

# Essential Tremors

## A Family of Neurodegenerative Disorders?

Elan D. Louis, MD, MSc

**E**ssential tremor (ET) is the most common pathologic tremor in humans. The traditional view of ET, as a monosymptomatic condition, is being replaced by an appreciation of the spectrum of clinical features, with both motor and nonmotor elements. These features are not distributed homogeneously across patients. In addition, postmortem studies are now demonstrating distinct structural changes in ET. There is growing evidence that ET may be a family of diseases rather than a single entity. Furthermore, this aging-associated, progressive disorder is associated with neuronal loss and postmortem changes that occur in traditional neurodegenerative disorders.

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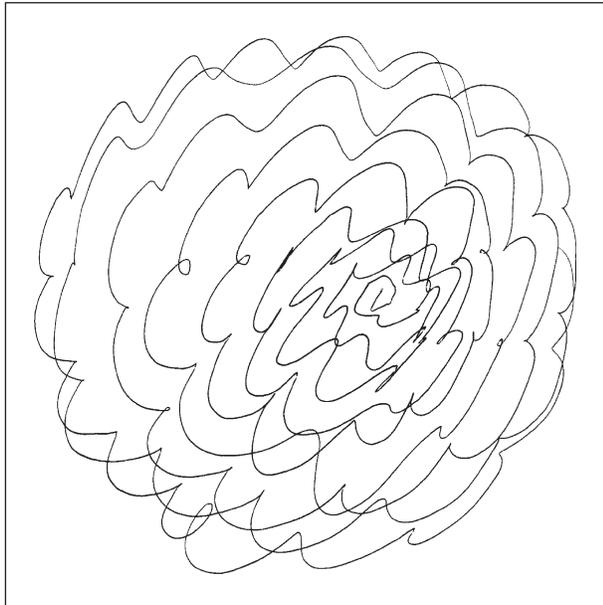
Essential tremor (ET), the most common pathologic tremor in humans, is among the more ubiquitous neurologic diseases, with a prevalence (age  $\geq 40$  years) of 4.0%.<sup>1,2</sup> Its most recognizable clinical feature is an 8- to 12-Hz kinetic tremor of the arms (ie, tremor during voluntary movement) (**Figure 1**), which is often later accompanied by head and voice tremors. The condition is global, affecting human beings in a variety of settings, ranging from the remote Okapa subdistrict of Papua New Guinea to the urban Washington Heights–Inwood community in northern Manhattan, New York.<sup>1,2</sup> The traditional view of ET as a monosymptomatic condition characterized by only kinetic or postural tremor has been supplanted in recent years. First, the tremor phenomenology is broad and many patients have other motor manifestations<sup>3</sup> and nonmotor features, including cognitive and psychiatric.<sup>3,4</sup> Furthermore, this expanded constellation of clinical features is not distributed homogeneously across patients. For example, some patients develop head tremor while others do not. Some have dementia while others do not; some develop Parkinson disease (PD) while others do not.<sup>5</sup> Recent

studies of the pathology of ET have demonstrated several distinctive structural changes, including neuronal loss.<sup>6-10</sup> With evidence of clinical and pathologic heterogeneity emerging, several important questions arise. First, is ET a single disease entity or a family of diseases? Second, is ET neurodegenerative?

### ESSENTIAL TREMOR OR THE ESSENTIAL TREMORS?

Neurology is replete with historical examples in which clinical-pathological investigations have resulted in the partitioning of disease entities and the refinement of classification. For example, many patients with upper motor neuron signs were clinically lumped together, yet in the 1800s, Charcot and others observed that among such patients who had sclerosis on postmortem examination, 1 subgroup had a pattern that could be characterized as amyotrophic lateral sclerosis (ALS), while a second subgroup had a pattern that could be characterized as multiple sclerosis (MS). We now know that ALS and MS are different diseases with distinct mechanisms, clinical features, and treatments. Likewise, in the mid-20th century, advances in neuropathology and careful clinical-pathological studies redefined the concept of parkinsonism as a family of disease

**Author Affiliations:** Gertrude H. Sergievsky Center, Department of Neurology, and Taub Institute for Research on Alzheimer's Disease and the Aging Brain, College of Physicians and Surgeons; and Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, New York.



