Tremor

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Dr Louis serves on the clinical advisory boards of CADENT Therapeutics and SAGE Therapeutics, Inc and receives publishing royalties from Elsevier for *Merritt's Neurology*.

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Dr Louis discusses the unlabeled/investigational use of alprazolam, benzodiazepines, carbidopa/levodopa, clonazepam, gabapentin, primidone, and topiramate for the treatment of essential tremor; trihexyphenidyl for the treatment of dystonic tremor; acetazolamide, baclofen, carbamazepine, clonazepam, ethosuximide, and phenytoin for the treatment of orthostatic tremor; pregabalin for the treatment of neuropathic tremor; benzodiazepines for the treatment of parkinsonian resting tremor; and phenobarbital to treat the side effects of acute nausea and unsteadiness that occur as a result of other treatments for tremor.

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ABSTRACT

PURPOSE OF REVIEW: **Tremor may be defined as an involuntary movement that is rhythmic (ie, regularly recurrent) and oscillatory (ie, rotating around a central plane) and may manifest in a variety of ways; accordingly, tremor has a rich clinical phenomenology. Consequently, the diagnosis of tremor disorders can be challenging, and misdiagnoses are common. The goal of this article is to provide the reader with straightforward approaches to the diagnosis and treatment of tremors.**

RECENT FINDINGS: **Focused ultrasound thalamotomy of the ventral intermediate nucleus of the thalamus is an emerging and promising therapy for the treatment of essential tremor.**

SUMMARY: **The evaluation should start with a detailed tremor history followed by a focused neurologic examination, which should attend to the many subtleties of tremor phenomenology. Among other things, the history and examination are used to establish whether the primary tremor is an action tremor (ie, postural, kinetic, or intention tremor) or a resting tremor. The clinician should then formulate two sets of diagnoses: disorders in which action tremor is the predominant tremor versus those in which resting tremor is the predominant tremor. Among the most common of the former type are essential tremor, enhanced physiologic tremor, drug-induced tremor, dystonic tremor, primary writing tremor, orthostatic tremor, and cerebellar tremor. Parkinson disease is the most common disorder of resting tremor. This article details the clinical features of each of these disorders, as well as those of additional tremor disorders.**

INTRODUCTION

Humans have been documenting their tremors for thousands of years.[1] Tremor is defined as an involuntary movement that is both rhythmic (ie, regularly recurrent) and oscillatory (ie, rotating around a central plane).[2] Tremor may manifest in a vast array of ways. As such, the clinical phenomenology is very rich, and it should be no surprise that numerous methods for classifying tremors exit. Thus, tremors may be classified based on speed (ie, frequency measured in hertz), regions of the body affected (eg, arm, voice, head), activation state in which tremor manifests (eg, when the body part is at rest), occurrence of associated medical conditions (eg, hyperthyroidism), and the brain region from which the tremor arises (eg, basal ganglia, cerebellum). Because there are many ways to classify and divide tremor, a large nomenclature applies to tremor. The richness of the clinical phenomenology and its associated nomenclature can be daunting

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to the clinician. The goal of this article is to provide the reader with a basic approach to the diagnosis and management of the patient with tremor. This approach includes a medical history, a focused neurologic examination, diagnosis, and, finally, treatment.

APPROACH TO EVALUATING THE PATIENT WITH TREMOR

The approach to the patient involves a medical history followed by a neurologic examination.

Medical History

The first set of questions should be directed at determining whether the tremor is one that occurs with action or at rest. It is best to begin with an initial question that is open-ended (eg, "Can you tell me about your tremor?" or "What type of tremor do you have?" or "When do you notice tremor?"). After this initial question, more specific questions, such as "Does your hand shake when you are writing?" or "Does your hand shake when you are trying to eat something?" may be asked to further ascertain whether the tremor is an action tremor or a resting tremor. This is then followed by additional questions that elicit information on the following items:

- The body areas that seem to be shaking (eg, arms, head, voice)
- The limb positions that bring on the tremor and, conversely, those that seem to lessen it
- The age at which tremor began
- How the tremor has changed over the years
- The presence of other involuntary movements
- The presence of other neurologic symptoms aside from tremor
- The presence of pulling sensations or discomfort in the body part that is shaking
- The use of medications that seem to produce or exacerbate tremor
- Dietary factors that exacerbate tremor (eg, coffee and other forms of caffeine)
- Symptoms of thyroid diseases (eg, weight loss, heat intolerance)
- Family history of "shaking" or tremor (eg, the presence of affected first-degree relatives is often reported by patients with essential tremor, among whom the pattern of inheritance may resemble that of an autosomal dominant disease)

Neurologic Examination

After the medical history, a detailed and focused neurologic examination should be performed. First, the examiner should ask the patient to raise his or her arms against gravity, with the palms down in front and then in the wing-beat position with the hands facing one another in the midline. If a postural tremor is present during sustained arm extension, the examiner should assess the following:

- Whether the tremor is regularly recurrent and oscillatory
- Which joints are involved (eg, elbow, wrist, metacarpophalangeal joints) and in what directions (eg, for the wrist, flexion-extension, pronation-supination)
- Whether the tremor in each arm is synchronous with that of the other arm (ie, in phase or out of phase)
- Whether the tremor has a reemergent quality (ie, initially absent and the time it takes to emerge)

