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Clinical and Neurophysiologic Spectrum of Orthostatic Tremor: Case Series of 26 Subjects

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Abstract: Orthostatic tremor (OT) is a condition described as high-frequency tremors predominantly in the legs and trunk, which are present not only in the standing position but also during isometric contraction of the limb muscles. This report is one of the largest OT series describing clinical and neurophysiologic findings in 26 subjects with OT. The main findings included 13.0 to 18.6 Hz leg tremors while standing with varied patterns of phase relationships between the antagonists of the ipsilateral leg and between the homologous muscles of the contralateral leg, short latency tremor onset upon standing with abrupt cessation after sitting, coexistence of tremors in the cranial structures and the arms, and sense of unsteadiness without actual falls. Although the oscillator of OT is most likely located in the brainstem, cerebral cortex, basal ganglia, and cerebellum may also be involved in its pathogenesis. © 2005 Movement Disorder Society

Key words: orthostatic tremor; clinical manifestation; neurophysiologic findings; tremor analysis; phase relationship

Orthostatic tremor (OT) is a condition manifested by high-frequency tremor predominantly involving the trunk and legs while standing. Although Heilman[1] first coined the term OT in 1984; this condition had been earlier described in an Italian study in 1970.[2] OT is believed to be driven by a central oscillator[3–5]; however, its pathophysiology, oscillator location, and circuitry are unknown. Possible anatomic regions of the oscillator include the cerebellum, brainstem, and spinal cord.[6–8] The role of dopaminergic system in OT has been raised recently.[9] Although termed OT, the tremors may occur during isometric contraction of the arm or leg muscles independent of stance and are absent in the upright position without weight bearing.[5,10] Because of the coexistence of lower-frequency tremors (6–8 Hz) resembling essential tremor (ET) and a positive family history of ET in some patients, it is controversial as to whether OT is a variant of ET,[11–15] or perhaps the lower-frequency activity represents a subharmonic of the primary 13 to 18 Hz tremor. There are also conflicting reports regarding the phase relationship (co- or alternating contraction) of electromyographic (EMG) bursts in ipsilateral antagonist and contralateral homologous muscles of the legs.[4,12,16] This study describes clinical manifestations and neurophysiologic findings in 26 subjects with OT examined at the Clinical Motor Physiology Laboratory at Columbia University Medical Center.

SUBJECTS AND METHODS

Medical records of 26 subjects with clinically suspected and neurophysiologically confirmed orthostatic tremor were reviewed. There were 21 women (age range, 47–83 years; mean age, 67.3 years) and 5 men (age range, 46–83 years; mean age, 66.8 years). All subjects had computerized quantitative tremor analysis using piezoresistive accelerometry recording movement and surface EMG recording muscle activity from the arms and legs while sitting comfortably; sitting with arms extended (without and with inertial loading); sitting and performing specific tasks: moving finger-to-nose, pouring water from one cup to another and writing; sitting and extending one leg; standing on both legs (arms extended or hanging by sides); standing on one leg; and walking in place. In 3 subjects, isometric contraction of

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the leg muscles while sitting was performed to test whether leg tremors similar to OT could be reproduced.

Tremor amplitudes were derived off-line by double integration of accelerometric data after filtering out low-frequency drift (<2 Hz) and averaging. Tremor frequencies were calculated from accelerometry and electromyography using a fast Fourier transform to generate autospectra. Coherence analysis was then applied to determine phase relationship of EMG bursts in ipsilateral antagonist and contralateral homologous muscles. Statistically significant coherence between two muscle burst discharge signals was determined as 0.25 or greater. A similar methodology as described by Boose and coworkers[17] was used to interpret EMG phase relationships. An EMG phase difference of −45° to 45° was defined as co-contraction and a phase difference of 135° to 225° was considered as alternating contraction. Phase differences that fell outside these ranges were considered neither co-contraction nor alternating contraction. In addition, bispectral and bicoherence analyses were used to assess quadratic nonlinear coupling between high frequency (OT range) and low frequency (ET range) in 8 subjects with leg tremor frequencies in both OT and ET ranges. Thirty-two windows for each EMG were used for calculation.

