Diagnosis and Management of Tremor

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Tremor is the most common involuntary movement disorder. It is differentiated from other involuntary movement disorders, such as chorea, athetosis, ballismus, tics, and myoclonus, by its repetitive, stereotyped, movements of a regular amplitude and frequency. Tremor can be defined as an involuntary, rhythmic, periodic, mechanical oscillation of a body part. Since small-amplitude tremors may not be visible to the naked eye and may only be detectable by sensitive recording devices, amplitude of the tremor is therefore not critical to the definition. Accurate diagnosis of tremor is important because appropriate treatment depends on the accuracy of the clinical diagnosis. This article reviews the classification and management of tremor.

Arch Intern Med. 2000;160:2438-2444

Tremor is the most common movement disorder. There are many varieties of tremors, each with characteristic features. It is important to recognize and diagnose them accurately and confidently for their successful management.

CLASSIFICATION AND MANAGEMENT

Tremors can be classified according to their specific clinical features or by etiology (Table 1). Because of the numerous and ever expanding etiologies of tremor, etiologic classification is not helpful, whereas classification based on clinical features is more useful to the clinician. Tremors can be divided into the following types.

Resting Tremor

Resting tremor occurs when there is no voluntary muscle activity and the limb is fully supported against gravity. Unlike essential tremor, resting tremor typically becomes less prominent with voluntary movement and therefore rarely results in motor disability. As with all forms of tremor, resting tremor becomes more evident with stress and is ameliorated by rest.

The tremor amplitude increases with movements of another body part. Resting tremor is most commonly found in Parkinson disease but seldom in other conditions. It may initially involve the legs, a feature uncommon in essential tremor.

Action Tremor

This occurs with voluntary muscle contraction and includes postural, kinetic, and isometric tremor. Postural tremor is produced by voluntary maintenance of a particular posture held against gravity. Examples are physiologic tremor, essential tremor, certain drug-induced tremors, and postural tremor of Parkinson disease. Some postural tremors continue when the limb is supported, thus making it difficult to differentiate from resting tremor. However, tremor amplitude almost always diminishes during target-directed movements in resting tremor, while increasing or constant tremor amplitudes are found during voluntary movements in postural tremor.1

Kinetic tremor is evident during any voluntary movement. It can be intention tremor, task-specific tremor, or simple kinetic tremor. Kinetic tremor, which is exacerbated toward the end of a visually guided goal-directed movement, is called
intention tremor. It is characterized by a variant of essential tremor while others believe it is a type of focal dystonia. However, unlike intention tremor, primary writing tremor is usually seen in cerebellar disorders. The etiology of primary writing tremor is controversial. Some authors believe it is caused by a rigid stationary object. It may occur sporadically or be inherited as an autosomal dominant trait. It has 2 forms. Type A is characterized by tremor appearing during writing only, and type B occurs when the hand adopts a writing position. Simple pronation and supination movements test simple kinetic tremor.

Isometric tremor occurs when a voluntary muscle contraction is opposed to a rigid stationary object. It can be tested while making a fist or squeezing the examiner’s fingers.

Physiologic Tremor

Physiologic tremor is an action tremor and is present in every healthy person. It becomes more pronounced during periods of muscular fatigue, anxiety, emotional stress, and fear or excitement. Other causes of enhanced physiologic tremor are thyrotoxicosis, pheochromocytoma, catecholamine infusion, methylxanthine administration, drug withdrawal states, and alcohol intoxication. These tremors are mostly reversible if the cause of the tremor is identified and corrected. The frequency of physiologic tremor in young adults is 8 to 12 Hz, gradually decreasing with age to around 6 to 7 Hz in persons older than 60 years. β-Receptor agonists enhance physiologic tremor whereas nonselective β-blockers and β-2 antagonists are effective in preventing such tremor.