**Figure 1.** Kinetic tremor is apparent in this drawing of an Archimedes spiral in a patient with essential tremor.

entities rather than a single disease. Idiopathic PD could be distinguished from other entities like progressive supranuclear palsy and corticobasal ganglionic degeneration. It is conceivable that we are now arriving at such a primary juncture in our understanding of ET. Evidence of clinical heterogeneity and pathologic heterogeneity is emerging, raising the question as to whether it is possible to reformulate ET as a cluster of separable clinical-pathological entities, that is, a family of diseases—the essential tremors.

#### CLINICAL, THERAPEUTIC RESPONSE, PATHOLOGIC, AND ETIOLOGIC HETEROGENEITY

Although clinical phenotypic variability by itself is not an argument for separate diseases, its presence further opens that possibility. Clinically, the view of ET as a single neurologic sign no longer seems tenable. First, the tremor phenomenology itself is multifaceted. Although kinetic and postural tremors are the core features upon which diagnostic criteria are generally based (**Table 1**), intention tremor<sup>18</sup> and tremor at rest<sup>19</sup> may also occur in subsets of patients. The relative severity of different tremor types (kinetic more severe than postural),<sup>20</sup> the favored sites of anatomical involvement (arm more often than head, and head more often than jaw),<sup>21</sup> and the typical direction of spread over time (from arms to head rather than the converse)<sup>22</sup> are distinctive, adding a degree of subtlety and complexity to the recognition and diagnosis of a disorder that is often viewed as relatively ordinary and featureless. Indeed, perhaps owing to a lack of familiarity with these features, misdiagnosis is exceedingly common; 30% to 50% of patients diagnosed with ET do not have ET,<sup>23</sup> which may make this one of the most commonly misdiagnosed neurologic disorders. Moreover, kinetic tremor of the arms, though not the head, may be an adverse effect of many medications, further

**Table 1. Clinical Diagnostic Criteria for Definite Essential Tremor**

#### Consensus Statement of the Movement Disorder Society on Tremor<sup>a,11,12</sup>

##### Inclusion criteria

Bilateral postural tremor with or without kinetic tremor, involving the hands and forearms, that is visible and persistent  
Duration >5 y

##### Exclusion criteria

Other abnormal neurological signs (except the Froment sign)  
Presence of known causes of increased physiological tremor  
Concurrent or recent exposure to tremorogenic drugs or the presence of a drug withdrawal state  
Direct or indirect trauma to the nervous system within 3 mo before the onset of tremor  
Historical or clinical evidence of psychogenic origins  
Convincing evidence of sudden onset or evidence of stepwise deterioration

#### Washington Heights–Inwood Genetic Study of Essential Tremor Criteria<sup>b,13</sup>

On examination, a +2 postural tremor<sup>c</sup> in  $\geq 1$  arm (a head tremor might also be present, but is not sufficient for the diagnosis)

On examination, there must be a +2 kinetic tremor during  $\geq 4$  tasks, or a +2 kinetic tremor on one 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 maneuver, and drawing spirals

If on examination the tremor is present in the dominant hand, then by report it must interfere with  $\geq 1$  activity of daily living (eating, drinking, writing, or using one's hands). If on examination the tremor is not present in the dominant hand, then this criterion is irrelevant

Medications, hyperthyroidism, ethanol, and dystonia are not potential etiological factors

Symptoms are not psychogenic (eg, bizarre features, features inconsistent in character, the patient is distractible, or other psychiatric features on examination)

<sup>a</sup>The Movement Disorder Society has proposed consensus criteria for essential tremor.