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- Whether the tremor is accompanied by abnormal postures
- Whether any features of psychogenic tremor are present, including distractibility (ie, a decrease or cessation of tremor when volitionally performing a task [eg, finger tapping with opposite hand]), entrainment (ie, the tremor may be brought into a specific rhythm), or suggestibility (ie, the examiner may induce tremor with certain stimuli)

Next, the examiner should attempt to elicit kinetic tremor—a tremor that occurs during voluntary movements. Thus, the examiner may ask the patient to perform the finger-nose-finger maneuver, pour water between cups, draw spirals, or write a sentence. The examiner should assess the following items:

- Does the tremor have an intentional component (ie, does the tremor worsen as the limb approaches a target [eg, during the finger-nose-finger maneuver])?
- Are dystonic movements or postures present (eg, do some of the fingers flex, extend, or twist during the finger-nose-finger maneuver)?
- What is the relative severity of the kinetic tremor that is being observed to that which was observed during sustained posture (above)?

Next, the examiner should assess whether there is any tremor at rest in the patient's arms or legs. Tremor at rest in the arms can be assessed while the patient is seated, standing, walking, and lying down. Resting tremor in the legs can be assessed while the patient is seated or lying down. In addition, tremor while standing (ie, orthostatic tremor) may be assessed while the patient is standing in a stationary position.

Finally, the examiner may assess for tremor in the head (ie, neck) (while the patient is seated and lying down), jaw (with the patient's mouth closed and then with the mouth held open), facial muscles (eg, forehead, cheek), chin, tongue, and voice (during sustained phonation and during speech).

DIAGNOSIS

The history and physical examination are first used to establish whether the main type of tremor is an action tremor (ie, postural, kinetic, or intention tremor) or a tremor at rest. Indeed, this is a primary point of divergence: those diseases in which action tremor is the predominant tremor versus those diseases in which resting tremor is the predominant tremor, each of which will be discussed in turn, beginning with the former because these are both of a larger variety and more prevalent.

DISEASES IN WHICH ACTION TREMOR IS PREDOMINANT

This section discusses the most commonly encountered diseases and those diseases that have a particularly distinctive set of clinical features.

Essential Tremor

The central clinical feature of essential tremor is kinetic tremor. This is generally observed during numerous activities of daily living, ranging from eating to writing, and may be elicited on neurologic examination during a variety of maneuvers (eg, finger-nose-finger maneuver, spiral drawing, pouring water between two cups) (**VIDEO 4-1**, *links.lww.com/CONT/A278*). Rather than being totally symmetric, the tremor is usually slightly asymmetric, affecting one arm more than the other. In approximately 5% of patients, this tremor is markedly asymmetric or unilateral.[3] In approximately 50% of patients with essential

KEY POINTS

- Tremors are involuntary movements that are both rhythmic and oscillatory.
- An initial step in evaluating patients with tremor is to determine whether the tremor is primarily present at rest or with activity.
- The key feature of essential tremor is kinetic tremor.
- The kinetic tremor of essential tremor is typically slightly asymmetric.
- Approximately one-half of patients with essential tremor exhibit intention tremor during the finger-nose-finger maneuver.

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tremor, the tremor has an intentional component, with observed worsening as the patient approaches the target during the finger-nose-finger maneuver. Interestingly, intention tremor in essential tremor is not limited to the arms; in fact, 10% of patients exhibit such tremor in their neck when their head approaches a target. This may be observed when the patient lowers his or her head, for example, to meet an approaching cup or a spoon. In addition to kinetic tremor, patients with essential tremor often have a postural tremor (ie, tremor that occurs when the body part is held motionless against the force of gravity), although the amplitude of this tremor is generally lower than that of the kinetic tremor.[4] The tremor in the two arms is generally out of phase, creating a seesaw effect when the arms are being held in a wing-beat position. This lack of phasic synchrony accounts for the observation that functionality may improve when two hands rather than one hand are used to hold a glass or cup because the tremors in each arm cancel one another out to some degree.

The postural tremor of essential tremor is generally of greatest amplitude at the wrist joint and generally involves wrist flexion-extension rather than rotation-supination, although this is not always the case.[5] Tremor at rest, without other cardinal features of parkinsonism such as bradykinesia or rigidity, occurs in approximately 1% to 35% of patients with essential tremor, depending on the method of ascertaining the cases (eg, population, brain repository), but in contrast to that of Parkinson disease (PD), it is a late feature and has only been observed in the arm (ie, does not involve the leg).

CASE 4-1

A 68-year-old woman presented with tremor, which she noticed when holding an eating utensil and when writing. The tremor had begun about 5 years previously, and it seemed to be getting worse, little by little, with each passing year. Her father and one of her two sisters had had a similar tremor. Although she was unaware of it herself, one of her children told her he sometimes noticed a mild, side-to-side head tremor.

She had previously been treated with propranolol but was unable to tolerate more than 80 mg/d because her heart rate dropped below 60 beats/min. Furthermore, this dose had resulted in only a modest (ie, 10%) reduction in her tremor. She had also taken primidone, 50 mg in the morning, but the initial dose made her nauseated, and she did not take it again.

