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Tremor and Other Hyperkinetic Movements

Reviews

Orthostatic Tremor and Orthostatic Myoclonus: Weight-bearing Hyperkinetic Disorders: A Systematic Review, New Insights, and Unresolved Questions

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Abstract

Background: Orthostatic tremor (OT) and orthostatic myoclonus (OM) are weight-bearing hyperkinetic movement disorders most commonly affecting older people that induce "shaky legs" upon standing. OT is divided into "classical" and "slow" forms based on tremor frequency. In this paper, the first joint review of OT and OM, we review the literature and compare and contrast their demographic, clinical, electrophysiological, neuroimaging, pathophysiological, and treatment characteristics.

Methods: A PubMed search up to July 2016 using the phrases "orthostatic tremor," "orthostatic myoclonus," "shaky legs," and "shaky legs syndrome" was performed.

Results: OT and OM should be suspected in older patients reporting unsteadiness with prolonged standing and/or who exhibit cautious, wide-based gaits. Surface electromyography (SEMG) is necessary to verify the diagnoses. Functional neuroimaging and electrophysiology suggest the generator of classical OT lies within the cerebellothalamocortical network. For OM, and possibly slow OT, the frontal, subcortical cerebrum is the most likely origin. Clonazepam is the most useful medication for classical OT, and levetiracetam for OM, although results are often disappointing. Deep brain stimulation appears promising for classical OT. Rolling walkers reliably improve gait affected by these disorders, as both OT and OM attenuate when weight is transferred from the legs to the arms.

Discussion: Orthostatic hyperkinesias are likely underdiagnosed, as SEMG is often unavailable in clinical practice, and thus may be more frequent than currently recognized. The shared weight-bearing induction of OT and OM may indicate a common pathophysiology. Further research, including use of animal models, is necessary to better define the prevalence and pathophysiology of OT and OM, in order to improve their treatment, and provide additional insights into basic balance and gait mechanisms.

Keywords: Electrophysiology, imaging, shaky legs

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Introduction

Orthostatic tremor (OT) and orthostatic myoclonus (OM) are weight-bearing hyperkinetic disorders affecting station and gait, primarily in older patients. These hyperkinesias were first described in the literature over 30 years ago. OT was described by Heilman[1] in 1984 as a tremor of the lower body that occurs upon standing, is absent when seated or lying, and is alleviated by walking or leaning (Figure 1). However, cases reported in the 1970s have been retrospectively recognized as probably reflecting OT.[2,3] Original patient descriptions generated the term, "shaky legs syndrome."[4,5] OT is divided into "classical" and "slow" OT forms. Classical OT has a frequency ⩾13 Hz on electromyographical recordings,[6] whereas slow OT has a tremor frequency of <13 Hz (most often <10 Hz).[7] In 2007, a similar disorder associated with myoclonus rather than tremor was reported by two separate groups and termed OM[8,9] (Figure 2). As with OT, similar cases were likely noted many years earlier and can be retrospectively identified.[10]

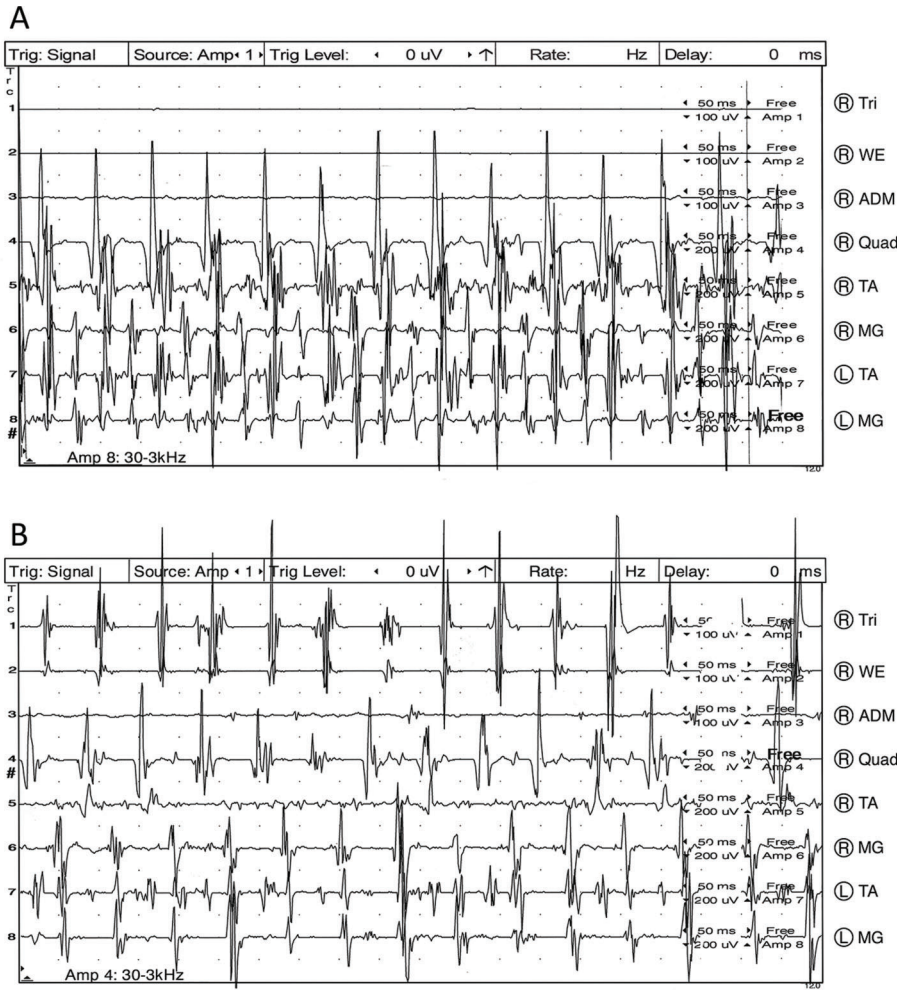

Figure 1. **Classical Orthostatic Tremor**. (A) A 14 Hz, highly synchronized tremor is present in the patient's legs as the patient stands. (B) As the patient leans onto a chair, the tremor transfers to the left triceps. It remains in the legs, but its amplitude is reduced. ADM, Abductor Digiti Minimi; MG, Medial Gastrocnemius; Quad, Quadriceps; TA, Tibial Anterior; Tri, Triceps; WE, Wrist Extensors.

