ESSENTIAL TREMOR – PATHOGENESIS AND DIAGNOSIS OVERVIEW

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ABSTRACT

Although essential tremor (ET) is a common movement disorder, the neural mechanism underlying this condition remains unknown. Because no diagnostic pathologic findings or biologic markers are available, correct diagnosis often depends on the clinician's skill in recognizing the clinical features of ET. This article tries to provide an overview of the current concepts in pathophysiology and diagnosis of ET.

Key words: essential tremor, epidemiology, pathogenesis, clinical features, diagnosis.

Essential tremor (ET) is a syndrome characterized by a slowly progressive postural and/or kinetic tremor, usually affecting both upper extremities. ET was first described in 1817 by James Parkinson, who differentiated between parkinsonism and what was later defined as essential tremor.

EPIDEMIOLOGY

ET is considered one of the most common neurologic movement disorders. Latest papers suggest that ET may be as much as 10 to 20 times as prevalent as Parkinson's disease. Estimates of the prevalence of ET are extremely variable, ranging from 0.08 to 220 cases per 1,000 individuals. Among four studies that provided age-stratified data, the prevalence of ET in persons over the age of 60 years was 13.0 to 50.5 cases per 1,000.

ET affects all ethnic and geographic populations, with the possible exception of certain isolated communities in New Guinea. The frequency of ET appears to be independent of gender and increases with age. Apparently, head tremor are more frequent in women, while postural hand tremor are more severe in men.

Age of onset has bimodal peaks: one in late adolescence to early adulthood and a second in older adulthood, with a mean of about age 45. ET usually manifests by age 65 years and virtually always by 70 years. Tremor amplitude slowly increases over time. Tremor frequency decreases with increasing age. An 8 to 12 Hz tremor is seen in young adults and a 6 to 8 Hz tremor is seen in elderly people. Rare cases of ET have been reported in newborns and infants. Although ET is progressive, no association has been found between age of onset and severity or disability.

GENETICS AND PATHOPHYSIOLOGY

Several genes are believed to help determine an individual's risk of developing ET. Environmental factors may also be involved.

Although sporadic and familial ET are widely considered to be phenotypically similar, this premise remains unsubstantiated. According to some reports, familial ET appears to have an earlier age at onset, indicating the increased influence genetic susceptibility may have in hereditary cases.

It is reported that 50% or more of ET patients will demonstrate a positive family history. However, more accurately stated, the estimated range varies from as low as 17% to as high as 100%. Because many epidemiologic studies have not included control subjects, it remains unclear the degree to

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which the observed aggregation of cases within families exceeds that beyond chance. In addition, most studies have assessed genetic effect based solely on positive family history. However, the likelihood of a positive familial history may be proportional to the size of the family, the age of relatives, and the genetic relationships among the family group.

Familial ET has been shown to have autosomal dominant inheritance. Gene penetrance is high but variable by the age of 65 to 70 years.

Some studies have found the DRD3 gene to be associated with essential tremor. The DRD3 gene provides instructions for making a protein called dopamine receptor D3, which is found in the brain. This protein responds to a chemical messenger (neurotransmitter) called dopamine to trigger signals within the nervous system, including signals involved in producing physical movement. A DRD3 variant seen in some families affected by essential tremor may cause the corresponding dopamine receptor D3 protein to respond more strongly to the neurotransmitter, possibly causing the involuntary shaking seen in this condition.

During a genome scan for familial ET in 16 Icelandic kindreds with 75 affected members, investigators identified linkage to chromosome 3q13. The gene was designated as FET1.

Another study evaluated a large American kindred of Czech descent in whom ET affected 18 of 67 family members. In this kindred, a gene for ET (ETM2) was mapped to chromosome 2p22-p25.

The chromosome 2p gene has been proposed to be HS1-BP3 (hematopoietic-specific protein 1 binding protein 3). Genotyping carried out on 73 individuals with dominantly inherited ET from 73 families showed that 12 of 73 ET individuals (16.4%) were heterozygous for the HS1-BP3 828C-G variant, versus none of 304 unaffected controls. ET patients with the variant had no atypical features and were classified as definite ET by clinical criteria. Age at onset was significantly younger for those with the variant compared to those without (26 years vs. 44 years).