On examination, the tremor was noticeable when she drew spirals and performed the finger-nose-finger maneuver, and it worsened slightly as she approached her nose during this maneuver. She also had a postural tremor, but it was considerably less than the tremor observed while she used her hands to write. She was started on topiramate 25 mg/d and was gradually increased to 200 mg/d, resulting in a moderate reduction in the amplitude of her tremor.

COMMENT

This case illustrates the slowly progressive and often familial nature of essential tremor, the fact that the central defining clinical feature of essential tremor is kinetic tremor, and the presence of head tremor in some patients with essential tremor, particularly women.

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The motor features of essential tremor are not limited to tremor. Another motor feature of essential tremor is gait ataxia, which may be brought out by asking patients to walk tandem. The number of missteps in essential tremor is in excess of that seen in control subjects of similar age. In most patients with essential tremor, this ataxia is mild, although in some patients it may reach moderate severity. In general, the ataxia results in a reduction in patients' confidence in balance and a mild but significant increase in the number of near falls and falls in patients with essential tremor compared with age-matched controls.[6]

In most individuals with essential tremor, the tremor worsens over time, and several patterns of progression have been described; the two most common are late-life onset (after the age of 60) with steady progression and early-life onset (ie, before the age of 40) with mild, stable tremor for many years that then, in the sixties and onward, progresses steadily (**CASE 4-1**). The least common pattern is that of early-life onset with marked worsening over the ensuing decade. Surprisingly few prospective, longitudinal natural history studies of essential tremor exist; however, the best estimates are that the average annual increase in tremor severity from baseline is between 3.1% and 5.3%, and the median annual increase from baseline is between 1.8% and 2.0%.[7]

Over time, the tremor has a tendency to spread beyond the upper limbs as patients develop cranial tremors involving the neck (most common), voice, or jaw. These cranial tremors are particularly prevalent in women with essential tremor, among whom the prevalence of neck tremor is several times higher than that of men with essential tremor.[8] Neck tremor in essential tremor often begins as a unidirectional tremor, either "no-no" (ie, horizontal) or "yes-yes" (ie, vertical); with time this can evolve into a more complex, multidirectional tremor.[9] Unless it is particularly severe, the neck tremor, which is a postural tremor, should resolve while the patient is lying on his or her back with the head fully at rest. An interesting feature of the neck tremor is that patients with essential tremor are often unaware of its presence (ie, they have an agnosia for it), particularly when it is mild. The jaw tremor is more often seen when the patient's mouth is open rather than closed; the latter is more a feature of the jaw tremor found in patients with PD.

The presence of dystonic posturing in essential tremor cases is controversial, although it is likely that a mild dystonic posture in the tremulous arm in some cases does not preclude a diagnosis of essential tremor, especially when the dystonic posture is a late finding in a patient with essential tremor with long-standing and severe tremor.[2]

The overdiagnosis of essential tremor is common. Indeed, studies show that 30% to 50% of "essential tremor" cases have diagnoses other than essential tremor, with many of these patients having PD or dystonia.[10] Differentiation from PD may be achieved, however, by the absence in essential tremor of rigidity, hypomimia, and bradykinesia accompanied by decrement (ie, patients with essential tremor have absence of a sequential decrement in amplitude during finger taps). The characteristics of the tremor are also important in distinguishing a patient with essential tremor from one with PD. The presence of isolated resting tremor, isolated postural tremor (ie, postural tremor with minimal kinetic tremor), postural tremor predominantly involving the metacarpophalangeal joints rather than the wrist, or postural tremor characterized by greater wrist rotation than wrist flexion and extension are indicators that the likely diagnosis is PD rather than essential tremor. Reemergent tremor is a

KEY POINTS

- The postural tremor in essential tremor is generally out of phase; this can create a seesaw effect when the patients' arms are held in the wing-beat position.
- Resting tremor may occur in patients with severe or long-standing essential tremor, but it is restricted to the arms.
- Neck tremor is several times more common in women with essential tremor than in men with essential tremor.

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type of postural tremor that commences after a brief latency of several seconds and is another feature of PD. The use of dopamine transporter (DAT) imaging can be useful in distinguishing patients with essential tremor from those with parkinsonism, although its use is supplemental to clinical information derived from the history and examination.[11,12]

Aside from a mild dystonic posture, noted above, dystonic postures, movements, or tremor are not features of essential tremor. In addition, dystonic tremor is often neither rhythmic nor oscillatory. The patient should be assessed for the presence of neck dystonia, which is characterized by head tilt or rotation, hypertrophy of the sternocleidomastoid or other neck muscles, the presence of a tremor null-point, or a sensory trick by history (ie, a maneuver such as touching the chin or back of the head that lessens the tremor).

Scanning or dysarthric speech or nystagmus may be present in patients with spinocerebellar ataxias; however, these are not features of essential tremor. Hyperthyroidism can be assessed by clinical history (eg, symptoms of weight loss or heat intolerance) as can the use of medications (eg, lithium, prednisone, valproate) or other substances (eg, tobacco, caffeine) that may produce or exacerbate action tremor.

A difficult differential is between that of mild essential tremor and enhanced physiologic tremor, although the presence of neck tremor should exclude the latter. Computerized tremor analysis with inertial loading can assist with this differential, although this is often not available outside of research-oriented tertiary referral centers. In patients with a tremor of central origin (eg, essential tremor), the primary tremor frequency should not change with inertial loading; in patients with enhanced physiologic tremor, the frequency will reduce. Other features that support an essential tremor diagnosis are the presence of essential tremor in one or more first-degree relatives. A reported reduction in tremor with ethanol use is often used as a diagnostic tool; however, this is not very specific and of limited utility. Indeed, patients with most tremor disorders often experience a reduction in tremor following ethanol consumption.