Essential Tremor

Essential tremor is an action tremor, either postural or kinetic in characteristics, mainly affecting the hands. It is bilateral and largely symmetrical. It affects 0.3% to 1.7% of the population and is the most common movement disorder. Half the cases are familial, with an autosomal dominant pattern of inheritance. The median age of onset is 15 years and both sexes are affected with equal frequency and severity. It commonly affects the head, neck, facial muscles, voice, jaw, tongue, and upper extremities, but except for upper extremities, does not affect the other parts of the body in isolation. The condition commonly progresses in severity with increasing age. The frequency of the tremor is 4 to 8 Hz. The diagnostic criteria include exclusion of other abnormal neurologic signs, especially dystonia. Positron emission tomography in patients with essential tremor reveals increased cerebellar activity even at rest.

Indeterminate Tremor Syndrome

Patients with indeterminate tremor syndrome have classic essential tremor in addition to other neurologic signs not sufficient to make a diagnosis based on other criteria. Indeterminate tremor is defined as a tremor that has clinical features and/or etiologic evidence insufficient for a recognizable syndrome.

<table>
<thead>
<tr>
<th>Type of Tremor</th>
<th>Clinical Features</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resting Tremor</strong></td>
<td>Occurs when limb is fully supported against gravity; becomes less prominent with voluntary movement</td>
<td>Parkinson disease</td>
</tr>
<tr>
<td><strong>Action Tremor</strong></td>
<td>Occurs when a posture is maintained against gravity</td>
<td>Physiologic tremor, essential tremor, drug-induced tremor</td>
</tr>
<tr>
<td>Postural tremor</td>
<td>Occurs during voluntary movement</td>
<td>Parkinson disease, cerebellar lesions (intention tremor), primary writing tremor, Holmes tremor, drug-induced tremor</td>
</tr>
<tr>
<td>Kinetic tremor</td>
<td>Occurs when voluntary muscle contraction is opposed by a rigid stationary object</td>
<td></td>
</tr>
<tr>
<td>Isometric tremor</td>
<td>Occurs when voluntary muscle contraction is opposed by a rigid stationary object</td>
<td></td>
</tr>
<tr>
<td>Indeterminate tremor syndrome</td>
<td>Essential tremor associated with other neurologic signs, but not sufficient for a recognizable neurologic disorder</td>
<td></td>
</tr>
<tr>
<td>Orthostatic tremor</td>
<td>16-Hz tremor of lower limbs, which appears on standing and remits on walking and sitting</td>
<td>Aqueduct stenosis, relapsing polyradiculoneuropathy, pontine lesions, head trauma</td>
</tr>
<tr>
<td>Isolated chin tremor</td>
<td>Episodic contraction of mentalis muscle; autosomal dominant</td>
<td></td>
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<tr>
<td>Isolated voice tremor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dystonic tremor</td>
<td>Tremor in a part affected by dystonia</td>
<td>Spasmodic torticollis</td>
</tr>
<tr>
<td>Monosymptomatic resting tremor</td>
<td>Resting and/or postural tremor in the absence of bradykinesia and rigidity</td>
<td></td>
</tr>
<tr>
<td>Palatal tremor</td>
<td>Essential or symptomatic</td>
<td>Cerebrovascular disease, encephalitis, multiple sclerosis, trauma, neurodegenerative diseases</td>
</tr>
<tr>
<td>Neuropathic tremor</td>
<td>X-linked bulbospinomuscular atrophy, hereditary motor-sensory neuropathy, multifocal motor neuropathy, Charcot-Marie-Tooth disease, Guillain-Barré syndrome, human T-lymphotropic virus 1–associated neuropathy, dysgammaglobulinemic neuropathy</td>
<td></td>
</tr>
<tr>
<td>Psychogenic tremor</td>
<td>Does not involve the fingers; tremor amplitude decreases during distraction</td>
<td></td>
</tr>
</tbody>
</table>

*Ellipses indicate no particular clinical features and/or unimportant or unknown etiology.
Orthostatic Tremor

