Clinical Classification of Borderline Cases in the Family Study of Essential Tremor: An Analysis of Phenotypic Features

Elan D. Louis \(^1,2,3,4*\), Ruth Ottman \(^1,2,4,5\) & Lorraine N. Clark \(^3,6\)

\(^1\)G.H. Sergievsky Center, College of Physicians and Surgeons, Columbia University, New York, New York, United States of America, \(^2\)Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, New York, United States of America, \(^3\)Taub Institute for Research on Alzheimer’s Disease and the Aging Brain, College of Physicians and Surgeons, Columbia University, New York, New York, United States of America, \(^4\)Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, New York, United States of America, \(^5\)Division of Epidemiology, New York State Psychiatric Institute, New York, New York, United States of America, \(^6\)Department of Pathology and Cell Biology, College of Physicians and Surgeons, Columbia University, New York, New York, United States of America

Abstract

**Background:** In genetic research on essential tremor (ET), certain individuals may be particularly challenging to categorize diagnostically.

**Methods:** In the Family Study of Essential Tremor (>200 enrollees), 28 participants with borderline clinical findings who did not meet strict criteria for ET were assigned final diagnoses of ET. We scrutinized the clinical features of these cases and the sensitivity/specificity of certain features that best separated them from 19 unaffected individuals.

**Results:** Borderline ET cases differed from unaffected individuals in eight features: total tremor score, at least one kinetic tremor rating >1.5, at least one kinetic tremor rating >1.5 in the dominant arm, tremor rating during spiral drawing >1.5, higher spiral axis score, head tremor, complaint of tremor, and comment on tremor by others. The combination of at least one kinetic tremor rating >1.5 in the dominant arm and the presence of at least three of the remaining seven features predicted the clinician-assigned diagnosis in 88.6% of borderline ET vs. unaffected individuals (sensitivity 84.6%, specificity 94.4%).

**Discussion:** In a family study, a small number of clinical features characterized borderline ET, and a particular combination of these separated the majority of these borderline cases from normals. These analyses may help researchers minimize diagnostic misclassification.

**Keywords:** Essential tremor, classification, genetic, clinical, epidemiology

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*To whom correspondence should be addressed. E-mail: EDL2@columbia.edu

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Introduction

The search for essential tremor (ET) genes is ongoing,\(^{1,2}\) In such research, certain individuals may be particularly challenging to diagnose because their clinical findings are borderline. Such individuals may be difficult to classify as either normal or emerging ET cases. Diagnostic misclassification reduces the likelihood of finding an ET gene.

In the Family Study of Essential Tremor (FASET), we enrolled 242 individuals (61 probands, 181 relatives). Approximately 15% had borderline clinical findings that did not meet strict diagnostic criteria for ET, but were nonetheless categorized by the study clinician as ET.

We scrutinized the clinical features of these cases as well as the sensitivity and specificity of features that best separated them from normals. These analyses may clarify issues related to diagnostic misclassification in genetic studies of ET, and are intended to help researchers minimize diagnostic misclassification.

Methods

Ascertainment of probands

ET cases (probands) and their reportedly affected first-and second-degree relatives were enrolled in FASET, a genetic study of ET at
The Center for Digital Research and Scholarship
Columbia University Libraries/Information Services

Tremor and Other Hyperkinetic Movements
http://www.tremorjournal.org

Classification Borderline ET Cases

Louis ED, Ottman R, Clark LN Classification Borderline ET Cases et al.). The presence of a single identifiable tremor orientation axis has been reported in ET, and was noted as present or absent on each of four spirals (see example in Louis et al.), and a spiral axis score (range = 0 [none of four spirals had a single identifiable tremor orientation axis] to 4 [a single axis was observed on all four spirals]) was assigned to each person. The study was approved by the CUMC Institutional Review Board and all participants gave written informed consent.

**Diagnoses**

All ET diagnoses were reconfirmed based on a review of the questionnaires and videotaped neurological examinations. Diagnoses of ET were assigned based on published diagnostic criteria with demonstrated reliability and validity (moderate or greater amplitude kinetic tremor during three or more activities or a head tremor in the absence of PD, dystonia, or another known cause, including medication-induced tremor). Medication-induced tremor was excluded based on clinical history (e.g., the onset of tremor preceded the use of the medication, the severity of the tremor did not change in response to reductions or increases in dose of medication), and physical examination features (e.g., the presence of severe and/or asymmetric tremor). A borderline ET category was created for enrollees who did not fully meet these strict diagnostic criteria for ET but were nonetheless considered by the study clinician to have clinical features that aligned them more with ET than normal.

