Is Essential Tremor Symmetric?
Observational Data From a Community-Based Study of Essential Tremor
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Background: Essential tremor (ET) has been variably portrayed in the literature both as a symmetric arm tremor and as an asymmetric arm tremor. Few quantitative clinical or neurophysiological data specifically address the issue of tremor asymmetry in ET.

Objectives: To examine a community-dwelling cohort of subjects with ET to (1) estimate the prevalence of tremor asymmetry and (2) quantify the magnitude of tremor asymmetry.

Methods: Fifty-four subjects with ET, identified in a community-based study of ET in New York City, underwent a Tremor Interview and a videotaped Tremor Examination. The examination included 6 tasks: sustained arm extension, pouring water, drinking water, using a spoon, finger-to-nose movements, and drawing spirals with each arm. Two neurologists rated the severity of tremor using a 0 to 3 clinical rating scale and a total tremor score was calculated (range, 0-36). Fourteen (25%) of 54 subjects also underwent quantitative computerized tremor analysis.

Results: The prevalence of asymmetry depended on the definition of asymmetry; small to moderate differences between sides were common. The mean side-to-side difference in clinical ratings for each of the 6 tasks was 0.54 of 3 points, which represented a 1.32-fold difference between sides. Clinical rating scores were higher in the nondominant arm in 39 subjects (72%), higher in the dominant arm in 9 (17%), and equal in 6 (11%). The 2 left-handed subjects had higher clinical ratings on the right. During quantitative computerized tremor analysis, there was a 1.71-fold mean difference between tremor amplitudes in the dominant and nondominant sides, and in 12 subjects (86%), the maximum tremor amplitude was in the nondominant arm.

Conclusions: Small to moderate differences between sides were common in ET. In most community-dwelling subjects, tremor amplitude was greatest in the nondominant arm. In contrast, clinic-based studies have reported greater tremor in the dominant arm; those with ET who seek medical attention are more likely to exhibit severe tremor in their dominant arms. This study documents that mild asymmetry is a fundamental property of ET and that tremor is more severe in the nondominant arm.

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ESSENTIAL TREMOR (ET) is one of the most common neurologic disorders.1 Published statements2-14 differ regarding the asymmetry of arm tremor, providing the reader with a confusing set of contradictory statements. Some studies7-9 have suggested that asymmetry is uncommon, while others3-6 have suggested that it may be common. Many others1,10-14 have not commented. In fact, the prevalence of asymmetry and the magnitude of asymmetry of arm tremor have been the focus of little systematic investigation. The importance of such an investigation is that it might provide additional insight into the underlying physiological features of ET, a disorder with as yet no consistently identified pathological changes at autopsy.2 In this study, using data from a large population-based study examining the prevalence, clinical features, and the familial aggregation of ET, we examined the issue of whether ET is symmetrical. The specific aims of this study are (1) to estimate the prevalence of asymmetry of arm tremor in ET and (2) to quantify the magnitude of asymmetry of arm tremor using clinical and neurophysiological measures.

RESULTS

SUBJECT CHARACTERISTICS

To date, 236 subjects have been enrolled in WHIGET, including 33 subjects with ET, 40 control subjects, and 163 rela-
SUBJECTS AND METHODS

SOURCE POPULATION

A number of subjects (n = 2117), aged 65 years or older, who were residents of Washington Heights–Inwood, northern Manhattan, NY, were enrolled in a longitudinal, community-based study of health issues in the elderly, the Northern Manhattan Aging Project.1 Subjects underwent a 90-minute medical interview and a standardized medical and neuropsychologic examination conducted by a neurologist, and subjects with ET were identified.1

These subjects with ET are currently being enrolled in a second study, the Washington Heights–Inwood Genetic Study of Essential Tremor (WHIGET). The WHIGET is an ongoing study aiming to obtain a valid estimate of the extent of familial aggregation of ET.15,16 In addition to the subjects with ET, the following subjects are also being enrolled in WHIGET: (1) control subjects, (2) first- and second-degree relatives of the subjects with ET, and (3) first- and second-degree relatives of the control subjects. The control subjects were matched by age, sex, and ethnicity to the ET cases. All control subjects had undergone a medical interview, and all but 5 also underwent a standardized medical and neuropsychologic examination as part of the Northern Manhattan Aging Project.

For ethnic group classification, we used the format suggested by the 1990 US Census Bureau that identified Hispanics as a cultural group, reporting this population as a proportion of the total.17 For this study, we used the categories African American, white (non–Hispanic white), and Hispanic.