<sup>b</sup>The Washington Heights–Inwood Genetic Study of Essential Tremor criteria specify the minimal severity of tremor that is required and are also widely used in genetic and epidemiological studies.<sup>1,14-17</sup>

<sup>c</sup>Tremor ratings: 0, no visible tremor; +1, tremor is of low amplitude, barely perceivable or intermittent; +2, tremor is of moderate amplitude (1-2 cm) and usually present and is clearly oscillatory; +3, tremor is of large amplitude (>2 cm), violent and jerky, resulting in difficulty completing the task because of spilling or inability to hold a pen to paper.

contributing to this diagnostic difficulty. The following medications may produce kinetic tremor: amiodarone, bronchodilators, cyclosporin, lithium, methylphenidate, phenylpropanolamine, procainamide, pseudoephedrine, selective serotonin reuptake inhibitors, steroids, theophylline, thyroxine, tricyclic antidepressants, and valproic acid. Second, there are motor features aside from tremor. In a large number of studies,<sup>18,24</sup> postural instability and mild to moderate gait ataxia, beyond that observed in normal aging, have been demonstrated in subgroups of patients with ET. In addition to these gait problems, eye motion abnormalities (impaired smooth pursuit initiation and pathologic suppression of the vestibulo-ocular reflex time constant) were recently described in a study of 17 ET cases.<sup>25</sup> Third, there is a growing appreciation of the existence of a variety of nonmotor features, including cognitive, psychiatric, and sensory. Cognitive features, especially mild problems with executive function and memory, were first reported in 2001<sup>26</sup>

**Table 2. Medications Used to Treat Essential Tremor**

Medication	Dosage	Potential Adverse Effects
Acetazolamide	≤500 mg/d	Weakness, fatigue
Alprazolam	0.125-3 mg/d	Sedation, fatigue, potential for abuse
Atenolol	50-150 mg/d	Light-headedness, nausea, cough, dry mouth, sleepiness
Botulinum toxin A (hand tremor)	50-100 U	Hand/finger weakness, reduced grip strength, pain at injection site, stiffness, cramping, hematoma, paraesthesias
Botulinum toxin A (head tremor)	40-400 U	Neck weakness, postinjection pain
Botulinum toxin A (voice tremor)	0.6-15 U	Breathiness, weak voice, swallowing difficulty
Clonazepam	0.5-6 mg/d	Drowsiness
Clozapine	≤200 mg/d	Sedation, potential agranulocytosis (0.8% at 1 y)
Flunarizine	10 mg/d	Sedation, weight gain, depression, dystonia, parkinsonism
Gabapentin	1200-1800 mg/d	Lethargy, fatigue, decreased libido, dizziness, nervousness, shortness of breath
Levetiracetam	≤3000 mg/d	Depressed mood, drowsiness, fatigue
Methazolamide	≤300 mg/d	Somnolence, nausea, paresthesias, headache
Nimodipine	120 mg/d	Headache, heartburn
Nadolol	120-240 mg/d	None
Olanzapine	20 mg/d	Drowsiness, sedation, weight gain, diabetes
1-Octanol	1 mg/kg/d	Lethargy, asthenia, headache
Phenobarbital	≤150 mg/d	Drowsiness, fatigue ataxia
Pregabalin	≤600 mg/d	Dizziness, somnolence
Primidone	≤750 mg/d	Sedation, drowsiness, fatigue, nausea, giddiness, vomiting, ataxia, malaise, dizziness, unsteadiness, confusion, vertigo, acute toxic reaction
Propranolol	60-800 mg/d	Reduced arterial pressure, reduced pulse rate, tachycardia, bradycardia, impotency, drowsiness, exertional dyspnea, confusion, headache, dizziness
Long-acting propranolol	80-320 mg/d	Skin eruption, transient dizziness
Sodium oxybate	≤7.5 g/d	Dizziness, headache, sedation, ataxia
Sotalol	75-200 mg/d	Decreased alertness
Topiramate	≤400 mg/d	Appetite suppression, weight loss, paraesthesias, anorexia, concentration difficulties
Zonisamide	≤200 mg/d	Ataxia, dizziness, somnolence, agitation, anorexia

