Essential Tremor

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Essential tremor (ET) is one of the most common movement disorders. Although often considered a monosymptomatic disorder (postural and kinetic tremor), ET has more recently been considered a more heterogeneous syndrome, with motor and nonmotor features. The diagnosis is clinical and pharmacologic and surgical therapies exist. ET is frequently misdiagnosed as Parkinson disease or dystonia. The traditional notion of ET as a benign disorder has been challenged by those who view ET as a slowly progressive neurodegenerative disorder.


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Essential tremor (ET) is a common movement disorder seen in neurologic practice. Once considered benign (benign essential tremor), the recognition that it could often lead to significant disability in activities of daily living prompted the neurologic community to drop that adjective. There has been recent interest in investigating ET as a more heterogeneous disorder with both motor and nonmotor characteristics. Over the past decade, research has advanced our understanding of the pathophysiology of ET and broadened treatment options for patients with ET. We review the diagnosis and clinical characteristics of ET and the treatment options available. We also discuss recent developments in etiology and physiology of ET and address the controversies that now surround this common disorder.

Epidemiology
ET is the most common tremor worldwide. Prevalence of this disorder varies with age, with a higher incidence seen in older individuals. The prevalence of ET in individuals between age 50 and 80 years ranges from 6% to 9%. Although ET was once thought to be a benign disorder that did not affect mortality, new questions were raised in a recent study conducted in central Spain that showed the risk of mortality was increased 45% in 201 individuals with ET when compared with 3337 age-matched control subjects. Risk factors for developing ET include age, family history, and ethnicity. Whites have a higher
prevalence than Hispanics and African Americans. There is no identified gene responsible for ET, but it has been recognized for decades that there are many families with a strong autosomal dominant inheritance pattern for ET.

Clinical Characteristics and Diagnosis
ET affects the upper limbs with frequent involvement of the head and voice. There is infrequent involvement of the face, trunk, or lower limbs. The term essential likely has its origin in the 1900s when it was used to imply that the clinical problem was an inherent or innate characteristic of the patient with no clear medical cause. Although tremor is the distinctive feature of ET, nonmotor signs are increasingly recognized.

The first step in the diagnosis of ET is determining that the patient has a tremor instead of another movement disorder. The term tremor implies rhythmicity of the movement as well as oscillation within a central plane. The movements are involuntary. Several other abnormal movements can be confused with tremor. Choreiform movements in the hands might confuse the physician; however, unlike tremor, chorea is nonoscillatory and arrhythmic. Myoclonus can resemble tremor; however, it is often arrhythmic and palpation of muscle contraction can detect the shock-like nature of the movement. There is often a jerky quality to the movement, hence the term kinetic. The tremor frequently intrudes into activities such as writing, shaving, using utensils, and other fine motor tasks that require manual dexterity. Changes in posture can affect the character of the tremor, hence the term postural. The tremor may appear to occur at rest (if the limb is supported the resting component often ceases); however, there is almost always a prominent postural or kinetic component as well. ET usually presents in a symmetric manner, although almost 50% of patients may present with some asymmetry. Although the tremor may be asymmetric, it is almost always bilateral. ET progresses slowly over time. With progression over years or decades, the amplitude of the tremor increases, whereas the frequency decreases.

Tremor in ET can affect other parts of the body other than the upper extremities. Involvement of the head, voice, face, and tongue can be seen. In a recent clinical cohort study, over half of patients with ET had head and neck involvement. Less affected regions include the tongue (5%), jaw (7%), and trunk (5%). The lower limbs are affected in about 30% of individuals with ET. Head tremor occurs more frequently in women. Coexisting upper extremity tremor and head tremor is not uncommon. Since 1975, it has been widely recognized that ET is frequently responsive to alcohol consumption. Alcohol responsiveness can serve as a diagnostic clue, although unresponsiveness does not exclude ET as a diagnosis.