RESULTS

Clinical Findings

The study was composed of 26 OT subjects: 21 women and 5 men. Table 1 shows the summary of clinical findings. Ages of symptom onset ranged from 34 to 79.5 years in women and 36 to 81 years in men with respective mean ages of 58.7 and 55.4 years. Of the 26 subjects, 22 felt tremors in the legs and 19 had a sense of unsteadiness. Eighteen subjects complained of tremor elsewhere including lips, jaw, hands, and whole body. Only 4 subjects with a sense of unsteadiness actually fell. Three subjects reported pain in the legs. Tremors were present while standing in all subjects and were relieved by sitting, walking, or leaning against the wall in 24 subjects (no data in 1 subject and persistence of tremors while walking in the other). Of 11 subjects with available information regarding alcohol consumption, 2 subjects stated that their leg tremors were improved by drinking alcohol and 1 subject sometimes had less-severe tremors in the legs after drinking. One patient had pulmonary and cutaneous sarcoidosis, and peripheral neuropathy of unknown etiology. One patient had a past history of poliomyelitis predominantly involving the left leg. Two subjects had blepharospasm. None of the subjects had

TABLE 1. *Clinical information*

Subject no.	Sex	Age (yr)	Duration from onset to the test	Age of onset (yr)	Feeling tremor	Sense of unsteadiness	Actual falling
1	F	66	3 1/2 yr	62 1/2	Yes	Yes	No
2	F	82	2 1/2 yr	79 1/2	Yes	N/A	No
3	F	65	10–15 yr	50	Yes	Yes	No
4	F	73	>2 yr	71	No	Yes	No
5	M	81	22 yr	59	Yes	Yes	N/A
6	F	76	5 yr	71	Yes	Yes	N/A
7	M	83	2 yr	81	Yes	Yes	Yes
8	M	46	10 yr	36	Yes	N/A	N/A
9	F	70	17 yr	53	Yes	Yes	Yes
10	F	66	21 yr	45	Yes	N/A	N/A
11	F	68	15 yr	53	No	Yes	No
12	F	65	6 mo	64	Yes	Yes	No
13	F	74	8 yr	66	Yes	Yes	No
14	F	58	7 yr	51	No	Yes	No
15	F	73	10 yr	63	Yes	Yes	Occasional falls (“not pick my legs up”)
16	F	69	2–4 yr	65	Yes	Yes	No
17	F	54	20 yr	34	Yes	Yes	Fell in the bathtub twice
18	F	65	8 yr	57	Yes	Yes	No
19	F	59	6 yr	53	Yes	Yes	No
20	F	72	2 yr	70	Yes	N/A	N/A
21	F	83	25 yr	58	Yes	N/A	N/A
22	M	49	4 yr	45	No	Yes	No
23	F	47	4 yr	43	Yes	N/A	N/A
24	M	75	19 yr	56	Yes	No	No
25	F	67	6 yr	61	Yes	Yes	No
26	F	62	4 mo	62	Yes	Yes	No

parkinsonism or cerebellar dysfunction. There were family histories of Parkinson's disease in 3 subjects and family histories of tremors in 4 subjects (1 with tremors possibly induced by an antidepressant). In one subject, her mother had a history also suggestive of orthostatic tremor. Multiple medications were tried to treat OT, including clonazepam, gabapentin, propranolol, levetiracetam, valproic acid, primidone, phenobarbital, topiramate, zonisamide, carbidopa/levodopa, and pramipexole (Table 2). Although the information concerning the medication dosage was not available, by patients' report, leg tremors clearly diminished in 2 subjects treated with clonazepam and in 1 subject treated with combination of clonazepam and levetiracetam. There was some benefit in 3 subjects treated with gabapentin, 1 subject treated with valproic acid, and 1 subject treated with primidone. In another subject, propranolol reduced hand tremors but did not decrease leg tremors. Other medications did not show benefit for OT.

