

Tremor Disorders: A Clinical Approach

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ABSTRACT

Tremor may be a manifestation of underlying neurological disorders or systemic diseases. Its behaviour varies according to many factors such as posture, voluntary movements and emotional states. Its aetiology is heterogeneous ranging from inherited to a wide array of acquired disorders. Both medical and surgical treatment options are currently in use. Symptomatic therapy as well as treatment of underlying aetiology should always be considered in the management of tremor. We provide a concise summary of the classification, clinical characteristics, and management of commonly encountered tremor syndromes in clinical practice.

Keywords: classification, deep brain stimulation, stereotactic thalamotomy, treatment, tremor

INTRODUCTION

The first description of tremor in the scientific literature is found in Galen's short text published in the second century AD.¹ It is the most common movement disorder encountered in clinical practice. Tremor is defined as an involuntary, rhythmic, and oscillatory movement about a joint, which is repetitive and regular in amplitude and frequency. It is caused by alternating or synchronous contractions of reciprocally innervated agonist and antagonist muscles. This article provides an overview of tremors in general with special emphasis on certain tremor syndromes.

CLASSIFICATION

Tremors can be classified according to their anatomical distribution, frequency, amplitude, or behaviour with posture and voluntary movements.² Frequency generally remains unaltered with emotional states unlike amplitude (Table 1). Classification based on behaviour of tremor is perhaps the most useful in clinical practice (Table 2). However, it must be noted that there may be more than one type of tremor characteristics in a given clinical syndrome (Table 3). Tremor syndromes are defined according to their aetiology. The clinical approach to patients with tremor includes a detailed history and examination to classify

the tremor and elucidate its aetiology. Subsequent investigations should be based on clinical judgement. In general, Wilson's disease needs to be investigated in any tremor disorder with onset before the age of 50.

TREMOR SYNDROMES

Physiological Tremor

This is a benign postural tremor most apparent in the upper extremities. The tremor frequency tends to vary with age. It is usually asymptomatic.

Enhanced Physiological Tremor

Physiological tremor is enhanced and made visible by many factors (Table 4). Beta adrenergic blockers, primidone, benzodiazepines, and alcohol reduce the tremor amplitudes. However, the mainstay of treatment is correction of the underlying enhancing factor.

Essential Tremor

Essential tremor (ET) typically is a postural tremor of the upper extremities or other regions. Its prevalence increases with age and its onset demonstrates 2 peaks in second and sixth decades. Its inheritance is autosomal dominant with variable penetrance. ET is thought to arise from a central oscillator involving

Table 1. Approximate frequency range of tremor syndromes (in Hz).

Frequency	Tremor Syndrome
1.5–3	Palatal tremor
2–5	Holmes' tremor
2–10	Tremor in multiple sclerosis
2–12	Drug induced/neuropathic
3–5	Tardive tremor
3–7	Parkinson's disease
3–8	Voice tremor
3–8	Cerebellar in upper limbs (3 in lower limbs and 2–4 in trunk)
3–12	Dystonic tremor
4–12	Essential tremor
5–7	Primary writing tremor
7–12	Physiological and enhanced physiological tremor
13–18	Primary orthostatic tremor in lower limbs

Table 2. Classification of tremors.

According to frequency	<ol style="list-style-type: none"> 1. Low: <4 Hz 2. Medium: 4–7 Hz 3. High: >7 Hz
According to tremor behaviour	<ol style="list-style-type: none"> 1. Rest tremor: tremor in a body part which is completely supported with no gravity effect 2. Action tremor: tremor associated with voluntary contraction of skeletal muscles <ol style="list-style-type: none"> 2.1. Postural: tremor in a body part voluntarily maintained against gravity 2.2. Kinetic: tremor during any voluntary movement <ol style="list-style-type: none"> 2.2.1 Simple kinetic: tremor during directed voluntary movements 2.2.2 Intention tremor: increasing tremor amplitude upon reaching a target 3. Isometric tremor: evoked by isometric muscle contractions 4. Task-specific tremor: occurs only during a specific skilled task or movement
According to amplitude	<ol style="list-style-type: none"> 1. fine 2. medium 3. coarse
According to distribution	<ol style="list-style-type: none"> 1. unifocal 2. multifocal 3. generalised
According to anatomical localisation	Head, face, jaw, lips, tongue, voice, trunk, extremities

Table 3. Combinations of tremor characteristics in different clinical syndromes.

