Controversy

Essential Tremor: A Heterogenous Disorder

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Although essential tremor (ET) has been well characterized since 1887, there is still considerable controversy about the definition of ET, and there is no agreement among the experts as to whether ET is a symptom, a syndrome, or a specific disease entity. Some experts, including my esteemed colleague, Dr. Elble, have concluded that ET “may not be a single entity.” As I agree with this view, there seems to be no need for any debate. Nevertheless, I will briefly review the evidence to support the argument that ET is not a monosymptomatic disorder, but a heterogenous disorder probably caused by different pathogenic mechanisms. I will discuss the evidence based on clinical, physiological, metabolic, genetic, and therapeutic studies.

The uncertainty about the nosology of ET is partly due to a lack of a disease-specific diagnostic marker for ET and an absence of specific pathological changes in the brains of ET patients. Until such a biological, physiological, or genetic marker or markers are identified, the operational diagnostic criteria must rely on the presence or absence of certain clinical characteristics that may be used to categorize ET as definite, classic, probable, or possible (Table 1). The diagnostic criteria may be modified according to specific needs. For example, in genetic linkage studies, only definite ET may be acceptable, whereas in studies designed to explore the clinical spectrum of ET, including associated features, the possible ET category may be more appropriate (Table 2). More recently, core and secondary criteria were proposed to facilitate a practical approach to the diagnosis of ET. Core criteria include bilateral action tremor of the hands and forearms (but not rest tremor), absence of other neurological signs (except Froment’s sign), and isolated head tremor without signs of dystonia. Secondary criteria include long duration (>3 years), positive family history, and beneficial response to alcohol. There are diagnostic red flags that indicate diagnosis other than ET, such as unilateral tremor, leg tremor, rigidity, bradykinesia, rest tremor, gait disturbance, focal tremor, isolated head tremor with abnormal posture (head tilt or turning), sudden or rapid onset, and drug treatment that may cause or exacerbate tremor. For the purposes of this review, I will define ET operationally as a predominantly postural tremor of sporadic or genetic origin producing oscillatory movement of the hands, head, or both, without other known causes of tremor, such as drugs, metabolic or endocrine disorders, structural metabolic central nervous system lesions, or peripheral injury. Family history, alcohol sensitivity, and propranolol responsiveness, while characteristic of ET, should not be considered necessary for the diagnosis. Similarly, the presence of PD, dystonia, and other movement disorders should not necessarily preclude the diagnosis of ET.

Typically described as a postural tremor, ET often has a marked kinetic component suggesting cerebellar involvement in the pathophysiology of ET. Thus, patients with otherwise typical (classic) ET often exhibit kinetic tremor when the voluntary movement starts (initial tremor), during the course of the movement (dynamic tremor), and as the affected body part approaches the target, e.g., while performing the finger-to-nose or the toe-to-finger maneuver (terminal tremor, also called intention tremor). In one study, 25% of ET patients were found to have moderate or severe kinetic tremor and other physiological evidence of cerebellar dysfunction. Cerebellar dysfunction in ET is also suggested by abnormalities in tandem gait, noted in 50% of ET patients and by mild postural instability. That the cerebellum may be involved in ET is also supported by the report of a 71-year-old man with ET in whom postural tremor disappeared on the right side after an ipsilateral cerebellar infarct.
These clinical observations are consistent with a growing body of evidence based on various physiological and imaging studies indicating a critical role of the cerebellum and its afferent and efferent projections in the pathophysiology of ET.\textsuperscript{15} Physiological studies of patients with ET have found evidence of cerebellar involvement as suggested by a delay in the second agonist electromyography (EMG) burst during rapid wrist movements.\textsuperscript{16} Several metabolic and blood flow studies utilizing positron emission tomography (PET) have provided evidence that ET is associated with markedly increased blood flow to both cerebellar hemispheres.\textsuperscript{17–21} Additional evidence of increased activation of the cerebellum and red nucleus in ET has been provided by functional magnetic resonance imaging (MRI) studies.\textsuperscript{22}

