

Orthostatic tremor – a review

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INTRODUCTION

The term “orthostatic tremor” (OT) was first coined by Heilman in 1984, although an earlier Italian description of the condition was made in 1970 by Pazzaglia and coworkers. OT is considered a rare condition. It is an intriguing movement disorder characterized by debilitating unsteadiness on standing accompanied by a characteristic 13–18-Hz tremor of the legs (Thompson et al., 1986). Symptoms quickly resolve on sitting and characteristically most patients do not experience problems when walking. Polygraphic recording showing a fast and synchronous tremor is mandatory in order to confirm the diagnosis (Deuschl et al., 1998).

CLINICAL SPECTRUM OF ORTHOSTATIC TREMOR – SYNDROMIC ASSOCIATIONS

OT is considered rare, but there are no available epidemiological data. Women may be affected slightly more frequently, as suggested by two reviews involving 41 and 26 patients (Gerschlagler et al., 2004; Piboolnurak et al., 2005). Age of onset varies, although the mean onset of symptoms is in the sixth decade.

OT is frequently overlooked or misdiagnosed because physicians may not be aware of the syndrome, patients can report apparently bizarre symptoms, and routine examination is generally normal. On average it takes about 6 years until a correct diagnosis of OT is made (Gerschlagler et al., 2004).

A family history of OT seems to be uncommon and most cases occur sporadically. However, genetic factors are suggested by the few reports of familial cases such as the monozygotic twins with OT described recently (Contarino et al., 2006).

OT is characterized by unsteadiness on standing accompanied by a rapid 13–18-Hz tremor of the legs

(Fig. 35.1). Characteristically, the symptoms improve markedly on sitting or walking. The urge to sit down or to move can be so strong that patients often avoid situations where they have to stand still for a period of time, such as when queuing. When forced to stand still, some patients try to shift the weight from one leg to the other, walk on the spot, or lean against a wall. Patients are eventually forced to sit down or walk after a short time, ranging from seconds to several minutes, depending on the severity of the disease. As the disease progresses, tremor may encroach upon the stance phase of gait. Under these circumstances patients have difficulty walking slowly and managing stairs. Although OT is frequently considered a benign disorder, inability to stand still affects activities of daily living and has a serious impact on the patient's health-related quality of life. One study found that 11 of 20 OT patients were depressed as assessed by the Beck Depression Inventory (Gerschlagler et al., 2003).

Falls are rarely encountered in the course of the disease (McManis and Sharbrough, 1993; Piboolnurak et al., 2005) and frequent falls should alert the physician to re-evaluate the patient in order to rule out other causes such as stroke or parkinsonism. Patients report a feeling of unsteadiness and often a weakness of the legs when standing still; only some patients complain about a tremor of the legs. Rarely, subjects report pain in the legs as the main problem. The high-frequency leg tremor may not be visible on routine examination as it leads to partially fused muscle contraction. However, the tremor can be heard with a stethoscope placed over the affected thigh or calf, sounding rather like a distant “helicopter” (Brown, 1995). The latency from the onset of standing to the symptom onset is highly variable, so some subjects may have to stand still for several minutes in order

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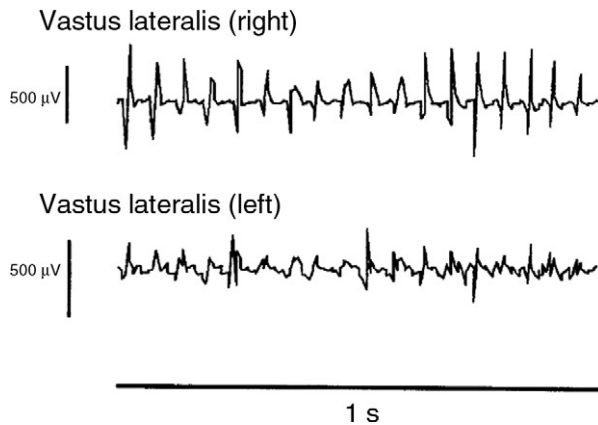


Fig. 35.1. Surface electromyography recordings showing high-frequency orthostatic tremor in the vastus lateralis muscles. Note that the rhythmic activity is bilaterally synchronous.

to provoke OT. In the advanced syndrome, there may be difficulty in tandem-walking.