**Final sample**

We enrolled 242 individuals (61 probands and 181 relatives). For the current analyses, we excluded enrollees who had been diagnosed with PD, dystonia, or psychogenic movements. The final sample included 207 individuals (52 probands and 155 relatives), including 160 ET, 28 borderline ET, and 19 normal.

**Statistical analyses**

Analyses were performed in SPSS (Version 20.0). Subject characteristics were compared across the three groups (ET, borderline ET, normal) using analysis of variance, chi-square tests and Jonckheere–Terpstra tests (a non-parametric test of trend). If the three group comparisons revealed a significant difference, we compared the groups two at a time using t tests, chi-square tests, and Mann–Whitney tests. We created receiver operating characteristic (ROC) curves for the clinical features, alone and in combination, in order to determine their diagnostic performance (i.e., their ability to separate borderline ET from normals).

**Results**

Clinical characteristics of the final sample are shown in Table 1. The majority of the borderline ET cases were children of probands. Total tremor score is shown by age across the three groups (Figure 1); although their tremor scores were low in absolute terms, borderline ET cases had a higher mean total tremor score than individuals who had been categorized as normal (Table 1). Compared with normals, borderline ET cases also had a higher spiral axis score (i.e., they exhibited a more clearly identifiable spiral axis), and a larger proportion had at least one or more kinetic tremor rating ≥1.5 (i.e., intermediate or greater tremor), including in their dominant arm, and a larger proportion had spiral scores ≥1.5 (Table 1). A marginally
large proportion also had head tremor (Table 1). When compared with normals, borderline ET cases were more likely to have complained of tremor that they could not control and were more likely to have had other people tell them that they had tremor (Table 1).

We combined these eight clinical features into an index. On this index, ET cases averaged 6.6 ± 1.0 (median = 5), compared with 4.7 ± 1.4 (median = 5) for borderline ET cases and only 1.7 ± 1.7 (median = 2) for normals (Jonckheere–Terpstra test p < 0.001).

With ROC modeling, we found that a total tremor score ≥ 10 did a satisfactory job of separating those who were categorized as borderline ET from those who were categorized as normal (sensitivity = 77.8%, specificity = 94.7%, correct classification = 84.7%). Further ROC modeling revealed that the combination of one or more kinetic tremor rating > 1.5 in the dominant arm and the presence of three or more of the remaining seven features predicted the clinician-assigned diagnosis (borderline ET vs. normals) with 88.6% accuracy (sensitivity = 84.6%, specificity = 94.4%).

