

## Essential Tremor: A Comprehensive Overview

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### Abstract

Essential tremor is the most prevalent form of movement disorders in the world and is 10 times more prevalent than that of Parkinson's disease. Even though it is traditionally considered as a benign disease all the patients of essential tremor have tremor induced disabilities. Essential tremor which shows kinetic, postural and resting is tremor mimicker of all tremor associated disease so often misdiagnosed and mismanaged. This article is authors' endeavor to summarize the facts in different publications on essential tremor. Electronic databases like MEDLINE/Pub Med, Google Scholar, IMSEAR (Index Medicus for South-East Asia Region) and Scopemed were extensively searched with MeSH (Medical Subject Headings) terms "essential tremor", "clinical features" "pathophysiology" and "treatment" from the earliest possible date of 1966 to Feb 2017. Articles in any languages especially those published in recent years were given preference. This review deals mostly with the clinical features and evidence-based management of essential tremor.

**Keywords:** Essential tremor; Clinical features; Treatment

### Introduction

Essential tremor is considered as the most prevalent form of movement disorder in the world [1]. Its prevalence is 0.9% for all ages. Above age 40, 65 and 95 its prevalence increases to 4%, 4.6% and 21.7% respectively [2]. In the USA 2.2% of population has an essential tremor which is 10 times more than that of Parkinson's disease [1]. Even though traditionally it is considered as benign tremor all the patients of essential tremor have tremor induced disabilities and feelings social embarrassment [2].

### Methods

Electronic databases like MEDLINE/PubMed, Google Scholar, IMSEAR (Index Medicus for South-East Asia Region) and Scope med have extensively searched with Mesh (Medical Subject Headings) terms like "essential tremor", "clinical features", "pathophysiology" and "treatment" from the earliest possible date of 1966 to Feb 2017. Articles in any language especially those published in recent years were given preference.

### Pathophysiology

The evidence had shown the link between the cerebellum and essential tremor. In the last few years, advanced neuroimaging has tried to confirm this evidence. Indeed, the vast majority of studies have found functional and structural abnormalities in several parts of the anterior and posterior cerebellar lobules, however, to what degree of these neural changes contribute to clinical symptoms of essential tremor, is not established yet [3]. Though the exact pathophysiology of essential tremor is not known, one of the proposed theory for the pathophysiology of essential tremor is GABAergic dysfunction in the cerebellar dentate nucleus and brainstem caused by neurodegeneration in these regions that lead to tremulous activity within the cerebellothalamocortical circuit [4]. Functional imaging studies have suggested that tremors in ET are of central in origin associated with olivocerebellar and cerebellothalamo-cortical pathways, Positron emission tomography studies have indicated the role of gamma-aminobutyric-acid dysfunction in tremor generation while most of the structural imaging studies along with magnetic resonance spectroscopic imaging have pointed toward neurodegeneration [5]. Currently, advanced neuroimaging has confirmed the involvement of the cerebellum in pathophysiological processes of ET though there is high variability in results. For this

reason, the translation of this knowledge of pathophysiology of essential into daily clinical practice is partially limited, although new advanced multivariate neuroimaging approaches are now proving interesting changes in different perspectives of the pathophysiology of essential tremor [3].

### Clinical Features

Essential tremor shows autosomal dominant inheritance pattern though some sporadic cases are also reported. Its prevalence increases with age and shows a bimodal pattern of distribution. The most common body part involved in essential tremor is upper limbs (95%) followed by head (34%), lower limbs (20%), voice (12%) face (5%) and trunk (5%) which exhibit a mixed postural and kinetic tremor without other neurologic abnormalities [6]. The tremor is mostly progressive and symmetrical. Hand tremor which is greater at the wrist joint may be kinetic or postural usually precedes the head tremor. The amplitude of kinetic tremor is more than that of postural tremor. In the upper limbs amplitude of wrist, tremor is greater than that of metacarpal joint tremor and they show flexion extension type of movement. Intention tremor can occur in 50 percent of cases. On drawing the Archimedes spiral single orientation axis is identifiable. Head tremor is another feature of essential tremor more common in women which resolve in a supine position which shows either yes-yes or no-no phenomenon [7]. The most important factors associated with increased tremor severity are older age, longer disease duration and the presence of voice tremor [8]. Table 1 shows diagnostic criteria for essential tremor [9]. Essential tremor can mimic any other tremor associated disease like enhanced physiological tremor, Parkinson's disease and tremor associated with peripheral neuropathy. It should be differentiated from the Parkinson disease as there is a vast difference in the management of two diseases. The difference between two conditions is shown in Table 2.