Many OT patients also experience tremor involving the face, hands, or trunk. Tremor of the outstretched arms is a very common finding – 24 of 31 patients in the study of [Gerschlager et al. \(2004\)](#) and 24 of 26 patients in the study of [Piboolnurak et al. \(2005\)](#). Postural and kinetic tremor is most common and usually occurs between 5 and 10 Hz, a frequency band also found in essential tremor (ET) ([Piboolnurak et al., 2005](#)). Alcohol benefit is occasionally found in OT patients ([Gerschlager et al., 2004](#); [Piboolnurak et al., 2005](#)). Perhaps not surprisingly, OT was initially classified as a variant of ET ([Papa and Gershanik, 1988](#); [FitzGerald and Jankovic, 1991](#)). However, the results of coherence and bispectral analysis suggest that the lower-frequency postural upper-limb tremor, and similar lower-frequency components in the legs, may be a subharmonic of the high-frequency OT tremor and thus not generated independently ([McAuley et al., 2000](#); [Piboolnurak et al., 2005](#)).

Most cases of OT are idiopathic, with normal magnetic resonance imaging of the brain. Symptomatic OT does occur ([Fig. 35.2](#)) and has been described in patients with ET ([Papa and Gershanik, 1988](#); [FitzGerald and Jankovic, 1991](#)), pontine lesions ([Benito-Leon et al., 1997](#); [Setta and Manto, 1998](#)), cerebellar degeneration ([Manto et al., 1999](#)), head trauma ([Sanitate and Meerschaert, 1993](#)), aqueduct stenosis, relapsing polyradiculoneuropathy ([Gabellini et al., 1990](#)), paraneoplastic syndrome associated with small-lung cancer ([Gilhuis et al., 2005](#)), Graves' disease ([Tan et al., 2008](#)), parkinsonism, restless-legs syndrome ([Gerschlager et al., 2004](#)), and thiamine deficiency ([Nasrallah and Mitsias, 2007](#)). Of particular interest is the association of OT with parkinsonism. So far, 12 cases of OT have been reported in Parkinson's

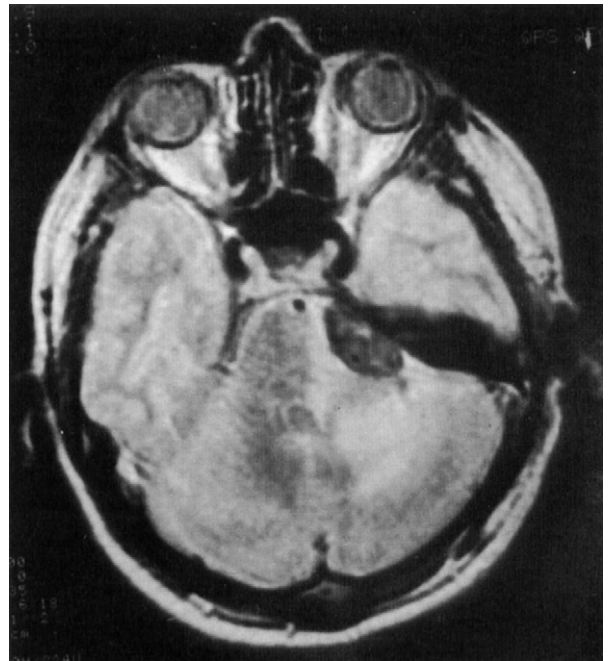


Fig. 35.2. Symptomatic orthostatic tremor caused by a lesion in the fossa posterior. Proton density axial magnetic resonance imaging (2200/35) demonstrating a mass in the left cerebellopontine angle with low-intensity signal and cerebellar edema. Case 2 from [Benito-Leon J, Rodriguez J, Orti-Pareja M, et al. \(1997\)](#). Symptomatic orthostatic tremor in pontine lesions. *Neurology* 49: 1439-1441.

