Diagnostic Criteria for Essential Tremor

A Population Perspective

Elan D. Louis, MD, MS; Blair Ford, MD; Helen Lee, MS; Howard Andrews, PhD; Gabriella Cameron, MD

Background: Prevalence estimates vary 2750-fold among the 20 studies of essential tremor (ET). It is not clear how the choice of diagnostic criteria affects research results.

Objective: To determine the impact of alternative sets of diagnostic criteria on the diagnosis of ET.

Methods: As part of the Washington Heights-Inwood Genetic Study of ET (WHIGET), a population-based study of ET, 285 subjects who include 36 case subjects with probable or definite ET, 34 case subjects with possible ET, and 215 normal subjects were interviewed and examined. All diagnoses in WHIGET were assigned by 2 neurologists. Ten of the 20 published prevalence studies of ET provided diagnostic criteria for ET. Criteria differed in terms of requirements for the distribution, duration, and severity of tremor. These 10 sets of criteria were then each separately applied to the subjects in the WHIGET cohort to determine their impact on the diagnosis of ET.

Results: Depending on which diagnostic criteria were applied to the WHIGET cohort, the proportion of WHIGET case subjects with definite or probable ET who would have been diagnosed as having ET was as low as 14% and the proportion of WHIGET normal subjects who would have been diagnosed as having ET was as high as 51%. Diagnostic criteria that included a positive family history of ET or a lengthy duration of tremor would have classified many WHIGET case subjects with ET as normal, whereas criteria that did not specify a minimal tremor severity would have classified many WHIGET normal subjects as having ET.

Conclusions: Alternative sets of diagnostic criteria for ET greatly impact on the diagnosis of ET. For population-based studies, information on tremor type and severity rather than family history should be included in diagnostic criteria.

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ESSENTIAL tremor (ET) is one of the most common adult neurologic disorders,1-4 as much as 20 times more prevalent than Parkinson disease.3 Prevalence estimates vary tremendously, from 0.008% to 22%, representing a 2750-fold difference.1,5-23 Some portion of this variability is probably due to true genetic or environmental differences between study cohorts and another similarly unknown portion is probably due to differences in study methodologies and diagnostic criteria for ET. The diagnosis of ET is based on clinical findings; biological markers and diagnostic pathologic findings are not available.2 There is disagreement among movement disorder specialists regarding diagnostic criteria for ET,1-3 and each of the published prevalence studies used a different set of diagnostic criteria.1,3-23

None of these numerous diagnostic criteria for ET have been compared within the same population. Thus, it is not precisely known to what extent different diagnostic criteria may affect prevalence estimates of ET. For example, do different diagnostic criteria account for a 1-fold, 10-fold, 100-fold, or 1000-fold difference in prevalence estimates? This question must be addressed before investigators can begin to determine the role that ethnic and environmental factors play in the pathogenesis of ET. The purpose of our study is to demonstrate the impact of alternative sets of diagnostic criteria on the frequency of diagnosis of ET in a single population-based cohort of case subjects with ET and normal control subjects.
SUBJECTS AND METHODS

SOURCE POPULATION FOR WASHINGTON HEIGHTS-INWOOD GENETIC STUDY OF ET (WHIGET)

The Northern Manhattan Aging Project,1 a longitudinal, community-based study of health issues in the elderly, enrolled 2117 subjects, aged 65 years and older, who were residents of Washington Heights-Inwood, northern Manhattan, NY. Subjects underwent a 90-minute medical interview and a standardized medical and neurologic examination conducted by a neurologist and subjects with ET were identified using published criteria.1

Subjects with ET were then enrolled in a second study, the WHIGET which is an ongoing 5-year study aiming to estimate the extent of familial aggregation of ET.25-27 In addition to subjects with ET, the following subjects were also enrolled in WHIGET: (1) control subjects, (2) first- and second-degree relatives of case 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 case subjects with ET. All control subjects had undergone a medical interview, and all but 5 also underwent a standardized medical and neurologic examination as part of the Northern Manhattan Aging Project.1

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

All participants in WHIGET (including case subjects with ET, control subjects, and their respective relatives) underwent a 30-minute semistructured tremor interview and a 10-minute videotaped tremor examination as described elsewhere.25-27

The 94-item tremor interview was conducted in person by a study physician and included 12 questions designed to screen for ET. 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 the use of medications. Subjects were not required to withhold from caffeinated beverages on the day of the evaluation. Hyperthyroidism was excluded by asking about the symptoms of this disorder, asking whether a diagnosis of thyroid disease had been made in the past, and examining the patient’s medication use to see whether they were currently under treatment for thyroid disease. Thyroid hormone levels were not assessed.

