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Case Report

Levodopa-Responsive Primary Slow Orthostatic Tremor: A Premotor Sign of Parkinson's Disease?

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Keywords
Orthostatic tremor · Dopaminergic drug · Dopamine transporter · Premotor sign · Parkinson's disease

Abstract
We present a case of primary orthostatic tremor (OT) responsive to dopaminergic medication. The patient was a 62-year-old woman, who had leg tremor on standing for 2 years. No parkinsonian or other neurological signs were observed. Surface electromyography of the quadriceps muscles showed regular 5–6 Hz muscle discharges. [^{123}I]-FP-CIT DAT-SPECT imaging revealed decreased specific binding ratio values in the striatum compared with age-matched controls. Her leg tremor almost completely disappeared following administration of levodopa 200 mg and pramipexole 0.75 mg. Since her OT with low-frequency discharge was responsive to dopaminergic medication, we speculate that it may be a premotor sign of Parkinson's disease.

Introduction

Orthostatic tremor (OT) is characterized by high-frequency tremor of the legs that appears on standing and is relieved by sitting, walking, or leaning against a wall. Patients often report a feeling of unsteadiness on standing. OT is idiopathic without any associated features

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(primary OT) in about 75% of patients [1], while about 25% have additional neurological features (secondary OT/OT plus), such as Parkinson's disease (PD), cerebellar degeneration, restless legs syndrome, peripheral neuropathy, head injury, or aqueduct stenosis. Surface EMG recordings reveal rhythmic discharge of lower limb muscles on standing, with pathognomonic frequencies between 13 and 18 Hz. This rhythmic activity disappears when the patient walks or sits. Although the clinical features are quite well defined, treatment options are limited.

Several recent studies have furthered our understanding of the central oscillatory network involved in OT. fMRI (functional magnetic resonance imaging) and ^{18}F-FDG-PET (fluorodeoxyglucose positron emission tomography) studies have identified ponto-cerebello-thalamic-primary motor cortical network abnormalities in primary OT [2]. However, the underlying pathophysiology remains largely unknown.

We report a female patient with primary OT who presented with tremor frequencies of 5–6 Hz in surface electromyography (slow OT; also known as pseudo-OT). [^{123}I]-FP-CIT DAT-SPECT (dopamine transporter single-photon emission computed tomography) imaging showed a decreased specific binding ratio (SBR) in the striatum compared with age-matched normal subjects. She showed a dramatic improvement of tremor in response to dopaminergic medication.

Case Report

A 63-year-old woman presented with complaints of leg tremor and unsteadiness in the standing position for the previous 2 years. She had a history of angina 5 years before and was taking a calcium antagonist for a short period, but there was no history of mental illness or intake of psychotropic drugs.

On examination, she showed incessant quivering in her lower limbs while standing, but the movement disappeared when she was asked to walk, sit, lie down, or lean against the wall for support. While she was standing, the quadriceps muscles showed fine ripples. No such movement was observed in other parts of the body. No parkinsonian signs such as bradykinesia, muscle rigidity, or gait disturbance (small steppage gait, frozen gait, etc.) were found. She did not show supranuclear gaze palsy, cerebellar signs, autonomic dysfunction, restless legs syndrome or cognitive dysfunction either. She showed no REM sleep behavioral disorder or insomnia (known prodromal manifestations of PD). Alcohol did not improve the tremor, and there was no family history of tremor or parkinsonism.

Blood tests, including a complete blood count, various electrolytes, glucose evaluation, renal and liver functions, vitamin B_{12}, and thyroid function, were all normal, and chest X-ray and electroencephalogram were noncontributory. Head MRI was normal except for small infarctions in the cerebral white matter. Surface electromyography of the lower leg muscles showed rhythmic spontaneous motor unit potentials at the frequency of 5–6 Hz with a burst duration of 100 ms and an amplitude of 200–400 μV (Fig. 1). There was a clear left-right difference in the motor burst, and the amplitude on the right side was larger than that on the left side. The tremors were not coherent among muscles and legs. No discharges were recorded while she was supine or sitting with her feet dangling.