This is a rare entity first described by Heilman in 1984. It is a disorder of middle-aged or elderly people that is characterized by unsteadiness on standing secondary to a 16-Hz tremor of the lower limbs, which remits on walking or sitting. Patients stand on a wide base but walk normally. Only a fine ripple of muscle activity is visible. Lifting the standing patient off the ground abolishes the tremor, and when walking, tremor disappears from the non-weight-bearing limb. Tremor persists in the weight-bearing leg and in truncal muscles. Standing on “all fours” also induces a 16-Hz tremor in proximal upper limb muscles. It is most pronounced in leg and trunk muscles and usually does not involve the face, although a single case report of orthostatic jaw tremor has been described. Thirty percent of patients may also have essential tremor of the arms, which does not attenuate on walking. Recently it has been shown that orthostatic tremor is invariably present during stance or other weight-bearing positions; however, it is not always associated with orthostasis. Isometric contraction of the arm and leg muscles also induces 16-Hz tremor in some patients when supine or suspended upright with orthostatic tremor, implying that muscle contraction seems to be the critical factor in generating the 16-Hz tremor and that it is not a true orthostatic tremor. Symptomatic orthostatic tremor has been described in non-tumoral aqueduct stenosis, relapsing polyradiculoneuropathy, pontine lesions, and following head trauma. Only electromyographic recordings can confirm the diagnosis. The tremor frequency of 16 Hz has not been described in any other kind of tremor and is pathognomonic of orthostatic tremor. However, it has been suggested that auscultation with the diaphragm of a stethoscope over quadriceps and hamstrings during stance may reveal a repetitive thumping sound, thus obviating the need to recourse to electromyographic recordings.

Isolated Chin Tremor

Isolated chin tremor, also called geniospasm, is an autosomal dominant hereditary syndrome characterized by episodic, usually stress-induced, high-frequency, contraction of the mentalis muscle. The onset is typically in infancy or childhood. Usually there is no evidence of any other nervous system abnormality, although abnormal electroencephalographic findings, sleep disorders, and involvement of other facial muscles have been described in rare cases.

Isolated Voice Tremor

Isolated voice tremor occurs in 2 variants. One is considered to be a form of focal dystonia of the vocal cords; the other is considered to be a variant of essential tremor.

Dystonic Tremor

Dystonic tremor is mainly a postural and kinetic tremor in an extremity or body part affected by dystonia. A typical example is tremulous spasmodic torticollis. Although essential tremor commonly accompanies dystonia, dystonic tremor is considered a separate entity. It is localized, asymmetric, and irregular in amplitude and periodicity. Some patients with dystonia have tremor of the body part not affected by dystonia. For example, patients with cervical dystonia often show an enhanced essential tremor of the upper limb. Isolated head tremor is also found in patients with first-degree relatives with spasmodic torticollis.

Monosymptomatic Resting Tremor

Monosymptomatic resting tremor is a resting and/or postural tremor in the absence of bradykinesia or rigidity significant enough to diagnose Parkinson disease.

Parkinson Disease

A pill-rolling resting tremor is characteristic of Parkinson disease, but postural tremor is also present in most cases. In many patients, 2 separate tremor peaks may be distinguished by spectral analysis and this pattern is considered pathognomonic of basal ganglia disease. Typically the parkinsonian tremor is asymmetrical, at least initially and affects the upper limb before involving the ipsilateral leg after a period of about 2 years. Tremor of the lips, jaw, or tongue may also occur, but head or voice tremor is rare.

Cerebellar Tremor

Intention tremor is the most common form of cerebellar tremor. There may be postural tremor, but resting tremor is not found in cerebellar diseases.

Holmes Tremor

This is a symptomatic tremor caused by lesions in the brainstem, cerebellum, or thalamus. It has been labeled in the past as rubral tremor, midbrain tremor, thalamic tremor, myorhythmia, and Benedikt syndrome, but the Ad Hoc Scientific Committee on Movement Disorders has applied the term “Holmes tremor” to all these forms of tremor. The tremors attributed to these different lesions are postural and/or action in nature and worsen during movement and markedly increase during goal-directed movements. These tremors affect predominantly proximal limbs and are of low frequency.