Tasks included 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.25-27

The reviewers rated the severity of tremor as observed during different postures and tasks. Ratings were on an ordinal scale (0 to +3), similar to that of Fatkin and coworkers.28 (Table 1). The ratings were 0 (no visible tremor), +1 (low-amplitude, barely perceptible 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 because of spilling or inability to hold a pen to paper). A total tremor score (maximum, 36) was calculated for each subject by addition of each of the postural and task-specific scores.25-27

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 (Table 1). Diagnostic criteria have been published.25-27,29 A final designation as a case subject with ET or as a control subject was based on WHIGET criteria. The WHIGET criteria for ET25-27,29 were far more stringent than the Northern Manhattan Aging Project criteria for ET.1

Table 1

<table>
<thead>
<tr>
<th>Tremor Examination</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posture 1</td>
<td>0-3</td>
</tr>
<tr>
<td>Posture 2</td>
<td>0-3</td>
</tr>
<tr>
<td>Posture 3</td>
<td>0-3</td>
</tr>
</tbody>
</table>

Ten studies4,14-23 did not specify diagnostic criteria. Diagnostic criteria from the remaining 10 studies (Table 2)1-5,13 were applied to the 285 subjects enrolled in WHIGET. More stringent and less stringent criteria were applied. Hence, a total of 20 sets of criteria were applied to the WHIGET cohort (10 sets, each with more and less stringent criteria).

The percentage of WHIGET case subjects with definite or probable ET (group 1) who would have been diagnosed as having ET using the 20 alternative criteria varied from 14% to 97%, representing a 7-fold difference (Figure 1). The proportion of WHIGET case subjects with possible ET (group 2) who would have been diagnosed as having ET using the alternative diagnostic criteria was 0% to 94% (not shown). The percentage of WHIGET normal subjects (group 3) who would have been diagnosed as having ET using alternative diagnostic criteria varied from 0% to 51% (Figure 2).
This diagnostic protocol was highly reliable. Two neurologists (E.D.L. and B.F.) used this protocol to assign diagnoses to 226 subjects (52 case subjects with ET and 174 control subjects) and demonstrated excellent interrater reliability (weighted \( k \) statistic = 0.84, indicating near perfect to perfect agreement) and excellent intrarater reliability (weighted \( k \) statistic = 0.98, indicating near perfect to perfect agreement).30

**APPLICATION OF DIAGNOSTIC CRITERIA FROM THE LITERATURE TO SUBJECTS IN THE WHIGET COHORT**

Ten of the 20 published ET prevalence studies3-13 specified diagnostic criteria for ET (Table 2). While these criteria specified that postural tremor and/or action tremor must be present, the following issues were not specified: (1) Was a mild, intermittent, or low-amplitude postural tremor (ie, equivalent to a WHIGET tremor rating score of +1) considered “present” or “absent”? (2) Was a kinetic tremor that was present during one task (eg, finger-to-nose movements) but not other tasks (eg, writing) considered “present” or “absent”? (3) Did the term action tremor include kinetic tremor (tremor while performing purposeful movements such as finger-to-nose movements, pouring water, or writing), postural tremor (tremor that was present while maintaining an antigravity posture), either, or both?

To allow us to apply the 10 published sets of diagnostic criteria to data collected on the WHIGET subjects, for each of the 10 sets of criterion, we specified (1) more stringent and (2) less stringent criteria. These criteria were based on prior experience with the identification of sources of diagnostic disagreement in the WHIGET cohort.31 In the more stringent criteria, a mild, intermittent, low-amplitude postural tremor was considered absent and a kinetic tremor was considered absent unless it was rated as +2 during 4 of 5 tasks (pouring water between 2 cups, drinking water from a cup, using a spoon to drink water, finger-to-nose movements, and drawing spirals). An action tremor was defined as both a postural and a kinetic tremor. Conversely, in the less stringent criteria, a mild, intermittent, low-amplitude postural tremor was considered present and a kinetic tremor was considered present when it was rated as +2 on only 1 of 5 tasks. An action tremor was defined as either a postural or a kinetic tremor.