WHIGET PROTOCOL (TREMOR INTERVIEW, EXAMINATION, AND ASSIGNMENT OF DIAGNOSES)

All participants in WHIGET (including subjects with ET, control subjects, and their respective relatives) underwent a 30-minute semistructured Tremor Interview and a 10-minute videotaped Tremor Examination.15,16 The 84-item Tremor Interview was conducted in person by a study physician and included 12 questions designed to screen for ET.15,16 The interviewer also collected information on the distribution and severity of tremor, change in these parameters over time, effects of alcohol, cigarettes, and caffeine consumption, the use of different tremor medications and the effectiveness of these medications, change in tremor with activity or rest, specific functional impairments resulting from tremor, concurrent medical conditions, and medications.

The 26-item, 10-minute videotaped Tremor Examination was designed to elicit tremor during 6 different tasks.15,16 The 6 tasks were sustained arm extension, pouring water between 2 cups, drinking water from a cup, using a spoon to drink water, finger-to-nose movements, and drawing spirals. Each task was first performed with the dominant arm and then performed with the nondominant arm.

Two neurologists (E.D.L. and B.F.) specializing in movement disorders, who were shielded from the individual’s status as a case subject, a control subject, or a relative, randomly and independently reviewed each subject’s Tremor Interview and videotaped Tremor Examination.15,16 The reviewers rated the severity of tremor as observed during different tasks. Ratings were on an ordinal scale (from 0 to 3), similar to that of Fahn et al.18 The ratings were 0, no visible tremor; 1, low amplitude/barely perceivable tremor or intermittent tremor; 2, tremor of moderate amplitude (1-2 cm), clearly oscillatory, and usually present; and 3, large amplitude (>2 cm), violent, jerky tremor resulting in difficulty completing the task due to spilling or inability to hold a pen to paper. A total tremor score (maximum, 36) was calculated for each subject by the addition of the 6 task-specific scores on each side.15,16 Head tremor was rated as either present or absent.

Each reviewer independently assigned a diagnosis of ET (definite, probable, or possible) or normal based on tives. A diagnosis of ET was made for 56 subjects that included the 33 subjects with ET and 23 affected relatives. Diagnoses in these 56 include definite ET (n = 15), probable ET (n = 21), and possible ET (n = 20), based on previously published diagnostic criteria.15,16 Two subjects with possible ET had missing data points. Hence, the analyses were conducted on 54 subjects with ET (Table 1). The subjects were largely untreated and had tremor of moderate severity (mean total tremor score, 18.4 of 36) and of moderate duration (mean duration, 18.2 years).

CLINICAL RATINGS

All 54 subjects had bilateral arm tremor. The prevalence of asymmetry depended on the definition of asymmetry (Table 2). When asymmetry was defined as a difference of 0.5 or more between the dominant and the nondominant side tremor scores, the prevalence was 89% (48 of 54 subjects); when asymmetry was defined as a difference of 3.0 or more between the dominant and the nondominant side tremor scores, the prevalence was 37%; and when asymmetry was defined as a difference of 6.0 or more between the dominant and the nondominant side tremor scores, the prevalence was 6% (Table 2). The nondominant side tremor score was higher than the dominant side tremor score in 39 subjects (72%) vs 9 subjects (17%) in whom the converse was true. In 6 subjects (11%), the 2 scores were identical.

For each subject, the tremor rating for each of 6 tasks on the nondominant side (range, 0-3) was subtracted from the tremor rating for the same task on the dominant side (range, 0–3), and the absolute value of the difference was obtained (range, 0–3). The mean side-to-side difference for each of the 6 tasks was 0.54 of 3 rating points. Given the fact that these subjects exhibited a mean clinical rating score of 1.53 points of a potential 3 points, there was a 1.32-fold mean difference between the 2 sides for each of the 6 tasks.