Although tremor is clearly the most troublesome symptom, it is not necessarily the only symptom in patients with ET.\textsuperscript{23} Some patients, for example, start with ET as a monosymptomatic disorder and later develop parkinsonism, dystonia, balance difficulties, and hearing loss; and in others postural tremor may start after the onset of these neurological disorders. Although no epidemiological studies have been conducted to confirm that the frequency of the associated comorbidities is significantly higher than would be expected in a general, age-matched population, the reported clinical studies, coupled with clinical experience, provide overwhelming support for the higher-than-expected co-occurrence of these disorders with ET. Furthermore, several well-studied families have been described in which some members have typical ET, while others have dystonia, parkinsonism, or a combination of all three disorders.\textsuperscript{24,25,25A} A possible relationship between ET and Parkinson’s disease (PD) has been suggested by some\textsuperscript{4,24–28} and disputed by others.\textsuperscript{29,30} We found that relatives of patients with PD have at least a 2.5-fold higher prevalence of postural tremor than normal controls, providing additional support for the association of ET and PD.\textsuperscript{31} Similarly, a fourfold increase in prevalence of isolated tremor among relatives of patients with PD as compared with controls was found by Payami and colleagues.\textsuperscript{32} Finding a 17% prevalence of uncomplicated tremor in immediate family members of 159 patients with PD, Lang and associates\textsuperscript{27} concluded that “some individuals with a family history of tremor may be genetically predisposed to the development of PD.”

\begin{table}
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\caption{Proposed classification of essential tremor (TRIG)}
\begin{tabular}{ll}
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I. Definite ET \\
A. Inclusions: & Bilateral postural tremor with or without kinetic tremor involving hands or forearms, which is visible and persistent, and long-standing in duration (> 5 years). Tremor involving body parts other than upper limbs may be present, the tremor may be asymmetrical, amplitude may fluctuate, and the tremor may or may not produce disability. \\
B. Exclusions: & 1. Neurological signs, except for Froment’s sign (a “cogwheel” phenomenon on passive movement of the affected limb with voluntary movement of the contralateral limb) \\
& 2. causes of enhanced physiologic tremor \\
& 3. concurrent or recent exposure to tremorgenic drugs \\
& 4. direct or indirect trauma to the central and peripheral nervous system \\
& 5. historical or clinical evidence of psychogenic origins of tremor \\
& 6. convincing evidence of sudden onset or evidence of stepwise deterioration \\
II. Probable ET \\
A. Inclusions: & the same as for definite ET, but the tremor may be confined to body parts other than hands and the duration is greater than 3 years. \\
B. Exclusions: & 1. primary orthostatic tremor, which is an isolated, high frequency (14–18 Hz), bilaterally synchronous leg tremor on standing or voluntary contraction of leg muscles \\
& 2. isolated voice, tongue, or chin tremors \\
& 3. position- and task-specific tremors \\
III. Possible ET \\
A. Inclusions: & Type 1. Satisfy criteria for definite or probable ET, but exhibit other recognizable neurologic disorders, such as: \\
& a. parkinsonism, dystonia, myoclonus, peripheral neuropathy or restless legs syndrome \\
& b. other neurological signs of uncertain significance not sufficient to make a diagnosis of a recognizable neurological disorder, such as mild extrapyramidal signs (hypomimia, decreased arm swing and mild bradykinesia). \\
& Type 2. Monosymptomatic and isolated tremors of uncertain relationship to ET. This includes position- and task-specific tremors such as occupational tremors (primary writing tremors); primary orthostatic tremor; isolated voice, chin, tongue and leg tremors; and unilateral postural hand tremor. \\
B. Exclusions: & 2–6 under Definite ET \\
\hline
\end{tabular}
\end{table}

Members of the Tremor Investigation Group TRIG: M. Brin, C. Contant, R. Elble, L. Findley, J. Jankovic, W. Koller, P. LeWitt, A. Rajput [Findley and Koller, 1995]
TABLE 2. Diagnostic criteria for essential tremor NIH essential tremor consortium

