History and evolution of the term *Essential Tremor*

Rodger Elble  
Southern Illinois University  
Springfield, Illinois  
[rodger.elble@gmail.com](mailto:rodger.elble@gmail.com)
Disclosures

• Consultant for Biohaven, Cadent, Cavion, Merz, Sage and Praxis Precision Medicines

• Paid reviewer of patient video exams for InSightec and Cavion.

• Medical advisory board of the International Essential Tremor Foundation.

• Medical director of Illinois-Eastern Iowa District Kiwanis Neuroscience Foundation

• Research grant from Illinois-Eastern Iowa District Kiwanis Neuroscience Foundation
Learning objectives

1. Know the origin of the term *essential tremor*

2. Know how this term has evolved and is presently defined

3. Discuss continuing controversies in the differential diagnosis of essential tremor
Historical underpinnings of the term *essential tremor* in the late 19th century

**Conclusions:** Toward the end of the 19th century, several clinicians attempted to provide a nosologic separation for a tremor diathesis that was often familial and occurred in isolation of other neurologic signs. This disorder, which was termed *essential tremor*, was later recognized as one of the most common neurologic disorders. *Neurology*® 2008;71:856-859

**Monosymptomatic tremor diathesis syndrome.**
ET has never been defined 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 - 1990</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>
<tr>
<td>MDS - 2018</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>3 yr</td>
</tr>
<tr>
<td>Many others...</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Louis et al. *Arch Neurol* 1998; 55: 823-8
Jankovic. *Mov Disord* 2002; 17: 638-44
Bhatia et al. *Mov Disord* 2018; 33: 75-87
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
Patient populations vary greatly depending on the definition of a syndrome.

Generalization among patient populations is not possible.

**ET must be defined consistently to be useful.**
Essential tremor
1) isolated tremor syndrome of bilateral upper limb action tremor
2) at least 3 years’ duration
3) with or without tremor in other locations (e.g., head, voice, or lower limbs)
4) absence of other neurological signs, such as dystonia, ataxia, or parkinsonism.

The product of 6 years of discussion.
New tremor classification scheme
MDS Tremor Task Force 2018

Patient with tremor

Axis 1 classification

Isolated tremor syndromes

Combined tremor syndromes

ET

Writing tremor

Orthostatic tremor

Dystonic tremor

Rest tremor, bradykinesia, rigidity
Skills and opinions vary

Bilateral UE action tremor ± tremor in head or voice

- Truncal and LE tremor
- Ataxia
- Parkinsonism
- Dystonia
- Myoclonus

ET → imprecise, simplistic labeling of patients
Video examples of “ET”

ET or PD?
ET versus dystonia with tremor
Kappa analysis of 65 videos

Balint

0.08
Deuschl
0.44
Gövert

0.18
Elble
“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</td>
</tr>
<tr>
<td></td>
<td>Hands ± head ± lower limbs, often hereditary</td>
</tr>
<tr>
<td></td>
<td>Central neurogenic oscillation at 5-7 Hz</td>
</tr>
<tr>
<td>Type 3</td>
<td>Severe pathologic essential tremor</td>
</tr>
<tr>
<td></td>
<td>Hands ± head ± lower limbs, frequently no family history</td>
</tr>
<tr>
<td></td>
<td>Central neurogenic oscillation at 4-6 Hz</td>
</tr>
<tr>
<td>Type 4</td>
<td>Symptomatic essential tremor</td>
</tr>
<tr>
<td></td>
<td>Associated with other neurologic conditions, such as dystonia, peripheral neuropathy, and Parkinson disease</td>
</tr>
</tbody>
</table>

Monosymptomatic disorders

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

ET is a heterogeneous disorder.

- There is genetic heterogeneity.
- Many cases are sporadic.
- It is a phenotype of dystonia, hereditary ataxia, and Parkinson disease.
- Late-onset ET (age > 65) is associated with increased risk of dementia and other morbidity and mortality.

Deuschl et al. *Mov Disord* 2015; 30: 1327-34
ET subtypes – more specificity?