We demonstrated a 7-fold difference in the proportion of WHIGET case subjects with definite or probable ET who would have been diagnosed as having ET based on alternative diagnostic criteria in the ET literature. Several of the diagnostic criteria were more conservative, requiring either a positive family history of ET or a long-standing history of ET,7,8 or both a postural and a kinetic tremor as prerequisites for the diagnosis of ET.10 Using these criteria, as few as 14% of WHIGET case subjects with definite or probable ET would have been diagnosed as having ET. The extent of familial aggregation of ET is not precisely known, and sporadic cases of ET may account for as many as 87% of all cases of ET. Studies that do not include all sporadic cases will underestimate the true prevalence of ET.3,34 In addition, subjects with mild or early ET who are ascertained from the community often demonstrate isolated postural
tremor or isolated kinetic tremor rather than manifesting both, and studies that require both postural and kinetic tremor may underascertain mild cases of ET. The more conservative published diagnostic criteria would have classified a large proportion of WHIGET case subjects with definite or probable ET as normal (Figure 1) and would have classified few of the WHIGET normal subjects as having ET (Figure 2).

Table 1. Diagnostic Criteria for Essential Tremor (ET)

<table>
<thead>
<tr>
<th>Criteria for definite ET (all 5 must be true)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. On examination, a +2 postural tremor of at least 1 arm (a head tremor may also be present, but is not sufficient for the diagnosis)</td>
</tr>
<tr>
<td>2. On examination, there must be</td>
</tr>
<tr>
<td>a. a +2 kinetic tremor during at least 4 tasks or</td>
</tr>
<tr>
<td>b. a +2 kinetic tremor on 1 task and a +3 kinetic tremor on a second task; tasks include pouring water, using a spoon to drink water, drinking water, finger-to-nose, and drawing a spiral</td>
</tr>
<tr>
<td>3. If on examination, the tremor is present in the dominant hand, then by report, it must interfere with at least 1 activity of daily living (eating, drinking, writing, or using the hands). If on examination, the tremor is not present in the dominant hand, then this criterion is irrelevant</td>
</tr>
<tr>
<td>4. Medications, alcohol, parkinsonism, dystonia, other basal ganglionic disorders, and hyperthyroidism are not potential etiologic factors</td>
</tr>
<tr>
<td>5. Not psychogenic (bizarre features, inconsistent in character, changing, subject is distractable, or other psychiatric features on examination)</td>
</tr>
</tbody>
</table>

Criteria for probable ET (either 1 or 1 b must be true; 2 and 3 must be true)

1. Same as 2 above (see definite ET)
2. Use of medications, alcohol, parkinsonism, dystonia, other basal ganglionic disorders, and hyperthyroidism are not potential etiologic factors
3. Not psychogenic

Criteria for possible ET

1. On examination, a +2 kinetic tremor must be present on 3 tasks
2. No visible tremor
3. Low amplitude, barely perceivable tremor, or intermittent tremor
4. Tremor is of moderate amplitude (1-2 cm) and usually present
5. Large amplitude (>2 cm), violent, jerky tremor resulting in difficulty completing the task due to spilling or inability to hold a pen to paper