disease (PD). OT may precede the onset of PD by several years ([Wills et al., 1999](#); [Gerschlager et al., 2004](#)), or develop in long-standing PD after 10 years ([Apartis et al., 2001](#); [Leu-Semenescu et al., 2007](#)). The age of onset of OT in PD patients is older (> 70 years) than in primary OT (mean age of 50–54 years). Related to this, dopaminergic drugs may be helpful, at least temporarily, in some patients suffering from OT.

PROGRESSION

The natural history of the disease has not been systematically studied. Progression of symptoms is anecdotally described in the literature. In a series of 41 patients, follow-up visits in six patients confirmed progression of symptom severity ([Gerschlager et al., 2004](#)). Some patients reported that they were able to go shopping and to queue for some minutes in the first year but subsequently became dependent on walking aids 5–6 years into the disease. Moreover, four of these six patients demonstrated a spread of tremor activity over time, from leg muscles to trunk and arm muscles ([Gerschlager et al., 2004](#)). A minority of OT patients develop other neurological disorders over prolonged follow-up, especially PD ([Wills et al., 1999](#);

Gerschlager et al., 2004) and progressive supranuclear palsy (de Bie et al., 2007), but whether this is coincidental is not known.

DIFFERENTIAL DIAGNOSIS

A new syndrome, orthostatic myoclonus, has been described. Leu-Semenescu et al. (2007) reported three PD patients developing “unsteadiness on standing” in the course of their disease. Electromyogram (EMG) analysis showed high-frequency myoclonic jerks ranging from 9.5 to 15 Hz on standing. Bursts were irregular and nonrhythmic and coherence analysis demonstrated a lack of synchrony between the right and left legs, unlike in OT. The duration of EMG bursts was also shorter (below 30 ms) as compared to OT. Glass et al. (2007) also described “orthostatic myoclonus” in 15 elderly subjects. Surface EMG recordings revealed non-rhythmic and irregular bursts that occurred predominantly in the upright position. In seven of the 15 patients, the myoclonus was associated with a neurodegenerative process: 2 cases of possible PD, and 1 case each of possible multiple-system atrophy, dementia with Lewy bodies, probable Alzheimer’s disease, mild cognitive impairment, and cerebral amyloid angiopathy. Two additional patients suffered from a systemic illness (systemic necrotizing vasculitis and chronic renal failure), which might have been responsible for the myoclonus. In most, however, the cause of orthostatic myoclonus is unclear.

Low (4–6-Hz)-frequency leg tremor while standing is a rare feature in PD and has a good response to dopaminergic drugs (Kim and Lee, 1993; Leu-Semenescu et al., 2007). Tremor of the legs may occasionally occur in ET, but always with upper-limb tremor and at frequencies under 12 Hz. A family history of tremor is common in ET but not OT. EMG recordings are very helpful in distinguishing alternative diagnoses in patients complaining of unsteadiness on standing.

PATHOPHYSIOLOGY

The evidence suggests that OT might be caused by a central generator located in the posterior fossa. High-frequency EMG bursts are time-locked in arm, leg, truncal, and even facial muscles and are bilateral (McAuley et al., 2000). OT has been associated with lesions in the pons or with cerebellar atrophy (Benito-Leon et al., 1997; Manto et al., 1999). In addition, OT can be reset by electrical stimulation over the posterior fossa, whereas peripheral stimulation is ineffective (Wu et al., 2001). A functional imaging study has shown that OT is associated with hyperactivity in the cerebellum and cerebellar connections. Similar abnormal bilateral hyperactivity is also found in other

tremulous disorders such as essential and dystonic tremor, suggesting that such activation may not reflect a distinct causal mechanism (Wills et al., 1996). OT is not necessarily related to the upright position of the body, since the tremor can be modulated by load-bearing tasks when patients are lying in a horizontal position (Boroojerdi et al., 1999).

