

PRIMER

A patient with tremor, part 2: from diagnosis to treatment

Hrishikesh Kumar MD DM, Mandar Jog MD

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Tremor is one of the most common movement disorders seen in the community. A wide variety of disorders can present with tremor, and a methodic approach is needed to evaluate possible causes. The following descriptions of prototypical presentations of tremor will use the approach described in part 1 of this series and highlight the typical presentation of individual conditions.¹

Case 1

A woman in her mid-30s presented with fine tremor of the hands of six months' duration. She also reported increased appetite, progressive loss of weight and palpitations. Examination showed wide-eyed, staring gaze, tachycardia, dry, warm extremities and symmetric postural tremor of the hands.

Approach

The patient had rhythmic, involuntary oscillations (tremor) of both upper limbs, predominantly involving her wrists and the distal portions of her fingers, present during activities (kinetic tremor) and outstretching of hands (postural tremor). The tremor had high frequency and small amplitude. There was neither entrainment nor change on distraction. Associated signs suggested thyrotoxicosis.

Diagnosis

Enhanced physiologic tremor, related to thyrotoxicosis, was diagnosed. The term enhanced physiologic tremor encompasses the reversible tremor caused by anxiety, caffeine, drugs, alcohol, withdrawal of drugs or alcohol, and metabolic and endocrine disorders. Amiodarone, amphetamines, β -adrenergic agonists, lithium, thyroid hormones, tricyclic antidepressants and valproic acid are commonly used drugs that can enhance physiologic tremor. This tremor is believed to result from an enhanced form of central oscillations that are also seen in healthy

people and hence is called enhanced physiologic tremor. The tremor frequency band of 8–12 Hz is similar to that of the physiologic tremor. Easy visibility of the tremor, postural nature and no evidence of underlying neurologic disease are the defining features of this entity. Enhanced physiologic tremor is quite common, but it is only physiologic tremor becoming more evident in specific situations. No prevalence study of enhanced physiologic tremor is available, probably because of the tremor's transient nature.

Treatment

Treatment of enhanced physiologic tremor involves correction of the underlying disorder.

Case 2

A 77-year-old woman presented with a 20-year history of tremor involving both her hands (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.101598/-/DC1). For the past two years, the tremor in her hands had worsened, and she had noticed some tremor in her head. Her family had noticed that her voice had become "tremulous" or "shaky" during the past year. The tremor in her hands was present during

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Correspondence to:

Dr. Hrishikesh Kumar, rishi_medicine@yahoo.com

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KEY POINTS

- An etiologically focused diagnostic method is helpful in determining the diagnosis in a patient presenting with tremor.
- Asymmetric resting tremor is the hallmark of Parkinson disease, but those affected may also have associated postural tremor.
- Essential tremor is usually monosymptomatic and is characterized by symmetric postural tremor.



See the following videos online:

Appendix 1: Essential tremor.

Appendix 2: Tremor in Parkinson disease.

Appendix 3: Dystonic tremor.

Appendix 4: Primary writing tremor.

www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.101598/-/DC1

rest, but was more pronounced when she held something in her hands or when she outstretched her arms. Her handwriting had deteriorated over time. General, systemic and neurologic examinations were normal. The finger–nose test was negative for intention tremor, and there was no bradykinesia or rigidity. She had noticed some improvement in the tremor with intake of alcohol. She reported that several members of her family also had shaky hands.

Approach

The patient had rhythmic, involuntary oscillations of both upper limbs, predominantly involving her wrist and the distal portions of her fingers. It increased on outstretching of hands (postural tremor) and during activities (kinetic tremor). It was of moderate frequency and amplitude. There was neither entrainment nor change on distraction. Tremor of the head and vocal tremor were also present. The tremor was very slowly progressive (over decades), monosymptomatic and sensitive to alcohol. Family history was suggestive of autosomal dominant mode of inheritance.

