Orthostatic Tremor
Overview

- History
- Assessment
- OT and OT PLUS
- Treatment
- Pathophysiology
General characteristics

- A bilateral leg tremor leading to unsteadiness when standing that is relieved when sitting or walking
History

- Coined in 1984 by Dr. Heilman
- No population incidence info available
- Most patients first develop OT around 60 years of age, (range from 13 to 85 years)
- Typically sporadic, but family history of “tremors” found in 50% of patients
- Diagnosis delayed by an average of 8 years
The tremor spectrum

**Tempo**

Rhythmic: PD, ET tremor, orthostatic tremor
Arrhythmic: myoclonus, dystonic tremor

**Frequency**

Slower: rubral tremor
Faster: essential tremor
Fastest: orthostatic tremor

**Amplitude**

Large: essential tremor, rubral tremor
Fine: orthostatic tremor, physiological tremor

**Position**

At rest:
Parkinsonian tremor

During posture:
Physiological tremor, Drug-induced tremor, essential tremor, some cerebellar and dystonic tremors

With action:
Cerebellar tremor, essential tremor, dystonic tremor

Standing:
orthostatic tremor
orthostatic myoclonus
# Tremor Disorders

## Table 2: Tremors and Their Characteristics

<table>
<thead>
<tr>
<th>Tremor Disorder</th>
<th>Rest</th>
<th>Postural</th>
<th>Action</th>
<th>Frequency</th>
<th>Average Age of Onset</th>
<th>Family History</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebellar tremor</td>
<td>-</td>
<td>+</td>
<td>+++</td>
<td>2-5 Hz</td>
<td>Variable</td>
<td>Variable</td>
<td>May be severe with action</td>
</tr>
<tr>
<td>Drug-induced tremor</td>
<td>+/-</td>
<td>++</td>
<td>+</td>
<td>Variable</td>
<td>None</td>
<td>None</td>
<td>Improves with drug discontinuation</td>
</tr>
<tr>
<td>Dystonic tremor</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>Irregular, 3-8 Hz</td>
<td>Adulthood</td>
<td>Variable</td>
<td>Irregular</td>
</tr>
<tr>
<td>Essential tremor</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>6-8 Hz or 8-12 Hz</td>
<td>Early adult</td>
<td>Common</td>
<td>Usually slightly asymmetric, involves hands most commonly.</td>
</tr>
<tr>
<td>Orthostatic tremor</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>10 Hz or 14-16 Hz</td>
<td>Late</td>
<td>Rare</td>
<td>Occurs only on standing still</td>
</tr>
<tr>
<td>Palatal tremor</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>1-4 Hz</td>
<td>Variable</td>
<td>Rare</td>
<td>EPT* may be accompanied by a click; SPT* may persist in sleep</td>
</tr>
<tr>
<td>PD tremor</td>
<td>+++</td>
<td>+</td>
<td>+/-</td>
<td>4-9 Hz</td>
<td>Middle age</td>
<td>Occasional</td>
<td>Variable in appearance; improves with levodopa in 60% of individuals</td>
</tr>
<tr>
<td>Physiological tremor</td>
<td>-</td>
<td>++</td>
<td>+</td>
<td>8-12 Hz</td>
<td>Childhood</td>
<td>Common</td>
<td>Present in all individuals</td>
</tr>
<tr>
<td>Post-traumatic tremor</td>
<td>+/-</td>
<td>++</td>
<td>++</td>
<td>Variable</td>
<td>None</td>
<td>None</td>
<td>Appearance varies with site of trauma. Myoclonus frequently present.</td>
</tr>
<tr>
<td>Rubral tremor</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>2-5 Hz</td>
<td>Variable</td>
<td>None</td>
<td>Large amplitude</td>
</tr>
<tr>
<td>Task-specific tremor</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>4-7 Hz</td>
<td>Adulthood</td>
<td>Occasional</td>
<td>Tremor with task or task-associated position.</td>
</tr>
</tbody>
</table>

References: Biary\(^{27}\), Deusch\(^{20, 29}\), Eible\(^{21, 26}\), Grosse\(^{30}\), Hailman\(^{31}\), Koller\(^{32}\), Miles\(^{33}\), Orti-Pareja\(^{34}\), Schneider\(^{36}\)
OT patients usually report a feeling of unsteadiness during stance without problems when sitting and lying. However, they rarely report tremor sensation or leg pain as a presenting symptom.

Many patients try to reduce the feeling of unsteadiness by standing with a widened stance and clawing the floor with their toes.