Both orthostatic hyperkinesias can be definitively diagnosed and distinguished from each other by surface electromyography (SEMG).[8] Other methods, such as leg muscle palpation and auscultation, are neither sufficiently sensitive nor specific to diagnose OT and OM reliably.[11,12] OT is designated as "primary OT" when it occurs in isolation (with or without an associated postural arm tremor) and as "OT-plus" when associated with parkinsonism or other neurological disorders.[13] However, OT appears to evolve independently, whether isolated or associated with additional neurological disorders.[14] There is controversy whether OM occurs in isolation.[8,15] Unlike other forms of tremor and myoclonus, which may be present in a person's lower limbs while a patient is standing, the orthostatic hyperkinesias are isometric phenomena; i.e., they abate or significantly attenuate when a standing individual takes weight off their legs, such as by leaning onto an object.[16,17]

In this paper, the first joint review of these disorders, we draw from the literature and our collective experience, to discuss the demographic, clinical, electrophysiological, neuroimaging, pathophysiological, and treatment features of these disorders.

Methods

A systematic literature search of PubMed was performed in July 2016 using the search terms "orthostatic tremor" (1,158 articles), "orthostatic myoclonus" (169 articles), "shaky legs" (16 articles), and "shaky leg syndrome" (72 articles). The MeSH entry term of "primary orthostatic tremor" is a unique identifier for both orthostatic tremor and shaky legs since 2010 and yielded 1,053 articles. There is no unique identifier in MeSH for orthostatic myoclonus. A manual review of all 1,485 abstracts was then performed to exclude duplicated articles, irrelevant articles (e.g., orthostatic hypotension) and those with non-English abstracts. In total, 246 reviews, case reports, case series, and clinical studies (from 1970 to 2016) were evaluated for this review.

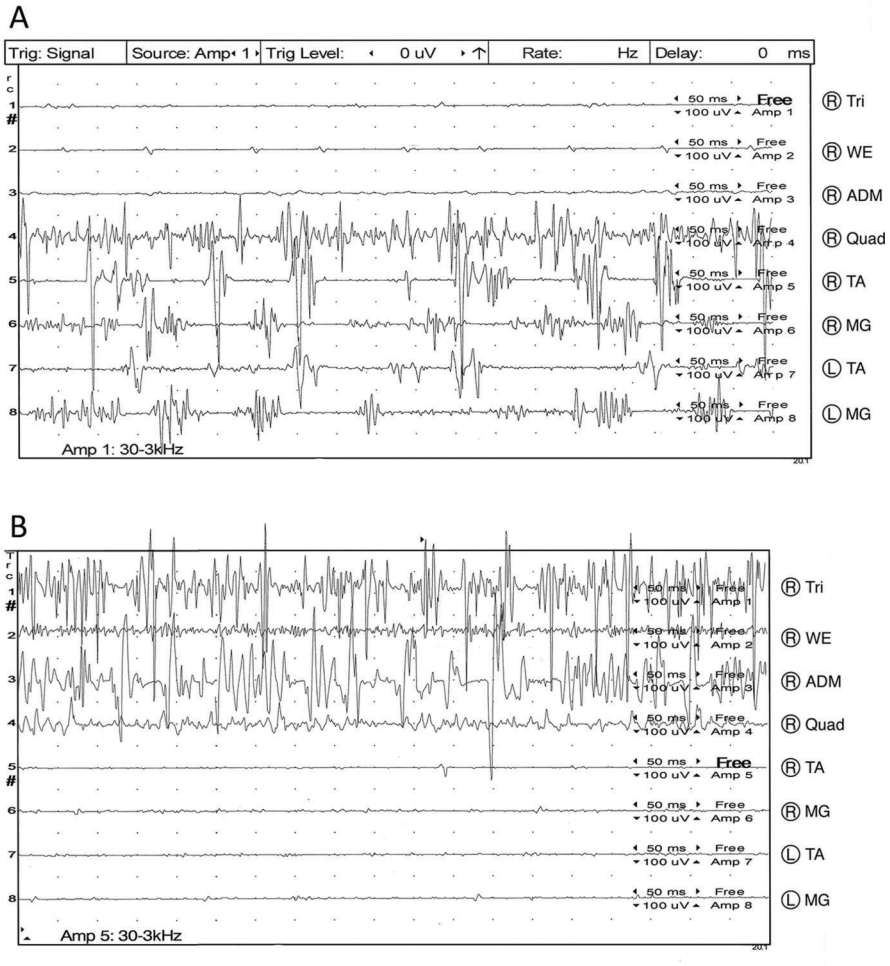

Figure 2. **Typical orthostatic myoclonus**. (A) While the patient stands, frequent bursts of motor activity lasting <50 ms are present in the TAs and MGs. These are often synchronous between homologous muscles and occasionally have an alternating pattern between ipsilateral muscle antagonists. (B) Leaning onto a chair, the activity in the legs becomes virtually quiescent and high amplitude, tonic motor activity is present in the arm. ADM, Abductor Digiti Minimi; MG, Medial Gastrocnemius; Quad, Quadriceps; TA, Tibial Anterior; Tri, Triceps; WE, Wrist Extensors.

