Diagnostic Criteria for Essential Tremor

A Population Perspective

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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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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 neuropsychologic 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.26-28 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 3 also underwent a standardized medical and neuropsychologic examination of all 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.26-27 The 84-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.

The total tremor score is shown with respect to each of the 3 groups (Table 3). Those with probable or definite ET (group 1) had a higher mean total tremor score than those with possible ET (group 2) (t = 4.47; P < .001) or the normal group (group 3) (t = 11.71; P < .001).

Ten studies24-29 did not specify diagnostic criteria. Diagnostic criteria from the remaining 10 studies (Table 2)1,3-13 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 $\kappa$ statistic = 0.84, indicating near perfect to perfect agreement) and excellent intrarater reliability (weighted $\kappa$ statistic = 0.98, indicating near perfect to perfect agreement).29

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

Ten of the 20 published ET prevalence studies1,5-13 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.29 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.

For each subject in the WHIGET cohort, data on the type of tremor and the distribution of tremor were available on the videotaped tremor examination. The tremor interview included variables that asked about functional disability, difficulty with activities of daily living, tremor duration, and family history of ET.

We applied more stringent and less stringent diagnostic criteria from each of the 10 published studies to the WHIGET cohort to determine the proportion of WHIGET subjects who would have been diagnosed as having ET according to a particular set of diagnostic criteria. For example, using the more stringent criteria from Moghal et al,12 a WHIGET subject was diagnosed as having ET if he/she met the following criteria: tremor was present for a long period and according to both neurologists there was a head tremor or a +2 postural tremor in either arm or a +2 kinetic tremor during 4 of 5 tasks (Table 2). Alternatively, using the less stringent criteria of Salemi et al,7 a WHIGET subject was diagnosed as having ET if he/she met the following criteria: according to both neurologists there was a head tremor or a voice tremor or a +2 kinetic tremor during 1 of 5 tasks or a mild, intermittent, low-amplitude postural tremor. The subject’s tremor must have been present for at least 1 year or 1 first- or second-degree relative must have a history of ET (Table 2).

Two of the studies specified that tremor of long duration was required for the diagnosis of ET. For the purposes of our analyses, long duration was interpreted conservatively as 5 years or longer.

ANALYSES AND STATISTICS

Diagnostic criteria from each of the 10 published studies were converted into a series of Boolean logical statements on which the diagnosis of ET would be based. The data were stored using the Scientific Information Retrieval Data Management system. Data were output to an SPSS system file and the algorithms that quantified the criteria from each study were applied within an SPSS program (SPSS Inc, Chicago, Ill). Tests of significance included the Student t test.

The percentage of all the 285 WHIGET subjects who would have been diagnosed as having ET varied from as low as 2.1%8 to as high as 62.1%,6 representing a 30-fold difference (not shown).

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.2,3,4 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).

We demonstrated that a large proportion of WHIGET normal subjects would have been diagnosed as having ET based on several of the published diagnostic criteria. For example, applying the less stringent diagnostic criteria from each of the 10 prevalence studies, as many as 51% of the WHIGET normal subjects would have been diagnosed as having ET. Mild clinically detectable tremor is extremely common in the population; it is pres-

<table>
<thead>
<tr>
<th>Table 1. Diagnostic Criteria for Essential Tremor (ET)</th>
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<tr>
<td>Criteria for definite ET (all 5 must be true)</td>
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<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>
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<td>2. On examination, there must be</td>
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<td>a. a +2 kinetic tremor during at least 4 tasks or</td>
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<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>
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<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>
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<td>4. Medications, alcohol, parkinsonism, dystonia, other basal ganglionic disorders, and hyperthyroidism are not potential etiologic factors</td>
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<td>5. Not psychogenic (bizarre features, inconsistent in character, changing, subject is distractable, or other psychiatric features on examination)</td>
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<td>Criteria for probable ET (either 1 a or 1 b must be true; 2 and 3 must be true)</td>
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<td>1. a. Same as 2 above (see definite ET)</td>
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<td>b. Head tremor is present on examination</td>
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<tr>
<td>2. Use of medications, alcohol, parkinsonism, dystonia, other basal ganglionic disorders, and hyperthyroidism are not potential etiologic factors</td>
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<tr>
<td>3. Not psychogenic</td>
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<td>Criteria for possible ET</td>
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<td>1. On examination, a +2 kinetic tremor must be present on 3 tasks</td>
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<td>0 +3 Tremor ratings</td>
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<td>0. No visible tremor</td>
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<td>+1. Low amplitude, barely perceivable tremor, or intermittent tremor</td>
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<td>+2. Tremor is of moderate amplitude (1-2 cm) and usually present It is clearly oscillatory</td>
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<td>+3. Large amplitude (&gt;2 cm), violent, jerky tremor resulting in difficulty completing the task due to spilling or inability to hold a pen to paper</td>
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<th>Table 2. Diagnostic Criteria Used in Each of the Prevalence Studies of ET*</th>
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<td><strong>Source, y</strong></td>
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<tr>
<td>Louis et al., 1995</td>
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<td>Snow et al., 1989</td>
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<td>Rajput et al., 1984</td>
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<td>Salemi et al., 1994</td>
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<td>Haerer et al., 1992</td>
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<td>Bharucha et al., 1988</td>
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<td>Larsson and Sjogren, 1960</td>
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<td>Rautakorpi et al., 1982</td>
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<td>Moghal et al., 1994</td>
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<td>Khatter et al., 1996</td>
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*ET indicates essential tremor; ADLs, activities of daily living; and NS, not specified. 
†A history of either familial ET or tremor of a certain duration was required for the diagnosis of ET.*
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 was estimated in 96% of normal control subjects.\textsuperscript{27} Hence, diagnostic criteria 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 1) with few WHIGET case subjects with definitive criteria 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 to be 0%. 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, 1.2-1.7-fold differences).\textsuperscript{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} 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}

**FAMILY HISTORY**

The presence of a positive family history for ET as a diagnostic criterion excludes sporadic cases of ET. Two stud-
ies,8 required either a positive family history of ET or a tremor of certain duration. These would have classified a large proportion of WHIGET case subjects with probable or definite ET as being normal (Figure 1). In a questionnaire completed by 98 neurologists specializing in movement disorders that asked about diagnostic criteria for definite ET, only 4% stated that a family history of ET should be a diagnostic criterion.24

**DURATION OF TREMOR**

While formes frustes of Parkinson disease and dystonia may present as action tremor,32-35 criteria that require lengthy duration of tremor would have classified many WHIGET case subjects with definite and probable ET as being normal because many of them did not acknowledge a tremor or did not know when their tremor began (Table 3). Fifty-nine percent of neurologists specializing in movement disorders who responded to a diagnostic questionnaire24 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 arbitrary 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 alternative sets of diagnostic criteria for ET impact on the frequency of diagnosis of ET in prevalence studies, accounting 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 previously tested and the extent to which it may have impacted on the observed differences in prevalence estimates was not known. Further knowledge about appropriate diagnostic criteria for ET may arise from studies on genetic linkage,36,37 particularly knowledge about the extent of phenotypic variation among individuals with identical genotypes. While the diagnosis of ET is somewhat arbitrary 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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**REFERENCES**