All individuals performed 6 tasks with each arm and these tasks were rated. In 35 (65%) of 54 subjects, 3 or more of the 6 tasks received higher ratings on 1 of the 2 sides (on the nondominant side in 28 subjects and on the dominant side in 7 subjects). In most subjects (87%), 3 or more of the 6 tasks received higher
Tremor amplitudes were derived off line by double integration of wrist accelerometric data after filtering out low-frequency drift (<2 Hz) and averaging. 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 as described previously.19,20

DATA ANALYSIS

Analysis of clinical data was performed using 2 neurologists’ (E.D.L. and B.F.) mean tremor rating scores. Tremor scores based on clinical ratings included (1) a dominant side tremor score (range, 0-18), which was the sum of the tremor ratings for each of the 6 tasks performed with the dominant arm; (2) a nondominant side tremor score (range, 0-18), which was the sum of the tremor ratings for each of the 6 tasks performed with the nondominant arm; and (3) a total tremor score (range, 0-36), which was the sum of each of the previous 2 scores. Tremor asymmetry was the arithmetic difference between the dominant and the nondominant side tremor scores; the potential range was 0 to 18. Using QCTA data, a total right-sided tremor amplitude was calculated for each subject by summing the mean tremor amplitude during right arm extension, finger-to-nose movements, and pouring. A similar calculation was performed with data derived from tasks performed with the left arm. Tremor asymmetry was defined neurophysiologically as any difference in total right-sided and total left-sided tremor amplitudes.

Side-to-side comparisons between continuous variables were made with the paired t test and analysis of variance. Forward stepwise linear regression analysis was performed. The outcome variable was the difference in the dominant and nondominant side tremor scores, a measure of the magnitude of tremor asymmetry. The independent variables were age, sex, ethnicity, tremor duration, and total tremor score.

NEUROPHYSIOLOGICAL (QCTA) DATA

The 14 subjects who were randomly selected to undergo QCTA were similar to the 40 subjects who did not undergo QCTA in terms of their sex (64% female vs 53% female) ($\chi^2 = 0.58; P = .44$), median age (78 years vs 73 years), and mean total tremor score (22.8 vs 18.1; $t = 1.8; P = .09$).

There were side-to-side differences in tremor amplitude for each of the 6 items (distal arm extension, proximal arm extension, distal finger-to-nose movements, proximal finger-to-nose movements, distal pouring water, and proximal pouring water) in all the subjects (Table 4). For each of the 14 subjects, a total right-sided tremor amplitude and a total left-sided
The prevalence and magnitude of asymmetry of arm tremor in ET have been the subject of numerous incidental comments in the neurologic literature; however, the topic has been the focal point of few prior systematic investigations, and quantitative neurophysiological data on tremor asymmetry are limited. Precise clinical data are important because the diagnosis of ET is still based exclusively on clinical information rather than serologic study findings, neuroimaging results, or pathologic findings. Quantitative data such as these could serve as a reference in diagnostic settings. In our study, using data from a large population-based cohort of subjects with ET, we documented the prevalence of asymmetry in ET and quantified its magnitude using clinical and neurophysiological measures of tremor severity. One of the strengths of this study was that subjects were all ascertained from the community rather than a clinic. Subjects attending clinics are more likely to have been self-selected for the presence of severe or disabling tremor in the dominant arm, and this type of selection bias could significantly alter the results of a study focusing on the phenomenon of tremor asymmetry.

We demonstrated that the prevalence of tremor asymmetry depended on the definition of asymmetry. A small difference between sides (≥0.5 points by clinical ratings) was detected in 89% of subjects, a moderate difference (between 2.0 and 5.0 points by clinical ratings) was detected in 15% to 48% of subjects, and large differences (≥10.0 points by clinical ratings) was detected in few subjects. The magnitude of asymmetry was examined both clinically and neurophysiologically, and the results were similar (1.32-fold vs 1.71-fold mean difference between sides), implying that on average there was a modest (<2-fold) difference between sides. During QCTA, this translated into a side-to-side difference in maximally observed tremor amplitudes of 0.03 to 15.4 mm (mean, 3.9 mm).

Tremor frequencies were assessed with QCTA. The range of frequencies was 0.7 to 11.1 Hz, and the predominant frequencies were identical on the 2 sides.

### Table 1. Characteristics of 54 Subjects With Essential Tremor

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24 (44)</td>
</tr>
<tr>
<td>Female</td>
<td>30 (56)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>18 (33)</td>
</tr>
<tr>
<td>African American</td>
<td>19 (35)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>17 (32)</td>
</tr>
<tr>
<td>Mean age, y (range)</td>
<td>70.3 (20-96)</td>
</tr>
<tr>
<td>No. of subjects ≤40 y</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Handedness</td>
<td></td>
</tr>
<tr>
<td>Right-handed</td>
<td>52 (96)</td>
</tr>
<tr>
<td>Left-handed</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Mean total tremor score*</td>
<td>(range) 18.4 (5-34.5)</td>
</tr>
<tr>
<td>Answered “yes” to at least 1 screening question for essential tremor†</td>
<td>28 (52)</td>
</tr>
<tr>
<td>Mean tremor duration, y (range)</td>
<td>18.2 (1-68)</td>
</tr>
<tr>
<td>No. currently treated with a tremor-suppressing medication</td>
<td>2 (4)</td>
</tr>
<tr>
<td>No. with head tremor</td>
<td>4 (7)</td>
</tr>
</tbody>
</table>