Results

Demographic features

The prevalence of OT and OM is unknown. Both are deemed uncommon disorders, although OM may be four times as common as OT.[15] Together, they likely represent less than 50% of elderly patients complaining of "shaky" legs while standing.[15] Restricted access to SEMG in clinical practice limits precise estimates of the prevalence of OT and OM.[15] Both disorders primarily affect older adults. Although OT is far more common in women, no gender disparity has been described in OM.[13–16,18–21] A family history is reported in 5–7% of OT cases and a few case reports describe familial OT.[14,22–25] Thus far, familial OM is not officially recognized.

Clinical features

Leg symptoms when standing are reported by all OT patients compared to 84% of OM patients.[14,15] Various symptoms, including "shaky," "wobbly," "jerking," and "jelly" legs, as well as gait unsteadiness, imbalance, a sense of leg weakness, or leg discomfort, are reported in both.[8,14,15] Some OT patients also report arm, head, or, rarely, jaw tremor on standing.[14] Lower limb symptoms in both OT and OM attenuate or extinguish when affected patients lean on an object, in contrast to other forms of tremor and myoclonus affecting the legs.[14,15] Thus a frequent complaint from patients with OT and OM is that they have difficulty with prolonged standing (e.g., while in line at a store), which is alleviated by leaning on an object (such as a shopping cart).[14,15] Both OT and OM can transmit to the arms after the patient leans on an object.[15,18] Although this is almost universal in OT patients, it is uncommon in OM patients.[14,15] Additionally, OT has been reported without an upright posture, e.g., tremor can occur in the arms and legs when a patient is on all fours, or when affected individuals contract their leg muscles against resistance while sitting or lying supine.[26–28] The frequency of these latter findings in OT patients is unknown, as these maneuvers are not commonly employed in

movement disorders laboratories. These characteristics are consistent with an isometric phenomenon rather than a purely orthostatic one.[17] The station of OT patients may entail larger amplitude swaying involving the legs and trunk. In contrast, OM is associated with very low amplitude standing leg movements, predominantly in the tibialis anteriors (TAs) and medial gastrocnemii (MGs).[15] Most OM patients ambulate with a reduced stride and wide base. They may appear very tentative, as if they are "walking on ice," yet they demonstrate a lengthened stride, narrower base, and less fear of falling if they use a rolling walker or shopping cart.[15] This likely reflects abolition of the myoclonus secondary to weight reduction on the legs.[15] Intriguingly, some of the originally reported OM patients previously had been diagnosed with normal pressure hydrocephalus (NPH), but none improved with ventriculoperitoneal (VP) shunting.[8,15] Whether the presence of OM is a poor prognostic indicator for VP shunting in suspected NPH patients is currently under investigation. At least early in its course, primary OT improves with walking, particularly briskly, unlike OM and OT-plus. OT is typically a slowly progressive disorder (91% of reported cases in large series) that increasingly compromises gait, with about 25% reporting falls.[14,19] OM is also usually associated with early postural instability and may be a cause of "drop attacks," perhaps because OM may consist of negative myoclonus as well as positive myoclonus.[8,15] Currently, an in-depth clinical characterization of slow OT is limited, because of the scarcity of reported cases (Table 1). Henceforth, unless the modifier "slow" is used, "OT" refers to the classical form.

Coexistent neurological disorders

Approximately 25% of OT patients have coexistent essential tremor (ET) and up to 50% report a family history of tremor.[20,26,29,30] About 40% of OT patients have additional neurological disorders, i.e., they have OT-plus.[19] The frequency of parkinsonism (9%) or a family history of parkinsonism (11%) is higher than expected.[14] Other neurological disorders associated with OT include dystonia,[14,19] cerebellar ataxia,[31–33] pontine lesions,[34,35] left-midbrain lesions,[36] aqueductal stenosis,[37] head trauma,[38] paraneoplastic small cell lung cancer,[39] SPG31 spastic paraplegia,[40] and stiff-person syndrome.[41] Non-neurological associations reported include vitamin B12 and thiamine deficiency,[42,43] medications,[44] Graves' disease,[45–47] biclonal immunoglobulin(Ig)G and IgA lambda gammopathy of uncertain significance,[48] GAD-65 antibodies,[41] spinal fluid monoclonal IgG band,[49] prominent muscle hypertrophy,[50] and other disorders.[14,37] However, many of these associations may be coincidental.

Similarly, OM rarely occurs in isolation. Approximately one-third of OM patients have PD or atypical parkinsonism, one-third have severe microvascular encephalopathy, and one-third have multifactorial neurological disease.[15] Recently OM was putatively linked with Caspr2 antibodies but the clinical and SEMG findings are atypical for OM.[51,52] Finally, reports regarding iatrogenic OM, e.g., secondary to tricyclic antidepressants, are conflicting.[12,15]

In the few existing reports on slow OT, co-occurrence with multiple sclerosis, Graves' disease, cerebellar ataxia, PD, and paraneoplastic disorders have been noted.[7,53] The strength of these associations is unclear. Interestingly, OM and slow OT may coexist (see under "Electrophysiological findings").

Cognitive performance has been evaluated in OT. Relative to healthy controls, OT patients had poorer performance on tests of executive function, visuospatial ability, verbal and visual memory, and language.[54]

Radiological findings

In the vast majority of OT patients, definite and plausibly causal lesions are not apparent on cranial magnetic resonance imaging (MRI) or computed tomography (CT) scans.[14] However, isolated case reports describe cerebellar and pontine lesions in OT.[31–35] A recent study by Gallea et al. entailed volumetric MRI studies of 17 OT cases versus 17 controls.[55] OT patients had bilateral decreased grey matter volume in the lateral cerebellum, and bilateral increased grey matter volume in the supplementary motor area (SMA) and vermian grey matter. They hypothesized that lateral cerebellum atrophy was related to disease, and that SMA and vermian hypertrophy reflected compensatory changes. This raises the possibility of previously unrecognized mild volumetric changes in OT. However, the temporal occurrence of these findings is unknown, and the findings require validation in additional, larger studies.