Palatal Tremor

Palatal tremor can be either symptomatic due to brainstem and/or cerebellar lesions or essential without any demonstrable brain lesion. In symptomatic palatal tremor, olivary hypertrophy can be demonstrated on magnetic resonance imaging. In the essential palatal tremor, the patient usually has ear clicks, which do not occur in symptomatic variety. The symptomatic form is often associated with pendular vertical nystagmus. Rhythmic movements of tensor veli palatini and levator veli palatini muscles occur in essential and symptomatic palatal tremor, respectively.

Symptomatic palatal tremor has been observed in patients with ce-
Drug-Induced Tremor

The most common form of drug-induced tremor is enhanced physiologic tremor due to sympathomimetic use, antidepressant use, or alcohol withdrawal. Neuroleptics or dopamine antagonists cause classic parkinsonian tremor. Long-term neuroleptic treatment can result in a postural tremor with a frequency of 3 to 5 Hz, but is also present at rest and during goal-directed movements. This is called tardive tremor. Lithium intoxication can cause a cerebellar tremor. Treatment is withdrawal or dose reduction of the offending agent if possible.

Neuropathic Tremor

Tremor has been described in many neuropathies including X-linked bulbospinal muscular atrophy, hereditary motor-sensory neuropathy, multifocal motor neuropathy, Charcot-Marie-Tooth syndrome, Guillaumin-Barre syndrome, and human T-lymphotropic virus 1-associated neuropathy, but demyelinating neuropathies and dysgammaglobulinenic neuropathies are the most common causes of such tremors. Characteristically, an action tremor resembling essential tremor is found in these patients.

Psychogenic Tremor

Psychogenic tremor is usually a combination of resting and postural or intention tremors. Onset and remission of the tremor is sudden and tremor amplitude decreases during distraction. The tremor does not involve the fingers. There may be a history of somatization, and additional unrelated neurologic signs might appear.

TREATMENT

Table 2 lists treatment for various tremor types.

Medical Treatment

The first line of treatment for tremor is oral medication. β-Blockers, anticholinergic medication, and levodopa are useful modalities for resting tremor. Kinetic tremor may respond to β-blockers, primidone, anticholinergic medication, and alcohol.

Physiologic Tremor. Usually no treatment is required for physiologic tremor. However, it may interfere with activities requiring extreme precision. Treatment of exaggerated physiologic tremor requires identification and removal or treatment of the precipitating cause such as thyrotoxicosis, hypoglycemia, emotional stress, pheochromocytoma, and use of tricyclic antidepressants, neuroleptics, and lithium. In cases in which the precipitating cause cannot be removed or highly skilled fine motor function is desired, treatment with propranolol may be effective.

Essential Tremor. Alcohol intake will temporarily cause dramatic tremor reduction lasting 45 to 60 minutes in the majority of patients with essential tremor. This temporary improvement is followed by a rebound phenomenon when the alcohol effect wears off. Moreover, tolerance develops to the effect of alcohol and with time larger amounts of alcohol may be needed to cause tremor reduction. The mechanism of action of alcohol is unknown. However, in a positron emission tomography study, alcohol has been shown to reduce the overactivity of cerebellar connections seen in essential tremor.

Propranolol was discovered by chance to improve essential tremor. β-Adrenergic blocking drugs (mainly a nonselective blocker such as propranolol or a β2-selective blocker) have been the mainstays for the treatment of essential tremor. They are, however, less effective in the treatment of essential voice and head tremor. Propranolol reduces tremor amplitude but not tremor frequency. The clinical response to propranolol is variable and often incomplete. Nipradilol, a new β-blocker, has been shown to be effective in essential tremor in a study involving 20 patients.

Gabapentin has been used in the treatment of essential tremor. In a comparative double-blind crossover placebo-controlled trial of patients with essential tremor, both propranolol and gabapentin demonstrated significant and comparable efficacy in reducing tremor. Theophylline has been shown to be a useful agent in the treatment of essential tremor. In a blind crossover trial, theophylline reduced tremor to the same extent as propranolol. Primidone has been shown to be effective in the treatment of essential tremor. It reduces tremor more than propranolol and its anti-tremor effect is maintained over the first year of therapy. Benzodiazepines have been used in the treatment of tremor. However, their efficacy is limited. Thompson et al found no effect of clonazepam on essential tremor. Clozapine can substantially improve essential tremor, but its use is limited as it can cause
The dysphasia, however, can be complicated with essential head and voice tremors. Use of botulinum toxin for pharmacologically, botulinum toxin treatment should be tried before recourse to other modalities. Use of botulinum toxin for essential head and voice tremors, however, can be complicated with dysphasia.