Data from one subtype may not be generalizable to other subtypes.
ET-like tremor
Bilateral UE action tremor ± tremor in head and voice
(no exclusion criteria)

Axis-1 assessment – deep phenotyping

- Sporadic
- Familial
- Neuropathy
- Mental status
- Late onset
- Rapidly progressive
- Ataxia
- Parkinsonism
- Comorbidities
- Medication response
- Dystonia
- Myoclonus

Ancillary tests:
- Imaging
- Neurophysiology

Cluster Analysis

ET subgroups, endophenotypes, and ET plus syndromes
We need natural history studies.

Hopfner et al. Parkinsonism Relat Disord 2016; 33: 27-35
Consensus Statement on the Classification of Tremors. From the Task Force on Tremor of the International Parkinson and Movement Disorder Society

Kailash P. Bhatia, MD, FRCP,1 Peter Bain, MD, PhD,2 Nin Bajaj, MD, PhD, FRCP,3 Rodger J. Elble, MD, PhD,4 Mark Hallett, MD, PhD,5 Elan D. Louis, MD,6 Jan Raethjen, MD, PhD,7 Maria Stamelou, MD, PhD,8 Claudia M. Testa, MD, PhD,9 Guenther Deuschl, MD, PhD10,7* and the Tremor Task Force of the International Parkinson and Movement Disorder Society†


Alfonso Fasano, MD, PhD,1,2 Anthony E. Lang, MD, FRCPC,1,2 and Alberto J. Espay, MD, MSc13*

Essential Pitfalls in “Essential” Tremor

Alberto J. Espay, MD, MSc,1* Anthony E. Lang, MD, FRCPC,2,3 Roberto Erro, MD, PhD,4 Aristide Merola, MD, PhD,1 Alfonso Fasano, MD, PhD,2,3 Alfredo Berardelli, MD,5,6 and Kailash P. Bhatia, FRCP7
Correspondence

Rajalingam et al.

Essential tremor plus is more common than essential tremor: Insights from the reclassification of a cohort of patients with lower limb tremor

Table 1
Classification changes with new IPMDS tremor criteria for patients seen in our clinic between January 2000 and August 2017.

<table>
<thead>
<tr>
<th>Previous tremor diagnosis</th>
<th>n</th>
<th>New tremor classification</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential tremor</td>
<td>133</td>
<td>Essential tremor</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Essential tremor-plus</td>
<td>110</td>
</tr>
<tr>
<td>Drug-induced parkinsonism with</td>
<td>5</td>
<td>Drug-induced tremor</td>
<td>5</td>
</tr>
<tr>
<td>antecedent essential tremor</td>
<td></td>
<td>Indeterminate tremor</td>
<td>3</td>
</tr>
<tr>
<td>Parkinsonian tremor</td>
<td>30</td>
<td>Classic parkinsonian tremor</td>
<td>30</td>
</tr>
<tr>
<td>Parkinsonian tremor with</td>
<td>10</td>
<td>Classic parkinsonian tremor</td>
<td>10</td>
</tr>
<tr>
<td>antecedent essential tremor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dystonic tremor</td>
<td>58</td>
<td>Dystonic tremor</td>
<td>58</td>
</tr>
<tr>
<td>Tremor associated with dystonia</td>
<td>6</td>
<td>Tremor associated with dystonia</td>
<td>6</td>
</tr>
<tr>
<td>Psychogenic tremor</td>
<td>7</td>
<td>Functional tremor</td>
<td>7</td>
</tr>
<tr>
<td>Cerebellar tremor</td>
<td>13</td>
<td>Intention tremor</td>
<td>13</td>
</tr>
<tr>
<td>Holmes tremor</td>
<td>4</td>
<td>Holmes tremor</td>
<td>4</td>
</tr>
<tr>
<td>Drug-induced tremor</td>
<td>10</td>
<td>Isolated tremor syndrome (axis 2 = drug-induced)</td>
<td>10</td>
</tr>
<tr>
<td>Enhanced physiologic tremor</td>
<td>1</td>
<td>Enhanced physiologic tremor</td>
<td>1</td>
</tr>
<tr>
<td>Enhanced physiologic tremor</td>
<td>1</td>
<td>Enhanced physiologic tremor and</td>
<td>1</td>
</tr>
<tr>
<td>and psychogenic tremor</td>
<td></td>
<td>functional tremor</td>
<td></td>
</tr>
<tr>
<td>Tremor associated with</td>
<td>1</td>
<td>Isolated tremor syndrome (axis 2 = neuropathic)</td>
<td>1</td>
</tr>
<tr>
<td>peripheral neuropathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unclassified tremor</td>
<td>4</td>
<td>Indeterminate tremor syndrome</td>
<td>4</td>
</tr>
</tbody>
</table>
Impact on clinical recruitment