The HS1BP3 gene provides instructions for making a protein called hematopoietic-specific protein 1 binding protein 3. This protein is believed to help regulate chemical signaling in the brain region involved in coordinating movements (the cerebellum) and in specialized nerve cells in the brain and spinal cord that control the muscles (motor neurons). An HS1BP3 variant has been identified in some families affected by essential tremor, but it has also been found in unaffected people. It is unknown what relationship, if any, this genetic change may have to the signs and symptoms of this condition.

No pathological findings are known to be associated consistently with ET. Post-mortem studies of ET brain have identified groups with two different pathologic changes: cerebellar degenerative changes and brain stem Lewy bodies. The distribution of Lewy bodies differs from that in Parkinson's disease, being primarily in the locus ceruleus. These neurons are the primary source of norepinephrine in the brain, and project to Purkinje cells in the cerebellum. Based on these pathologic findings, it is possible that a dysfunction of inhibitory cerebellar output underlies both pathologic subtypes of ET.

Several theories of tremorogenesis have been proposed that implicate a central source of oscillation.

- ET is the result of an abnormally functioning central oscillator, which is located in the Guillain Mollaret triangle near the brain stem and involves the inferior olivary nucleus.
- The cerebellar-brainstem-thalamic-cortical circuits probably are involved.

More specifically, ET is thought to arise from oscillatory activity within a central network or cell group that becomes dysregulated, allowing spinal reflex loop oscillations. It has also been proposed that stretch loop circuits may become unstable and drive muscle contractions to produce tremor as in ET.

Harmaline, a monoamine oxidase inhibitor (MAOI), when administered to primates with lesions of the ventromedial tegmental tract or lateral cerebellum, produces an ET-like tremor. In these animals, inferior olivary nucleus neurons fire synchronously at the tremor frequency. C-2-deoxyglucose positron emission tomography (PET) studies demonstrate hypermetabolism in the inferior olivary nuclei of rats and cats with harmaline-induced tremor.

In patients with ET, [^{18}F]fluorodeoxyglucose PET studies identified increased glucose consumption in the medulla. [^{15}O]H_2O PET studies demonstrated increase in medullary regional cerebral blood flow in subjects with ET, only after the administration of ethanol, and bilateral overactivity of cerebellar circuitry.

C^{15}-labeled O_2 positron emission tomography (PET) of ET patients has suggested a possible abnormality in the olivocerebellar tracts with

midbrain activation in the region of the red nucleus. PET testing in patients with ET also revealed increased cerebellar activity even while at rest. These findings are consistent with the theory that the cerebellum plays an important role in the generation of tremor.

Increased glucose metabolism in the inferior olivary nucleus of the medulla has also been demonstrated, suggesting that this structure may be the source of the rhythmic discharge causing the tremors. This is further supported by the fact that lesions in the cerebellum or thalamus may result in cessation of tremor.

In another study, functional magnetic resonance imaging in 12 people with ET and 15 control subjects suggested that ET is mainly associated with an additional contralateral cerebellar pathway activation and overactivity in the cerebellum, red nucleus, and globus pallidus without significant intrinsic olivary activation.

Ingestion of ethanol (ETOH), which suppresses tremor in ET patients, lead to a bilateral decrease in cerebellar blood flow in both tremor patients and normal subjects, plus increased blood flow in the inferior olivary nuclei in the ET patients but not in the control subjects.

Peripheral factors may contribute to tremor as well. Beta-adrenergic blockers such as propranolol attenuate ET and physiologic tremor, possibly via peripheral $beta_2$ adrenoreceptors. In addition, intravenous and intra-arterial epinephrine enhance physiologic tremor via peripheral beta-adrenoreceptors, which are blocked by propranolol. However, beta-blockers may also affect central pathways.