Diagnosis

Essential tremor was diagnosed. In all age groups, the estimated prevalence of essential tremor is 0.4%–0.6%, but the prevalence increases to more than 4% in people over 60 years of age.² The diagnosis was suggested by the monosymptomatic nature, extremely slow progression, predominant postural tremor, autosomal dominant mode of inheritance and sensi-

tivity to alcohol. This patient had a positive family history, but more than 50% of patients with essential tremor may not report any family history.³ In some patients, impaired tandem walking, dysarthria and intention tremor may be observed.³ As compared with enhanced physiologic tremor, essential tremor has lower frequency but higher amplitude.

Essential tremor is characterized by both postural and kinetic tremor, but those affected may have associated resting tremor. On the other hand, patients with Parkinson disease frequently have postural tremor in addition to the hallmark resting tremor. As a result, it may be difficult to differentiate tremor in Parkinson disease from essential tremor (Table 1).^{3,4} A practical way to separate parkinsonian tremor from essential tremor is to examine the patient during target-directed movements, as in the finger–nose test or heel–knee–shin test. In instances of Parkinson disease, the amplitude of tremor diminishes during these tests, but in instances of essential tremor, the amplitude of tremor will remain the same or will increase.

Another helpful manoeuvre is to ask the patient to count backward or to move another body part. Resting tremor in instances of Parkinson disease usually increases during the manoeuvre but does not change in instances of essential tremor. Finally, when a patient with Parkinson disease outstretches his arms, postural tremor appears after a few seconds of latency (Appendix 2, www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.101598/-/DC1). In a patient with essential tremor, the postural tremor

Table 1: Differentiation between tremor in Parkinson disease and essential tremor ^{3,4}		
Characteristic	Parkinson disease	Essential tremor
Age at onset	Usually ≥ 50 yr	Bimodal distribution, peaks during teenage years and during the fifth decade
Family history	Only in a minority of patients (about 1%)	30%–50%
Characteristics of tremor		
• Predominant type	Resting tremor is more pronounced than the postural or kinetic component	Postural and action components dominate
• Symmetry	Asymmetric	Often symmetric
• Frequency	Slower (4–8 Hz)	Faster (4–12 Hz)
• Progression	Progressive	Very slowly progressive or stable
• Body parts or functions involved	Hands, legs, head, jaw	Hands, head, trunk, voice
• Latency	A few seconds	None
Treatment	Levodopa, dopamine agonist, anticholinergic agent	β-blocker, primidone

appears immediately on outstretching the arms (Appendix 1). Despite these diagnostic pointers, it is sometimes difficult to differentiate between instances of essential tremor and tremor in Parkinson disease. Long-term follow-up of these patients provides valuable information. In instances of Parkinson disease, signs like bradykinesia, rigidity, gait and postural abnormalities appear with time.

Treatment

Propranolol and primidone are the first-line options for treatment of essential tremor. Clonazepam, gabapentin and topiramate are other options that can be used as add-on treatment, or when the first-line medications were ineffective or could not be tolerated. Many open-labelled and double-blind case-control studies have shown the efficacy and safety of propranolol and primidone.^{5,6} In a double-blind, randomized crossover study, no significant difference in efficacy was found between propranolol and primidone.⁷ Some open-labelled studies have shown a response of essential tremor to clonazepam, but double-blind, controlled trials could not substantiate this response.⁸ Double-blind, placebo-controlled studies of gabapentin and topiramate in essential tremor have shown conflicting results.^{9,10}

Injection of botulinum toxin and surgical treatment with thalamic deep brain stimulation are other options for treatment in severe, medically refractory instances of essential tremor. Most of the evidence that supports these interventions comes from isolated case reports and case series. Brin and colleagues, in a placebo-controlled, double-blind study, found that treatment with botulinum toxin improved postural but not kinetic tremor of hands, resulting in limited functional efficacy.¹¹ Medically refractory tremor of the hands may respond to injection of botulinum toxin, as shown by Pahwa and coauthors in a double-blind study.¹² Thalamic deep brain stimulation carries a 1%–2% risk of cerebral bleeding and a small long-term risk of problems with speech and gait.¹³