Should a study include

– ET
– Subtypes of ET
– ET plus
– Subtypes of ET plus

The new classification scheme places greater diagnostic burden on clinicians.
Accurate phenotyping makes a difference

Signs of ataxia are a predictor of early tolerance.
Is ET still useful?

• If we live by the new MDS definition.
  – ET is a syndrome, not a specific disease.
  – Deep phenotyping of patients is needed – ET plus
  – Subtypes within ET and ET plus may improve the odds of discovering an etiology or new treatment.

• Consensus ≠ fact
  – Prospective multicenter collection of Axis 1 data
  – Statistical cluster analyses to identify subgroups.

Nonspecific monosymptomatic tremor diathesis syndrome.
Case studies
Skills and opinions vary

- Dystonic posturing
- Jerky
- Asymmetric
- Ataxia
- Bradykinesia

- Compensatory posturing
- Rhythmic
- Symmetric
- Unsteady tandem gait
- Aging

ET → imprecise, simplistic labeling of patients

ET → ET plus
Rest tremor in ET?

Poor test-retest and inter-rater reliability
ET or PD?

Parkinson rest tremor is suppressed during movement initiation.
“In our (clinic) sample, 1 in 5 patients with ET had rest tremor.”
Test-retest reliability FUS study
Ondo et al. Mov Disord Clin Pract 2018; 5: 60–65

<table>
<thead>
<tr>
<th>Item(s)</th>
<th>Intraclass Correlation†</th>
<th>95% Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FTM items</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kinetic tremor</td>
<td>0.79</td>
<td>0.69–0.86</td>
</tr>
<tr>
<td>Postural tremor</td>
<td>0.74</td>
<td>0.62–0.83</td>
</tr>
<tr>
<td>Rest tremor</td>
<td><strong>0.01</strong></td>
<td>−0.21, 0.24</td>
</tr>
<tr>
<td>Kinetic + postural + rest tremor composite score</td>
<td>0.81</td>
<td>0.71–0.88</td>
</tr>
<tr>
<td>Large spiral A drawing</td>
<td>0.76</td>
<td>0.65–0.84</td>
</tr>
<tr>
<td>Small spiral B drawing</td>
<td>0.82</td>
<td>0.74–0.89</td>
</tr>
<tr>
<td>Drawing straight lines</td>
<td>0.80</td>
<td>0.70–0.87</td>
</tr>
<tr>
<td>Pouring</td>
<td>0.74</td>
<td>0.62–0.83</td>
</tr>
<tr>
<td>Spirals + lines + pouring</td>
<td>0.88</td>
<td>0.82–0.93</td>
</tr>
<tr>
<td><strong>TETRAS items</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kinetic tremor</td>
<td>0.78</td>
<td>0.68–0.86</td>
</tr>
<tr>
<td>Postural tremor</td>
<td>0.75</td>
<td>0.63–0.83</td>
</tr>
<tr>
<td>Wing-beating tremor</td>
<td>0.82</td>
<td>0.71–0.89</td>
</tr>
<tr>
<td>Kinetic + postural + wing-beating tremor composite score</td>
<td>0.87</td>
<td>0.79–0.92</td>
</tr>
</tbody>
</table>
Clinical Study

Tremor is attenuated during walking in essential tremor with resting tremor but not parkinsonian tremor

Kei Uchida, Masaaki Hirayama, Fumitada Yamashita, Norio Hori, Tomohiko Nakamura, Gen Sobue *
ET, ET plus or ???

DBS tolerance
Case 1 – ET plus
12 months later
DBS tolerance
Tremor phenotype makes a difference

Case 2
Left Vim DBS off
DBS tolerance

1. Underreported
2. Poorly defined
3. Largely unstudied

Can DBS produce deleterious neuroplasticity?

ET, ET plus or ???