	Parkinson's disease	Essential tremor	Midbrain tremor	Cerebellar tremor
Rest	+++	+	+	–
Postural	+	+++	+++	+
Kinetic	+	++	+++	+++

Table 4. Factors enhancing physiological tremor.

Drugs	amphetamines, beta adrenergic agonists, butyrophenones, caffeine, dopamine agonists, epinephrine, fluoxetine, haloperidol, levodopa, lithium, metoclopramide, neuroleptics, phenothiazines, theophylline, thyroxine, tricyclic antidepressants, valproic acid
Alcohol and drug withdrawal	
Emotional states	anxiety, stress, fear
Exercise and fatigue	
Metabolic and endocrine disorders	hypoglycaemia, hypothermia, hyperthyroidism, pheochromocytoma
Toxins and heavy metals	lead, mercury, bismuth, arsenic, carbon monoxide

pathways through the cerebellum, thalamus, and brainstem.

Clinical Features

Diagnosis is based on characteristic clinical features. Though typically a postural tremor, some may demonstrate kinetic and rest components. Distal upper extremity tremor is the most common manifestation whilst head, leg, jaw, face, trunk, tongue and voice tremor may be evident in some. At the onset, it may be unilateral but can become bilateral and symmetrical later. The tremor is reduced by alcohol in 50 to 90% of patients. The effect can last for up to 60 minutes and may be followed by rebound effect.

Diagnostic Criteria

The major criteria for the diagnosis of ET are bilateral, symmetrical visible tremor involving the hand and forearm which is postural or kinetic in behaviour. Isolated or additional head tremor without abnormal posturing is also compatible with the diagnosis. Secondary criteria are duration of more than 3 years, positive family history and relief by alcohol.³

Medical Treatment

Treatment should be considered when the tremor causes significant functional impairment or social embarrassment. Beta adrenergic blockers are the first line drugs which effectively ameliorate symptoms in 40 to 50% patients. Propranolol is commonly used in dosages of 80 to 320 mg per day. Treatment should be started with a lower dosage and gradually titrated upward. Metoprolol and nipradilol have also been found to be effective. Primidone is an alternative which is administered in dosages ranging from 50 to 250 mg per day. Acute reactions to the initial dose in the form

of a flu-like syndrome or ataxia can be troublesome but is usually transient and the drug is well tolerated in the long term. Emerging therapies include gabapentine, topiramate, carbonic anhydrase inhibitors, clozapine, benzodiazepine and topical injection of botulinum toxin.

Surgical Treatment

Stereotactic thalamotomy of the ventral intermediate nucleus (surgical ablation of the nucleus using stereotactic techniques) has been shown to reduce contralateral tremor in 70 to 80% of patients. Thalamic deep brain stimulation (DBS) is an alternative technique where an electrode is implanted in the thalamic region with its wire tunneled under the skin to a stimulating device placed in the subclavicular pouch. The generator produces electrical impulses which are transmitted to the thalamus, suppressing genesis of tremor. This device can be turned on and off externally using a magnet. DBS is preferred over surgical ablation as the former has fewer side effects.

Tremor in Parkinson's Disease

Tremor is the first manifestation in about 50% of Parkinson's disease (PD) patients.⁴ It is typically a rest tremor, and classically seen in distal arm initially, with subsequent involvement of the ipsilateral leg. The tremor may also involve head, trunk, jaw, lips, and tongue. However, head and vocal tremor are rare in PD. Some patients may manifest postural or kinetic tremor with or without rest component. Tremor in PD usually improves by about 50% with dopaminergic medications. Anticholinergics are also effective, but should be used with caution, particularly in the elderly due to side effects. Beta adrenergic antagonists are an option for relieving postural tremor in PD. Clozapine has also been shown to be effective.