and soon after by numerous other investigators.<sup>27</sup> Furthermore, a population-based study in Madrid<sup>28</sup> first demonstrated in 2006 that the odds of prevalent dementia were nearly twice as high among the subset of ET cases with older-onset disease when compared with age-matched controls. The same group later demonstrated<sup>15</sup> that the risk of developing incident dementia was nearly twice as high in the ET cases than controls. Also, a number of psychiatric correlates have been observed. The presence of specific personality traits<sup>29,30</sup> has been demonstrated. In one such study,<sup>29</sup> the observed personality profile was not related to functional disability or tremor severity, suggesting that it could be a primary disease feature rather than a response to disabling tremor.<sup>29</sup> Anxiety,<sup>31</sup> depressive symptoms,<sup>32</sup> and social phobia<sup>33</sup> have been shown to occur in patients with ET more often than in controls. Traditionally, these have been viewed as psychiatric responses to disabling tremor. Yet in a recent prospective study,<sup>4</sup> depressive symptoms preceded the onset of the tremor by several years (ie, the presence of baseline self-reported depression was associated with an increased risk of developing incident ET during follow-up). Sensory abnormalities, including olfactory deficits in some studies<sup>34</sup> and hearing loss in others,<sup>35</sup> have been reported in ET cases compared with age-matched controls, further drawing attention to the domain of non-motor manifestations. Although a single disease may have a broad array of clinical manifestations (eg, Huntington disease), such clinical variety can also be an indication that one is dealing with a group of diseases (eg, parkinsonisms such as PD, progressive supranuclear palsy, and corticobasal ganglionic degeneration).

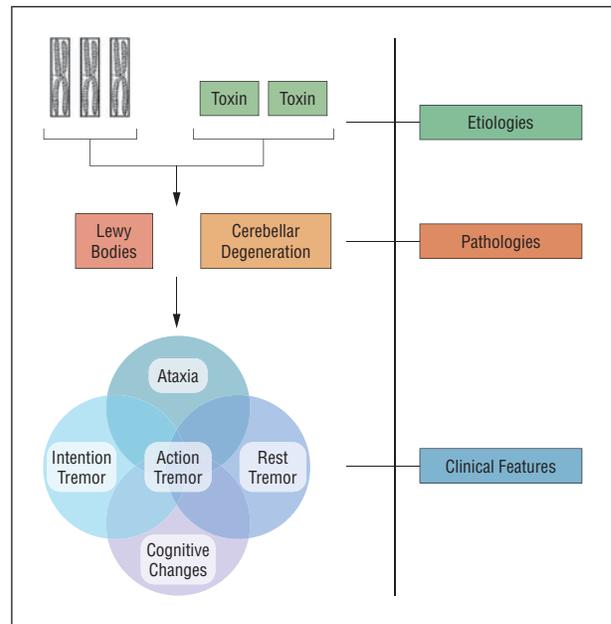
It is important to emphasize that these clinical features are heterogeneously distributed across patients with ET. Although some patterns are now becoming apparent (eg, patients with intention tremor have more gait difficulties and eye motion abnormalities<sup>25</sup>; patients with rest tremor generally have long-standing disease with severe kinetic tremor<sup>19</sup>; dementia is associated with older age of onset of ET<sup>5</sup>; and older age of onset and unilateral onset are associated with more rapid progression<sup>36,37</sup>), a clear separation of distinct clinical subtypes has yet to emerge.

The mainstays of therapy for ET are propranolol and primidone, though several promising new agents have been introduced in recent years (**Table 2**); surgical treatment (deep brain stimulation) is also highly effective.<sup>3</sup> One reoccurring feature of pharmacotherapeutic trials in ET is that the response to a particular medication is usually patchy, with approximately one-half of the patients showing some degree of tremor reduction and others none at all<sup>38</sup>; this phenomenon is frequently observed by practitioners as well. Among other possibilities (eg, differences in disease duration across treated patients), this heterogeneity of response could be a marker of different underlying disease mechanisms in subsets of patients, though this remains to be demonstrated.