In contrast to OT, a majority of OM patients have significant subcortical microvascular encephalopathy.[15] We have also identified two patients with asymmetric OM and a contralateral frontal lobe infarction (Figure 3).

Transcranial sonography in four OT patients demonstrated that all had substantia nigra echogenicity, three unilaterally and one bilaterally.[56] This may suggest nigrostriatal dopaminergic deficits in OT patients. Functional imaging of one OT patient revealed a dopaminergic deficit in [^{123}I]-FP-CIT-SPECT (Single Photon Emission Computerized Tomography), possibly supporting this theory.[57] However, follow-up studies found no difference in [^{123}I]-FP-CIT-SPECT among OT patients compared with matched controls.[58,59]

A positron emission tomography study of four patients with OT and postural arm tremor analyzed cerebral activation associated with right arm tremor with a sustained posture and at rest.[60] Regional cerebral blood flow at rest and during arm tremor was associated with increased bilateral cerebellar and contralateral lentiform and thalamic activation, similar to prior findings in ET and writing tremor. However, as orthostatic tremor was not provoked in this study, no definite conclusions can be reached.

A functional MRI (fMRI) study assessed resting state network connectivity in 13 OT patients and 13 matched healthy controls.[61] Compared with controls, OT patients had reduced connectivity in cerebellum and sensorimotor networks, which correlated with longer duration of OT. However, in the recent study by Gallea et al.,[55] fMRI connectivity between the cerebellum and SMA was abnormally increased in OT patients, and correlated positively with tremor severity. These findings contrast with the decreased connectivity reported by Benito-Leon.[61] Gallea et al.[55] also performed open-label,

Table 1. **Comparison of Clinical, Electrophysiological, Imaging, and Treatment Features of Classical OT, slow OT, and OM.**

	Classical OT	Slow OT	OM
Gender	Female predominant	Female predominant	No gender preference
Age of onset	Older adults	Older adults	Older adults
Coexistent ET	25%	No	No
Coexistent parkinsonism	11%	Unknown	33%
Coexistent neurological disease	40%	Unknown	100%
Family history OT/OM	5-7%	Unknown	No
Family history tremor	Up to 50%	Up to 37.5%	Unknown
Family history parkinsonism	9%	Unknown	No
Leg shaking provoked by standing	100%	100%	88%
Leg shaking improves with walking	93.6%	Unknown	No
Leg shaking improves with leaning	98.6%	Unknown	100%
Difficulty with prolonged standing in line	Yes	Unknown	Yes
Falls	24.1%	37–50%	Frequent at onset
Progressive disorder	91%	Unknown	Unknown
SEMG	Tremor bursts >13 Hz, (usually 15–16 Hz); shorter-duration discharges	Tremor bursts usually <10 Hz, longer-duration discharges	Myoclonic bursts 3–7 Hz, Very short burst duration (30–100 ms)
Synchronicity of bursts	Highly synchronous	Less synchronous	Synchrony of homologous muscles common
Transmits to arms on weight-bearing	Yes	Yes	Rare
Coexistent SEMG findings reported	Postural arm or leg tremor	Unknown	Coexistent arm myoclonus rarely
Medications of choice	Clonazepam, beta-blockers, gabapentin, valproate, primidone	Partial response – clonazepam, gabapentin, primidone, propranolol	Clonazepam, levetiracetam
Response to alcohol	Yes	Unknown	No
Response to DBS	Yes	Unknown	Unknown
Gait aid	Roller walker	Unknown	Roller walker
Imaging findings	Normal or age-related atrophy or leukoaraiosis	Unknown	Severe microvascular disease common

Abbreviations: DBS, Deep Brain Stimulation; ET, Essential Tremor; OT, Orthostatic Tremor; OM, Orthostatic Myoclonus; SEMG, Surface Electromyography.

