A Clinical Approach to Tremor

INTRODUCTION
Tremor is defined as a rhythmic and oscillatory movement of a body part with relatively constant frequency and variable amplitude. It is caused by either alternating or synchronous contractions of antagonistic muscles. Tremor is the most common of all movement disorders. It can occur even in normal individuals in the form of exaggerated physiological tremor. This review will cover classification, clinical features of various tremor syndromes and diagnostic approach to tremor.

CLASSIFICATION
Tremors are clinically classified mainly into two types—resting and action tremors. 

- Resting tremor occurs when the affected part is completely supported against gravity (e.g. hand resting in a lap). Its amplitude increases with mental stress, while it decreases with specific movement.
- Action tremors are initiated by voluntary muscle contraction. They are further subclassified into postural, isometric and kinetic tremors.
  - Postural tremors occur when affected part maintains a posture unsupported against gravity (extending arms in front of chest).
  - Isometric tremors occur on muscle contraction against fixed objects (squeezing other person’s fingers, pushing against a wall).
  - Kinetic tremors: These are divided in two types, i.e. simple kinetic tremors and intention kinetic tremors. Simple kinetic tremors increase on movements of extremities like flexion-extension and pronation-supination, while intention tremors increase on a target-directed movement like finger-nose or heel-shin test.

Usually this classification along with its anatomical distribution (e.g. leg, hands or head; unilateral or bilateral), symmetry (focal/segmental/generalized) and features like gait disturbance, extrapyramidal signs, bradykinesia, rigidity and family history form the keystone of diagnostic approach once psychogenic and drug-induced tremors have been ruled out.

TREMOR SYNDROMES

Action Tremors
Postural and action tremors comprise the largest group of tremors. They are elicited during examination under two circumstances: (1) with the arms suspended against gravity in a fixed posture (e.g. arms in front of chest with finger tips touching); and (2) during the course of goal-directed activity (finger-nose test, heel-shin test). Following tremor syndromes are predominantly part of this group.

Physiologic Tremor
It is low amplitude, high frequency tremor of 10–12 Hz, seen in normal people, not visible in normal circumstances. It is accentuated by increased sympathetic activity due to drugs or diseases.

Common drugs that increase adrenergic activity include beta-adrenergic agonists, such as salbutamol, terbutaline, amphetamines, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), levodopa, nicotine and xanthines.

Anxiety, excitement, muscle fatigue, hypoglycemia, alcohol and opioid withdrawal, thyrotoxicosis, fever and pheochromocytoma also increase sympathetic drive.

Enhancement of physiologic tremor is the most common cause of postural-action tremor. Thus, a medical rather than primary neurological cause for postural-action tremor should be considered in most cases. It is reversible once the cause is corrected. Patient with a tremor that comes and goes with fatigue, anxiety, medication or caffeine use does not need further testing.

Essential Tremor
Essential tremor (ET) is the most common neurological cause of action tremor with an estimated 5% prevalence worldwide. It is considered as familial tremor when there is a family history (approximately 50% of cases have an autosomal dominant pattern of inheritance) and as benign ET when it is sporadic. The incidence of ET increases with age, although it often affects young individuals, especially when it is familial.

Clinical features: Essential tremor most often affects the hands and arms and can be asymmetric. It can also affect the head, voice, chin, trunk and legs. Tremor becomes immediately apparent in the arms when they are held in front of chest bilaterally, and typically increases at the very end of goal-directed movements such as drinking from a glass or finger-to-nose testing. Cerebellar outflow tremor should be considered when the tremor oscillations increase steadily before arriving at the target rather than at the termination of goal-directed activity, although a distinction between the two is often difficult.

Tremor in the legs is unusual in ET. Head tremor may be vertical (‘yes-yes’) or horizontal (‘no-no’) and, although usually associated with hand or voice tremor, can be predominant or the only manifestation of ET in some patients. Ten to fifteen percent of ETs may have atypical features like resting tremors, and tongue or facial dyskinesia whereby it becomes important to distinguish it from parkinsonism.

Some patients with ET develop enhanced physiological tremor due to anxiety or other adrenergic mechanisms, thereby aggravating...
the underlying tremor. Essential tremor is typically relieved by small amounts of alcohol. Physiological tremor is aggravated by caffeine.

By definition, tremor should be the only neurological manifestation of ET. Hence, generally ET is a diagnosis of exclusion.

**Differential diagnosis:** When ET is thought of as a diagnosis, following features, which, if present, indicate a different disease—unilateral tremor, leg tremor, rigidity, bradykinesia, rest tremor (Parkinson’s disease), sudden or rapid onset (psychogenic, toxic tremor), isolated head tremor with abnormal posture: head tilt or turning (dystonic tremor), focal tremor (dystonic tremor), gait disturbance, ataxia, dysmetria (cerebellar disease), voice tremor (spasmodic dysphonia). Tremor of jaw and lips is more common in Parkinsonism whereas ET more commonly involves head.3 Generally, ET is easily distinguished from parkinsonism, but in severe ET, there may be a component of resting tremor; however, subtle bradykinesia and micrographia would clinch the diagnosis in favor of parkinsonism.