The main motivators for treatment in essential tremor are embarrassment and functional disability. Beta-blockers (especially propranolol) and primidone, alone or in combination, are the most effective pharmacologic agents, although many patients choose to discontinue these medications because of their limited efficacy and side effects.

Propranolol has been used in doses up to 360 mg/d, although doses in excess of 80 mg/d to 100 mg/d are rarely tolerated in patients who are elderly, with the main issue being bradycardia. A conservative starting dose is 20 mg/d, and this is gradually increased as noted above. Asthma is only a relative contraindication to the use of propranolol, and propranolol use should be considered on a case-by-case basis. Primidone can be given in doses up to 1500 mg/d, although lower doses (eg, starting with 25 mg and gradually increasing to 500 mg/d) are often effective. Acute nausea or unsteadiness is observed in approximately 25% of patients, irrespective of the starting dose, and in the author's experience, preloading with phenobarbital (ie, 30 mg 2 times a day for 3 days) is one method to avoid this unwanted side effect. Propranolol and primidone may result in mild to moderate reduction in the amplitude of tremor in 30% to 70% of patients with essential tremor. If the tremor is mild, it may be abolished.

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Other agents that have been used include topiramate, gabapentin, and benzodiazepines (alprazolam or clonazepam). IM botulinum toxin injections for wrist tremor are also beneficial for some patients.[13]

Deep brain stimulation (DBS) surgery (ventral intermediate nucleus of the thalamus) and gamma knife surgery (thalamus) markedly reduce the severity of the tremor in patients with severe pharmacologically refractory tremor, with reductions in upper limb tremor often of greater magnitude than can be achieved with the use of medication. More recently, focused ultrasound thalamotomy (ventral intermediate nucleus) has demonstrated similar effects, although long-term benefits are not fully known.[14] These surgeries are generally reserved for patients who have failed to adequately respond to appropriate pharmacologic trials.

KEY POINTS

- Neck tremor is always pathologic. It is not a feature of enhanced physiologic tremor.
- Although limb tremor may be present, head tremor should not be a feature of drug-induced action tremor.

Enhanced Physiologic Tremor

This type of action tremor occurs in the hands in virtually all people. The postural and kinetic components of this tremor are generally several hertz faster than those seen in essential tremor, and the amplitude is generally lower than that seen in essential tremor, with the major caveat that at disease onset patients with essential tremor have a low-amplitude tremor that may be difficult to distinguish from enhanced physiologic tremor.[15] In contrast to essential tremor, there is no intentional component on the finger-nose-finger maneuver. Enhanced physiologic tremor may be evident in the voice and hands; however, it is not present in the neck; neck tremor is always pathologic. A mild ratchetlike quality to arm movements or mild cogwheeling during passive arm movement may be present, but this is not accompanied by rigidity. On quantitative computerized tremor analysis, inertial loading reveals a pattern that is consistent with peripherally generated rather than centrally generated tremor (ie, an observed reduction in the primary tremor frequency with inertial loading).

Many of these individuals present to the doctor because they are also anxious; hence, treatment should begin by reassuring them that they do not appear to have either PD or essential tremor. Beta-blockers at a low dose (eg, propranolol up to 60 mg/d or used in a 10-mg to 60-mg dose on an as-needed basis) and judicious use of benzodiazepines may be effective.

Drug-Induced Action Tremor

A variety of medications may produce or exacerbate action tremors, and the severity of these tremors may range from mild to severe (**VIDEO 4-2,** *links.lww.com/CONT/A279*).[16] These medications are inclusive of but not limited to immunosuppressants (eg, cyclosporine), hormones (eg, levothyroxine), antiepileptics (eg, valproic acid), and methylxanthines (eg, theophylline). Several features can differentiate drug-induced action tremor from other forms of action tremor. First, historically, the onset of tremor follows the initiation of the medication. Second, there may be a dose-response relationship such that higher doses of the medication are associated with greater tremor amplitude. Third, discontinuing the medication should ultimately result in complete resolution of tremor. Fourth, head tremor should not be a feature of drug-induced action tremor. Finally, in the setting of a stable medication dose, the tremor should not progressively worsen; this stands in contrast to the tremors of essential tremor or PD, which progressively worsen with time.

The mechanisms that underlie drug-induced action tremors are not fully understood, although these tremors are thought to represent a form of enhanced

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physiologic tremor. Additional evidence also exists that drug-induced action tremor could be mediated through central mechanisms.[17]

The treatment of this type of tremor is to lower the dose of or discontinue the causative medication. When this is not possible, beta-blockers (eg, propranolol, 10 mg/d to 360 mg/d) may be of some benefit.