Because the frequency of her OT was similar to the resting tremor frequency seen in PD, we performed a [^{123}I]-FP-CIT DAT-SPECT study using the procedures described in our previous report [3]. For assessment of the DAT images, the SBR was calculated semi-quantitatively using DAT VIEW automated analysis software (Nihon Medi-Physics, Tokyo, Japan). The SBR

values were 3.31 in the right striatum and 3.50 in the left striatum (Fig. 2), which are decreased compared with age-matched normal subjects [4].

The patient was put on levodopa 100 mg per day initially and then increased to 200 mg per day, whereupon marked improvement was noticed. Her symptoms improved further with additional administration of pramipexole 0.75 mg per day. She continued taking this medication, and there was no evidence of progression during follow-up for several months.

Discussion

OT is defined as a rapid tremor that appears only while standing, and chiefly affects the lower limbs, with a characteristic frequency of 13–18 Hz. Other clinical syndromes have lower discharge frequencies (less than 13 Hz); this form has generally been referred to as "slow OT" or "pseudo-OT" and is included in the latest classification of tremor [5]. The tremor frequency of our patient was 5–6 Hz, which is consistent with slow OT. Slow OT is frequently associated with other diseases such as multiple sclerosis, Grave's disease, cerebellar ataxia, and PD. Because our patient did not show any other neurological disorders, we diagnosed her tremor as primary OT. Our patient also did not show gait unsteadiness or falls, which are frequently observed in patients with slow OT.

Orthostatic myoclonus (OM) is an important differential diagnosis, as it shows similar clinical features to slow OT. It manifests as unsteadiness or leg-jerking on standing and can lead to recurrent falls or difficulty in gait initiation. Leg shaking often does not improve with walking [6]. It rarely occurs in isolation and may develop on a background of neurodegenerative disease. Surface EMG shows 9–19 Hz, nonrhythmic (not periodic) muscle bursts with a duration of 50–100 ms. We think the clinical features and EMG findings exclude OM in our case.

While clonazepam and gabapentin are considered first-line therapeutics, there have been conflicting reports on the efficacy of dopaminergic agents in treating primary OT. Our case responded well to levodopa and pramipexole. One early study by Wills et al. [7] found significant improvement in 5 of 8 patients (62.5%) on levodopa (up to 750 mg/day), and another case report documented significant improvement of OT symptoms with pramipexole [8]. However, later studies have been less encouraging. Katzenschlager et al. [9] evaluated 7 OT patients with an acute levodopa challenge (200 mg levodopa in a single dose) and found only a small (nonsignificant) improvement on EMG. Gerschlager et al. [1] reported transient benefit in 7 of 15 (46.7%) patients on a mean levodopa dose of 425 mg/day; only 2 of the 15 (13.3%), both of whom had associated PD, showed sustained benefit. In a combined analysis of several larger case series on levodopa administration, only 10 of 70 patients (14.3%) had any reported benefit [10].

Our clinical observations gain additional support from the functional neuroimaging study. A [^{123}I]-FP-CIT DAT-SPECT scan is indicated for striatal dopamine transporter visualization to evaluate patients with suspected dopamine deficiency. The SBR values of our case were clearly decreased compared with age-matched normal subjects, suggesting presynaptic dopaminergic deficits at the striatum. Katzenschlager et al. [9] also demonstrated significantly reduced [^{123}I]-FP-CIT uptake in 11 OT patients as compared to 12 age-matched normal controls. Those patients did not have PD. On the other hand, Trocello et al. [11] reported that OT is not necessarily associated with DAT-SPECT abnormalities, although their cases were limited to a subtype of high-frequency OT. Subsequent studies also reported negative results. In a more recent study, uptake in 18 of 19 OT patients was normal, and the only abnormal result was

found in a patient with concurrent OT and PD [12]. Based on these reports, it seems likely that dopaminergic abnormalities are present in some patients with primary OT. However, at this point, the role of the nigrostriatal dopaminergic system in OT pathophysiology remains unclear.