Force platform recordings have demonstrated an increased sway path confirming objective instability in OT (Yarrow et al., 2001). One study has shown a puzzling dissociation between the subjective feeling of unsteadiness and objective measurements, as assessed by body sway under several conditions (Fung et al., 2001). The authors of this study postulated that unsteadiness is caused by a tremulous disruption of proprioceptive afferent activity from the legs causing a co-contraction of the leg muscles in order to increase stability. This results in increased tremor-locked muscle activity, further blocking proprioceptive input in a vicious cycle. However, another study showed that a 16-Hz tremor can be recorded in healthy subjects when made extremely unsteady either by vestibular galvanic stimulation or by leaning backwards. This suggested that the fast and synchronous tremor might be an exaggerated physiological postural response under conditions of extreme imbalance (Sharott et al., 2003).

Involvement of the dopaminergic system has been suggested by clinical reports of an association with parkinsonism as well as improvement in OT following dopaminergic agents, such as levodopa or dopamine agonists. A ¹²³I-FP-CIT single-photon emission computed tomography study showed a significant, albeit modest, dopaminergic deficit in a group of 11 OT patients (Katzenschlager et al., 2003). Those patients did not suffer from other neurological syndromes, and olfactory function on the University of Pennsylvania Smell Identification Test was normal, supporting the fact that the patients did not suffer from PD (Fig. 35.3). In accordance with these findings, Spiegel and coworkers (2005) demonstrated an echogenic substantia nigra in six OT patients using transcranial sonography, consistent with involvement of the dopaminergic system. However, evidence of a dopaminergic deficit has not been found in other functional imaging studies (Vaamonde et al., 2006; Trocello et al., 2008; Wegner et al., 2009). A dopaminergic deficit may not be found in all cases of OT. Perhaps primary OT is caused by direct involvement of an oscillator in the posterior fossa, whereas some cases of secondary OT might occur when subclinical or clinical dysregulation of dopaminergic transmission results in release of the posterior fossa oscillator. Recently, it was speculated that OT might be a “soft sign” heralding the onset of PD (Trocello et al., 2008).