Dystonic Tremor

A range of tremors may occur among patients who have been diagnosed with dystonia, and a challenging differential is between the diagnosis of essential tremor and the diagnosis of dystonic tremor.[18–20] In patients who have been diagnosed with dystonia, tremor may occur both in limbs that exhibit dystonic postures or movements and in limbs that do not exhibit these. Furthermore, the tremor may occur in limbs at rest as well as in limbs that are active (ie, during sustained posture or during voluntary movements). What complicates matters is that, as noted above, patients with long-standing and clinically advanced essential tremor may develop mild dystonic posturing of the hand during arm extension. As a result, considerable debate exists as to where essential tremor as a disease ends and where dystonia as a disease begins and vice versa. One further point is that the tremor in patients with dystonia is not always regularly recurrent. This raises the issue in these patients as to whether the "tremor" is indeed, in the strictest sense of the word, a tremor. This author sometimes uses the term *tremulous* rather than *tremor* to describe such movements.

With this uncertainly in mind, when a clinician is confronted with an individual patient, several issues should be taken into consideration. First, what

CASE 4-2

A 56-year-old woman presented with a chief complaint of head tremor with some mild associated right-sided neck pain. The pain had begun 10 years previously. For 4 years, she had also felt an intermittent pulling sensation in the neck region. She further noted that her head had been turning to one side and sometimes it even felt a little shaky. She did not report any tremor in her hands.

On examination, she had a mild to moderate postural tremor of the right arm, with a little bit of flexed posturing of her index and middle fingers. On the finger-nose-finger maneuver, no tremor was observable. Her right sternocleidomastoid muscle was slightly hypertrophic, and her head tended to preferentially turn to the left and shake intermittently; the shakiness was irregular. This head tremor persisted even when she lay down on her back on the examining table.

She was treated with IM botulinum toxin injections to several neck muscles, which helped diminish her symptoms, although they did not resolve completely.

COMMENT

This case illustrates several important features of dystonic head (neck) tremor: the tremor is often nonrhythmic, and it often persists in the recumbent position. Furthermore, it may be accompanied by pain or pulling sensations of the neck.

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are the features of the tremor itself? Second, does the patient exhibit dystonic movements or dystonic postures? In terms of the first question, the tremor itself in patients with dystonia may not be rhythmic or oscillatory (VIDEO 4-3, *links.lww.com/CONT/A280*); these features distinguish the tremor from that of essential tremor. In terms of the second question, patients with dystonia may exhibit a variety of sustained postures and/or twisting movements involving the neck, which do not occur in essential tremor. Patients may also exhibit one or more of a variety of dystonic postures during arm extension (eg, difficulty maintaining both hands strictly parallel while outstretched in a karate chop position, thumb flexion during arm extension). These should not occur in essential tremor unless the disease is advanced; furthermore, in essential tremor they should be of mild severity relative to the tremor itself.

Tremor in the neck or voice is another issue worth discussing. Patients with neck dystonia (ie, torticollis) may also have neck tremor. This tremor is generally neither strictly rhythmic nor oscillatory (VIDEO 4-3, *links.lww.com/CONT/A280*), and it may be accompanied by twisting or tilting of the neck, jerklike or sustained neck deviation, hypertrophy of neck muscles, or pulling sensations or pain in the neck (CASE 4-2). These clinical features do not occur in patients with essential tremor. In addition, in contrast to the head tremor of essential tremor, which generally resolves when the patient is lying on his or her back, dystonic head tremor often persists while the patient is recumbent.[21] Voice tremor may also be present in patients with vocal cord dystonia (ie, spasmodic dysphonia) but, in contrast to the voice tremor of essential tremor, is often associated with voice breaks or strangulated speech.

The treatment of dystonic tremor includes the use of medications used to treat dystonia (ie, trihexyphenidyl in a dose up to 10 mg/d in adults, baclofen up to 60 mg/d), benzodiazepines, or beta-blockers. For dystonic neck tremor, other options include IM botulinum toxin injections or DBS surgery.

KEY POINTS

- The tremor in dystonia may be neither rhythmic nor oscillatory.
- Dystonic head tremor often persists after the patient lies on his or her back; this is generally not true of essential tremor.
- Primary writing tremor is a tremor that occurs mainly while writing but not during other tasks that involve the hands.

Primary Writing Tremor

Primary writing tremor is a task-specific tremor that occurs primarily or only during writing and not at all or less so during other tasks that involve the use of the hands.[22] The current definition of primary writing tremor excludes patients who have dystonic postures with hand tremor while writing (ie, dystonic writing tremor). The disorder may be sporadic or inherited as an autosomal dominant trait. Primary writing tremor has a frequency similar to that seen in patients with essential tremor (ie, 4 Hz to 8 Hz), and it is relieved by ethanol consumption in 30% to 50% of patients. The mechanisms that underlie primary writing tremor are unclear; it is debated whether it represents a variant of essential tremor or a variant of focal dystonia, and there are families in which all three conditions are indeed present.[23]

Treatment of primary writing tremor includes the use of propranolol, primidone, and anticholinergic medications (trihexyphenidyl 2 mg/d to 10 mg/d) as well as the use of writing and hand orthotic devices. IM injections of botulinum toxin have exhibited some benefit as well, as has stereotactic surgery in a limited number of patients.[22–24] Finally, some patients switch to writing with the other hand.[23]

Orthostatic Tremor

This is a rare syndrome characterized by unsteadiness on standing and high-frequency tremor in the legs.[25,26] The typical onset is in the sixth decade of life.