**Cerebellar Tremor**

It classically presents as a disabling low frequency intention tremor and is generally caused by stroke, brain stem tumor and multiple sclerosis. It worsens with approach to specific target leading to abnormal finger to nose, finger to finger (dysmetria) and heel to shin (dysynergia) tests. Other neurological signs might accompany like gait disturbance, difficulty in rapidly alternating hand and leg movement (dysdiadochokinesis), abnormal ocular movement and titubation.4

**Uncommon Action Tremors**

- **Primary writing tremor:** Many action tremors are particularly severe during the act of writing. Tremor that occurs exclusively while writing and not during other voluntary motor activities is referred to as primary writing tremor.
- **Orthostatic tremor:** Orthostatic tremor is limited to the legs and trunk and occurs exclusively while standing.
- **Rubral tremor:** Rubral tremor is caused by disturbances of cerebello-ponto-thalamic projections. It is usually present at rest, maintenance of posture and voluntary activity.
- **Neuropathic tremor:** It is sometimes associated with large fiber peripheral neuropathy.

**Resting Tremor**

Resting tremor is usually due to drug-induced parkinsonism or idiopathic Parkinson’s disease. Resting tremor is not typically disabling like action tremor and its amplitude varies with patient’s repose.

**Parkinsonism**

Parkinsonism is a clinical syndrome characterized by bradykinesia, rigidity, tremors (present in 50%), postural instability and with added features of masked facies, shuffling gait and micrographia.

Parkinson’s disease generally starts around 50 years of age, is more common in males than females and family history is present in 5–10% of cases. It has resting nondisabling tremor of low frequency, which starts generally in ipsilateral hands (pill rolling) and legs, associated with bradykinesia, rigidity and postural instability. It is generally unaffected by alcohol intake. However, 20–30% of idiopathic Parkinson’s disease will never have tremor as a part of natural history; similarly at other end of spectrum, there is a tremor predominant Parkinson’s disease too, which is benign and very slowly progressive.

Other disorders associated with resting tremor include Wilson’s disease, non-Wilsonian hepatocerebral degeneration and midbrain injury due to stroke, trauma or demyelinating diseases. Resting tremor may also occur as a “spillover” phenomenon in a variety of disorders in which very severe postural-action tremors predominate, such as Wilson’s disease, severe forms of ET, and other cerebellar or extrapyramidal syndromes.

**Drug-Induced and Metabolic Tremor**

Drug-induced tremors may be caused by drug withdrawal (alcohol, benzodiazepine and opioids), toxic ingestion (lithium) or simply as side effects of drug intake (salbutamol, valproate).

Sympathomimetics and tricyclic antidepressants lead to enhanced physiological tremor. Withdrawal of benzodiazepines, alcohol and opioids can lead to tremors. Tremors also appear commonly as side effects of long-term valproate. Lithium toxicity is known to cause fine postural tremor, which is directly proportional to lithium concentration. Even amiodarone may sometimes cause tremors in first week of its therapy. Antidopaminergic medicines are well known to cause parkinsonism like resting tremors. Alcohol temporarily can suppress physiologic and essential tremor while taken acutely, but can cause intention tremor on chronic intoxication and postural tremor on withdrawal.

Metabolic causes of tremors are varied such as hepatic encephalopathy, hypoglycemia, hyponatremia, vitamin B12 deficiency, etc.

**Psychogenic Tremor**

Psychogenic tremors are characterized by abrupt onset, spontaneous remission, relief with distraction and changing tremor patterns. Typically, patient is told to beat the limbs opposite to affected limb. If the tremor decreases (distractibility) or shifts its frequency (entrainment) to tapping, then psychogenic tremor is suspected.

**Wilson’s Tremor**

Wilson’s disease is a rare but important cause of treatable tremor usually presenting under 40 years of age with wing-beating pattern in its characteristic form. It is confirmed by serum ceruloplasmin and 24-hour urinary copper excretion. Additional clinical features include ascites, jaundice and chronic liver disease in a young nonalcoholic patient and by presence of Kaysar-Fleischer ring, dystonia, dystarthish, drooling in neurological phenotype patients.

**DIAGNOSTIC APPROACH**

The diagnostic approach to patients with tremor involves the history, physical examination and selected laboratory studies. Firstly, tremor should be classified on basis of its activating stimulus (rest, kinetic, postural, isometric), frequency and topographic distribution.5 Action tremor is most common and, of these, ET and enhanced physiological tremor are the most frequent diagnoses. Patients with tremor due to other disorders, such as hyperthyroidism, Parkinson’s disease, dystonia or Wilson’s disease, frequently have additional signs or symptoms that help point to the diagnosis, although this is not always the case (Flow chart 1).