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Received April 19, 2017; Accepted May 23, 2017; Published May 28, 2017

Citation: Shah B (2017) Essential Tremor: A Comprehensive Overview. J Neurol Disord 5: 343. doi:10.4172/2329-6895.1000343

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Criteria for definite essential tremor (all 5 must be true)	
1	On examination, a +2 postural tremor of at least 1 arm (a head tremor may also be present, but is not sufficient for the diagnosis).
2	On examination, there must be a. a +2 kinetic tremor during at least 4 tasks or b. a +2 kinetic tremor on 1 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 and drawing a spiral.
3	If on examination, the tremor is present in the dominant hand, then by report, it must interfere with at least 1 activity of daily living (eating, drinking or using the hands). If on examination, the tremor is not present in the dominant hand, then this criterion is irrelevant.
4	Medication, alcohol, parkinsonism, dystonia, other basal ganglionic disorders, and hyperthyroidism are not potential etiological factors.
5	Not psychogenic (bizarre features, inconsistent in character, changing, subject are distractable, or other psychiatric features on examination).
Criteria for probable ET (either 1 a or 1b must be true; 2 and 3 must be true)	
1	Same as 2 above (see definite ET)
2	Medication, alcohol, parkinsonism, dystonia, other basal ganglionic disorders, and hyperthyroidism are not potential etiological factors.
3	Not psychogenic
Criteria for possible ET	
	On examination, a +2 kinetic tremor must be present on 3 tasks 0 to +3 tremor ratings.
0	No visible tremor
1	Low amplitude, barely perceivable tremor, or intermittent tremor
2	Tremor is of moderate amplitude (1-2 cm) and usually present. It is clearly oscillatory.
3	Large amplitude (> 2 cm), violent, jerky tremor resulting in difficulty completing the tasks due to spilling or inability to hold pen to paper.

Table 1: Diagnostic criteria for essential tremor [9].

Characteristics	Essential tremor	Parkinson disease
Type	Kinetic, Postural tremor	Resting tremor
Progression	Slow progression	Rapid progression
Symmetry	Symmetrical	Asymmetrical
Body part involved	Hand, head, voice	Hands, legs, tongue
Effect of alcohol	Improves	No improvement

Table 2: Difference between essential tremor and Parkinson disease.

### Laboratory evaluation

Accelerometry of 95% of a patient of essential tremor showed frequency of 5-8 Hz whereas in 95% of Parkinson's disease showed the frequency of 4-8 Hz [10]. Archimedes spiral is another tool to differentiate the Essential tremor from Parkinson disease where single axis and multiple axes are seen in essential tremor and Parkinson disease respectively [11].

### Treatment

Even though essential tremor doesn't shorten the lifespan of the individual, it makes person social disable and may have a great psychological impact. Treatment of essential tremor should be individualized based on the severity of tremor, functional impairment caused by tremor, co-morbid conditions of the patient and patient preference for treatment. The management of essential tremor includes.

- Behavioral techniques and physical therapy
- Medical therapy
- Surgical treatment [12]

### Behavioral techniques and physical therapy

Essential tremor is a benign but progressive condition. There is no definitive treatment for a cure for it till now so the patient should be counseled regarding the course of the disease, impact of anxiety on tremor and expected response to treatment. Handling embarrassment and the social effects of tremor have been highlighted by ET patients as one of the major issues not being addressed in their health care [13]. Depressive symptoms are common in patients with essential tremor and have more embarrassment thus earlier treatment of depressive symptoms in ET patients might be a better strategy to lessen the burden of social embarrassment [14]. These include relaxation therapies and

reducing emotional stress, using the less disabled hand to write or eat, using wrist weights and minimizing exposure to tremorogenic foods (eg; caffeine) and drugs (e.g. sympathomimetics) [12].

### Medical therapy

**Beta blockers:** Propranolol is first line therapy for essential tremor (level A). It is only one beta blocker approved by united states FDA for the treatment of essential tremor. The mechanism of antitremor effect of the drug is blocking effects of peripheral beta-2 receptors which are located in muscle spindles. The starting dose of propranolol is 20 mg BD which can be increased up to 320 mg/day. The response of drug is seen in 50% individual [15]. Long-acting propranolol is superior in efficacy than conventional propranolol in the management of essential tremor. Better compliance with once a daily dose offers an advantage over the short-acting propranolol [16]. Acute adverse reactions occurred in 8% of patients and chronic side effects seen in 17% of patients with propranolol [17]. Common side effects noticed are a headache, bradycardia, fatigability, sleep disturbances, and lightheadedness. Contraindication of beta blockers are a congestive cardiac failure, bronchial asthma, atrioventricular block and peripheral vascular disease Other beta blockers like atenolol, Sotalol and metoprolol also decrease the tremor and useful in a patient where non-selective beta blockers are contraindicated though its efficacy is lower than that of propranolol in essential tremor (level B) [18].