Parkinsonian Tremor. The response of parkinsonian tremor to treatment is variable. Several drugs have been tried. Both trihexiphenidyl hydrochloride and carbidopa-levodopa combination have been shown to significantly reduce the tremor of Parkinson disease. In a study comparing the effects of trihexiphenidyl, carbidopa-levodopa, and hexiphenidyl, carbidopa-levodopa, levodopa76 or gabapentin77,78 may also improve orthostatic tremor.

Dystonic Tremor. Pharmacologic treatment of dystonic tremor is usually disappointing; however, clonazepam or anticholinergics may be tried.79-82 Treatment of the underlying dystonia with botulinum toxin often results in significant improvement of tremor.81

Orthostasic Tremor. Orthostatic tremor rarely responds to ß-blocker therapy but can be ameliorated by clonazepam alone or in combination with primidone.73 In one small study,74 8 of 9 patients responded to clonazepam. The patient who did not respond to clonazepam, responded to chloridazepoxide. In another study,75 10 of 18 patients showed improvement with clonazepam and the remaining 8 patients responded to valproic acid. Levodopa83 or gabapentin77,78 may also improve orthostatic tremor.

Cerebellar Tremor. There is no effective treatment of cerebellar tremor. However, some success has been reported with clonazepam.82 It may also respond to levodopa and anticholinergic agents or clozapine when a clinically significant resting tremor is present. Odansetron, a 5-hydroxytryptophan-3 antagonist, has been shown to improve cerebellar tremor in a placebo-controlled double-blind crossover study involving 20 patients.83

Holmes Tremor. Treatment of Holmes tremor is usually unsuccessful. Some success with carbidopa-levodopa and clonazepam has been reported.84,85

Neuropathic Tremor. Treatment of neuropathy may or may not improve neuropathic tremor. The tremor of hereditary motor-sensory neuropathy often responds to treatment with propranolol and alcohol.86

Surgical Treatment

The minimal criteria for a patient to be considered a candidate for neurosurgery are a lack of response to medical treatment, tremor resulting in severe disability, and the absence of contraindications to neurosurgery.

Thermocoagulation (thalamotomy) and deep brain stimulation target nucleus ventralis intermedius thalami. Thalamotomy and thalamic stimulation cause an improvement of the tremor in 80% to 90% of patients with Parkinson disease. Unilateral thalamotomy improves the contralateral tremor in 90% of patients.87 However, problems associated with bilateral thalamotomy, such as dysphagia and dysarthria, limit its use. Deep brain stimulation has similar benefits to thermocoagulation but fewer side effects, including lower perioperative mortality.88 Koller et al89 and Limousin et al90 have shown the benefits of deep brain stimulation in patients with Parkinson disease or essential tremor in controlled, prospective studies. Other targets for the treatment of parkinsonian tremor are internal pallidum (pallidotomy) and subthalamic nucleus. In a series of 239 patients who underwent pallidotomy for parkinsonian tremor, complete relief of all symptoms on the contralateral side occurred in 81.9% of patients. Nearly 77% of the remaining patients experienced substantial improvement.91 Pallidotomy also improves akinesia and decreases levodopa-induced dyskinesia.92 The side effects associated with pallidotomy are visual field defects, hemiparesis, dysarthria, and cognitive deficits.

Stimulation of subthalamic nucleus improves not only tremor but also akinesia by about 70%.93 Thalamotomy can achieve a permanent satisfying tremor relief in
CONCLUSIONS
Tremor is the most common movement disorder. There are many varieties of tremors, each with characteristic features. It is important to recognize and diagnose them accurately and confidently for their successful management.

Accepted for publication April 18, 2000.

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