**History**

The history concerning the onset of tremor is usually obvious due to its visibility. Examination of previous handwriting samples may be useful in determining the precise time of onset. Precipitating, aggravating or relieving factors, such as coffee, alcohol, drugs of abuse, medications, exercise, fatigue or stress should be elicited.

Patient with sudden onset of tremor should arouse suspicion about brain tumor, stroke, cerebellitis, multiple sclerosis, psychogenic tremor and intoxication, while gradual onset points toward parkinsonism. Generally, tremors are symmetric and asymmetry would point to focal lesion like brain tumor. Family history in ET reflects an autosomal dominant pattern of inheritance.
in approximately half of patients, while approximately 5–10% of Parkinson’s disease cases.\(^6\)

History should also assess for severity and disability.

**Examination**

Examination begins with observations of the tremor during the interview. Many patients with tremor are more symptomatic during the early part of the examination. Patients should be observed while seated, lying down with the affected body part fully supported and while walking.\(^7\) Horizontal or vertical head tremor is usually associated with ET, but it may also occur in cervical dystonia and midline cerebellar syndromes. Localized face, jaw and lip tremors are more commonly a manifestation of parkinsonism. Essential voice tremor is readily audible and may be further enhanced by having the patient hold a prolonged note.

Tremor in the arm is observed with the affected limb fully supported at rest, with the limb elevated against gravity and during goal-directed movements.

Most resting tremors cease with action but reappear again in maintenance of posture (re-emergence). Patients with resting tremor should be further examined for supportive signs of parkinsonism.

Intention tremor is generally identified by finger to nose or finger to finger test. These patients should be further analyzed for evidence of stroke (headache, vertigo, difficulty in balance, uneven gait, nystagmus) and multiple sclerosis (difficulty in vision, diverse neurological signs).

Postural and action tremors are best elicited with the arms held outstretched, with the shoulders abducted, elbows flexed and index fingers held an inch apart in front of the chest. Writing and drawing may demonstrate large, tremulous, angulated loops of ET or micrographia of parkinsonism. Stigmata of chronic liver disease and hyperthyroidism should also be looked for in these patients.\(^8\)

Cognitive impairment may be seen in Fragile X syndrome, late stage of Parkinson’s disease and Wilson’s disorder.

Eye signs like nystagmus, abnormality of saccades and pursuits are indicative of cerebellar disorders.

Symmetry is the hallmark of ET and enhanced physiological tremor, while asymmetry is predominant in Parkinson’s disease and focal tremors due to structural brain lesions like stroke, tumor and multiple sclerosis.

Distractibility and entrainment as described above point toward psychogenic tremor.

Leg tremor is more commonly due to parkinsonism than ET.

The gait is almost always normal in patients with ET, while it is characteristically narrow-based and shuffling in Parkinson’s disease, and is wide-based and ataxic in cerebellar disorders.

**Laboratory Studies**

The routine laboratory evaluation of tremor should include tests of thyroid function, glucose, complete blood count (CBC), liver function test, gamma-glutamyl transpeptidase (GGT), other diagnostic studies to exclude Wilson’s disease, and screening for heavy metal poisoning such as mercury or arsenic, if an environmental cause is suspected.\(^9\)

Wilson’s disease should be suspected in anyone under age 40 who has tremor or other involuntary movements. Hypoglycemia and pheochromocytoma may need to be ruled out in patients with enhanced physiologic tremor. Lithium levels might be done in those suspected of intoxication.

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Flow chart 1: Diagnostic algorithm
Brain imaging can be useful in patients suspected clinically of having a structural cause for tremor, such as Wilson’s disease, brain trauma, stroke or mass lesion, but it is otherwise not indicated.

Positron emission tomography (PET) or single photon emission computed tomography (SPECT) might be done for atypical presentation of Parkinson’s disease.

**TREATMENT**

The treatment of tremor depends upon the underlying cause.

**Rest Tremor**

Management of rest tremors, such as those associated with Parkinson’s disease or other parkinsonian disorders, is accomplished by treatment of the underlying disorder, holding antidopaminergic drugs and usually consists of anticholinergic drugs or other antiparkinson agents like Levodopa and other dopamine agonists.

**Essential Tremor**

Propranolol and primidone are the most effective and well-studied medications for the treatment of ET. Initial propranolol is given followed by primidone if ET is refractory to propranolol. Trials of clonazepam, gabapentin, topiramate, botulinum toxin have been done in medically refractory cases with varying efficacy. Deep brain stimulation and unilateral thalamotomy are effective for the treatment of medically refractory ET.

**Enhanced Physiologic Tremor**

Enhanced physiologic tremor is best managed by reduction or removal of the responsible offending medication or toxin; diagnosis and treatment of possible associated endocrine disorders, and dealing with stress, anxiety or fatigue. Single doses of propranolol taken in anticipation of stress inducing scenarios might be efficacious.

**Cerebellar Tremor**

There is no useful pharmacotherapy for cerebellar tremor. The rare patient with severe tremor and little or no ataxia can be helped by deep brain stimulation of the ventral intermediate nucleus of the thalamus.

**REFERENCES**