Imaging

Of 13 subjects who had brain magnetic resonance imaging (MRI) scans, results were normal in 9 subjects, showed microvascular ischemic diseases in 2, an old infarct in the right posterior temporoparietal lobe in 1, and mild diffuse atrophy in another.

Neurophysiologic Findings

EMG and nerve conduction studies were performed in 6 subjects, which revealed peripheral neuropathy in 1 patient (a subject with sarcoidosis) and normal results in the other 5 subjects.

Tremor analysis revealed high-frequency leg tremors in a standing position in all subjects. The frequencies predominantly ranged from 12.0 to 18.6 Hz. The latencies from the onset of standing to the tremor onset were 200 to 1,000 msec, based on data from 4 subjects. And, based on data from 2 of those 4 subjects, the latencies from sitting to the tremor cessation were 2 to 3 seconds (see Fig. 1). There were 2 subjects with leg tremors of higher and lower frequency than in general range. In one, tremor frequencies were 19.0 to 23.0 Hz, but the tremors were inconsistent and of low power and low amplitude. In the other, leg tremors while standing were from 10.0 to 12.0 Hz.

In 8 subjects, conventional-frequency spectra from leg EMG showed that there were two dominant frequency bands, i.e., ET (5.0–8.4 Hz) and OT (12.2–17.4 Hz). Further analysis showed that 79% of EMG recordings had peak appearance of these two frequencies in the bicoherence spectrum. This finding suggests that cross-quadratic nonlinear coupling may exist between high-frequency EMG signals in the OT band and the lower-frequency signals in the ET band. Although EMG signals were coherent in the ipsilateral antagonist leg muscles and between side-to-side homologous leg muscles, EMG phase relationship between these signals varied among individuals as well as within the same individual (see Table 3). This variation included co-contraction, alternating contraction, or neither pattern. Mixed patterns were the most common findings, followed by co-contraction.

High-frequency leg tremors similar to OT were reproducible through isometric contractions of leg muscles in one of 3 cases. Leg tremors diminished or disappeared in the non–weight-bearing legs in 10 of 10 subjects. Walking in place also decreased or abolished the leg tremors in 9 of 12 subjects.

Six subjects had leg tremors while sitting. The frequencies were in the same range as tremors while standing in 4 subjects, were in the range of postural leg tremors in 1 subject, and were neither in the range of leg tremors in standing position nor postural tremors in 1 subject. Of 14 subjects evaluated with the legs extended, 6 had postural leg tremors with frequency ranges of 5.0 to 9.7 Hz.

Arm tremor data were available in 24 of 26 subjects. Tables 4 and 5 demonstrate the type and frequencies of the arm tremors. The frequencies of the postural tremor in a sitting position and kinetic tremor were predominantly in the range of ET, whereas the postural arm tremors while standing were mostly in the range of OT. When standing with arms by sides, 4 subjects had arm tremors in the ET range and 6 in the OT range. In 3 subjects, there were also arm tremors at rest: 2 in the frequency range of ET and the other in two frequency ranges (parkinsonian tremor and OT).

TABLE 2. *Response to medications*

Medication	Subjects (n)		
	No benefit	Some benefit	Good benefit
Clonazepam	3	1	2
Gabapentin	1	3	—
Propranolol	2[a]	—	—
Primidone	1	1	—
Valproic acid	1	1	—
Phenobarbital	1	—	—
Clonazepam and levetiracetam	—	—	1
Topiramate	1	—	—
Zonisamide	1	—	—
Levodopa/carbidopa	1	—	—
Pramipexole	1	—	—

[a]Only benefit on hand tremors in 1 subject.

