Should we redefine essential tremor?

Rodger Elble
Southern Illinois University
Springfield, Illinois

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www.siumed.edu/neuro/research/PDResearch.html

No

Yes, if we all agree to live by the new definition.
Neurologists can achieve the impossible!

Perhaps we can agree on a definition of ET.

In 1954, Roger Bannister ran the mile in 3 min. 59 sec.

Why is the definition of ET so difficult?

• ET is a syndrome, not a specific disease.
  – There is genetic heterogeneity.
  – Many cases are sporadic.
  – It is a phenotype of dystonia and Parkinson disease.
  – Late-onset ET (age > 65) is associated with increased risk of dementia and other morbidity/mortality.

• We cannot agree on the clinical characteristics of ET.

Deuschl et al. Mov Disord 2015; 30: 1327-34
ET is an isolated tremor syndrome.

Observations on essential tremor
Critchley. Brain 1949; 72: 113-139

“Occasionally, other involuntary movements may accompany the tremor”
- choreiform contractions of the face or of the head
- choreoathetosis
- spasmodic torticollis

“...but there is no”
- alteration in muscle tone
- “real ataxia”
- abnormal reflexes
- sensory disturbances
- sign of a Parkinsonian syndrome
“Benign essential tremor is not a single entity”
Marsden, Obeso and Rothwell - 1983

<table>
<thead>
<tr>
<th>Type 1</th>
<th>Exaggerated physiologic tremor. Mild tremor in the hands.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2</td>
<td>Benign pathologic essential tremor&lt;br&gt;Hands ± head ± lower limbs, often hereditary&lt;br&gt;Central neurogenic oscillation at 5-7 Hz</td>
</tr>
<tr>
<td>Type 3</td>
<td>Severe pathologic essential tremor&lt;br&gt;Hands ± head ± lower limbs, frequently no family history&lt;br&gt;Central neurogenic oscillation at 4-6 Hz</td>
</tr>
<tr>
<td>Type 4</td>
<td>Symptomatic essential tremor&lt;br&gt;Associated with other neurologic conditions, such as dystonia, peripheral neuropathy, and Parkinson disease</td>
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</tbody>
</table>


Marsden’s Type 2 and Type 3 ET
Do they have the same etiology?

- 71 yo right-handed man
- Tremor started in adolescence
- Mother, maternal grandmother, maternal uncle, 1 of 2 brothers and 2 of 4 children with tremor
- Now has Lewy body dementia

- 60 yo right-handed woman
- Tremor started at age 20
- Grade 4 tremor in UEs by age 34
- 74 yo mother has very mild tremor. Maternal aunt reportedly has PD. None of 4 children has tremor
- Afraid to have surgery
A study of hereditary essential tremor


Examine 20 probands and 131 relatives (93 first-degree).

“The typical phenotype was a mild symmetrical postural tremor of the upper limbs. Tremor of the legs, head, facial muscles, voice, jaw and tongue occurred but never in isolation, and rest, task specific (e.g. primary writing tremor) and primary orthostatic tremors were not found.”

Age of onset is virtually always before age 65.

This is the phenotype of Marsden’s Type 2 ET.

There is a tendency to broaden the definition of ET.
International survey of movement disorder specialists – circa 1996

Compatible with the diagnosis of ET

- Dystonia in the tremulous arm – 29%
- Dystonia elsewhere – 52%
- Position or task specific arm tremor – 46%
- Isolated head tremor – 81%
- Isolated voice tremor – 70%

Chouinard et al. *Mov Disord* 1997; 12: 973-6
ET is still not defined consistently.

**ET has no value if it is not defined and used consistently.**

<table>
<thead>
<tr>
<th></th>
<th>Other signs?</th>
<th>Isolated head tremor?</th>
<th>Amplitude criteria?</th>
<th>Duration criteria?</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRIG</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>5 yr</td>
</tr>
<tr>
<td>MDS</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>WHIGET</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>NIH ET consortium</td>
<td>Dystonia</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>NEDICES</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>1 yr or fam hx</td>
</tr>
</tbody>
</table>

Many others...

Louis et al. *Arch Neurol* 1998; 55: 823-8

Jankovic. *Mov Disord* 2002; 17: 638-44

Epidemiologic approach to elucidating a disease

Classification of disease
Parkinson disease
"Clinically, the view of ET as a single neurologic sign no longer seems tenable."

However, an etiology of ET may cause other neurological signs.
Should we include other signs in the definition of ET?

- Impaired tandem walking
- Questionable dystonia
- Mild cognitive impairment
- Dementia
- Mild bradykinesia
- Mild rigidity

We need to define ET and live by this definition.