On occasion, it may start suddenly with position changes, from sitting to standing and vice versa. Other patients with milder OT may have to stand still for several minutes in order for the symptoms to appear. (latency)

It is characteristic that the symptoms of OT decrease markedly on sitting, walking, or when leaning against a wall.
Assessment

- The need to sit down or to walk can be so disturbing that patients express that they tend to avoid situations in which they have to stand still for a long period, such as taking a shower, waiting in line, or standing at a kitchen counter to prepare a meal.

- In these situations, the patients usually try to alternate weight from one leg to the other, walk in place, or lean on an object such as a chair or a countertop.

- Auscultation using a stethoscope of the gastrocnemius muscles can sometimes reveal a characteristic of barely audible noise akin to the sound of distant rotor blades of a helicopter.
Neurophysiological recording by the presence of a fast tremor of 13–18 Hz in the legs, trunk, and, sometimes, the arms, which is coherent in all muscles studied.
No neurologist? No problem!

- An electrocardiogram recorded in the standing position could also be a simple non-invasive tool to screen for or to support the clinical diagnosis of OT.

- In this sense, Littmann et al reported a patient with OT in whom telemetry strips while standing revealed continuous gross 13–18 Hz of oscillatory artifact.
Fast Fourier Transform of Orthostatic Tremor Accelerometer Recordings. Tremor was recorded from the lower leg using a smartphone placed in the patient’s sock. There is a 16.4 Hz Y-axis peak present in both legs, a feature characteristic of orthostatic tremor.
Apart from in the legs, tremor is often present in other areas such as the hands, cranial muscles, and even the trunk.

In fact, only a small proportion of patients have isolated leg tremors.

Most OT patients have such postural tremor, with the proportion ranging from 77.4% to 92.3%.

Orthostatic tremor in the arms may manifest if the patient is examined while he or she is on all fours.

Most cases of OT are idiopathic, with normal brain neuroimaging, normal laboratory work-up, and no evidence of other associated conditions.
Associations

- non-tumoral aqueduct stenosis
- relapsing polyradiculoneuropathy
- head trauma
- pontine and midbrain lesions
- cerebellar degeneration
- spinal cord lesions
- paraneoplastic syndrome associated with small cell lung cancer
- stiff-person syndrome
- multiple sclerosis
- Graves’ disease
- biclonal immunoglobulin (Ig)G and IgA lambda gammopathy
- thiamine deficiency
- vitamin B12 deficiency
- recreational use of solvents
No studies to assess mortality

Progression studies are few. Measured by “time patient can stand still”

Tremor initially only involves the leg muscles and then spreads proximally to involve the trunk and arm muscles
DDx

- ET with leg involvement
- Orthostatic Myoclonus
There have been a few reports of patients whose OT was associated with other movement disorders, mainly parkinsonism and specifically Parkinson’s disease.

Of the 41 patients included in the clinical series by Gerschlager et al., 5 other additional neurological features were evident in 10 patients. Specifically, six had parkinsonism (four had typical Parkinson’s disease, one vascular parkinsonism and restless leg syndrome, and one had drug-induced parkinsonism).

Of the remaining four patients, two also had restless leg syndrome, one had tardive dyskinesia of uncertain etiology, and one had orofacial dyskinesias of uncertain etiology.
Psychological Burden of Disease

1) SF-36 and the Beck Depression Inventory to measure health-related quality of life and depression, respectively, in 20 OT patients.

All dimensions of the SF-36 were markedly reduced in OT patients and depression was found in 11 out of 20 patients.

2) Using a modified Parkinson’s disease questionnaire (PDQ-39), observed in five OT patients that mobility, activities of daily living, bodily discomfort, emotional wellbeing, and cognition dimensions were domains that were affected in patients with OT, and these problems improved slightly with gabapentin.

Overall, these two studies suggest that OT strongly impacts on health-related quality of life.
Management