ET is a clinical diagnosis that should be suspected in patients who complain of longstanding tremor that interferes with daily activities and who have a positive family history for the disease. The diagnosis is confirmed by neurologic examination.
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bring out a wavy pattern. Walking is a useful means to observe resting tremor but does not usually bring out a postural or kinetic tremor.\textsuperscript{13,14}

Although tremor is the pathognomonic feature of ET, several other motor features are described. Individuals with ET can have impaired postural stability that is greater than expected with normal aging. Tandem gait can be difficult, and may represent impairment of cerebellar function.\textsuperscript{15} Orally administered alcohol has been shown to improve gait ataxia in patients with ET.\textsuperscript{16} Subtle eye movement deficits have been described, particularly in patients with advanced ET. Although difficult to assess at the bedside, deficits in pursuit and in abnormal discharge of velocity storage mechanisms have been described. The eye movement anomalies imply vestibulocerebellar dysfunction.\textsuperscript{17} Abnormalities of tone, particularly in a cogwheeling pattern, represent a palpable component of the underlying tremor. Of note, rigidity and bradykinesia are not associated with ET, and in the setting of a resting tremor, are signs of PD.\textsuperscript{1}

Controversy surrounds some of the recently described nonmotor features of ET. Whether ET is associated with cognitive impairment is the subject of debate. Several studies have shown deficits indicating frontal lobe dysfunction in patients with ET; however, these patients did not have cognitive complaints.\textsuperscript{18} There currently is no evidence that ET itself causes symptomatic cognitive impairment.\textsuperscript{1} Personality traits such as increased anxiety are more common in individuals with ET.\textsuperscript{19}

Other nonmotor features that may be more common in patients with ET include impairments in olfaction and hearing loss.\textsuperscript{20,21} More studies are needed to verify many of these nonmotor associations.

Although there can be confounding motor and nonmotor features in ET, the disorder is characterized by a postural and kinetic tremor that affects the upper extremities with frequent involvement of the head and voice. Involvement of the face, jaw, and lower limbs can be seen, and asymmetric presentations of the tremor are common. Determining that the movement is a tremor instead of another type of movement disorder is essential to making the correct diagnosis. ET is a clinical diagnosis based on characteristic historical features and examination. Tremor is the hallmark feature; however, other motor abnormalities such as gait impairment, eye movement anomalies, and other cerebellar signs can coexist. The etiology and character of nonmotor features, particularly cognitive impairment, remain controversial and are subject to further investigation.

Diagnostic Criteria

In 1998, the Movement Disorder Society (MDS) sponsored a symposium on tremor in an effort to standardize terminology and diagnostic standards. The MDS criteria for ET are the most accepted criteria for diagnostic and research purposes. They emphasize that ET is a clinical diagnosis made on history and examination. Table 1 demonstrates the MDS criteria for ET.\textsuperscript{22}

Differential Diagnosis

A common dilemma facing the physician making a diagnosis of ET in a patient with an upper extremity tremor is distinguishing it from PD, dystonia, or an enhanced physiologic tremor. A recent study examining misdiagnosis of ET demonstrated that 1 in 3 patients with tremor were misdiagnosed as having ET. PD was the most common misdiagnosis in this study, followed by dystonia.\textsuperscript{21} Subtle red flags in the character of the tremor can help separate ET from PD. In ET, the tremor can occur at rest; however, it is much more prominent with movement, and a resting tremor in ET often occurs in the setting of a severe kinetic tremor.\textsuperscript{24} Often the resting component is seen because the limb is not fully supported. Tremor involving the arm and leg on one side of the body is not characteristic of ET, and far more suggestive of PD. Cogwheel rigidity can be confused with a palpable tremor in ET, but patients with ET should not have bradykinesia or clear rigidity.\textsuperscript{15}

Enhanced physiologic tremor is commonly mistaken for ET, and historical clues can help solidify the diagnosis. Physiologic tremor is present in normal individuals and represents a normal oscillation in any freely moving muscle or joint. A complete review of medications, as well as caffeine and tobacco use should be completed. Medications commonly associated with worsening physiologic tremor include asthma inhalers, sodium valproate, tricyclic
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antidepressants, and lithium. Hyperthyroidism can cause a tremor with similar characteristics to ET. Caffeine and tobacco use can exacerbate enhanced physiologic tremor.14,15

There are several uncommon tremors in the differential of ET that can be recognized clinically. Primary orthostatic tremor is a rare tremor in the legs that occurs only with standing and resolves upon walking. The history of the patient being able to walk but not stand due to a leg tremor is pathognomonic.25,26 Primary writing tremor or other occupational and task-specific tremors occur when the individual is performing a specific task, such as writing. Individuals with a primary head tremor should be evaluated for cervical dystonia. Abnormal postures of the head or a sensation of the head and neck pulling in a specific direction is not seen in ET, and is suggestive of cervical dystonia. Patients with cervical dystonia frequently have a head tremor in association with the abnormal head posture.23