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Although most cases are sporadic, rare familial cases have been reported. Patients more often note unsteadiness while standing rather than tremor per se. Because of these symptoms, patients typically avoid situations in which they have to stand still (eg, standing in lines). Indeed, they are eventually forced to sit down or walk after a short time (ie, seconds to minutes), depending on the severity of the disease. As the disease progresses, the tremor may begin to encroach upon the stance phase of walking. On examination, the patient may see or feel a rapid (14 Hz to 16 Hz) fine tremor in the calves. Due to its high frequency and low amplitude, orthostatic tremor may be difficult to appreciate on visual inspection. In some cases, the tremor may be heard when a stethoscope is placed over the affected calf, sounding like a distant helicopter. The EMG indicates the presence of a 14 Hz to 16 Hz synchronous tremor in the leg (especially in calf) muscles. A slower, larger-amplitude tremor may also be superimposed on top of this tremor, perhaps representing a subharmonic of the high-frequency tremor, and this can be more disabling for patients than the faster tremor. Numerous cases occur in the setting of comorbid PD.

The treatment of orthostatic tremor is challenging.[25] Many agents have been used and often to little avail. The most commonly used agents are clonazepam (0.5 mg/d to 4 mg/d), gabapentin (300 mg/d to 1800 mg/d), and carbidopa/levodopa (25 mg/100 mg per day to 250 mg/1000 mg per day). Many other agents have also been tried, including propranolol, primidone, phenytoin, carbamazepine, ethosuximide, baclofen, and acetazolamide, although given the rarity of the disorder no large-scale clinical trials have been conducted. DBS surgery can also provide benefit to some patients.

Cerebellar Tremor

The term *cerebellar tremor* has classically been used to describe tremor that can occur in patients with spinocerebellar ataxias and other classical disorders originating in the cerebellum.[27] In modern times, cerebellar tremor has become equated exclusively with intention tremor.[28] This is a tremor that occurs with goal-directed movement (eg, finger-to-nose maneuver) and worsens when approaching a target. However, cerebellar tremors (ie, tremors of cerebellar origin) do not always present exclusively as intention tremor. Indeed, the clinical phenomenology of tremor of cerebellar origin is heterogeneous, and it extends beyond that of intention tremor to include postural tremor, kinetic tremor, resting tremor, and orthostatic tremor.[28] This heterogeneity is consistent with the seminal work of Holmes,[29] who described a variety of tremors aside from intention tremor in the setting of cerebellar lesions.[30]

On examination, patients with classically defined cerebellar tremor often have other cerebellar signs, including saccadic eye movement abnormalities, dysarthric or scanning speech, gait ataxia, and hypotonia. When these patients are examined, it is important, although often difficult, to separate the tremor (ie, rhythmic oscillatory movements) from problems with force and timing of motion (ie, dysmetria); both may occur during the finger-nose-finger maneuver, but the former generally improves with DBS surgery whereas the latter might worsen.

A number of medications have been used to treat cerebellar tremor, although their efficacy is limited. The most effective treatment for severe cerebellar tremor is thalamic DBS surgery, with the caveat noted above.[31]

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Holmes Tremor

Holmes tremor is also referred to as *rubral tremor* or *midbrain tremor*.[32] In most cases, the tremor is a unilateral and has three components: tremor at rest, postural tremor, and kinetic/intentional tremor, with the relative severity generally being such that kinetic tremor is greater than postural tremor which is greater than resting tremor (VIDEO 4-4, *links.lww.com/CONT/A281*). The tremor is slow (<5 Hz).

In some cases, the tremor is severe and disabling and can render the affected limb functionally useless. Patients generally have other neurologic signs as well, including hemiparesis, cranial nerve abnormalities, ataxia, hypoesthesia, and dystonia involving the same body region as the tremor. The tremor may occur in a variety of clinical settings (eg, in the setting of stroke, head trauma, or a variety of other processes, which can include multiple sclerosis), and when occurring after an infarct, the tremor may arise after a latency of 1 month to 2 years.

On brain imaging, a lesion is often but not always present in the pontine-midbrain region, affecting cerebellar outflow tracts and dopaminergic nigrostriatal fibers,[33] although lesions often occur elsewhere (eg, the thalamus),[32,34] which is one of the motivations for referring to the tremor as *Holmes tremor* rather than *rubral tremor* or *midbrain tremor*.

As the dopaminergic system is involved in most cases, treatment with carbidopa/levodopa (25 mg/100 mg per day to 250 mg/1000 mg per day) has been reported to be beneficial, improving all three components of tremor (ie, resting, postural, and kinetic).[32] In addition, medications that are used for the treatment of essential tremor may be effective in alleviating the postural or kinetic components of the tremor.[32] DBS surgery has proven beneficial in some cases as well, treating all three components of tremor.[32]

Psychogenic (Functional) Tremor

By history, the tremor in patients with psychogenic or functional tremor often has an abrupt beginning with maximal tremor at onset rather than an insidious onset followed by a slowly progressive course, as is typical of many organic tremor disorders.[35] Also, the tremor may fluctuate and have periods of remission.