*The possible range of the total tremor score is 0 to 36, with 0 indicating no tremor.
†Twelve screening questions were included in the 84-item Tremor Interview.

### Table 2. Clinically Rated Tremor Asymmetry and Diagnostic Categories

<table>
<thead>
<tr>
<th>Tremor Asymmetry†</th>
<th>All Subjects (N = 54)</th>
<th>Definite ET (n = 15)</th>
<th>Probable ET (n = 21)</th>
<th>Possible ET (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.5</td>
<td>48 (89)</td>
<td>13 (87)</td>
<td>20 (95)</td>
<td>15 (83)</td>
</tr>
<tr>
<td>≥1.0</td>
<td>37 (69)</td>
<td>8 (53)</td>
<td>18 (86)</td>
<td>11 (61)</td>
</tr>
<tr>
<td>≥2.0</td>
<td>26 (48)</td>
<td>6 (40)</td>
<td>11 (52)</td>
<td>9 (50)</td>
</tr>
<tr>
<td>≥3.0</td>
<td>20 (37)</td>
<td>6 (40)</td>
<td>7 (33)</td>
<td>7 (39)</td>
</tr>
<tr>
<td>≥4.0</td>
<td>14 (26)</td>
<td>5 (33)</td>
<td>5 (24)</td>
<td>4 (22)</td>
</tr>
<tr>
<td>≥5.0</td>
<td>8 (15)</td>
<td>3 (20)</td>
<td>3 (14)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>≥6.0</td>
<td>3 (6)</td>
<td>1 (7)</td>
<td>2 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>≥10.0</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Values are number (percentage). ET indicates essential tremor.
†Tremor asymmetry was the arithmetic difference between the dominant and the nondominant side tremor scores.

### Table 3. Magnitude of Clinically Rated Tremor Asymmetry During Different Tasks

<table>
<thead>
<tr>
<th>Posture or Task</th>
<th>Difference Between Dominant and Nondominant Side Tremor Scores*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pouring water between 2 cups</td>
<td>0.72</td>
</tr>
<tr>
<td>Drawing spirals</td>
<td>0.68</td>
</tr>
<tr>
<td>Using a spoon to drink water</td>
<td>0.60</td>
</tr>
<tr>
<td>Arm extension</td>
<td>0.48</td>
</tr>
<tr>
<td>Drinking water from a cup</td>
<td>0.42</td>
</tr>
<tr>
<td>Finger-to-nose movements</td>
<td>0.33</td>
</tr>
</tbody>
</table>

*Maximum difference equals 3.0. All values are absolute values.
in 87% of subjects, 3 or more of the 6 tasks received higher ratings on one side, with the remaining tasks predominantly rated as equal. Hence modest side-to-side differences were commonly observed during multiple tasks, representing a true fixed property of ET.

While the extent of tremor asymmetry observed in ET in this study was modest in comparison with differences commonly observed in subjects with Parkinson disease and cerebellar disorders, this does not diminish the finding that mild to moderate side-to-side differences in ET are common.

There are numerous incidental comments in the literature regarding the asymmetry of ET. Several studies provided data on the prevalence of clinically rated asymmetry, with different estimates including 6 (18%) of 34 cases, 9 (22%) of 41 cases, 7 (23%) of 30 cases, and 5 (36%) of 14 cases. Biary and Koller reported more than 25% asymmetry in 60 (62%) of 97 cases. Some of the variability in prevalence estimates may be due to differences in tremor rating scales and differences in the definitions of asymmetry.

Only 1 of the above studies clinically or neurophysiologically quantified the magnitude of tremor asymmetry. Using accelerometry to quantify tremor amplitude as less than 25%, 25% to 50%, or more than 50% different between sides, a difference of 25% or more was observed in 67% of subjects.
more was reported in 60 (62%) of 97 subjects. One additional study examined the magnitude of clinically rated tremor asymmetry during arm extension and drawing in 91 subjects with mild familial ET. The group's right arm tremor score was similar to the left. However, side-to-side asymmetries within individuals may not be reflected in mean statistics of entire groups.