POSITIVE DIAGNOSIS

Clinical

ET is considered to be monosymptomatic (tremor only), although some patients have abnormalities in gait and balance; if patients have such abnormalities, the diagnosis should be carefully reconsidered.

- The tremor is characteristically postural (occurring with voluntary maintenance of a position against gravity) and kinetic (occurring during voluntary movement).
- Tremor usually begins in one upper extremity and soon affects the other. ET rarely extends from the upper extremity to the ipsilateral leg.
- A mild degree of asymmetry is not unusual.
- In about 30% of cases, tremor involves the cranial musculature; the head is involved most frequently, followed by voice, jaw, and face.
- Tremor may be intermittent initially, emerging only during periods of emotional activation. Over time the tremor becomes persistent.
- At any point of time the frequency of tremor is relatively fixed, but amplitude is highly variable depending on the state of emotional activation. Tremor amplitude is worsened by emotion, hunger, fatigue, and temperature extremes. The baseline tremor amplitude slowly increases over several years.
- A degree of voluntary control is typical, and the tremor may be suppressed by skilled manual tasks.
- The tremor dissapear during sleep.
- Ethanol intake temporarily reduces tremor amplitude in an estimated 50-70% of cases.
- A family history of ET is noted in 50-60% of cases.
- Visible tremor is generally pathologic, but distinguishing between ET and enhanced physiologic tremor can be difficult. Causes of enhanced physiologic tremor, such as medications, substances such as caffeine, hyperthyroidism, fever, and anxiety, should be excluded.
- Muscle tone and reflexes are normal.
- Parkinsonian features such as bradykinesia and rigidity are absent.
- In a population-based sample of untreated patients with essential tremor, cases performed more poorly on formal neuropsychological testing than did their counterparts without tremor. A complaint of forgetfulness was also marginally more common in patients with essential tremor.

Although no single test is pathognomonic for ET, several tools are available to evaluate the condition. Methods used to assess tremor include physical examination, physiologic techniques, subjective clinical measures, objective functional performance tests, and assessment of the impact of tremor on patients' lives.

a) According to experts reccomandations, a complete ***physical examination***, that may assist in differential diagnosis and provide information regarding tremor severity and progression, must include:

- Muscle tone checked throughout the body.
- Cranial structures (including the mouth and jaw) examined at rest and in action.

- The tongue observed during rest and protrusion.
- The upper extremities examined while the patient is seated with the arms fully supported.
- The upper extremities examined in an outstretched position with the hands supine, prone, and in the wing position (i.e., with apposition of the index fingers close to each other but not touching).
- Goal-directed activities performed, such as finger-to-nose, heel-to-shin, and toe-to-finger movements. In addition, the patient may be evaluated while pouring water from one cup into another.
- The patient is asked to recite a standard paragraph and enunciate a sustained vowel.
- Handwriting samples are obtained (e.g., script, numbers, Archimedes spirals).
- Gait is evaluated and Romberg (station) and balance testing are conducted.
- Careful evaluation performed for signs of other neurologic disease, including PD and dystonia.

b) ***Physiologic techniques*** are used to obtain objective measures of tremor magnitude and frequency. These may include linear accelerometric studies, short-term or long-term EMG, and graphic digitizing tables for the measurement of tremor during drawing and writing. Also available are gyroscopic techniques that sense trunk and limb rotation rate and computer tracking tasks that measure the error resulting from tremor during performance of manual tasks.

c) ***Subjective clinical measures*** of tremor include clinical rating scales and rating handwriting or spiral drawings, known as Archimedes spirals. ET patients typically have handwriting that is shaky and large, whereas that of PD patients may initially be of normal size and progressively become smaller (micrographia). Archimedes spirals drawn by ET patients tend to illustrate natural fluctuations in tremor magnitude.

d) ***Objective functional performance tests*** tend to be inexpensive, are simple to use, and objectively evaluate the performance of actions involved in real-life activities. Such tests may include measuring the amount of water spilled while pouring water from one cup to another or holding a cup for 1 minute; the 9-hole pegboard test; or maze tests, such as assessment of the number of times a patient's drawn line crosses the boundaries of a preprinted spiral.

e) ***Assessment on the impact of tremor on patients' lives*** includes measures of disability, handicap, and quality of life. Functional disability is a measure of the difficulty encountered in performing activities of daily living whereas resultant handicap is often described as the consequence of having certain disabilities. The quality of life is typically viewed as a patient's subjective assessment of his or her state of affairs. Such measures may be quantified using generic or disease-specific questionnaires.