Major clinical features in our case were consistent with primary slow OT. Thomas et al. [13] reported 4 patients with a slow debilitating standing tremor, described as pseudo-OT, that appeared years before parkinsonian symptoms were seen. In all 4 patients, the tremor, whose dominant frequency was 6.2–6.9 Hz (slow OT), responded dramatically to levodopa administration. All these patients had dopamine transporter abnormalities. Similarly, there have been some reports of cases with slow OT that responded to levodopa [14] or showed decreased dopamine transporter uptake at the posterior putamen and caudate [15]. These cases were similar to our case. We think these reports support the idea that slow OT is a consequence of dopamine depletion. However, even in the case of conventional fast tremor, dopaminergic medication was effective in some patients [7, 8].

Considerable efforts have recently been made to define prodromal stages of PD, before motor signs permit classical diagnosis. There is clear evidence that hyposmia, REM sleep behavior disorder, constipation, decline in executive function and depression can be present in prodromal PD. It is unclear at this time whether our case will develop PD in the future, but based on the dopamine imaging, we think it is plausible that primary "slow OT" could be a premotor sign of PD with potentially high sensitivity and specificity.

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Statement of Ethics

All authors hereby declare that all work was conducted in accordance with the Declaration of Helsinki (1964), and the submission of this manuscript for publication has been approved by Saiseikai Shonan Hiratsuka Hospital, Tokai University Oiso Hospital and Isehara Kyodo Hospital.

The patient was informed of the purpose of the case presentation, and informed consent was obtained from the patient.

Disclosure Statement

All authors declare that there is no conflict of interest regarding the publication of this article.

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Author Contributions

Fumihito Yoshii, MD (the principal researcher), examined the patient, contributed to data collection, interpretation, and wrote the manuscript. Wakoh Takahashi, MD, examined the patient together with Dr. Yoshii and reviewed the manuscript. Koji Aono, MD, performed surface electromyography and reviewed the manuscript.

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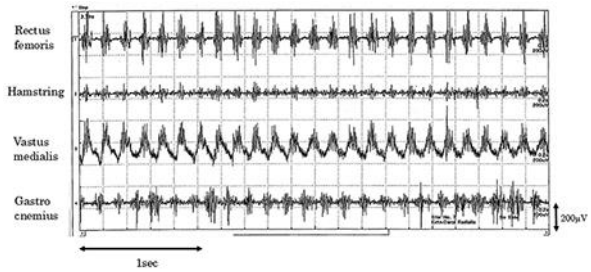

Fig. 1. Surface EMG showed slow (5- to 6-Hz) tremor of the right legs on standing. Highly synchronized discharges are present in the patient's legs.

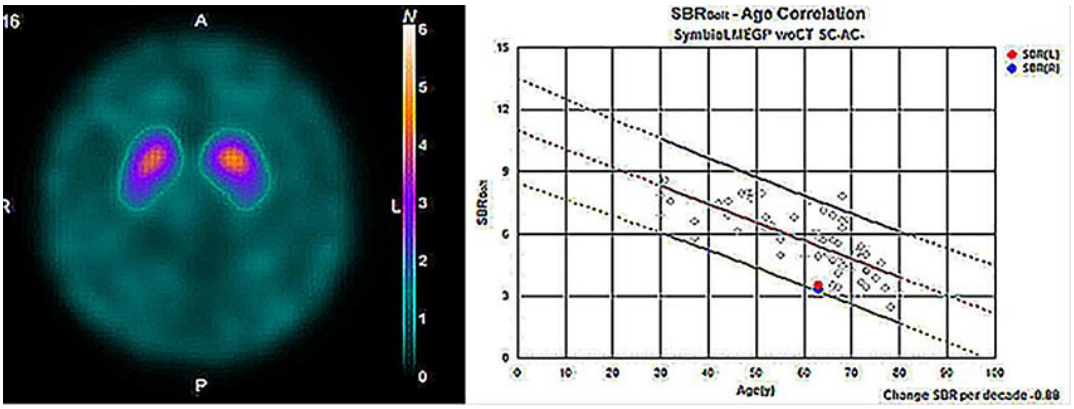

Fig. 2. [^{123}I]-FP-CIT DAT-SPECT imaging showing decreased dopamine transporter uptake at the striatum compared with age-matched normal subjects. Left figure: SPECT image of the patient. Right figure: scatter plot of SBR as a function of age in normal subjects. Patient's SBR value: right 3.31 (blue circle), left 3.50 (red circle).