**Primidone:** Primidone is an anticonvulsant that is metabolized to phenobarbital and phenyl- ethylmaleimide. It reduces high-frequency repetitive firing of neurons and alteration of transmembrane sodium and calcium channels ion movements which is the probable mechanism of antitremor activities [15]. It can be an alternative to propranolol when beta-blockers are contraindicated in the management of essential tremor (Level A) [19]. The starting dose of primidone is 50 mg/day which can be increased up to 750 mg/day. The response rate is 50% to 70%. Common side effects noticed during primidone treatment are drowsiness, fatigue, nausea, vomiting and bone marrow suppression. It should be tapered after 6 months of use due to chances development of suicidal thought. It is contraindicated in porphyria, severe renal insufficiency, and advanced hepatic failure.

**Benzodiazepines:** Benzodiazepines potentiate GABAergic neurotransmission which results in hyperpolarization of the cell

membrane and, thus, inhibition of action potential firing. This accounts for their anxiolytic, anticonvulsant, sedative, muscle relaxant, and likely also anti-tremorogenic effects. Even in a patient not responding to first-line therapy for essential tremors like propranolol and primidone, clonazepam may be effective in controlling the tremor (Level C) [20]. Alprazolam another short acting benzodiazepine may reduce the tremor of essential tremor (Level B) [21]. Common side effects of benzodiazepines are drowsiness, cognitive impairment, and drug dependence.

**Pregabalin:** Pregabalin acts on the alpha 2-delta protein, an auxiliary subunit of voltage-gated calcium channels which reduces the synaptic release of several neurotransmitters thus the neuronal excitability [22]. Though pregabalin was proposed to have tremorolytic action, the effects of pregabalin for treating essential tremor are uncertain because the quality of the evidence is very low [23]. The starting dose is 50 mg BD which can be increased up to 600 mg/day. Common side effects of pregabalin are dizziness, vertigo, incoordination, balance disorder, ataxia, diplopia, blurred vision, amblyopia, tremor, somnolence, confusional state, and disturbance in attention, thinking abnormal, euphoria, asthenia, fatigue and peripheral edema [24].

**Gabapentin:** Gabapentin was proposed to have action on an auxiliary subunit of voltage-sensitive  $Ca^{2+}$  channels and reduce the neuronal excitation [25]. It can be used in the management of essential tremor if first line therapy fails (Level B) It was compared with propranolol for the management of essential tremor which showed comparable efficacy in reducing tremor from baseline in all tremor measures [26]. The initiating dose is 300 mg TDS which can be increased up to 3600 mg/day. Use of gabapentin as monotherapy is recommended only if there is a contraindication for propranolol and primidone. Common side effects of gabapentin are sedation, dizziness, and dry mouth.

**Topiramate:** Topiramate has multifactorial action and involves blockade of voltage-dependent sodium channels, potentiation of GABAergic transmission and inhibition of excitatory pathways through an action at AMPA receptor sites [27]. Topiramate is effective in the treatment of moderate to severe essential tremor (Level B). Functional improvements accompany tremor reduction, such as in motor tasks, writing, and speaking [28]. The most common treatment-limiting adverse events in topiramate-treated patients are paresthesia, nausea, concentration/attention difficulty, and somnolence.

### Surgical therapy

Surgical therapy is recommended if the tremor is disabling and non-responsive or contraindicated to the medical treatment. Deep brain stimulation therapy and ultrasound thalamotomy are two recent surgical approaches for the management of the essential tremor.

**Deep brain stimulation therapy:** All medically refractory essential tremor patients should be considered for DBS. DBS of the Ventral intermediate area and the Posterior subthalamic area appears to be a safe and effective treatment for medically refractory ET [29]. Tremor and handwriting improvements in long-term follow-up are stable. The patients' perception of their outcome is good [30]. Side effects of deep brain stimulation are personality changes, mood disorders and risk-taking behaviors, parenchymal haemorrhage and lead infection [31].

**Ultrasound thalamotomy:** Ultrasound thalamotomy is an option for management of medically refractory essential tremor. It reduces the disability and improved the quality of life. The most common side effect is alteration in sensation, gait disturbance, dysmetria, and ataxia [32].

### Conclusion

Essential tremor is the most prevalent form of movement disorder in the world. The cerebellum is the proposed site for the pathophysiology of essential tremor. Propranolol and Primidone are first line therapy whereas in medically refractory patient deep brain stimulation therapy and ultrasound thalamotomy is showing promising therapeutic role.

### Acknowledgements

The author acknowledges Prof. Dr. Sanjib Sharma, Dr. Lekhjunga Thapa, Dr. Roshan Chhetri, Dr. Bijay Bartaula, Dr. Manish Subedi and Ms. Piyush Dahal for constantly motivating and guiding me to write this review article.

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