<table>
<thead>
<tr>
<th>Possible:</th>
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<tr>
<td>1. Isolated 1+ cranial—cervical tremor.</td>
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<tr>
<td>2. Task/position specific hand/arm tremor.</td>
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<tr>
<td>3. Unilateral arm tremor.</td>
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<td>4. Orthostatic tremor.</td>
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<td>Explanation of tremor rating:</td>
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<tr>
<td>0 = none perceived.</td>
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<td>1 = slight (barely noticeable).</td>
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<tr>
<td>2 = moderate, noticeable, probably not disabling (&lt;2 cm excursions).</td>
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<tr>
<td>3 = marked, probably partially disabling (2–4 cm excursions).</td>
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<tr>
<td>4 = severe, coarse, disabling (more than 4 cm excursions).</td>
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Definite:

1. Bilateral arm tremor with ≥2+ amplitude rating in at least one arm and ≥1+ in the other arm. 
or
2. Predominant cranial—cervical tremor with ≥2+ amplitude rating and ≥1+ rating in at least one arm. The head tremor is rhythmic, without directional preponderance, and without asymmetry of cervical muscles.
3. Exclude obvious secondary causes of tremor: physiologic, drug-induced, CMT, PD, etc. (Co-existent dystonia is allowed, but co-existent PD is not).

Probable:

1. 1+ arm tremor bilaterally. 
or
2. Isolated cranial—cervical tremor with ≥2+ amplitude rating. 
or
3. Convincing history of ET.
4. Exclude obvious secondary causes of tremor: physiologic, drug-induced, CMT, etc. (Co-existent dystonia is allowed; co-existent PD is allowed if there is a convincing history of pre-existing ET).


ET, essential tremor; PD, Parkinson’s disease; CMT, Charcot-Marie-Tooth disease.

Suomotor impairment in 8 of 23 patients (35%) with ET, Schwartz and coworkers concluded that, “considering the presence of similar impairments in patients with early PD and the increased prevalence of parkinsonism in patients with ET, it is possible that preclinical parkinsonism exists in patients with ET.”

The coexistence of ET and PD may be difficult to recognize because once a patient develops symptoms of PD, the postural tremor is usually attributed to PD. Before discussing the relationship between ET and PD, it is important to note that there are many other causes of postural tremors that appear phenomenologically identical to ET, including PD-related tremors. Postural tremor has been reported to occur in as many as 93% of patients with clinically diagnosed PD. It is this action-postural tremor that seems to correlate with motor disability rather than the typical rest tremor, which correlates chiefly with social disability. Different mechanisms have been proposed for this postural tremor in patients with PD. For example, postural tremor in patients with PD has been attributed to enhanced physiological tremor. Some patients with PD exhibit flexion—extension hand (wrist) tremor when arms are outstretched in front of the body or abducted at the shoulder and flexed at the elbow (”wing-beating position”); it emerges after a latency of a few seconds. This tremor, referred to as the re-emergent tremor, probably represents a rest tremor that has been reset during posture holding. The relationship of this re-emergent tremor to the typical PD-related rest tremor is supported by the observation that the re-emergent tremor shares many characteristics with the PD rest tremor: it has the same 3- to 6-Hz frequency and also responds to dopaminergic therapy. In addition to well-defined clinical characteristics that reliably differentiate between postural tremor of ET and of PD, patients with ET may exhibit akinesia or bradykinesia, as evidenced by increased reaction times and slow movement velocities, respectively, similar to patients in early stages of PD. To help differentiate between ET and postural tremor as the initial manifestation of PD, we have insisted that our studies explore an ET–PD association based on the presence of monosymptomatic postural tremor (ET) for at least 5 years prior to the onset of any other symptom of PD. Initially arguing that the coexistence of the two disorders simply “represents a chance occurrence of two common diseases,” Pahwa and Koller later concluded that “the frequency of PD in ET is more than would be reported in the general population.” This revised view was based on the finding of higher-than-expected (6.1%) prevalence of concomitant PD among 678 patients diagnosed with ET. Tanner and colleagues found that, of 196 twins with postural or kinetic tremors, 137 (70%) had PD or a twin with PD. These findings provide support for the notion that some ET patients later develop parkinsonism. Whether the parkinsonism in patients with ET is predominantly due to PD or some other form of parkinsonism is still uncertain. Although there are no postmortem reports of patients with a ET–PD combination, most of our patients with this phenotype are responsive to levodopa. The weight of reported evidence supports the conclusion that at least a subgroup of ET patients has an increased risk for developing PD. This, of course, may have important implications for possible neuroprotective therapy that may need to be targeted to this at-risk population.