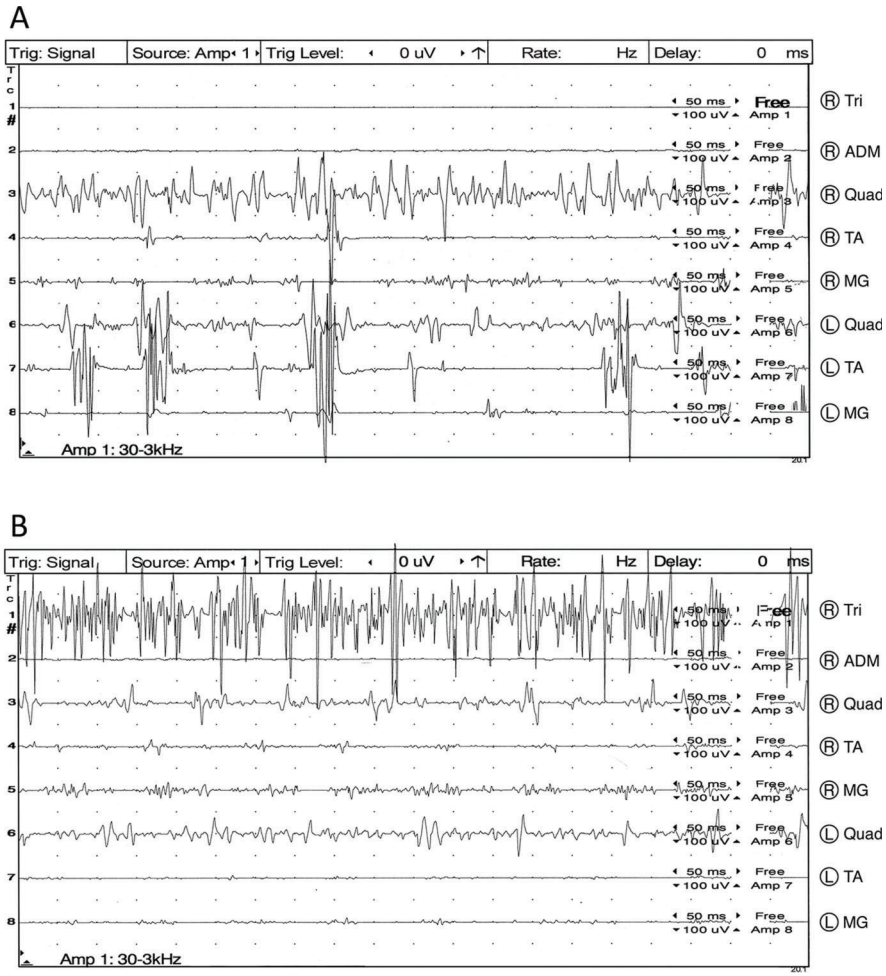

Figure 3. **Asymmetric Orthostatic Myoclonus in a Patient Who Suffered a Remote Right MCA (Middle Cerebral Artery) Stroke**. (A) As he stands, frequent, high amplitude bursts lasting <50 ms are present in his left TA, while only an isolated, lower amplitude burst <50 ms is present in the right TA. (B) Leaning onto a chair, the activity in both legs is tonic and of very low amplitude, predominantly in the quadriceps. It is tonic and high in amplitude in the triceps. ADM, Abductor Digiti Minimi; MG, Medial Gastrocnemius; Quad, Quadriceps; TA, Tibial Anterior; Tri, Triceps.

repetitive cerebellar transcranial magnetic stimulation (TMS) in nine patients; tremor severity and functional connectivity between the lateral cerebellum and SMA were reduced.[55] Limitations of this work are that the recordings occurred in the absence of OT; the temporal resolution of fMRI limited the ability to assess for high frequency activity in the cerebellothalamocortical network; and coexistent clonazepam usage in some subjects may have impacted the results.

Electrophysiological findings

Surface electromyography. The typical montage and recording methods used for evaluating the orthostatic hyperkinesias are described in detail elsewhere.[15] Recording from at least eight muscles is preferable when studying a patient with a possible orthostatic hyperkinesia, including in the bilateral lower limbs, two or three in an upper extremity, and possibly paraspinals. Tremor is defined as a sinusoidal oscillation of a body part with a fixed frequency, but a potentially variable amplitude.[62] In comparison, myoclonus is a "lightning-like" jerk with an irregular frequency, but potentially semi-rhythmical, and of lower amplitude.[62] Voluntary motor activity corresponds electromyographically to burst durations of greater than 100 ms and a sustained contraction of a muscle produces "tonic" motor activity lasting many hundreds of milliseconds.[62] The duration of tremor bursts may fall within the voluntary range, whereas myoclonus generated rostral to the spinal cord is of <100 ms duration, and often <50 ms.[15,62,63] In addition to the frequency and burst durations of the SEMG activity, its synchrony (the simultaneous occurrence of the activity in different muscles, i.e., intermuscular coherence) is also important diagnostically.

The electrophysiological features of OT were first reported in a patient with lower limb tremors that alternated between antagonist muscle groups at a rapid frequency (16 Hz) only during certain postures.[64] A fast frequency tremor between 13–18 Hz, and most commonly 15–16 Hz, is a diagnostic criterion of classical OT.[6,14] However, tremor frequencies as high as 20 Hz or greater are

