subjects with both arm and head tremor were 21.4%, 14 35%, 1 52.9%, 15 and 75.4%, 16 respectively, and the proportions with isolated head tremor were similarly low: 0%, 15 1%, 1 and 9.1%, 16 respectively.

Variation in the rate of progression of ET has not been studied previously. We found that the rate of progression varied considerably, and that the variance was distributed exponentially. There was a large cluster of individuals with a slower rate of progression, and a smaller number who had considerably faster rates of progression (Figures 2 and 3).

We demonstrated differences between ET cases in terms of age of onset, anatomic distribution of tremor, and rate of progression. We tested whether this clinical variability was a result of the existence of distinct clinical subtypes of ET, and demonstrated that several forms
of ET (defined by age of onset and location of tremor) differed in rate of progression. There was an association between age of onset and rate of progression; patients with older age of onset (>60 years) progressed more rapidly ($P < .001$). Also, subjects with both head and arm tremor experienced slower progression in arm tremor.

Our data suggest that ET cases with older age of onset progress more rapidly than those with younger age of onset. There are no other studies of rate of progression in ET, but clinicians have previously commented on this phenomenon. Critchley\(^2\) noted that “in later life . . . the tremor may . . . progress with some rapidity.” Similarly, Hornbrook and Nagurney\(^16\) noted that “a slow progression seems to occur in most people, and this may be accelerated by old age.”

Cases of ET with head tremor progressed more slowly in terms of arm tremor than did those without any head tremor. There is other evidence to suggest that patients with ET with head tremor may form a distinct clinical subtype. Groups of patients with head tremor differ in sex distribution (there is a positive association between head tremor and female sex),\(^2\) and they may respond differently (ie, either less or more responsive) than individuals with arm tremor to numerous standard therapies, including \(\beta\)-blocking agents,\(^18\) methazolamide,\(^19\) and barbiturates.\(^20\)

This study was not without limitations. First, estimates of rate of progression were not based on longitudinal prospective assessments of the change in tremor severity; rather, rate of progression was estimated based on the severity of tremor at the time of the evaluation divided by tremor duration in years. Prospective longitudinal data would not be subject to the issue of recall bias. Second, while we have demonstrated that patient’s estimates of age of onset are highly reliable (ie, patients are consistent in their reporting),\(^10\) there are no data on the validity of these reports or on the validity of age of onset data in ET in general. A systematic bias in retrospective recall of age of onset is hypothetically possible. For example, if older subjects systematically underestimated the duration of their tremor, then we would have overestimated their rate of progression. We tested this hypothesis by examining our data on reported age of onset of our 27 patients with ET who were older than 80 years, finding that 9 (33.3%) reported an age of onset older than 80 years; 8 (29.6%), between 70 and 79 years, and the remaining 10 (37.1%), prior to age 70 years. In the 1 incidence study of ET,\(^13\) 30.6% of ET cases arose after age 80 years; 27.8%, between 70 and 79 years; and the remaining 41.6%, prior to age 70 years. These published epidemiological data on age of onset in ET are consistent with our data on reported age of onset above.

Third, in these analyses, we assumed a linear rate of progression. If rate of progression were initially rapid and then leveled off, late-onset cases would more likely be classified as rapid progressors. Conversely, if rate of progression were initially slow and then more rapid, and late-onset cases had not yet reached the more rapid phase, they might be classified as slow progressors. Fourth, among those with head tremor, most cases had considerable arm tremor, and we studied the rate of progression of arm rather than head tremor. Finally, we chose to study a small and focused number of clinical features of ET, and did not examine all of the sources of variability in the expression of ET (eg, responsiveness to alcohol or electrophysiological properties), which have been examined previously.\(^4,12\)

In summary, ET is not a uniform disorder. There are differences between cases in their age of onset, anatomic distribution of tremor, and rate of progression. We demonstrated that some forms of ET differ with regard to rate of progression, suggesting that several clinical measures (age of onset and location of tremor) may define distinct clinical subtypes of ET. These subtypes should be assessed further for the possible presence of etiologic and genetic heterogeneity as well as different responses to therapy.

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REFERENCES