Although postmortem studies, while limited, have not provided evidence of nigrostriatal pathology in ET, there is indirect evidence suggesting nigrostriatal impairment in some patients with ET. Evidence of nigrostriatal deficiency in ET has been suggested by some but not all imaging studies. A 10 to 13% reduction in 18F-dopa...
uptake in the striatum of patients with ET as compared with controls suggests a physiologically important compromise of the dopaminergic system in ET patients. Furthermore, 18F-dopa uptake constants (K) in 5 of 32 “asymptomatic” relatives of patients with PD who had isolated postural tremor were reduced on average by 23% (P < 0.001). The mean K, for the other 27 asymptomatic relatives was decreased by 17% (P < 0.001). Using 123I-IPT single photon emission computed tomography to image the striatal dopamine transporter, Lee and associates found the mean bilateral uptake in 9 patients with isolated postural tremor (probably ET) to be slightly lower than in normal control subjects but this difference did not reach statistical significance. However, 6 other patients in whom rest tremor developed 4 to 18 years after the onset of postural tremor without other parkinsonian features had a significant reduction in the dopamine transporter compared with normal controls (2.61 vs. 3.83; P < 0.05) but lower than PD patients (1.97 contralateral and 2.35 ipsilateral). The investigators concluded that “some patients with postural tremor may acquire rest tremor in association with mild substantia nigra neuronal loss.”

In addition to a dystonic tremor, patients with dystonia frequently have postural ET-like tremor, present in body parts distal to the dystonia, and they have a higher-than-expected family history of postural tremor (about 25% of patients with cervical dystonia have postural hand tremor). The relatively frequent coexistence of a postural tremor similar to ET in patients with dystonia supports the notion that there is a pathogenic link between the two disorders. Although linkage analysis excluded the dystonia (DYT1) gene on chromosome 9 in hereditary ET, this does not mean that there is no genetic link between the two disorders. The genes for these two disorders may be on separate loci, or the relationship between the two disorders may be physiological rather than genetic. Münchau and coworkers studied 11 patients with classic ET and compared them with 19 patients with cervical dystonia and arm tremor. Although they concluded that the physiological mechanism of arm tremor in patients with ET was different from that of arm tremor in patients with cervical dystonia, this does not rule out the possibility that coexistent ET may account for the postural arm tremor in some patients with cervical dystonia. The overlap between ET and dystonia suggests by the observation that some patients (or their relatives) with typical ET also manifest task-specific tremors or dystonias that occur only during, or are markedly exacerbated by, a certain task, such as writing (primary handwriting tremor or dystonic cramp), speaking or singing (voice tremor or spasmodic dysphonia), or performing certain occupations, sport activities, or other tasks. Position-specific tremors or dystonias that occur while holding a certain posture (e.g., the wing-beating position or holding a cup close to the mouth); or isometric tremors that occur during a voluntary contraction of muscles without an accompanying movement or a change in position of the body part, such as maintaining a tightly squeezed fist or standing (e.g., orthostatic tremor).

Orthostatic tremor, first described by Heilman in 1984, is a fast (14- to 16-Hz) tremor involving mainly the legs and trunk. In support of the association between ET and orthostatic tremor are the relatively high occurrence of familial, postural tremor in patients with orthostatic tremor and similar PET findings indicative of bilateral cerebellar (and contralateral lentiform and thalamic) dysfunction. Rarely, leg tremor, phenomenologically similar to orthostatic tremor, is the initial manifestation of PD, and some patients with orthostatic tremor respond to levodopa. The involvement of the cranial muscles and a high degree of EMG coherence between right and left muscle groups suggest that supraspinal mechanisms are involved in the generation of the tremor. This is further supported by the finding of high intermuscular coherence between both sides, providing evidence that the tremor originates from a common site. Some authors have suggested that orthostatic tremor merely unmasks 16-Hz central oscillators involved in postural tremor. In contrast to ET, orthostatic tremor responds well to clonazepam and gabapentin, but some patients with orthostatic tremor benefit from levodopa.