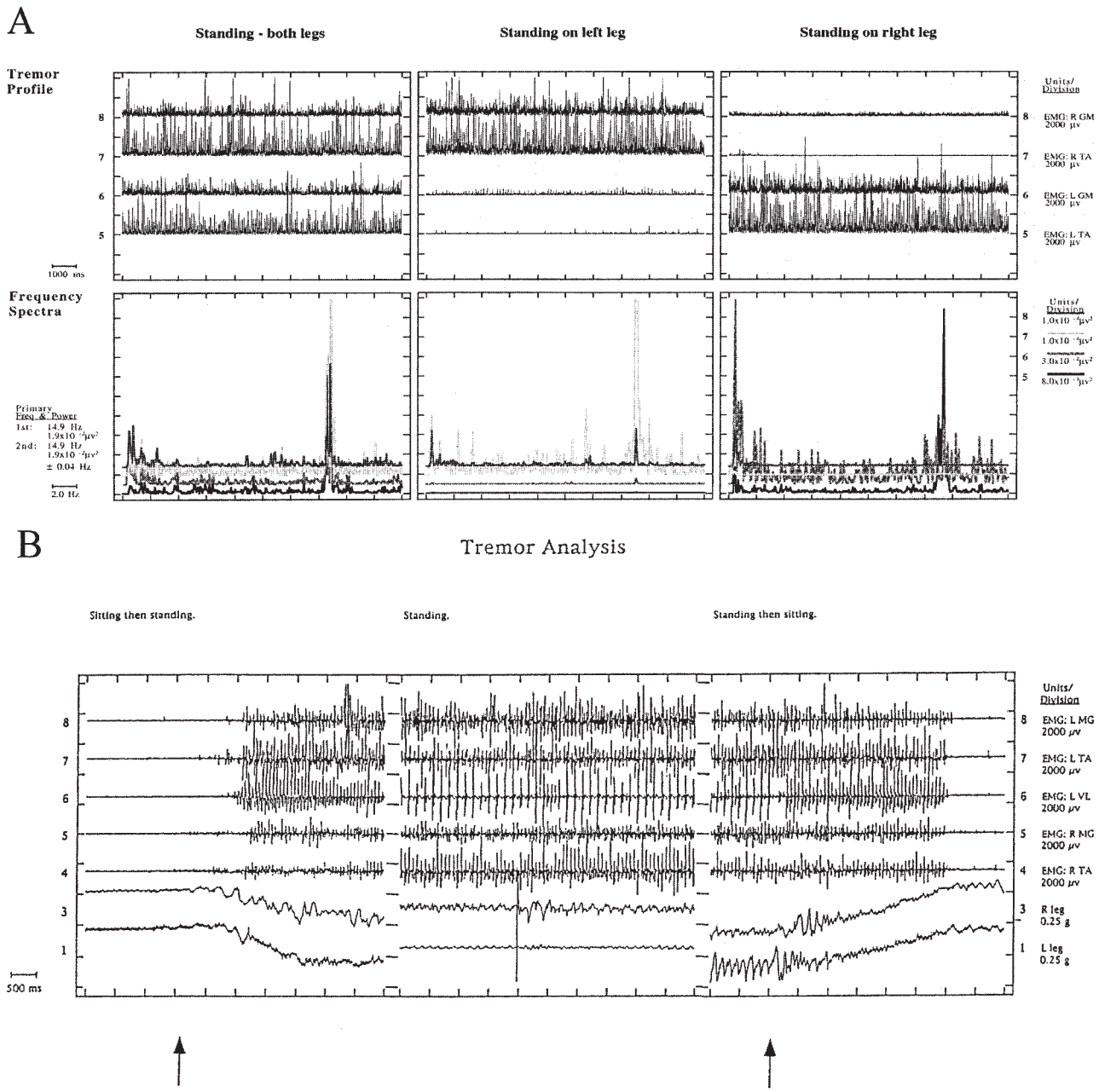

FIG. 1. Sample tracings from patients with orthostatic tremor (OT). Tremor analysis tracings of patients with OT illustrating leg tremors in different conditions. **A:** The tracings show tremor profiles and frequency spectra when the subject stood on both legs and while standing on one leg at a time. The data were obtained from bilateral tibialis anterior (TA) and bilateral gastrocnemius (GM) muscles. There were 14.9 Hz leg tremors in both legs while standing on both legs. When standing on one leg, tremors significantly diminished in the non–weight-bearing leg. **B:** Tracings obtained from a different subject demonstrating that leg tremors developed and disappeared with a notably short latency after changing the position from sitting to standing and from standing to sitting, respectively, as demarcated by the arrows.