### Table 1. Clinical and Demographic Characteristics of Enrollees

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ET (N = 160)</th>
<th>Borderline ET (N = 28)</th>
<th>Normal (N = 19)</th>
<th>Significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.0 ± 18.0*</td>
<td>48.0 ± 12.5</td>
<td>49.3 ± 17.9</td>
<td>&lt;0.001¹</td>
</tr>
<tr>
<td>Female gender</td>
<td>82 (51.3)*</td>
<td>16 (57.1)</td>
<td>15 (78.9)</td>
<td>0.07²</td>
</tr>
<tr>
<td>Education (years)</td>
<td>16.3 ± 3.7</td>
<td>16.6 ± 2.0</td>
<td>16.5 ± 3.5</td>
<td>0.90¹</td>
</tr>
<tr>
<td>Tremor duration (years)</td>
<td>32.8 ± 19.3</td>
<td>17.8 ± 12.8</td>
<td>Not applicable</td>
<td>&lt;0.001¹</td>
</tr>
<tr>
<td>Relationship</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001²</td>
</tr>
<tr>
<td>Proband</td>
<td>50 (31.3)*</td>
<td>2 (7.1)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Child</td>
<td>37 (23.1)</td>
<td>18 (64.3)</td>
<td>8 (42.1)</td>
<td></td>
</tr>
<tr>
<td>Sibling</td>
<td>38 (23.8)</td>
<td>5 (17.9)</td>
<td>5 (26.3)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>35 (21.9)</td>
<td>3 (10.7)</td>
<td>6 (31.6)</td>
<td></td>
</tr>
<tr>
<td>“Other people tell me that I have tremor”</td>
<td>126 (78.8)**</td>
<td>12 (42.9)***</td>
<td>3 (15.8)</td>
<td>&lt;0.001²</td>
</tr>
<tr>
<td>“I sometimes have tremor that I can’t control”</td>
<td>154 (96.3)**</td>
<td>21 (75.0)***</td>
<td>8 (42.1)</td>
<td>&lt;0.001²</td>
</tr>
<tr>
<td>Total tremor score</td>
<td>20.1 ± 5.2**</td>
<td>11.4 ± 2.6*</td>
<td>7.3 ± 1.8</td>
<td>&lt;0.001¹</td>
</tr>
<tr>
<td>Spiral axis score</td>
<td>2.2 ± 1.3 (2.0)**</td>
<td>1.1 ± 1.0 (1.0)***</td>
<td>0.4 ± 0.5 (0.0)</td>
<td>&lt;0.001³</td>
</tr>
<tr>
<td>Any kinetic tremor score ≥ 1.5</td>
<td>160 (100)**</td>
<td>27 (96.4)***</td>
<td>10 (52.6)</td>
<td>&lt;0.001²</td>
</tr>
<tr>
<td>Any kinetic tremor score ≥ 1.5 in dominant arm</td>
<td>157 (98.1)**</td>
<td>25 (89.3)***</td>
<td>7 (36.8)</td>
<td>&lt;0.001²</td>
</tr>
<tr>
<td>Spiral score ≥ 1.5</td>
<td>126 (78.8)**</td>
<td>8 (28.6)***</td>
<td>0 (0.0)</td>
<td>&lt;0.001²</td>
</tr>
<tr>
<td>Rest tremor</td>
<td>16 (10.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0.08²</td>
</tr>
<tr>
<td>Head tremor</td>
<td>72 (45.0)**</td>
<td>4 (14.3)***</td>
<td>0 (0.0)</td>
<td>&lt;0.001²</td>
</tr>
<tr>
<td>Voice tremor</td>
<td>26 (16.4)***</td>
<td>1 (3.6)</td>
<td>0 (0.0)</td>
<td>&lt;0.001²</td>
</tr>
<tr>
<td>Intention tremor</td>
<td>62 (38.8)*</td>
<td>1 (3.6)</td>
<td>2 (10.5)</td>
<td>&lt;0.001²</td>
</tr>
</tbody>
</table>

Abbreviation: ET, Essential Tremor.
All values represent mean ± standard deviation (median) or number (percentage).
¹Chi-square test comparing all three groups.
²Analysis of variance test comparing all three groups.
³Jonckheere–Terpstra test comparing all three groups.
* p < 0.05 compared with normals; ** p < 0.01 compared with normals; *** p = 0.05–0.09, compared with normals.
Note: For some items, data were available on <207 enrollees.
Discussion

In a family study of ET, a small and definable number of clinical features differentiated borderline ET from normals, and a combination of these features separated the majority of these borderline cases from those who were considered normal. The search for ET genes is currently ongoing and intensive. Attention to these features may help lessen diagnostic misclassification.

The clinical features that best aligned with the clinician-assigned diagnosis were both historical and examination based. Historical features included patient reports that tremor was at times difficult to control and that others were aware of the tremor. Examination features that differentiated borderline ET from normals included a total tremor score \( \geq 10 \) (horizontal line) separated the borderline ET cases from normals with a sensitivity of 77.8% and a specificity of 94.7% (correct classification, 84.7%). One borderline ET did not have a total tremor score and two others had identical total tremor scores and ages.

Figure 1. Total Tremor Score (y-Axis) by Age (x-Axis) Across the Three Diagnostic Groups. Essential tremor (ET), green diamonds; borderline ET, blue squares, and normals, red circles. A total tremor score \( \geq 10 \) (horizontal line) separated the borderline ET cases from normals with a sensitivity of 77.8% and a specificity of 94.7% (correct classification, 84.7%).

Other disorders. These analyses may clarify issues related to diagnostic misclassification in genetic studies of ET. Inclusion of borderline cases should proceed with caution, with one option being to perform parallel analyses, one of which includes these cases with ET cases, and another that excludes them altogether rather than including them with unaffected normals.

References