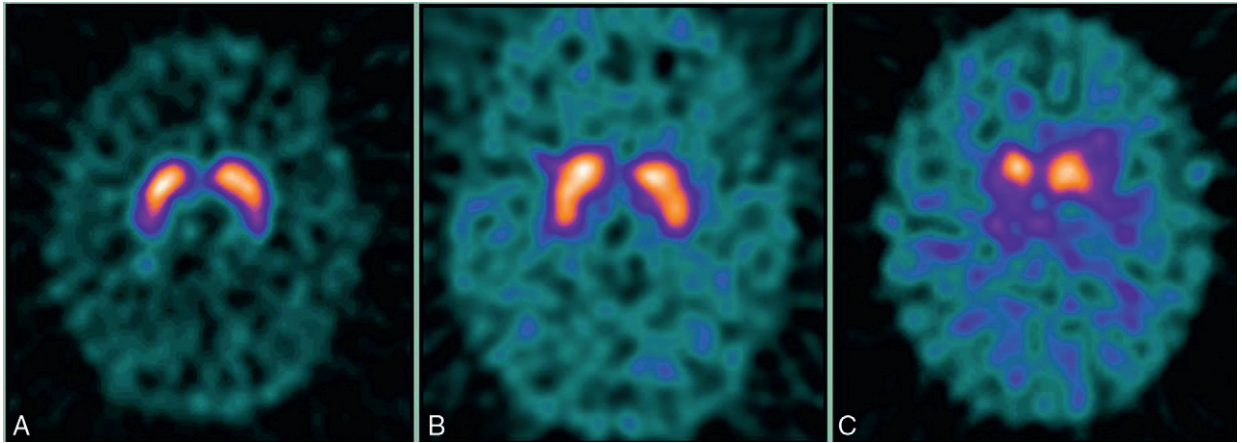


Fig. 35.3. ^{123}I -FP-CIT single-photon emission computed tomography images of (A) a normal control; (B) a patient with idiopathic orthostatic tremor; and (C) a patient with Parkinson's disease. Transaxial slices at the level of the striatum. The images are displayed normalized to the maximum striatal counts per pixel in the normal control. The images show a mild dopaminergic deficit in orthostatic tremor, whereas in Parkinson's disease there is marked as well as asymmetric dopaminergic deficit in the striatum. (Courtesy of Regina Katzenschlager, MD.)

TREATMENT

Overall the response to treatment is poor. Clonazepam is widely used as a first-line agent and some studies report a beneficial effect on tremor severity, although whether this is sustained or not remains unclear (Papa and Gershanik, 1988; Uncini et al., 1989; FitzGerald and Jankovic, 1991; Britton et al., 1992; McManis and Sharbrough, 1993; Gerschlager et al., 2004; Piboolnurak et al., 2005). Several small studies indicate that gabapentin may be an efficient treatment in doses ranging from 300 to 2400 mg/day, at least in the short term (Evidente et al., 1998; Onofrj et al., 1998; Rodrigues et al., 2005, 2006). Occasionally primidone has been reported to have a positive effect, whereas in other patients improvement lasted only a few months (van der Zwan et al., 1988; FitzGerald and Jankovic, 1991; McManis and Sharbrough, 1993; Gerschlager et al., 2004). Other drugs used with variable benefit include beta-blockers, sodium valproate, carbamazepine, and phenobarbital (Gerschlager et al., 2004; Rodrigues et al., 2005).

Pramipexole, a dopamine agonist, was effective in a single case report (Finkel, 2000). Wills et al. (1999) reported a series in which six out of eight OT patients improved with levodopa. One patient had classical OT and developed PD 9 years after its onset. Levodopa improved both parkinsonian symptoms and the high-frequency tremor. Another patient had sustained benefit to levodopa and then developed PD. However, only one patient, out of the eight treated with levodopa (Wills et al., 1999), had a benefit sustained longer than 24 months (Gerschlager et al., 2004). An open-label

study with levodopa treatment over 2 months employing 600 mg/day led to some improvement in two of five patients but no significant overall change and no sustained benefit (Katzenschlager et al., 2003). In summary, dopaminergic agents may be helpful in some patients over a short period of time, particularly those with, or at risk of developing, parkinsonism.

Finally, deep-brain stimulation (DBS) may be an option in severe, medically refractory OT. Recently, 2 cases of sustained benefit were reported with bilateral thalamic (ventralis intermedius nucleus) DBS. The tremor was successfully controlled over a period of 1.5 and 4 years (Espay et al., 2008; Guridi et al., 2008). However, in another patient who underwent unilateral thalamic DBS, clinical benefits diminished after 3 months (Espay et al., 2008). In addition, chronic spinal cord stimulation at the level of the lower spinal cord was reported to be effective in 2 cases of medically intractable primary OT (Krauss et al., 2006).

SUMMARY

OT is a rare, enigmatic, and poorly understood condition. It can lead to debilitating unsteadiness on standing, accompanied by a characteristic 13–18-Hz tremor of the legs. Symptoms resolve quickly on sitting and characteristically most patients do not experience problems when walking. The syndrome can be primary or secondary and associated with a variety of disorders, most commonly parkinsonism. The cause of the tremor is unknown, although most evidence points to a generator in the brainstem or cerebellum that can autonomously produce tremor or does so once released from inhibitory,

particularly dopaminergic, control. The response to treatment is poorly documented, particularly with regard to whether or not treatment responses are sustained. Clonazepam, gabapentin, and dopaminergic agents are worth trying.

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