As noted earlier, one advantage of this cohort is that the subjects with ET were not selected from a specialty clinic. Subjects in clinic-derived cohorts are self-selected to express severe and disabling tremors in their dominant arms. One study of a clinic-based sample of patients with ET demonstrated that right-handed subjects with ET had a significantly greater incidence of right-sided tremors than left-sided tremors and that left-handed patients had a significantly greater incidence of left-sided tremors.

We found that the tremor was usually more severe on the nondominant side. Interestingly, the 2 left-handed subjects had tremor that was clinically more severe on the right (nondominant side). Hornbrook and Nagurney, in a community-based study of 175 subjects with ET in Papua, New Guinea, also noted that both postural and kinetic tremor were more marked in the nondominant arm. In contrast, as noted earlier, clinic-based samples are more likely to demonstrate severe tremor in the dominant arm because of referral bias.

There are several possible explanations for the observed greater severity of ET in the nondominant arm in subjects recruited from community-based studies. The most likely explanation is that tremor severity is related to the phenomenon of human hand preference (handedness). Several physiological and developmental observations support a possible relation between handedness and tremor severity. There are anatomical and physiological asymmetries in the human nervous system that are associated with handedness. The human corticospinal tract is asymmetric at the time of birth, with the left pyramids (ie, those innervating the dominant side of the body) larger than and decussating prior to the right pyramids. Findings from transcranial magnetic stimulation studies reveal that the excitement threshold of cortical neurons is lower on the side that is contralateral to the dominant hand, regardless of whether the subject is right- or left-handed. Learned, repetitive, highly skilled motor behaviors may lead to further motor cortical reorganization and side-to-side asymmetries. For example, the motor cortical representation of the reading finger in Braille readers is enlarged on the side contralateral to the dominant reading hand. Although the physiological basis of ET is not known, it seems plausible that a lack of fine motor development and dexterity in the nondominant arm allows a greater limb perturbation during fine tasks. The higher amplitude of ET in the nondominant arm may reflect a lesser degree of precision and control of motor programs in the nondominant arm and the inability to filter unwanted mechanical reflex perturbations. Differential central processing of afferent information may also play a role in the development of side-to-side amplitude differences in ET. Studies have noted that physiological tremor is also of lower amplitude in the dominant arm, perhaps reflecting a similar modulation of tremor by motor programs in the dominant arm. Alternatively, one might hypothesize that our results are related to the issue of onset of tremor. Essential tremor is often asymmetric at onset. One might hypothesize that for unclear reasons ET usually first manifests itself pathologically in the nondominant cerebellar hemisphere, and the arm in which ET first develops might always exhibit a more severe tremor. Arguing against this is the observation that all our patients who complained of tremor either first noticed the tremor in their dominant arm or in both arms simultaneously. None of these patients first noticed tremor in their nondominant arm. However, tremor may be very mild at onset, and tremor in the nondominant arm may be asymptomatic in the early stages of the disease.

One limitation of this study is that the clinical tremor ratings were restricted to 4 gradations (0 to 3). Subtle differences between sides might not have been measurable using a 0 to 3 scale. The ultimate effect on our results might have been to create more conservative estimates for the prevalence and magnitude of clinically rated tremor asymmetry. On the other hand, the total tremor score was 36, consisting of the addition of ratings during multiple tasks. Some of these tasks (eg, pouring or drinking water) may have been measuring similar underlying physiological phenomena, and the addition of multiple similar items may have overestimated the true difference between sides. Despite these caveats, the QCTA served as an independent measure of tremor amplitude that confirmed the results of the clinical ratings. Finally, the cohort consisted predominantly of older individuals and our results may not be generalizable to younger subjects with ET.

To conclude, small to moderate side-to-side differences were commonly observed in ET (on the order of 1.32- to 1.71-fold), with several tasks (eg, pouring water and drawing spirals) being more asymmetric. In most community-dwelling subjects, tremor amplitude was greatest in the nondominant arm. In contrast, clinic-based studies have reported greater amplitudes in the dominant arm; those with ET who seek help are more likely to exhibit severe tremor in their dominant arms. Our study documents that modest asymmetry is a fundamental property of ET and that tremor severity is greater in the nondominant arm. These findings may provide additional clues regarding the underlying physiological features of ET.

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