Case 3

A man in his late 60s presented with a several-year history of unsteadiness and feeling of “internal shaking of legs,” only while standing. When he walked, his initial steps were unsteady with a wide-based gait, and he often groped for support. After the initial few steps, he was able to walk normally. No tremor was visible, but on palpation of his legs in the standing position, a fast tremor was felt to be present. Surface elec-

tromyography showed 16 cycles/s of low-amplitude tremor.

Diagnosis

Primary orthostatic tremor was diagnosed. This type of tremor is very rare; however, no prevalence data are available. Primary orthostatic tremor is present only when the patient is standing. Because it has a fine amplitude, it can be more easily palpated than seen. It has a characteristic high frequency in the range of 13–16 Hz.¹⁴ Tracings on surface electromyography done with the patient in the standing position show this characteristic frequency. The patient may not be aware of the tremulousness, and the problem of stance and gait may be the only symptom. It may be mistaken as ataxia or freezing of gait. Unlike ataxia or freezing, however, the problem with gait is present only during the initial few steps. Patients with primary orthostatic tremor rarely fall. If falls are the prominent symptom, alternative or associated diagnoses should be sought.

Treatment

In general, response of primary orthostatic tremor to treatment is unsatisfactory, but patients are often relieved to know the diagnosis. Isolated instances of successful response to clonazepam, clozapine, primidone, phenobarbital, levodopa, pramipexole and sodium valproate have been reported.¹⁴ Propranolol and alcohol are usually ineffective. A double-blind, placebo-controlled, crossover trial reported a 50%–70% reduction in symptoms during treatment with gabapentin in four instances of primary orthostatic tremor.¹⁵ Instances of successful treatment of medically refractory orthostatic tremor by thalamic deep brain stimulation have been reported.¹⁶

Case 4

A 36-year-old woman who was otherwise healthy presented with a three-year history of tremor of the head and neck (Appendix 3, www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.101598/-/DC1). It had gradually progressed and was associated with a sensation of aching and pulling of the neck. She also complained of abnormal involuntary posturing of the neck. Close observation of the posture of the neck suggested a mixture of extension (retrocollis), tilt toward left (left laterocollis) and turn toward right (right torticollis). The tremor was most severe when she flexed her neck with a tilt toward the right, and it reduced when she extended her neck with a tilt toward the left. Touching the chin resulted in reduction in tremor and partial straightening of her neck (sensory trick or geste antagoniste).

Diagnosis

Dystonic tremor was diagnosed. This tremor's true prevalence is difficult to estimate, but we believe this type of tremor is very rare. Abnormal involuntary posturing of the neck, presence of null point (reduced tremor at a specific position of neck) and sensory tricks (touching the chin reduced tremor and posturing) suggested the presence of cervical dystonia. Tremor is often observed in patients with dystonia and is called dystonic tremor if the dystonia and tremor affect the same body part. Unlike other tremors, dystonic tremor can be jerky and irregular, as seen in this patient.¹⁷

Treatment

Injection of botulinum toxin is the most effective treatment for cervical dystonia and associated dystonic tremor. A Cochrane systematic review concluded that injection of botulinum toxin type-A provided more objective and subjective benefit than trihexyphenidyl (an anticholinergic) to patients with cervical dystonia.¹⁸ The efficacy and safety of botulinum toxin have been shown in several double-blind, controlled, open-labelled trials. Overactive muscles for injection of botulinum toxin are identified by observing the position of the head and by palpation of individual neck muscles.

Case 5

A patient in late 40s presented with shaking of the hands while writing (Appendix 4, www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.101598/-/DC1). The problem had started several years before presentation and gradually progressed. There were no other neurologic symptoms. The patient was able to perform other tasks involving the hands without difficulty.