DISCUSSION

In our series, there are more women than men with OT, with similar age of onset, ranging from 34 to 81 in both sexes. Unlike the findings in the most recent review of 41 patients with OT,[18] none of our patients had parkinsonism. Clinical manifestations of our patients include tremors, sense of unsteadiness, and leg pain. Although many patients felt unsteady, they generally did not actually fall and did not have cerebellar dysfunction. It has been postulated that a sense of unsteadiness was

TABLE 3. *Phase relationship*

Phase relationship	Subjects (n)	
	Homologous muscles	Antagonist muscles
Co-contraction	7	8
Alternating contraction	0	0
Co-contraction or alternating contraction	2	0
Neither co-contraction nor alternating contraction	5	1
Mixed	9	11
No data	3	6

due to tremors disrupting the proprioceptive input from the legs.[19]

The tremors were present mainly in the legs but also in the other regions such as hands, lips, jaw, or even the whole body. Involvement of cranial muscles has also been reported in one study of 6 OT patients.[8] Only a minority of our patients had solely leg tremors. This finding supports the existing evidence of a supraspinal generator in OT. Because leg tremors are present in the weight-bearing leg and diminished in the non–weight-bearing leg, the underlying pathophysiology is not likely related to the upright position per se, but rather related to mechanisms or pathways that modulate the perception of weight bearing or upward force applied to the legs. Moreover, because the leg tremors can be reproduced by isometric contraction of the leg while sitting in 1 of 3 subjects, mechanisms that modulate muscle contraction may also underlie the pathogenesis of OT. In one study,[20] unsteadiness induced by vestibular galvanic stimulation or leaning backward in normal subjects caused 16 Hz EMG activity in tibialis muscles, resembling the findings in OT patients. However, this high-frequency EMG activity was not induced by muscle activation when the subjects were not unsteady, suggesting that OT might be an exaggeration of a physiological response to the instability.

TABLE 4. *Type of arm tremor in 24 subjects with arm tremor data*

Type of arm tremor	Subjects (n)
No tremors	3
Postural tremor in a sitting position	1
Postural tremor in a standing position	1
Kinetic tremor	3
Tremor in a standing position with arms extended or hanging by sides	1
Kinetic tremor and postural tremor in a sitting position	4
Rest tremor and postural tremor in a sitting position	1
Postural tremor in sitting and standing positions and kinetic tremor	1
Rest tremor, postural tremor in a sitting position, and kinetic tremor	1
Postural tremor in a sitting position, kinetic tremor, and tremor in a standing position with arms by sides	5
Postural tremor in sitting and standing positions, kinetic tremor, and tremor in a standing position with arms by sides	2
Rest tremor, postural tremor in sitting and standing positions, kinetic tremor, and tremor in a standing position with arms by sides	1

TABLE 5. *Types and frequencies of the arm tremor*

Tremor type	Frequency (Hz)			
	4–5	5–10	10–12	13–19
Rest tremor	1	2	0	1
Postural tremor in a sitting position	0	12	1	4
Postural tremor in a standing position	0	1	0	6
Tremor in a standing position with arms by sides	1	4	0	6
Kinetic tremor	1	15	1	4