On examination, the tremor has nonphysiologic or unusual features (eg, the tremor may exhibit variable frequency; the tremor may change direction; or there may be an unusual combination of resting, postural, and kinetic tremors). Positive signs may be seen that are suggestive of psychogenic tremor including entrainment, distractibility, and suggestibility.[35,36] Furthermore, many patients show excessive exhaustion during the examination.[35] Of note, during quantitative computerized tremor analysis, inertial loading may produce a paradoxical increase in tremor amplitude rather than the expected decrease in amplitude that is observed with organic tremors.[37]

The treatment of psychogenic tremor begins with a discussion of the diagnosis, recognition of the patient's symptoms, and a referral to a psychiatrist to explore underlying psychiatric issues. Some evidence exists that cognitive-behavioral therapy is effective.[38]

Wilson Disease With Associated Tremor

Patients with Wilson disease may present with a wide variety of involuntary movements, and common among these is tremor.[39] Tremor is usually

KEY POINTS

- In some cases, orthostatic tremor may be heard when a stethoscope is placed over the affected leg; the tremor makes a sound like a distant helicopter.
- The clinical phenomenology of tremor of cerebellar origin is heterogeneous, and it extends beyond that of intention tremor to include postural tremor, kinetic tremor, resting tremor, and orthostatic tremor.
- Rubral tremor is strikingly asymmetric, and it has resting, postural, and kinetic components.
- Psychogenic tremors often have an abrupt onset.

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accompanied by other neurologic signs, although rare reports exist of isolated tremor and even rarer reports exist of action tremor occurring in isolation.[40]

Although the prototypical tremor of Wilson disease is the wing-beat tremor (ie, a proximal tremor, present while the shoulders are abducted and the arms flexed at the elbows), it is not the most commonly observed tremor in Wilson disease. In actuality, the tremor phenomenology is quite varied. A wide range of tremors may occur, including kinetic, resting, postural, and intention tremors; tremors that are symmetric or asymmetric; those that are low amplitude; others that are of high amplitude; and those that are intermittent whereas others are constant and progressive.[41] Most of the large, published case series dealt with the broad panoply of neurologic signs, and detailed video-based modern characterization of the tremor phenomenology is lacking. According to one series, 32% of patients exhibited tremor at the time of their initial presentation to a tertiary care center[41]; in another report, 60% of patients exhibited tremor at some point.[42] Tremor most commonly occurs in the arms or hands, with one study reporting 72% of patients having such a tremor[39] and another study reporting 82% of patients with this tremor type.[43]

Most patients present well before the age of 40 years, and the laboratory workup may reveal a low serum ceruloplasmin level, an abnormal brain MRI (hyperintensity on T2-weighted and fluid-attenuated inversion recovery [FLAIR] images is characteristically present in the putamen, the most commonly involved structure in the basal ganglia, followed by the striatum and globus pallidus), a high 24-hour urine copper concentration, an abnormal slit-lamp examination (ie, presence of Kayser-Fleischer rings), or elevated liver function tests.[44]

Treatment with D-penicillamine, zinc, or trientine is recommended; little has been written about the specific treatment of tremor as a neurologic sign.

Fragile X Tremor-Ataxia Syndrome

Fragile X tremor-ataxia syndrome (FXTAS) is an inherited degenerative disorder that is associated with a broad range of neurologic symptoms and signs. The syndrome, which primarily affects older men, is caused by a CGG repeat expansion in the premutation range in the 5′ noncoding region of the fragile X mental retardation 1 (*FMR1*) gene.

As evident from the name of the disease, the core signs of FXTAS are tremor, ataxia, and cognitive symptoms. Aside from intention tremor (noted in 70% of patients in a series of 20),[45] kinetic and postural tremors are reported to be common findings in patients with FXTAS,[46] and these have variable severity; unfortunately, their relative prevalence has not been well documented. It deserves mention that, aside from these action tremors, resting tremor occurs in these patients as well. In one of the initial articles on FXTAS, Jacquemont and colleagues[45] described the clinical spectrum of 20 patients, and they documented the presence of resting tremor (in 10% of patients) in addition to the commonly observed intention tremor (in 70% of patients).

Controlled trials evaluating symptomatic therapies for tremor have not been reported in FXTAS. However, therapies used to treat similar tremors in patients with essential tremor and PD have been tried with variable success; furthermore, surgical therapy is effective for tremors associated with essential tremor and PD and is an option for patients with FXTAS who have medication-resistant and disabling tremors.[47]

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Peripheral Neuropathy-Related Tremor

Patients with several of the acquired and familial neuropathies may exhibit mild-to-moderate postural and kinetic tremors of the arms.[48,49] For some of these neuropathies, such as IgM demyelinating paraproteinemic neuropathy, up to 90% of patients have been noted to exhibit such a tremor.[50] These patients have a coexisting peripheral neuropathy in the same limb that is tremulous. The neuropathy and the tremor should be temporally linked, with tremor accompanying or following the onset of neuropathy.

On examination, a peripheral neuropathy characterized by weakness, wasting, or diminished/absent deep tendon reflexes is readily apparent in the tremulous arm or arms. Although the severity of neuropathy correlates with the presence of tremor,[49] the severity of neuropathy does not necessarily correlate with the severity of the tremor.[51] The tremor disappears if neuropathic weakness progresses to the point of paralysis.

The underlying mechanisms are likely to be diverse and may involve both central and peripheral components.[52] If the tremor occurs in the setting of an immunoglobulin-mediated disease, then immunosuppressive or immunomodulatory therapies, such as corticosteroids, IV immunoglobulin (IVIg), or plasma exchange may be used. Several studies report the use of pregabalin (up to 450 mg/d) for the treatment of neuropathic tremor.[48] The tremor may respond to IM botulinum toxin injections[53] and to DBS surgery.[54]

RESTING TREMOR

Entities that cause resting tremor are fewer than those that can cause kinetic tremor. The main entities are PD and drug-induced tremor.