Genetics and Pathology
ET often has an autosomal dominant pattern of inheritance, although no clear genetic locus has been confirmed. Over 50% of patients with ET have a family history with ET.30 In a 2006 postmortem study by Louis and colleagues,31 individuals with ET were shown to have Lewy body pathology in the locus ceruleus, whereas others had cerebellar degenerative changes. The cerebellar changes were characterized by Purkinje cell loss and the presence of axonal swellings termed torpedoes. Studies have been limited by small sample size and overlap of

Recently, a large genome-wide association study for ET identified the LINGO1 gene as possibly associated with hereditary ET.
postmortem samples. Although it is not generally accepted that ET is a neurodegenerative disorder, further research is required. Moreover, it may be that over long periods of time, the central oscillatory process may cause irreversible damage to underlying cerebellar and brainstem structures.29,30

**Treatment**

There are several available treatments for ET, and treatment choices depend on patient goals, severity of tremor, and comorbid factors. Treatments include behavior modifications, medications, and surgery. Social embarrassment and functional impairment are the 2 main issues when determining whether to start medications or consider surgical options. Patients with mild ET may not require any treatment at all. Biofeedback or limited alcohol use can be useful in mild cases. Wrist weights, which increase the functional load in the arms, can be useful in mild upper extremity ET.9

If the tremor does cause significant disability or social embarrassment, several medications are available. An evidence-based practice parameter sponsored by the American Academy of Neurology found convincing evidence that established propranolol and primidone as the primary medications recommended for treatment of ET.32 Propranolol, a nonselective \( \beta \)-adrenergic blocker, can be started at 10 mg/d and titrated to effect. The usual therapeutic dose is in the 160- to 320-mg/d range. Side effects include fatigue, depression, and bradycardia. Other \( \beta \)-blockers have been shown to have benefit in ET, but propranolol is the most widely studied, and likely more effective than the selective \( \beta \_1 \) antagonists. Primidone, an anticonvulsant, is also well studied and effective in treating ET. Typical starting doses are 25 mg/d and titrating up to effect, which can be as high as 750 mg/d. However, seldom is more than 100 to 150 mg required for effect. Primidone does have tolerability issues that may improve with starting at very low doses or slowing a titration schedule.33 Common problems include sedation and nausea. If the tremor does not adequately respond to propranolol or primidone, combination therapy can be tried.15 Several other medications have been shown to have variable benefit in ET. Topiramate is often recommended as the third option after propranolol and primidone. Alprazolam, atenolol, gabapentin (monotherapy), and sotalol are second-line choices that have been shown to be probably effective.32 Botulinum toxin injections can be considered in patients who have failed oral therapy. In upper extremity tremor, the risk of upper extremity weakness secondary to botulinum toxin should be weighed against the benefit of possible tremor reduction.34 Pharmacotherapy for treatment of head tremor in ET has been less studied than treatment of upper extremity tremor; however, propranolol is the drug of choice. Botulinum toxin injections have also shown benefit in treating head tremor, and should be considered.32,35

Surgical treatment of refractory or severe ET can be very effective, and should be considered in patients who have debilitating ET that markedly impacts their daily function.32 Continuous deep brain stimulation (DBS) with electrode placement in the ventral intermediate nucleus (VIM) of the thalamus can lead to almost complete resolution of the contralateral tremor (Figure 1).36 Unilateral VIM DBS can only suppress the contralateral limb tremor. Bilateral VIM DBS is necessary to suppress tremor in both limbs.35 Side effects of dystarthis, gait impairment, and paresthesias are more common in bilateral VIM DBS.38 The added advantage to VIM DBS over thalamotomy is that adjustments in the DBS settings can be made periodically to mitigate side effects and optimize tremor control over time.

**Tremor Case Studies**

**Case 1**

A 67-year-old man is referred for evaluation of a longstanding tremor of the upper limbs with mild involvement of the head. He has had the tremor since childhood, and has a strong family history of tremor. The tremor interferes with many activities, including drinking, writing, and using utensils. He is embarrassed by the tremor. In the past, the tremor improved temporarily with alcohol consumption. On examination, he has symmetric low-amplitude, high-frequency tremor of the upper extremities. There is a slight tremor of...
the head. He has significant difficulty writing and drawing a spiral. He takes propranolol, 160 mg, twice daily, which improves the tremor slightly. Primidone is prescribed and titrated to 100 mg twice daily. He returns for follow-up and reports that he tolerates the medications; however, there is minimal improvement in tremor.