Disease mechanisms in ET have been elusive. Despite its high prevalence, until recently few brains with ET were examined and little information was available about its pathology. An intensive effort was launched in 2003 to bank ET brains.<sup>6</sup> In contrast with previous studies, these brains were systematically examined to quantify cerebellar and other brainstem pathologies and were compared with control brains. These analyses, based on 33 ET brains, indicated that the structural pathologic

changes appeared to be of 2 types.<sup>6,7,9,39</sup> Most commonly (75%), brains were characterized by clear cerebellar degenerative changes, including a 40% reduction in the number of Purkinje cells, a 6-fold increase in the number of torpedoes (ie, swellings of the Purkinje cell axon that likely represent a cellular response to injury), and Purkinje cell heterotopia and dendrite swellings. These brains did not have Lewy bodies. The remaining brains were characterized by Lewy bodies confined mainly to the locus ceruleus relative to total sparing of other brainstem structures.<sup>6</sup> The prevalence of Lewy bodies was significantly greater than that observed in similarly aged controls, indicating that they were not likely incidental.<sup>6</sup> Furthermore, this particular pattern of Lewy body involvement in ET has not been described in series of atypical Lewy body brains (ie, brains that do not follow the Braak staging scheme).<sup>40</sup> The ET brains with Lewy bodies did not have excessive torpedoes or Purkinje cell loss.<sup>6</sup> These 2 pathological patterns were labeled cerebellar ET and Lewy body variant of ET.<sup>6,41</sup> Other recent series of ET brains have also confirmed a heterogeneous pathology involving Purkinje cell loss in the cerebellum in some cases and changes, including cell loss, in the locus ceruleus in others.<sup>8</sup> These recent postmortem studies have helped identify degenerative structural alterations in the cerebellum and its connecting pathways in ET. How changes in the locus ceruleus could produce ET is less clear, though neurons of the locus ceruleus synapse with cerebellar Purkinje cell dendrites.<sup>42</sup> These projections are important for the normal development and maintenance of Purkinje cells.<sup>43</sup> Impaired activity in the locus ceruleus could result in a diminution of stimulatory output from that locus to the Purkinje cells.

On an etiologic level, ET is often considered to be genetic.<sup>44</sup> There are many examples of families in which the proband and multiple relatives have ET and in which the pattern of inheritance is consistent with an autosomal dominant model. In 1997, linkage to a region on chromosome 2p was demonstrated,<sup>45</sup> and in that same year, to chromosome 3q in other families.<sup>46</sup> A third study demonstrated linkage to a region on chromosome 6p in several families.<sup>47</sup> Aside from these 3 studies, others have failed to demonstrate linkage to these 3 regions, indicating that there will likely be more than 3 genes responsible for this disease.<sup>44,48</sup> It is important to note, however, that the genetic studies have not progressed further and the specific ET genes have not yet been identified.<sup>44-47</sup> In the absence of a specific genotype for ET, there are as yet no specific genotype-phenotype correlations, though it appears that young-onset cases are generally familial (ie, likely to have a genetic susceptibility).<sup>49</sup> Aside from genetic factors, there is also a growing understanding that environmental factors likely contribute to the etiology of ET as well, indicating that there is further heterogeneity on an etiologic level. Several lines of evidence support the role of these factors. First, while commonly stated that 50% or more of ET cases have a genetic basis, the precise derivation of this estimate is unclear and its validity is also doubtful.<sup>50</sup> Indeed, some estimates are as low as 17%.<sup>50</sup> In twin studies,<sup>51,52</sup> concordance in monozygotic twins was only 60% in one study and 63% in another. Second, the well-known existence of intrafamil-