Laboratory:

- No biological markers exist for ET.
- If the family history and examination findings are not indicative of ET, laboratory and imaging studies should be considered.
- Laboratory investigations include standard liver function tests and serum ceruloplasmin (for Wilson disease), blood urea nitrogenum, serum creatinine, electrolyte panel, thyroid function tests.

Imaging Studies:

Findings on CT scanning and MRI of the head are normal in ET. MRI helps exclude structural and inflammatory lesions (including multiple sclerosis) and Wilson disease. MRI should be performed if the tremor has acute onset or stepwise progression. PET scanning, may also be required for selected patients, particularly those with tremor that is unilateral, of sudden onset, or associated with atypical clinical features.

Although there are no universally accepted criteria for ET diagnosis, classification schema, such as the NIH Collaborative Genetic Criteria and the Consensus Statement of the MDS on Tremor, provide a usefull tool for clinicians.

Differential Diagnosis

The differential diagnosis of ET includes a number of hereditary and idiopathic disorders, metabolic conditions, cerebral diseases, and peripheral neuropathies that may be characterized by postural, intention, or rest tremors or combinations of such tremor elements.

For example, isolated head tremor in ET must be excluded from head tremor seen in up to 40% of patients with cervical dystonia. In ET patients, head tremor is characterized by rhythmic, regular oscillations, whereas that associated with cervical dystonia tends to be irregular, occurs with tilting of the head or chin, and varies in intensity with position changes. ET and parkinsonian tremor may be characterized by postural, kinetic, and resting

Table 1. *NIH Collaborative Genetic Criteria*

Tremor Severity Scale:	0= None 1= Minimal (barely noticeable) 2= Obvious, noticeable but probably not disabling (<2 cm excursions) 3= Moderate, probably partially disabling (2 cm to 4 cm excursions) 4= Severe, coarse, and disabling (>4 cm excursions)
Definite ET:	2+ amplitude rating for bilateral arm tremor **or** 2+ amplitude rating in one arm and 1+ amplitude rating in other arm **or** 1+ amplitude rating in at least one arm and predominant cranial/cervical tremor with 2+ amplitude rating Head tremor is rhythmic with no directional preponderance and without asymmetry of cervical muscles. *Exclude:* obvious secondary causes (coexistent dystonia allowed; coexistent PD disallowed)
Probable ET:	1+ bilateral arm tremor **or** Isolated 2+ cranial/cervical tremor **or** Convincing history of ET *Exclude:* obvious secondary causes (e.g., enhanced physiologic tremor, drug-induced or toxic tremor, coexistent peripheral neuropathies [such as CMT], etc.) Coexistent dystonia allowed Coexistent PD allowed if there is a convincing history of pre-existing ET
Possible ET:	Isolated 1+ cranial/cervical tremor **or** Task- or position-specific arm tremor **or** Unilateral arm tremor **or** Orthostatic tremor
Unrateable ET:	Tremor is coexistent with other neurologic disease, therapy with anti-tremor or tremor-promoting drugs, untreated thyroid disease, caffeine withdrawal/abstention, etc.

tremor components. However, traditionally, Parkinson disease (PD) is primarily characterized by rest tremor that decreases with action, whereas ET is generally a postural/kinetic tremor with dampening upon rest. In addition, PD almost never involves tremor of the head or voice yet may involve the chin and perioral structures.