The phase relationship between the antagonist muscles in ipsilateral legs and between homologous muscles in the contralateral legs are reported differently in various studies.[4,12,16] In our report, the most common phase relationships are (1) a mixed co-contraction pattern with alternating contraction or no discernible pattern by phase analysis, and (2) pure co-contraction in antagonists and in homologous muscles. The onset and cessation of the leg tremor can be quite abrupt with position changes from sitting to standing and vice versa. The co-existence of arm tremor mainly in the form of postural and kinetic tremor of 5 to 10 Hz might suggest that OT is a variant of ET. Alternatively, because some OT subjects had leg tremors of both lower frequency similar to ET and the higher frequency of OT, the lower-frequency oscillations may represent a subharmonic of the higher-frequency leg tremors. Using bispectrum and bicoherence analyses, we found that the 13 to 18 Hz OT frequencies are significantly related, in a nonlinear manner, to the lower 6 to 8 Hz frequencies when both frequency bands coexist in the same patient. We speculate that OT may not be generated independently but results from central oscillators in common with ET.

At present, the pathophysiology of OT is unknown. Because this and other studies have shown that OT symptoms involve bilateral cranial structures, arms, trunk, and legs, the tremor generator is most likely located in the brainstem. The circuitry involving in OT pathogenesis may be complex, with feedback and feed

forward modulation, and might not involve one brain region. The findings that the transcranial magnetic stimulation over the motor cortex reset OT but lumbar stimulation had no effect on OT supported that OT was supraspinally generated.[21] There are some reports indicating that OT could be associated with Parkinson's disease.[18,22,23] Furthermore, a single-photon emission computed tomographic study[24] using (123) I-FP-CIT (2-β-carbomethoxy-3-β-(-4-iodophenyl)-N-(3-fluoropropyl)-nortropane) as a dopamine transporter tracer[9] reported a reduced striatal dopamine uptake in 11 OT patients without parkinsonism. These finding suggests that dopaminergic system is involved in OT. In our series, there was no parkinsonism in any subject, although 1 subject had arm rest tremor in the frequency range of parkinsonian tremor. Another study,[25] using H_2 ^{15}O positron emission tomography, demonstrated an activation in bilateral cerebellar hemisphere, cerebellar vermis, contralateral thalamus, as well as lentiform nucleus in 4 patients with OT, who also had postural arm tremor of 14 to 16 Hz while standing and occasional bursts of 14 to 16 Hz postural tremor in a supine position. Combination of these findings indicate that, although the OT generator is likely located in the brainstem, other regions such as motor cortex, basal ganglia, and cerebellum may also be involved.

Many agents, including benzodiazepines, dopaminergic agents, antiepileptics, β-blockers, and muscle relaxants, have been tried for OT. Among those agents, clonazepam appears to be the most effective. Although there is evidence that the dopaminergic system is involved in OT pathogenesis, the response to L-dopa or dopaminergic agonists varies.[18,23,24,26]

CONCLUSION

OT is a neurologic condition manifested by tremors, mainly in the legs, but also in the cranial structures, arms, and trunk. The patients tend to feel unsteady without actually falling. Leg tremors are predominantly present in the standing position, with a reduction in a sitting position, while walking or with a non–weight-bearing task. Neurophysiologic findings in our OT case series consisted of 13.0 to 18.6 Hz leg tremors while standing with different patterns of phase relationships between the antagonist muscles in the ipsilateral leg and between homologous muscles in the contralateral leg (a mixed pattern is most common, followed by co-contraction), short latency tremor onset upon standing with abrupt cessation after sitting, and co-existence of arm tremors mainly in the form of postural and kinetic tremors. Rest tremors were also present in a few cases, without other clinical parkinsonian features. In addition, we found that, in some patients with two coexisting frequency bands, those two bands (6–8 Hz and 13–18 Hz) were related in a nonlinear manner, which suggested that OT may be generated independently but results from central oscillators in common with ET. Although OT is most likely generated in the brainstem, other brain regions such as cerebral cortex, basal ganglia, and cerebellum are also involved in generating or modulating the tremors. The response to treatment varies and benzodiazepines appear to be the most-effective agents.

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