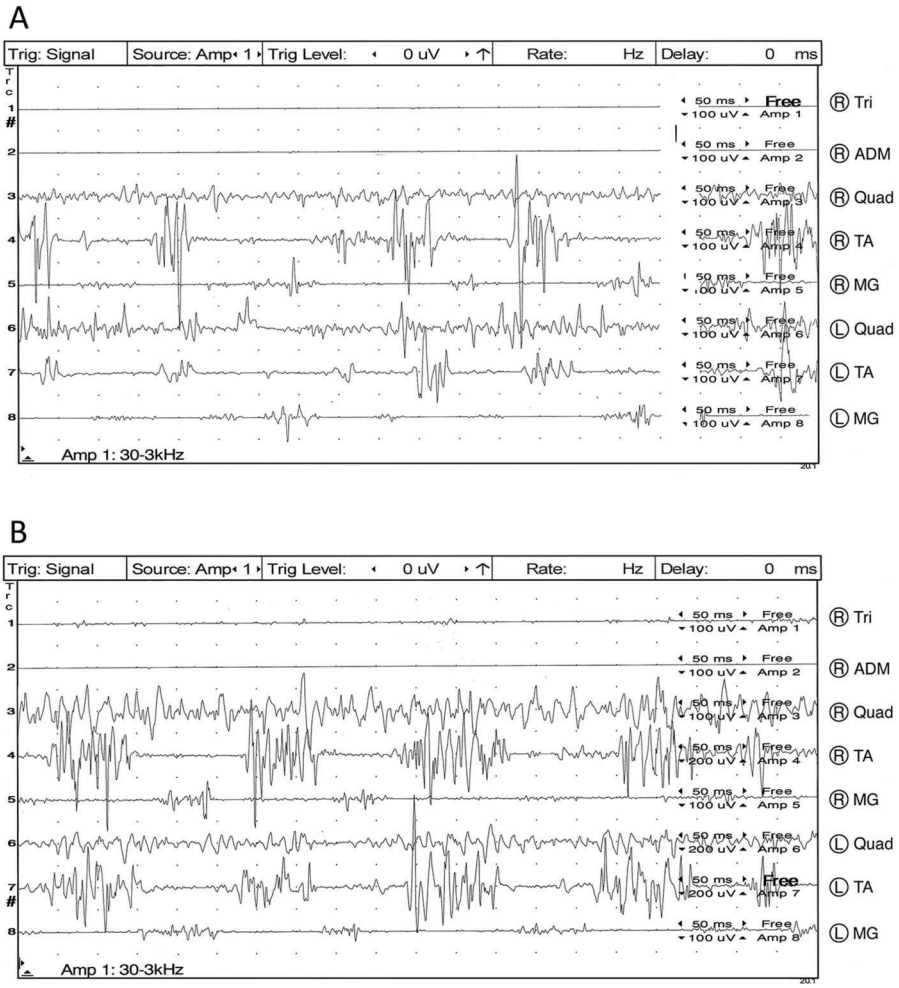

Figure 4. **Mixed Orthostatic Myoclonus and Slow Orthostatic Tremor**. (A) While the patient is standing in his preferred manner, intermittent bursts of motor activity lasting <50 ms are present, particularly in the TAs. He describes his legs as "trembling." (B) Standing with his knees slightly flexed, a synchronous 5 Hz tremor is present in the TAs, and he describes his legs as "shaky." ADM, Abductor Digiti Minimi; MG, Medial Gastrocnemius; Quad, Quadriceps; TA, Tibial Anterior; Tri, Triceps.

reported.[14,16] The tremor associated with classical OT is usually highly synchronous between leg and paraspinal muscles, and transmits to the arms with partial weight bearing (Figure 1). The tremor frequency can shift from low to high frequencies with forceful muscle contractions, but is unaffected by loading the limbs or peripheral stimulation.[27,65,66] As noted previously, a postural arm tremor at a slower frequency, consistent with ET, may coexist with OT. There may also be a postural leg tremor at the same frequency or a slower harmonic of OT.[14] Slow OT has similar characteristics to classical OT when its frequency is greater than 10 Hz. However, at lower frequencies, it is far less synchronous than classical OT and more similar to OM.[7] PD patients with leg tremor may have symptoms mimicking slow OT, but important distinctions exist: 1) PD patients usually manifest the leg tremor at rest, i.e., while seated, but slow OT patients do not; 2) PD leg tremor is typically highly asymmetric; 3) It is present in muscle antagonists whereas slow OT manifests in bilateral, homologous muscles and; 4) It is typically not isometric, remaining when the patient leans onto an object (Figure 4).

The frequency of OM is usually between 3 and 7 Hz, and its amplitude typically between 100 and 500 μV.[8,15] OM is most frequent in the TAs followed by MGs, and less so in the quadriceps.[8,15] Tonic motor activity is usually present in the paraspinals while a patient with OM is standing. The myoclonic bursts are often synchronous in homologous muscles, particularly the TAs, but occasionally alternate semi-rhythmically between the ipsilateral TAs and MGs (Figure 2).[15] This alternating activity has also been reported in slow OT <10 Hz. This, plus the coexistence of OM and slow OT in certain patients, depending on their stance, suggests a possible continuum between these hyperkinesias (Figure 4). Coexistent myoclonus in the upper and lower limb muscles of OM patients while they are seated is uncommon and occurs with sustained postures or movements, most often in isolation in an intrinsic hand muscle.[8,15]

When patients with OT lean onto a chair, the tremor in their leg muscles will extinguish or attenuate enough for their legs to feel far less shaky, and the tremor then transmits to their arms at the same frequency (Figure 1).[14] OM always abates with weight reduction on the legs, but does not always reappear in the arms.[15] If the myoclonus does not extinguish when weight is taken off the legs, then it is not isometric and multifocal myoclonus is the likely diagnosis. Slow OT <10 Hz, similar to OM, often abates with leaning but does not always transmit to the arms, although more research is required regarding this characteristic.[7,15] None of the orthostatic hyperkinesias attenuate with prolonged standing, and usually worsen.

Listening to the SEMG recordings of classical OT, slow OT, and OM can facilitate their recognition. They each have auditory signatures. Classical OT sounds like rotating helicopter blades. OM sounds like water boiling or popcorn popping.[15] Slow OT at 4–6 Hz sounds like a steam locomotive, and at 7–10 Hz like a rotating ceiling fan.

Other electrophysiological testing. Acoustic startle and blink responses were evaluated in seven OT cases versus 13 healthy controls. The blink reflex was normal in both groups, but the acoustic startle was suppressed in the OT cases.[67] These have not been studied in OM patients.

Posturography studies have employed an artificial neural network technique (ANNW) to assess postural sway patterns in normal controls, subjects with OT, and subjects with postural phobic vertigo, anterior lobe cerebellar atrophy, or acute unilateral vestibular neuritis. The ANNW differentiated postural sway patterns with high sensitivity and specificity (1.0) for OT.[68] Another study utilized posturography to screen for OT in 701 patients attending a balance clinic.[69] A retrospective review identified five patients with SEMG-confirmed OT (four women, mean age 56 years, age range 36–73 years) and narrow peaks in the spectral power distribution at 8.5–18 Hz. Therefore, spectral power analysis may be a simple, quick method to screen for OT.[69] A smart phone accelerometry app has also been reported to detect OT and holds promise as an easy, cheap, and sensitive screening tool.[70] Posturography is being studied in OM patients, but the data are preliminary.

Electroencephalography (EEG) has been studied in OT patients, with both seated and standing recordings. McManis and Sharbrough[18] reported that EEG studies are normal in most OT patients, but some have a midline electrographic discharge associated with the tremor. Hassan et al.[14] noted similar findings and that the EEG frequency could be identical, a harmonic or non-harmonic of the OT frequency. However, in these cases OT artifact was not unequivocally excluded.