Case 2
A 59-year-old woman is referred for evaluation of a mild left upper extremity tremor. She has noticed the tremor for approximately 2 years and it has been mildly progressive. The tremor occurs more frequently when she is at rest; however, it sometimes intrudes into her regular activities, such as writing. She reports that she has difficulty signing her name, noticing that the letters are smaller. On examination, she has a tremor that is worse when she is resting her left arm in her lap and when she is distracted. There is a fine kinetic tremor in the left hand when she holds her arms straight. She has difficulty walking on a straight line and shows mild postural instability.

Main Points
- Essential tremor (ET) is the most common tremor worldwide, with a higher incidence seen in older individuals. The prevalence of ET in individuals between age 50 and 80 years ranges from 6% to 9%.
- ET is a clinical diagnosis that can be suspected by history and confirmed on physical examination. A review of family history, nonprescription and prescription medications, caffeine and tobacco use, and alcohol responsiveness are important elements in the history.
- Tremor, which is an involuntary, rhythmic movement with oscillation within a central plane, must be distinguished from other abnormal movement disorders and is the hallmark feature of ET.
- When examining the tremor of ET, the tremor should be accentuated by movement, hence the term kinetic. Changes in posture and extending the arms against gravity can affect the character of the tremor, hence the term postural.
- Greater than 95% of patients with ET have an upper extremity tremor; there can be involvement of the head, voice, face, and tongue.
- Difficulties with tandem gait as well as mild postural instability are other motor features coexisting with tremor that can be seen in ET. Nonmotor features may include impairments in hearing and olfaction. It is unclear whether cognitive impairment is associated with ET.
- Common misdiagnoses include Parkinson disease, dystonia, and enhanced physiologic tremor.
- Treatment should be tailored to the individual patient and the severity of the tremor. Propranolol and primidone remain the mainstay first-line medications. Several other second-line agents, including botulinum toxin injections, have shown benefit, and can be considered.
- Deep brain stimulation (DBS) of the thalamic ventral intermediate nucleus is a safe and highly effective treatment of severe and refractory ET. Patients should be considered for DBS surgery when they have failed first-line therapies and when the tremor has significantly impaired their daily function.

Figure 1. Archimedes spiral before and after bilateral deep brain stimulation (DBS) of the thalamic ventral intermediate nucleus (VIM). The patient had longstanding essential tremor (ET) refractory to several medications. The first spiral (left), drawn prior to DBS surgery, shows severe difficulty, with a characteristic wavy or saw-toothed pattern seen in ET. The second spiral (right) demonstrates a dramatic improvement after the stimulating electrodes were programmed.
slower movements in her left hand. A fine tremor in her left leg is noticeable as well. Her right side is normal. She has been diagnosed with ET by her family physician, and was given propranolol, 80 mg, twice daily; however, the tremor has not improved.

**Diagnosis**

In case 1, the diagnosis is ET. The patient has strong family history, and an upper extremity kinetic and postural tremor with responsiveness to alcohol. The head tremor is present in the setting of a severe upper extremity tremor. Combination medical therapy was initiated with the addition of primidone and continuation of propranolol. Despite 2 first-line medications in combination, the tremor persists. It causes significant disability and social embarrassment, and should be considered refractory ET. The option of VIM DBS should be discussed with the patient for tremor control. This patient was referred for bilateral VIM DBS placement and had a significant response with almost complete resolution of his upper extremity tremor.

In case 2, the patient has an asymmetric resting tremor that is also present with movement. An asymmetric tremor can be seen in ET; however, a tremor that is greater at rest compared with movement is a red flag that this is not ET. Another red flag is the occurrence of the tremor in the left arm and leg (ie, a hemibody tremor). A resting tremor that affects the arm and leg on one side of the body while sparing the other is highly suggestive of PD. Cogwheel rigidity can be sometimes confused with a palpable tremor; however, bradykinesia should not be seen in ET. The diagnosis in this case is PD.

**References**