Diagnosis

Primary writing tremor was diagnosed. Primary writing tremor is a task-related tremor. This tremor is divided into type A (task-specific) when the tremor appears only during the task of writing and type B (position-specific) when the tremor also appears when the hand assumes the position as if performing the task.¹⁹ This patient had type-A (task-specific) tremor, because there was no tremor on assuming the position simulating the act of writing. This type of tremor is very rare; however, no prevalence data are available.

Treatment

Injection of botulinum toxin in long flexors and extensors of fingers have been shown to be useful in isolated case reports and open-labelled trials.²⁰

Case 6

A man in his mid-70s with diabetes and hypertension had acute-onset tremulousness of his right arm. The tremor was slow and of high amplitude, and present during both rest and activities. The tremor was predominantly proximal and had the appearance of wing-flapping. Several months before the onset of tremor, he had acute-onset weakness of his right side that recovered spontaneously. Magnetic resonance imaging of the brain showed an ischemic lesion in the left half of the midbrain.

Diagnosis

Holmes tremor was diagnosed. This tremor is very rare, and we are unaware of any study describing its prevalence. This type of tremor has both resting and intention components, and the tremor can be nonrhythmic. These tremors are slow, usually less than 4–5 Hz, and of high amplitude. If proximal, the appearance is similar to that of a beating wing. Holmes tremor usually results from lesions of the brainstem, cerebellum or thalamus. A variable delay of four weeks to two years between the lesion and the first occurrence of the tremor is typical.

The consensus statement of the Movement Disorders Society on tremor has preferred to use the term Holmes tremor over traditional terms such as rubral tremor, midbrain tremor, thalamic tremor and myorhythmia.¹⁹ Data from pathoanatomic and positron emission tomography studies suggest combined involvement of the dopaminergic and cerebellothalamic systems in patients with Holmes tremor.²¹ This explains the simultaneous presence of resting and intention tremor.

Treatment

Isolated reports have shown improvement in Holmes tremor with levodopa, propranolol, clonazepam, levetiracetam and thalamic surgery, but treatment of this type of tremor remains unsatisfactory.

Case 7

A man in his mid-20s presented with slowly progressive gait disorder, dysarthria, cognitive decline and tremor of his upper limbs and trunk. Examination showed square-wave jerks (inappropriate saccadic eye movements that take the eyes off the target and are followed by corrective saccades), hypermetric saccades, ataxic dysarthria and positive finger–nose and knee–heel–shin tests. Magnetic resonance imaging of the brain showed mild cerebellar atrophy. Results of a urinary copper study were normal,

and results of genetic testing for Friedreich ataxia were negative. His serum vitamin E level was very low.

Diagnosis

Cerebellar tremor related to ataxia with vitamin E deficiency was diagnosed. This tremor's true prevalence is difficult to estimate, but we believe this type of tremor is very rare. The patient had intention tremor, which is often characteristic of a cerebellar lesion. He also had oculomotor cerebellar signs (square-wave jerks, hypermetric saccades) along with signs and symptoms of ataxia of the gait and limbs.

Postural tremor found in essential tremor occasionally appears to be more prominent when the patient reaches toward a target and can be mistaken as intention tremor. However, in contrast to patients with cerebellar disorders, patients with essential tremor do not miss the target. Furthermore, cerebellar tremor is slower than essential tremor, with frequency less than 5 Hz. In a young patient with tremor and ataxia, screening for copper overload and vitamin E deficiency, genetic studies and neuroimaging may be warranted.

Treatment

The treatment for ataxia with vitamin E deficiency is lifelong, high-dose (20–40 mg/kg) oral supplementation with vitamin E.²²

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Affiliation: From the Movement Disorders Program, Division of Neurology, University of Western Ontario, London, Ont.

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