Diagnosis

Other disorders that can produce shaky legs and mimic OT and OM include functional (psychogenic) leg tremor, functional myoclonus, non-specific gait and balance disorders of the elderly, poor vision, orthopedic disorders, peripheral neuropathy, postural orthostatic intolerance (due to hypotension, deconditioning, hyperadrenergic states, dehydration), Parkinson's disease (PD) with prominent leg tremor, and cerebellar truncal tremor (titubation). These can be distinguished from OT and OM by meticulous clinical examination and SEMG.[14,15]

Treatment

Both OT and OM are challenging to treat. Clonazepam was recognized early as a treatment for OT.[1] There are also case reports of improvement of OT with primidone,[71] phenobarbital,[72] levodopa,[73] pramipexole,[74] and dual primidone and clonazepam therapy.[75] In two small, blinded, placebo crossover studies, gabapentin reduced tremor amplitude and sway area in OT patients, and improved the patients' quality of life.[76,77] Levetiracetam was studied in 12 OT patients in a double-blind, placebo-controlled trial for 4 weeks, but was ineffective for the primary end point of stance duration, and secondary endpoint of total track length of sway path and tremor total power.[78] A comprehensive medication review of 184 OT patients in the largest OT case series identified 46 medications administered over 416 medication trials.[14] Benzodiazepines were the most efficacious class of medication and produced at least mild benefit in over half of all patients (56%), and this was slightly higher for clonazepam (57%); at least moderate benefit in 33%; and marked benefit in 15%. The next most efficacious classes to produce at least mild benefit were beta-blockers (31%) and anticonvulsants (25%). The remainder were largely ineffective, including levodopa (Table 1).[14] OT is alcohol-responsive in about 50% of patients.[14]

For OM, levetiracetam is the pharmacological agent of choice and clonazepam is reportedly efficacious.[8,9,79] In slow OT patients, responses to oral medications are similar to those in classical OT, and intravenous immunoglobulin was used successfully in one case.[7,80]

Botulinum toxin injections into leg muscles were tested in one randomized, double-blind, placebo- controlled, crossover study of eight patients with electrophysiologically confirmed OT. Each patient received 200 units of abobotulinum toxin or saline into bilateral TAs with crossover after 20 weeks. No significant difference was seen in clinical symptoms or electrophysiological findings in the seven patients who completed the study.[81]

Deep brain stimulation (DBS) of bilateral, thalamic ventral intermediate nuclei (VIM) has been reported to benefit a small number of OT patients and requires further study.[14,20,82–87]

Patients with OT and OM may achieve remission or attenuation of their hyperkinesia when standing and ambulating using a gait aid, such as a rolling walker, to bear some of their weight.

Pathophysiology

Overlap with clinical disorders. An overlap between ET and OT has been suggested by several groups.[26,29,30,88,89] However, there are several differences. While both are centrally generated tremors, ET is a slower frequency action/postural tremor that can be reset by a peripheral stimulus, whereas OT is a fixed, weight-bearing tremor not altered by peripheral loading.[27,65] In patients with coexistent OT and ET, these separate electrophysiological features can be demonstrated.[18,90] Their demographic, clinical, and treatment features also

differ. ET has a bimodal distribution, whereas OT occurs overwhelmingly in seniors.[14,91] ET is commonly familial, whereas this is uncommon in OT.[14] OT is rare, while ET is the most common movement disorder. ET is often responsive to beta-blockers and primidone, whereas these produce only mild benefit in about a third of OT patients. Interestingly, alcohol responsiveness is similar for OT and ET.[14,92] Functional neuroimaging indicates different areas of the cerebellar hemispheres are involved in OT and ET: lobule VI in the former, and lobules V and VIII in the latter. Additionally, hypertrophy of the cerebellar vermis occurs in OT, but not in ET.[55]

An overlap between OT and cerebellar disorders has been suggested.[31,32,55] Limitations to this theory include that the majority of OT patients lack associated cerebellar lesions, or accompanying cerebellar symptoms and signs.[14,18] However, OT recently has been associated with atrophy of the lateral cerebellum and hypertrophy of the cerebellar vermis and SMA, as noted above.[55] Improvement of OT following VIM thalamic DBS suggests OT is generated within the cerebellothalamocortical pathway, similar to other tremor disorders.[83]

Given the greater than expected incidence of parkinsonian disorders in OT and OM, an underlying dopaminergic deficit could exist. However, this is unlikely in OT, because of its poor responsiveness to levodopa or dopamine agonists, its female predominance, and the lack of consistent correlation with abnormal DAT scan imaging. OM has not been systematically studied with DAT scan imaging, but its similar lack of responsiveness to dopaminergic therapy suggests it mirrors OT in this regard.

An overlap of OT with autoimmunity was suggested by single case reports.[48,49,80,93] However, there is not a greater than expected association with other autoimmune disorders; the cerebrospinal fluid (CSF) is usually normal in OT patients; and there is an absence of MRI features of inflammation or abnormal enhancement in this population.[14] Therefore, autoimmunity seems an unlikely mechanism for OT.