Table 2. Consensus Statement of the Movement Disorder Society

Classic ET: Inclusion Criteria	Bilateral, largely symmetric postural or kinetic tremor involving the hands and forearms that is persistent and visible
Classic ET: Exclusion Criteria	1. Other abnormal neurologic signs (particularly dystonia) 2. Presence of known causes of enhanced physiologic tremor 3. Historical or clinical evidence of psychogenic tremor 4. Convincing evidence of sudden onset or stepwise deterioration 5. Primary orthostatic tremor 6. Isolated voice tremor 7. Isolated position- or task-specific tremor 8. Isolated tongue or chin tremor 9. Isolated leg tremor

Table 3. *Differential Diagnosis of ET*

• Parkinson's disease • Multiple system atrophy (e.g., olivopontocerebellar atrophy, striatonigral degeneration) • Huntington's disease • Benign hereditary chorea • Wilson's disease • Fahr's disease • Paroxysmal dystonic choreoathetosis • Ataxia-telangiectasia • Familial intention tremor and lipofuscinosis • Ramsay-Hunt syndrome (progressive myoclonic ataxia) • Dystonia musculorum deformans • DOPA-responsive dystonia (Segawa's syndrome) • Spasmodic torticollis (cervical dystonia) • Meige syndrome • Task- or position-specific tremors (e.g., primary writing tremor, isolated voice tremor) • Space-occupying lesions of the brain (e.g., cerebrovascular insults, trauma, cysts, tumors, hematomas) • Various metabolic disturbances (e.g., hepatic encephalopathy, hypoglycemia, hyperthyroidism, hyperparathyroidism, hypocalcemia, etc.) - Toxin-related tremors (Alcohol, Arsenic, Caffeine, DDT, Lead, Nicotine, Toluene, Withdrawal of alcohol, cocaine) - Drug-induced tremors (Antidepressants, Beta-agonists, Dopamine, Lithium, Metoclopramide, Neuroleptics, Theophylline, Thyroid hormones, Withdrawal of drugs) • Peripheral neuropathies (e.g., Charcot-Marie-Tooth disease, Guillain-Barré syndrome, Roussy-Levy syndrome, dysgammaglobulinemic neuropathies, etc.)

Also included in the differential diagnosis are a number of syndromes that may be misinterpreted as tremor. These may include:

- Clonus or rhythmic, uniphasic contractions and relaxations of muscle groups.
- Rhythmic myoclonus, characterized by irregular or rhythmic, shock-like contractions of a muscle group due to CNS disease.
- Epilepsia partialis continua, a focal motor epilepsy associated with recurrent, rhythmic clonic movements of a specific muscle group.
- Asterixis, a condition in which sudden, periodic interruptions in muscle contraction lead to arrhythmic lapses of sustained posture associated with EMG pauses ranging from about 35 to 200 msec or greater. This condition is sometimes referred to as "negative myoclonus."

ET is sufficiently common that some patients will have coexistent tremorogenic or other neurologic disorders. Mild extrapyramidal signs, such as a masked face or balance difficulty, may be observed in some patients, particularly those of advanced age. Some studies have also supported a possible association between ET and dystonia and ET and parkinsonism, demonstrating that members of some kindreds may have ET whereas other family members have parkinsonism, dystonia, or signs of all three conditions. In addition, some patients with ET later develop concomitant dystonia, parkinsonism, or both.

- ET has been hypothesized to be a risk factor for the development of PD. Some patients with PD report a long-standing history of bilateral upper extremity postural tremor. Some patients with focal dystonia, such as torticollis, have mild bilateral upper extremity postural tremors.
- Without biological markers for these diseases, determining whether long-standing postural tremor is part of a PD syndrome/ a focal dystonia syndrome or reflects the presence of 2 diseases is still not possible.

Some researchers contend that the coexistence of ET and PD may represent the chance occurrence of two common conditions. However, others indicate that there appears to be a higher frequency of PD in ET than occurs in the general population. Concerning dystonia, although the condition is frequently associated with ET, the *DYT1* gene on chromosome 9 has been excluded in hereditary ET through linkage analysis, suggesting different genetic loci or a physiologic rather than a genetic relationship between the two conditions.

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