Parkinson Disease

Tremor in patients with PD is classically a tremor at rest. The resting tremor is generally asymmetric, affecting one side of the body (ie, arm, leg, or both) preferentially; it typically begins in one limb. In patients with upper limb tremor, the tremor typically involves distal joints (eg, fingers and wrist) rather than proximal joints (eg, elbow or shoulder). Aside from the arms, tremor may affect the jaw, although in contrast to essential tremor, it is more often noted when the patient's mouth is closed and relaxed rather than while the patient is speaking. In patients with PD, tremor rarely affects the head.

The treatment of parkinsonian resting tremor includes the use of anticholinergic agents (trihexyphenidyl 2 mg/d to 10 mg/d), amantadine (up to 300 mg/d), as well as carbidopa/levodopa (up to 500/2000 mg/d of carbidopa/levodopa), dopamine agonists, and rasagiline.[55,56] DBS surgery for tremor is reserved for patients with PD who have severe tremor and who are refractory to medications. Although resting tremor is one of the hallmark features of PD, a large proportion of patients also have postural or kinetic tremor (or both) of the arms. Sometimes the postural and kinetic tremors have a reemergent quality; this so-called "reemergent tremor" surfaces after a latency of 1 or several seconds, has a frequency that is similar to that of the resting tremor in PD, and often attains amplitudes greater than that seen in patients with essential tremor (VIDEO 4-5, *links.lww.com/CONT/A282*).[57] This tremor tends to increase in severity (ie, it crescendos) with sustained posture or during the course of repetitive movements during which much of the limb is immobile (eg, while pouring water between two cups, during which much of the movement is proximal rather than distal).

KEY POINTS

- Wing-beat tremor is considered a classic tremor in Wilson disease, but it is not the most common type of tremor in that disease.
- Although intention tremor is common in patients with fragile X tremor-ataxia syndrome, kinetic, postural, and resting tremors may also occur.
- The resting tremor in Parkinson disease is generally asymmetric.
- In contrast to essential tremor, the jaw tremor of Parkinson disease is more often noted when the patient's mouth is closed and relaxed rather than while the patient is speaking.

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The treatment of this type of tremor is similar to the treatment of the resting tremor of PD, although it is less responsive to medications than resting tremor.

Drug-Induced Resting Tremor

Several medications (eg, dopamine-blocking agents [eg, haloperidol] or dopamine-depleting agents [eg, tetrabenazine]) may cause resting tremor, which is generally accompanied by other features of parkinsonism, such as bradykinesia and rigidity. The tremor generally resembles a typical parkinsonian resting tremor and may even be asymmetric, affecting one arm more than the other.[58] As with other parkinsonian tremors, the tremor may have a reemergent component as well. By the patient's history, the medication use should precede the onset of the tremor, and there may be a dose-effect relationship. Unless there is an underlying disease of the basal ganglia, stopping use of the medication should result in complete resolution of tremor, although this may take weeks to months; rarely, it may take up to 1 year.[59]

The treatment of such tremor first involves the discontinuation of the causative drug or a reduction in dosage if this is possible; although often in the setting of a brittle underlying psychiatric problem, this is not possible.[60] Carbidopa/levodopa, amantadine, and anticholinergic agents (see dosages above) may lessen the severity of this type of tremor and may even be used with the tremor-producing medication if the latter cannot be discontinued.

CONCLUSION

Tremors are among the most common movement disorders. The diagnosis of these disorders is challenging. The approach to a patient with tremor involves a history and careful neurologic examination focused on the nuances of clinical phenomenology. When generating the differential diagnosis, it is important to first consider whether the primary type of tremor is an action tremor or a resting tremor. As is true for the diagnosis of most disorders of involuntary movement, arriving at the correct diagnosis is often based on pattern recognition.

VIDEO LEGENDS

VIDEO 4-1
Essential tremor. Video shows a man with essential tremor exhibiting a severe kinetic tremor while pouring water between two cups. The tremor is slightly asymmetric and is worse on the right.
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VIDEO 4-2
Drug-induced action tremor. Video shows a man with drug-induced action tremor due to lithium exhibiting both a postural and a kinetic tremor of mild to moderate amplitude.
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Courtesy of Amar Patel, MD.
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VIDEO 4-3
Dystonic tremor. Video show a man with dystonic tremor exhibiting a tremor in the neck that is neither rhythmic nor oscillatory.
links.lww.com/CONT/A280

Courtesy of Sule Tinaz, MD, PhD, and Sara Schaefer, MD.
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VIDEO 4-4
Holmes tremor. Video show a woman with Holmes tremor exhibiting a unilateral, slow tremor at rest, which worsens during sustained posture.
links.lww.com/CONT/A281

Courtesy of Sule Tinaz, MD, PhD.
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VIDEO 4-5
Parkinson disease tremor. Video shows a woman with Parkinson disease exhibiting a resting tremor, primarily on the left, while seated. A reemergent tremor is apparent, emerging after several seconds and then worsening, as she holds her arms in front of her body.
links.lww.com/CONT/A282

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