- Of all the medications, clonazepam is probably the first-line medication in the treatment of primary and secondary OT.
- This drug reduces tremors in about one-third of people who have the disorder. In some patients, it eliminates tremor almost entirely.
- Unlike essential tremor, OT does not improve either with alcohol or propranolol.
<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Clinical Efficacy</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonazepam</td>
<td>0.5–6 mg/day</td>
<td>+++</td>
<td>Documented effect</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>300–2400 mg/day</td>
<td>++</td>
<td>Documented effect</td>
</tr>
<tr>
<td>Levodopa</td>
<td>300–800 mg/day</td>
<td>++</td>
<td>Only short-term benefit</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>0.75 mg/day</td>
<td>+</td>
<td>Anecdotal effect</td>
</tr>
<tr>
<td>Primidone</td>
<td>125–250 mg/day</td>
<td>+</td>
<td>Anecdotal effect</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>500–1000 mg/day</td>
<td>+/-</td>
<td>Anecdotal effect</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>400 mg/day</td>
<td>+/-</td>
<td>Anecdotal effect</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>100 mg/day</td>
<td>+/-</td>
<td>Anecdotal effect</td>
</tr>
<tr>
<td>Intravenous immunoglobulin$^1$</td>
<td>2 g/kg over 3 days</td>
<td>+</td>
<td>Anecdotal effect</td>
</tr>
<tr>
<td>Propanolol</td>
<td>120 mg/day</td>
<td>–</td>
<td>Without effect</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>3000 mg/day</td>
<td>–</td>
<td>Without effect</td>
</tr>
<tr>
<td>Botulinum toxin</td>
<td>200 mU in the tibialis anterior bilaterally</td>
<td>–</td>
<td>Without effect</td>
</tr>
<tr>
<td>Alcohol</td>
<td>–</td>
<td>–</td>
<td>Without effect[1]</td>
</tr>
</tbody>
</table>

$^1$It was used in a case of slow orthostatic tremor associated with a novel antineuronal antibody.\(^9^3\)
Deep Brain Stimulation (DBS)
Deep Brain Stimulation of the Ventral Intermediate Nucleus of the Thalamus in Medically Refractory Orthostatic Tremor: Preliminary Observations

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PATHOPHYSIOLOGY
Tremors

- Circuits
- Location of oscillator(s)
Superior cerebellar peduncle (SCP), the contralateral red nucleus (RN), and VA/VL of the thalamus to various cerebral areas including the motor cortex (MC), the prefrontal cortex (PFC), the parietal cortex (PC), and the temporal cortex (TC).
Cerebellar outflow (dentato-rubro-thalamic) pathways are the target of deep brain stimulation, which may be effective in treating OT.

Further, functional connectivity between the lateral cerebellum and the supplementary motor area was abnormally increased in OT patients, and correlated positively with tremor severity.
Tractograms built off the data from diffusion tensor imaging
Where is the oscillator in primary OT? Akin to ET, it has been postulated that a central oscillator is perhaps the prime generator of tremor in primary OT.

This idea has largely been based on observations from electrophysiological studies. Koster et al. performed spectral analysis of EMG recordings from all of the affected muscles in six patients with primary OT, and revealed a high level of coherence. This high intermuscular coherence between all muscles suggests the existence of a unique central oscillator, which generates tremor.
Where’s the oscillator?

Accumulating evidence suggests that OT is a disease of the cerebellar and/or cerebellar system. For example, in a recent clinical series of 18 OT patients, careful clinical examination revealed that at least mild cerebellar ocular motor dysfunction such as saccadic smooth pursuit was found in all the patients with most of them also showing different forms of nystagmus and with 14 out of 18 showing additional ataxia of at least one limb.

Also, compared with healthy volunteers, gray matter volume in OT patients was 1) increased in the cerebellar vermis and correlated positively with the duration of the standing position; and 2) increased in the supplementary motor area and decreased in the lateral cerebellum, which both correlated with the disease duration.

One positron emission tomography study of four OT patients revealed bilateral activation of the cerebellar hemispheres as well as activation of the cerebellar vermis, thalamus, and lentiform nucleus.
Supporting studies

- fMRI: Reduced connectivity between cerebellar hemispheres and supplementary motor area
- Using MRSpect, Reduced NAA (N-Acetyl Aspartate) in cerebellar vermis, cerebellar white matter, and mid-parietal gray matter
Dopaminergic Involvement?

- Katzenschlager et al
- SPECT
- OT: 11 PD: 12 Controls: 12
- Striatal tracer binding in OT was significantly lower than that in controls and higher than that in PD, suggesting deficits in the dopaminergic system in OT
Orthostatic tremor

- Altered cerebello-thalamo-cortical network
- Neuro-degeneration
- Central oscillatory network
- Dopaminergic deficit
References

Clinical Overview of Movement Disorders
Michael S Okun et al

Orthostatic Tremor: An Update on a Rare Entity
Julia’n Benito-Leo’n et al

Orthostatic tremor: A review of 45 cases
Toby C. Yaltho et al

Deep Brain Stimulation of the Ventral Intermediate Nucleus of the Thalamus in Medically Refractory Orthostatic Tremor: Preliminary Observations
Alberto J. Espay et al

Smartphone Apps Provide a Simple, Accurate Bedside Screening Tool for Orthostatic Tremor
Danish Bhatti et al

Orthostatic tremor: a cerebellar pathology?
Ce´ cile Gallea et al