Table 2. Diagnostic Criteria Used in Each of the Prevalence Studies of ET

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Type of Tremor</th>
<th>Distribution</th>
<th>Bilateral</th>
<th>Interferes With ADLs</th>
<th>Duration</th>
<th>Familial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Louis et al, 1995</td>
<td>Postural or kinetic</td>
<td>Head or limbs</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Snow et al, 1989</td>
<td>Postural</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>Long-standing</td>
</tr>
<tr>
<td>Rajput et al, 1984</td>
<td>Postural and/or action</td>
<td>NS</td>
<td>Yes</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Salemi et al, 1994</td>
<td>Action</td>
<td>Head, limbs, or voice</td>
<td>NS</td>
<td>NS</td>
<td>1 †</td>
<td>Yes †</td>
</tr>
<tr>
<td>Haerer et al, 1992</td>
<td>Action</td>
<td>Head or limbs</td>
<td>NS</td>
<td>Handwriting, vocalization, or ADLs</td>
<td>10 †</td>
<td>Yes †</td>
</tr>
<tr>
<td>Bharucha et al, 1988</td>
<td>Action</td>
<td>Head, limbs, or voice</td>
<td>NS</td>
<td>Any severity</td>
<td>1 y</td>
<td>NS</td>
</tr>
<tr>
<td>Larsson and Sjogren, 1960</td>
<td>Postural and kinetic</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Rautakorpi et al, 1982</td>
<td>Postural or action</td>
<td>Head or limbs</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>Long duration</td>
</tr>
<tr>
<td>Moghal et al, 1994</td>
<td>Postural or kinetic</td>
<td>Head or limbs</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Khatter et al, 1996</td>
<td>Postural or kinetic</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 3. Clinical Characteristics of 285 Study Subjects in WHIGET

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Probable or Definite ET, Group 1 (n = 36)</th>
<th>Possible ET, Group 2 (n = 34)</th>
<th>Normal Subjects, Group 3 (n = 215)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y (range)</td>
<td>76 (23-97)</td>
<td>72 (18-94)</td>
<td>48 (18-93)</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td>Male</td>
<td>15 (42)</td>
<td>13 (38)</td>
</tr>
<tr>
<td>Ethnicity, No. (%)</td>
<td>Female</td>
<td>21 (58)</td>
<td>21 (62)</td>
</tr>
<tr>
<td>African American</td>
<td>13 (36)</td>
<td>7 (21)</td>
<td>57 (26)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>14 (39)</td>
<td>11 (32)</td>
<td>90 (42)</td>
</tr>
<tr>
<td>White</td>
<td>9 (25)</td>
<td>16 (47)</td>
<td>68 (32)</td>
</tr>
<tr>
<td>Mean tremor duration, y (range)</td>
<td>18 (1-68)†</td>
<td>6 (2-18)‡</td>
<td>NA</td>
</tr>
<tr>
<td>Report of at least 1 other first- or second-degree relative with ET, No. (%)</td>
<td>11 (36)</td>
<td>6 (18)</td>
<td>68 (32)</td>
</tr>
<tr>
<td>Mean (SD) total tremor score§</td>
<td>22.7 (6.7)</td>
<td>13.2 (4.2)</td>
<td>6.7 (4.0)</td>
</tr>
<tr>
<td>Mean No. of postures or tasks rated as ≥ +2]</td>
<td>9.1</td>
<td>4.0</td>
<td>1.2</td>
</tr>
<tr>
<td>No. (%) with +1 or higher postural tremor in at least 1 arm</td>
<td>29 (81)</td>
<td>13 (38)</td>
<td>29 (14)</td>
</tr>
<tr>
<td>No. (%) with +2 or higher kinetic tremor on at least 1 task in at least 1 arm</td>
<td>35 (97)</td>
<td>31 (91)</td>
<td>70 (33)</td>
</tr>
</tbody>
</table>