The possibility of additional cochlear involvement in ET is supported by the observation of high occurrence of partial or complete deafness in patients with ET. Although mental functioning is usually intact in patients with ET, detailed testing of cognitive performance has found some subtle abnormalities on tests of verbal fluency, naming, mental set-shifting, and verbal and working memory, as well as higher levels of depression (similar to the control group with PD). These deficits have been interpreted to suggest involvement of frontocerebellar circuits.

In addition to the observed coexistence of ET and other neurological disorders, the clinical heterogeneity of ET is exemplified by the variable course of the disease, suggesting that there may be different subtypes of ET. Indeed, Louis and colleagues found that patients who were older at onset (age >60 years) and those without head tremor progressed more rapidly than patients who were young at the onset of tremor and those with head tremor. We also found that some patients with ET and
those with the ET–PD combination had a significantly increased longevity.67

Family history of tremor has been reported in 17 to 100% of patients with ET.68,69 The reason for such a large discrepancy is that unless all the symptomatic and asymptomatic members of the family are examined, the number of affected relatives will be underascertained.24,70 Studies of large families with ET provide the most cogent evidence for heterogeneity of ET. In 252 members of four large kindreds with ET, we found that three kindreds with a total of 41 members had the combination of ET and dystonia and two kindreds had members with both ET and PD.24 Two of our families with pure ET and one with ET–PD-dystonia also mapped to the same locus, providing further support for the notion that a single genotype may be manifested by different phenotypes.71 Another marker for ET has been mapped to chromosome 4p14–16.3 in a family with autosomal dominant PD.25 The haplotype occurred not only in individuals with parkinsonism, but also in family members without parkinsonism who exhibited isolated postural tremor phenomenologically identical to ET. Finding a 17% prevalence of uncomplicated tremor in immediate family members of 159 patients with PD, Lang and associates27 concluded that “some individuals with a family history of tremor may be genetically predisposed to the development of PD.” A possible genetic link between ET and PD is also suggested by the finding of higher frequency of the 263-bp allele of the NACP-Rep1 polymorphism in patients with PD (odds ratio, 3.86) and ET (odds ratio, 6.42), but not in Huntington’s disease or other disorders.72 These data provide further evidence that ET and PD may be genetically related.73

Besides the evidence of an association between ET and PD and between ET and dystonia, there are many other disorders associated with ET. For example, ET-like tremor has been described in patients with hereditary myoclonus and with hereditary motor-sensory neuropathy (sometimes referred to as Roussy-Lévy syndrome).74 ET-like tremor occurs in other genetic diseases, the study of which may provide important insights into possible genetic heterogeneity in families with clinically similar tremors. For example, postural tremor similar to that seen in ET has been reported in patients with Kennedy’s disease, also called “X-linked recessive spinal and bulbar muscular atrophy,” which is caused by a mutation characterized by expansion of CAG repeats in the gene on the X chromosome.75

The validity and meaning of the observed associations between ET and PD, dystonia, myoclonus, deafness, and other neurological disorders, however, are not likely to be resolved until a disease-specific marker (e.g., an ET-linked gene mutation or mutations) is identified. A diagnostic marker for ET would also help to resolve the question of whether site-, position- and task-specific tremors, such as primary handwriting tremor and orthostatic tremor, are distinct entities, or whether these tremors represent clinical variants of ET. While it is desirable to define an entity under study as specifically as possible, until the different disorders manifested by postural tremor can be split into well-defined nosological entities with unique causative or pathogenic mechanisms, an open-minded approach is recommended in which ET is considered as a heterogenous disorder rather than merely a monosymptomatic clinical entity.

References
ESSENTIAL TREMOR: A HETEROGENEOUS DISORDER


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