**Figure 2.** One possible schema of the heterogeneity of essential tremor. The heterogeneity in essential tremor may be organized by (1) disease etiology, (2) tissue-level changes that occur after the disease process is initiated and as it develops, and (3) clinical features that are the end product of these underlying pathological processes.

ial differences in age of onset, location of tremor, and severity of tremor<sup>53</sup> also suggests that environmental (or perhaps other genetic) factors may be serving as modifiers of underlying susceptibility genotypes. In terms of environmental factors, a growing number of case-control studies<sup>54</sup> have implicated several specific toxins, namely  $\beta$ -carboline alkaloids (eg, harmine and harmaline, a group of highly tremorogenic dietary chemicals) and lead; and further studies of these putative environmental toxins are needed.

#### ORGANIZING THE HETEROGENEITY

Information presented in the previous section may be organized by etiologies, pathologies, and clinical features (**Figure 2**). Given the sheer prevalence and ubiquity of this condition, the historical tendency to divide disease entities as new knowledge arises, the appreciation of a broader variety of clinical features in several separate domains (eg, tremor, other motor, cognitive, and psychiatric), the observation that these are not uniformly present in patients with ET, the evidence that multiple genes will likely be responsible for this disease, and preliminary evidence of distinct pathologic patterns, it is likely that ET will turn out to be a family of diseases rather than a single disease entity. It is likely that this family of diseases, united by the presence of kinetic tremor, would be separable on the basis of etiologic, clinical, therapeutic response, and pathologic features, though further work is needed to explore these relationships.

#### IS ET NEURODEGENERATIVE?

A question implicitly raised in the above discussion is whether this disease (or these diseases) are neurodegen-

erative. The idea that ET could be neurodegenerative is not new. In 1948, Critchley and Greenfield wrote: "Although anatomical proof is as yet lacking, there are at least a number of clinical points to make question whether 'essential tremor' may not, at times any rate, represent an incomplete or a premature variant of one of the cer-



**Figure 3.** When quantified using different methods, Purkinje cell loss in essential tremor is significant compared with age-matched controls. Bielschowsky-stained section (original magnification  $\times 50$ ) of the cerebellar cortex in a 79-year-old individual with essential tremor showing normal Purkinje cellularity (right) vs a region with segmental loss of Purkinje cells (left).

ebellar atrophies."<sup>55</sup> Although not further elaborated on by those authors, these clinical points include its insidious onset, association with advanced aging (ie, both incidence and prevalence increase with aging), gradual yet progressive nature, and the presence of cerebellar features (eg, intention tremor and ataxia) on examination.

Neurodegenerative diseases traditionally have been defined as diseases that begin insidiously, pursue a gradually progressive course that may continue for many years, and are characterized by the selective involvement of anatomically and physiologically related systems of neurons owing to intrinsic processes rather than an identifiable outside influence (eg, vascular, autoimmune). Cell loss is also considered by many to be a prominent feature of these diseases.<sup>56</sup> Furthermore, their occurrence often increases markedly with advancing age. What is the evidence that ET is neurodegenerative? The clinical points noted above are important. Essential tremor has an insidious onset<sup>33,37</sup> and then follows a gradual yet progressive clinical course.<sup>36,37</sup> There is a marked and continued rise in disease occurrence in advanced ages.<sup>1,2</sup> This clinical constellation is somewhat compelling; however, none of these features in isolation is specific to neurodegenerative diseases. On a tissue-based level, the evidence is more compelling. Selective involvement of an anatomically and physiologically related system of neu-