Table 5. Clinical approach to a patient with tremor: a stepwise guide.

1.	Make the clinical diagnosis of tremor	
2.	Classify tremor	<ul style="list-style-type: none"> a. Frequency b. Amplitude c. Behaviour with posture and voluntary movements d. Anatomical localisation e. Distribution
3.	Find out aetiology	<ul style="list-style-type: none"> a. History: age of onset, mode of onset, anatomical sequence and rate of progression, family history, drug history, response to alcohol, associated other neurological disorders, movement disorders and systemic illnesses, aggravating and relieving factors b. Examination: extrapyramidal signs, cerebellar signs, dystonia, dyskinesia, signs of neuropathy, signs of stroke, signs of multiple sclerosis, hepatosplenomegaly, Kayser-Fleischer rings, signs of thyroid dysfunction c. Investigations: thyroid function tests, serum copper and caeruloplasmin, neuroimaging (magnetic resonance imaging, positron emission tomography, single photon emission computed tomography), genetic studies, nerve conduction studies, electromyography, neuropathy screening, toxicology
4.	Define the tremor syndrome based on above data	
5.	Assess severity and functional impact	<ul style="list-style-type: none"> a. Rating scale from 0 to 10 (0= none, 10= extremely severe) b. Draw a spiral c. Sample of hand writing
6.	Plan treatment according to the tremor syndrome, aetiology, severity and degree of disability	

Cerebellar Tremor

Cerebellar tremor is typically an intention tremor with irregular frequency and amplitude usually involving the proximal muscles. Lesions in the vermis cause postural tremor of the trunk and head, manifesting as titubation. There are anecdotal reports of improvement with isoniazid, beta adrenergic antagonists and antiepileptics, but the definitive therapy is not well established. Thalamic DBS is an emerging therapy.

Midbrain Tremor

This is also known as Holmes' or rubral tremor. It has rest, postural, and kinetic components with involvement of more proximal than distal muscles. It is due to interruption of pathways in the midbrain tegmentum. There is typically a variable delay between the occurrence of the underlying lesion and the appearance of tremor.⁵ Benzodiazepines, sodium valproate, beta adrenergic antagonists, anticholinergics, and dopamine agonists can be tried in the treatment but generally control is difficult. Stereotactic thalamotomy or thalamic DBS could be considered in resistant cases.

Primary Writing Tremor

Primary writing tremor is an asymmetrical, task specific tremor, which occurs during writing or on positioning

the hand for writing. There are anecdotal reports of improvement with alcohol, propranolol, primidone, and anticholinergics. Botulinum toxin injection and thalamic DBS have also been used successfully.

Orthostatic Tremor

Orthostatic tremor classically involves legs and trunk. It occurs during standing and improves with ambulation or sitting down.⁶ The tremor has a frequency of 13 to 18Hz (usually 16Hz) which could be detected on surface electromyography of weight bearing muscles. The majority of patients present during the sixth or seventh decade. Treatment options include clonazepam, primidone, sodium valproate, and phenobarbitone. The response to alcohol and propranolol is poor unlike in ET.

Psychogenic Tremor

Psychogenic tremor usually has wide variations in frequency. It may demonstrate rest, postural and kinetic components in various combinations. Its onset can be abrupt, followed by spontaneous remissions. Tremor characteristics may change with each examination. It tends to decrease with distraction and increase with attention. Frequency tends to change to match the frequency of voluntary movements of the contralateral limb. There is paucity of other neurological signs. Treatment is generally difficult and psychotherapy may be helpful.

Other important tremor syndromes include voice tremor, palatal tremor, dystonic tremor, post-traumatic tremor, tardive tremor, drug induced tremor, stroke-related tremor and tremor associated with peripheral neuropathy.

CONCLUSION

Tremor is a clinical diagnosis. It could be a physiological phenomenon or a manifestation of an underlying neurological or systemic disease. Having classified the tremor, one has to decide on appropriate investigations to elucidate its aetiology. The management approach should be individualised based on aetiology, severity, and degree of disability (Table 5).

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