1. ET is an isolated tremor syndrome, not a specific disease.
2. Patients with ET may develop other signs, at which time they cease to have ET.
### Criteria for classic ET

**TRIG criteria (1995)**

1. Bilateral postural tremor with or without kinetic tremor in the hands that is visible and persistent
2. Duration longer than 5 yr
3. No other neurologic signs

**MDS consensus criteria**

1. Bilateral, largely symmetric postural or kinetic tremor of the hands that is visible and persistent
2. Additional or isolated head tremor in the absence of posturing
3. No other neurologic signs

Deuschl et al. *Mov Disord* 1998; 13: 2-23

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### Criteria for (classic) ET

**TRIG criteria (1995)**

1. Bilateral postural tremor with or without kinetic tremor in the hands that is visible and persistent
2. Duration longer than 5 yr
3. No other neurologic signs

**NINDS workshop (2015)**

1. Bilateral upper limb tremor, postural or kinetic
2. Duration at least 3 yr
3. No other diagnostic neurologic signs
4. Difficulty with tandem walking is permissible, but gait should be normal

Isolated tremor
Aging-related tremor
Deuschl et al. *Mov Disord* 2015;30:1327-1334

Comorbidities


Proposed classification scheme
MDS Tremor Task Force

- ET
- Writing tremor
- Orthostatic tremor
- Dystonic tremor
- Rest tremor, bradykinesia, rigidity

Patient with tremor

Isolated tremor syndromes

Combined tremor syndromes
Isolated and combined tremor syndromes

We need ancillary tests.

- ET vs orthostatic tremor
  - EMG coherence analysis

- ET vs PD
  - DaTscan

- ET vs enhanced mechanical-reflex tremor
  - EMG/accelerometry with inertial loading

- ET vs dystonic tremor
  - Temporal sensory discrimination
    Tinazzi et al. *Neurology* 2013;80:76-84
ET subtypes vs isolated tremor syndromes

- Late-onset
- Familial
- Sporadic
- Rapidly progressive

ET subtypes vs isolated tremor syndromes

- Late-onset
- Familial
- Sporadic
- Rapidly progressive
- Isolated tremor syndrome
## Isolated tremor syndromes

<table>
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<tr>
<th>Tremor syndrome</th>
<th>Characteristics</th>
<th>Other diagnostic signs that may develop or may be missed</th>
</tr>
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<tbody>
<tr>
<td>Essential tremor</td>
<td>Bilateral upper extremity action tremor with or without tremor in the head, neck, voice and elsewhere; <em>slowly progressive over decades.</em></td>
<td>Focal dystonia in the neck, face, voice or upper limb; parkinsonism; ataxia; myoclonus; sensorimotor polyneuropathy</td>
</tr>
<tr>
<td>Rapidly progressive isolated tremor syndrome</td>
<td>Bilateral upper extremity action tremor with or without tremor in the head, neck, voice and elsewhere; <em>progressive over a few years.</em></td>
<td>Focal dystonia in the neck, face, voice or upper limb; parkinsonism; ataxia; myoclonus; sensorimotor polyneuropathy</td>
</tr>
<tr>
<td>Late-onset isolated tremor syndrome</td>
<td>Bilateral upper extremity action tremor with or without tremor in the head, neck, voice and elsewhere; <em>beginning after age 65</em></td>
<td>Focal dystonia in the neck, face, voice or upper limb; parkinsonism; ataxia; myoclonus; sensorimotor polyneuropathy; dementia</td>
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<tr>
<td>Focal isolated tremor</td>
<td>Isolated tremor in a single body part (e.g., face, neck, upper extremity)</td>
<td>Focal dystonia; parkinsonism; myoclonus</td>
</tr>
<tr>
<td>Task-specific isolated tremor</td>
<td>Isolated tremor that is induced by a specific motor task (e.g., writing, playing a musical instrument).</td>
<td>Focal dystonia; myoclonus</td>
</tr>
<tr>
<td>Primary (isolated) orthostatic tremor</td>
<td>Lower limb tremulousness or unsteadiness upon standing; generalized, <em>highly coherent, 13-18-Hz motor unit entrainment</em></td>
<td>Other upper body tremor, resembling essential tremor; parkinsonism, dementia, dystonia, ataxia</td>
</tr>
<tr>
<td>Isolated action tremor with rest tremor</td>
<td>Isolated action tremor with rest tremor in one or both upper limbs</td>
<td>Parkinsonism, dystonia, ataxia</td>
</tr>
</tbody>
</table>
We need natural history studies.

- Onset
- Progression
- Other signs
- Comorbidities

We need to connect the data silos.

Elble’s tremor lab in Illinois

World-wide ET network

Common data elements → compatible databases
We need to elucidate the “tremor network” to find clues for new treatments.

Muthuraman et al. Mov Disord 2015; 30: 1673-80

Should we redefine essential tremor?

• Only if we can define ET in a way that is universally acceptable.
  – We have too many definitions already.

• Defining isolated tremor and combined tremor syndromes is preferable

**ET and other isolated tremor syndromes are not etiologies. They are groups of signs and symptoms that occur repeatedly and are produced by one or more etiologies.**

**A patient with ET may evolve into another tremor syndrome.**
"How do we define ET?"

Thank you!

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