**Table 3. Evidence Suggesting That ET Is Neurodegenerative**

Evidence	Comment/Rationale	Feature Is a Characteristic of PD or AD		Cautionary Caveat
		PD	AD	
Purkinje cell loss or Lewy bodies on postmortem studies	Selective involvement of anatomically and physiologically related systems of neurons is considered an important feature of neurodegenerative disorders; Lewy bodies are a feature of PD, a neurodegenerative disease	Yes	Yes <sup>a</sup>	Additional postmortem studies are needed to confirm the results of currently emerging large postmortem series. <sup>6,8</sup>
Clinical resemblance to other cerebellar atrophies and Purkinje cell loss	This suggests shared disease mechanisms	No	No	
Marked rise in occurrence with advanced age	PD and AD are associated with advanced age	Yes	Yes	
Clinically progressive in most patients	PD and AD are relentlessly clinically progressive	Yes	Yes	Diseases that are not neurodegenerative may sometimes be clinically progressive
Somatotopic spread of tremor over time	Tremor often begins in one body region, and as the disease worsens, spreads to others	Yes	Yes <sup>b</sup>	
Olfactory deficit	Olfactory deficits are reported in PD and AD	Yes	Yes	Not specific to neurodegenerative disorders; not a consistent finding across all studies of ET
Loss of body mass index <sup>58</sup>	Neurodegenerative diseases are often associated with loss of body mass index	Yes	Yes	Not specific to neurodegenerative disorders; not a consistent finding across all studies of ET
Increased risk of mortality <sup>59</sup>	Neurodegenerative disorders are associated with increased risk of mortality	Yes	Yes	Not specific to neurodegenerative disorders; not a consistent finding across all studies of ET
Increased risk of AD	This association with ET suggests that ET may share pathogenic features with this neurodegenerative disease	Yes		
Increased risk of PD	This association with ET suggests that ET may share pathogenic features with this neurodegenerative disease		Yes	

Abbreviations: AD, Alzheimer disease; ET, essential tremor; PD, Parkinson disease.

<sup>a</sup>Neuronal loss in the hippocampus and neocortex is a feature of AD.

<sup>b</sup>As AD progresses, different cortical regions may become involved.

rons, Purkinje cells, has been reported recently in ET cases both in our series (**Figure 3**)<sup>6,7</sup> and in the other large series.<sup>8</sup> When quantified using different methods, Purkinje cell loss is significant. There is an approximate 40% loss of these cells in ET cases compared with age-matched control brains,<sup>6,7</sup> which persists even when one adjusts for age and other confounding pathologies (eg, mild Alzheimer-type changes). Additional evidence that the Purkinje cells are diseased is that there are significantly more torpedoes in the ET brain, where their numbers are 6 times higher than expected for age and a preponderance of displaced (ie, heterotopic) Purkinje cells as well as Purkinje cells with dendritic swellings.<sup>6</sup> In contrast to these cases, the ET cases with normal cerebella have Lewy bodies,<sup>6,9</sup> lesions that have long been considered important in the pathogenesis of another neurodegenerative tremor disorder, namely PD. While none of these pathologic changes in the cerebellum are disease-specific (eg, other forms of cerebellar degeneration may be characterized by Purkinje cell loss and torpedo formation), this just indicates that the changes seen in the cerebellum in ET occur more broadly in the cerebellar degenerations. Aside from this structural-pathologic evidence suggesting a neurodegenerative process, other evidence suggests that ET is neurodegenerative. While many of these features in isolation are not specific to neurodegenerative diseases, the constellation of findings, all present in the same disease, is more compelling (**Table 3**). For example, there is a long-standing clinical association between ET and PD; indeed, having ET increases the risk of developing incident PD 4- to 5-fold.<sup>60</sup> Furthermore, having older-onset ET increases the risk of developing Alzheimer disease nearly 2-fold.<sup>5</sup> This association between ET and subsequent development of these neurodegenerative diseases suggests that ET may share pathogenic mechanisms with these disorders.

There is some evidence to suggest that ET is a family of diseases rather than a single entity. These disorders, perhaps better termed the essential tremors, are aging-associated, progressive, and associated with cell loss and other types of changes (Lewy body formation) that traditionally occur in neurodegenerative disorders. Future study is needed to continue to shape our evolving notion of the entity that we currently refer to as essential tremor.

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**Correspondence:** Elan D. Louis, MD, MSc, Neurological Institute, Unit 198, 710 W 168th St, New York, NY 10032 (edl2@columbia.edu).

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