*WHIGET indicates Washington Heights-Inwood Genetic Study of Essential Tremor; ET, essential tremor; and NA, not applicable.
†Thirteen (36%) of 36 subjects did not acknowledge a tremor or did not know when their tremor began.
‡Thirty-one (91%) of 34 subjects did not acknowledge a tremor or did not know when their tremor began.
§Maximum possible total tremor score, 36.
||Total number of postures or tasks, 12 (ie, sustained arm extension and 5 tasks with the right hand, and sustained arm extension and 5 tasks with the left hand).
is generally considered to be between 1.3% to 5.1%.\textsuperscript{1,2,7-9} The prevalence of ET in the population older than 60 years is finite or probable ET classified as normal (Figure 1). The ET (Figure 2) with few WHIGET case subjects with definitive many WHIGET normal control subjects as having the tremor must be of a minimal severity would have classification that required tremor but did not specify that the tremor must be of a minimal severity would have classified many WHIGET normal control subjects as having ET (Figure 2) with few WHIGET case subjects with definite or probable ET classified as normal (Figure 1). The prevalence of ET in the population older than 60 years is generally considered to be between 1.3% to 5.1%.\textsuperscript{1,2,7-9} The WHIGET normal subjects (aged 71–93 years; Table 3) were examined twice by neurologists (initially as part of Northern Manhattan Aging Project and then as part of WHIGET) and diagnosed as normal (ie, not having ET). Hence, one would expect the true percentage of the WHIGET normal subjects with ET to be 0%. The proportion of all 285 WHIGET subjects who would have been diagnosed as having ET varied by 30-fold, implying that diagnostic criteria alone may account for much of the 2750-fold difference in prevalence estimates between various studies. Conversely, a 92-fold difference (ie, 2750 = 30) cannot be explained by diagnostic differences. Other methodologic issues such as service-based vs community-based study design, different methods of case ascertainment and evaluation (eg, assignment of disease status based on direct interview and examination vs indirect interview), and demographic (eg, age) differences between study populations probably account for much of the remaining 92-fold difference.\textsuperscript{2} For example, as few as 0.5% of community-dwelling individuals with ET seek medical attention, implying that community-based studies have the potential to ascertain 200-fold more ET cases than service-based studies.\textsuperscript{10} In studies in which subjects are diagnosed without direct interview and examination, the true prevalence of ET may be underestimated.\textsuperscript{2,28} Finally, while true ethnic differences between populations may account for some of the difference in prevalence estimates, differences in the prevalence of ET among different ethnic groups within the United States are small (eg, \textsuperscript{1,2,7-9} fold differences).\textsuperscript{1,18} 

**TYPE OF TREMOR**

While criteria that require both postural and kinetic tremor may underascertain early or mild cases of ET, more problematic for population-based studies is the misclassification of normal subjects with ET because normal and enhanced physiologic tremor are far more prevalent in the population than ET itself.\textsuperscript{27} Therefore, criteria specifying that only a mild postural tremor or only a mild kinetic tremor is sufficient for the diagnosis of ET will probably classify many normal subjects as having ET.\textsuperscript{3}

**SEVERITY OF TREMOR**

Severity of tremor should probably be specified by designating either a minimal tremor amplitude or a minimal functional disability associated with tremor. Diagnostic criteria that do not exclude mild tremor will probably classify normal subjects as having ET. This results in more misclassification than those diagnostic criteria that exclude mild cases of ET because physiologic and enhanced physiologic tremor are at least one order of magnitude more prevalent in the population than ET itself.\textsuperscript{27} 

**FAMILY HISTORY**

The presence of a positive family history for ET as a diagnostic criterion excludes sporadic cases of ET. Two stud-
ies, required either a positive family history of ET or a
tremor of certain duration. These would have classified
many WHIGET case subjects with definite ET as being nor-
mal because many of them did not acknowledge a tremor
or did not know when their tremor began (Table 3). Fiftynine
percent of neurologists specializing in movement disor-
ders who responded to a diagnostic questionnaire stated
that the duration of tremor was not an important diagno-
sic criterion for ET. The majority of those who stated that
duration was an important factor thought that 1 year was
appropriate. Conditions such as hyperthyroidism or drug-
induced tremor may exist for many years, and an arbi-
trary requirement of tremor of 1, 3, 5, or even 10 years’
duration does not always exclude these conditions.
To conclude, our study clearly demonstrates that alter-
native sets of diagnostic criteria for ET impact on the
frequency of diagnosis of ET in prevalence studies, ac-
counting for as much as a 30-fold difference in prevalence
estimates between studies. While it may seem intuitive that
different diagnostic criteria would account for differences
in prevalence estimates, this hypothesis had not been pre-
viously tested and the extent to which it may have im-
pacted on the observed differences in prevalence esti-
mates was not known. Further knowledge about appropriate
diagnostic criteria for ET may arise from studies on ge-
netic linkage, particularly knowledge about the extent of
phenotypic variation among individuals with identical
genotypes. While the diagnosis of ET is somewhat arbi-
trary in the absence of a pathognomonic diagnostic test,
for population-based studies of ET we suggest that data on
type of tremor and severity rather than family history should
probably be incorporated into diagnostic criteria.

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