OT generator. Shortly after OT was first reported, Thompson et al.[64] and others[28] posited that it was generated by a central oscillator. A supraspinal location for the generator was suggested after reports that TMS over the cortex could reset the tremor in both legs, but peripheral TMS over the lumbar spine did not.[94–96] However, these cortical TMS findings were not replicated by other groups.[97,98] Wu et al.[98] proposed an oscillator in the posterior fossa, since electrical stimulation over the posterior fossa, but not the cortex, could reset the tremor bilaterally. They hypothesized the stimulator may be influenced by cerebellar stimulation but not necessarily reside there. A midline location for a tremor generator is possible, as OT patients with EEG discharges at the same frequency as OT in the parasagittal region are reported.[2,18] This is uncommonly found, possibly reflecting the depth of the generator, and should be investigated further. Intriguingly, OT spread to the upper limbs following hip replacement surgery in one patient, which could suggest a mechanism of altered proprioceptive feedback resulting in increased tremor output.[99] It has been hypothesized that peripheral Ib interneurons are implicated in OT.[98] Muscle contraction under load activates muscle Golgi tendon organs, whereby Ib afferents project to interneurons in the spinal cord, motor neurons, dorsal and ventral spinocerebellar tracts, Clarke's column, and the spinal locomotor center. However, this could not be proven in a study of OT patients.[98] Additionally, the intriguing findings of Gallea et al., notably hypertrophy of the cerebellar vermis and SMA in OT, may be akin to the hypertrophy of the inferior olive in patients with lesions within various locations of the dentatorubral tract or central tegmental tract (Guillain–Mollaret triangle)[100] and reflect that there are potentially multiple OT generators within cerebellothalamocortical pathways.

OM generator. Investigations to establish the location of the generator for OM are limited but cortical or subcortical locations are hypothesized. The presence of enlarged cortical somatosensory evoked potentials (SEPs) or stimulus-sensitive myoclonus can support a cortical generator for myoclonus.[12] Gasca Salas et al.[101] found enlarged SEPs in 20% of their OM patients and van Gerpen found none.[15] Stimulus-sensitive myoclonus was also absent in OM patients.[15] Therefore, a subcortical generator for OM may be more likely, which is also supported potentially by imaging findings of severe subcortical cerebral microvascular encephalopathy in most OM patients.[15] Also, isolated cases of unilateral OM secondary to contralateral, frontal lobe infarctions have been identified (Figure 3). Thus, it is conceivable that the origin of OM is subcortical and frontal, though future studies utilizing functional neuroimaging will be necessary to verify, or refute, this hypothesis.

OM pathophysiology. Anticipatory postural adjustments (APAs) are involuntary movements to maintain balance in response to external perturbations.[102–104] When these forces are small, an "ankle strategy" is employed in which the TAs contract to counteract a backward tilt, and the MGs do the same to counteract a forward tilt. Patients with OM invariably have imbalance and postural instability, a greater tendency to retropulse, and myoclonic bursts in the TAs more than the MGs.[15] Interestingly, APAs precede step initiation to shift the center of mass laterally and forward over the stance limb through the activation of hip abductors and ankle dorsiflexors prior to foot lift. These have been associated with knee trembling during freezing of gait.[105] The knee trembling accompanying freezing of gait resembles OM. These similarities could indicate that OM represents hyperactivity of APAs in elderly patients with gait and balance disorders. Similar reasoning has postulated that OT is an exaggeration of a physiological response to instability.[106]

Animal studies. There are a handful of case reports of primary orthostatic tremor in dogs (Great Danes, Scottish deerhound, and giant breeding dogs).[107–109] The clinical and electrophysiological features are identical to humans. In addition, MRI, CSF, and muscle and nerve biopsies are reported as normal.[109] This animal model is ideal to further evaluate the pathophysiological underpinnings, genetic abnormalities, and treatment options for OT. There are no known animal models of OM.

Discussion

Both OT and OM share common clinical features including age of onset, induction by standing, abolition by sitting, a higher than expected association with parkinsonism, and responsiveness to benzodiazepines. A striking similarity is that weight bearing is fundamental to their genesis, which suggests that these hyperkinesias exist on a pathophysiological continuum. Nonetheless distinctions remain between these entities. When OT patients lean onto an object, tremor is transferred to their arms and the leg tremor diminishes or abolishes, whereas in OM and slow OT, the hyperkinesia extinguishes but uncommonly transfers to the arms. Perhaps this is a manifestation of the difference between the highly synchronized movements in OT, compared with OM and slow OT. We have recognized five patients who have OM when standing in their preferred manner, but have OT $<$10 Hz when standing with their knees flexed (Figure 4), suggesting overlap between these two hyperkinesias. Thus, if OT and OM are on a spectrum, perhaps OM and slow OT $<$10 Hz lie closer together than classical OT. In that vein, classical OT and slow OT $>$10 Hz are more clinically and electrophysiologically similar than OT $<$10 Hz.[7] We therefore propose that slow OT should be defined as $\leq$10 Hz and classical OT should include frequencies of 11–13 Hz.

The nomenclature of these disorders is misleading and problematic. Although they were first described on "standing straight" (i.e. "orthostatic"), this position is not necessary to generate these hyperkinesias, as they emerge with any type of weight bearing, such as kneeling on all fours in OT. They are also not truly "isometric," as changes in muscle length occur on standing when these hyperkinesias are present. We have chosen to relabel these hyperkinesias as "weight bearing," rather than "isometric," but have retained the term "orthostatic," as it is far more firmly entrenched in the literature.

The orthostatic hyperkinesias are likely underdiagnosed, given limited access to SEMG in clinical practice. Thus they may not be rare, particularly in the elderly population. The encouraging use of smart phone technology may increase the diagnostic sensitivity of OT, particularly where SEMG (or even access to neurologists) is limited. Referral for SEMG confirmation of the diagnosis of OT or OM could help elucidate the prevalence of these hyperkinesias and gather data in larger numbers of subjects. Additionally, greater utilization of SEMG in the evaluation of elderly patients with non-specific gait and balance disorders could be useful.

Further research is necessary to better define the true prevalence, pathophysiology, and optimal therapy of OT and OM. Toward that end, we recommend that future manuscripts accepted into the literature pertaining to these weight-bearing hyperkinesias only include patients who have been diagnosed with multi-channel SEMG.

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