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CASE REPORT

A Case of Tardive Dystonia with Task Specificity Confined to the Lower Extremities only during Walking

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Background: Task-specific dystonia (TSD) confined to the lower extremities (LE) is relatively rare. This report describes dystonia confined to the LE only during forward walking. This case required careful neurological and diagnostic assessment because the patient was taking several neuropsychiatric drugs that cause symptomatic dystonia, such as aripiprazole (ARP). **Case:** A 53-year-old man visited our university hospital with a complaint of abnormalities in the LE that appeared only during walking. Neurological examinations other than walking were normal. Brain magnetic resonance imaging revealed meningioma in the right sphenoid ridge. The patient had been treated for depression with neuropsychiatric medications for a long time, and his abnormal gait appeared about 2 years after additional administration of ARP. After the meningioma was removed, his symptoms remained. Surface electromyography showed dystonia in both LE during forward walking, although his abnormal gait appeared to be accompanied by spasticity. The patient was tentatively diagnosed with tardive dystonia (TD). Although dystonia did not disappear clinically, it was alleviated after discontinuing ARP. Administration of trihexyphenidyl hydrochloride and concomitant rehabilitation improved his dystonia until return to work, but some residual gait abnormalities remained. **Discussion:** We report an unusual case of TD with task specificity confined to the LE. The TD was induced by the administration of ARP in combination with multiple psychotropic medications. Careful consideration was required for clinical diagnosis, rehabilitation, and assessment of its relevance to TSD.

Key Words: aripiprazole; meningioma; task-specific dystonia

INTRODUCTION

Symptomatic dystonia includes diverse etiologies, with one representative instance being tardive dystonia (TD) induced by neuroleptics with dopaminergic blocking action. Adult-onset TD usually involves both craniocervical dystonia and segmental dystonia.[1)] Here, we report a patient who was hospitalized for the purpose of surgery for meningioma. Prior to hospitalization, the patient, who was also being treated for depression, showed TD in the lower extremities (LE) after additional administration of ARP (ABILIFY®, Otsuka Pharmaceutical), which is a partial dopamine (DA) agonist of the DA D2 receptor. Dystonia was ameliorated after ARP cessation, which suggested that it might have been induced by ARP. TD confined to the LE occurs at a low prevalence; in this case, the dystonia only appeared during walking. These findings indicate that the TD may have resembled task-specific dystonia (TSD). Although previous reports have described tardive syndrome that was attributed to ARP, dystonia appearing in the LE has not been reported.[2)] We report that TSD, which is similar to spastic gait and is localized to the LE during walking, is rare and should be

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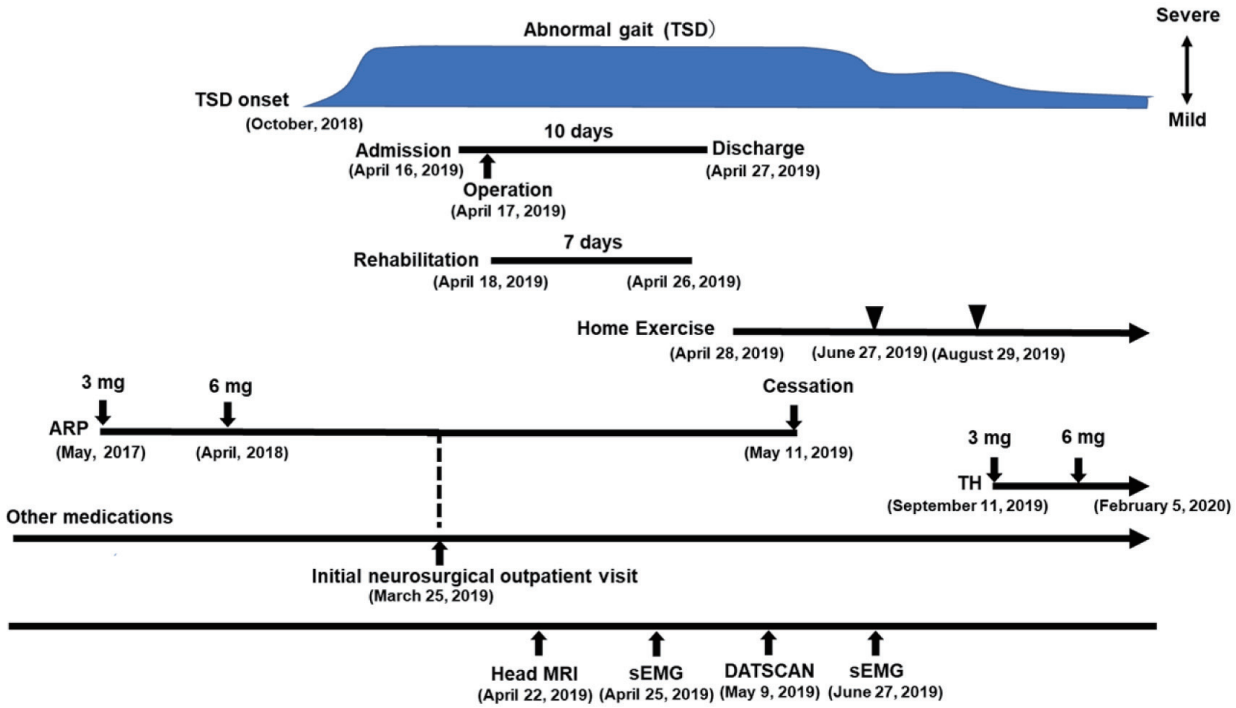

Fig. 1. Timeline of the clinical course. sEMG, surface electromyography; DATSCAN, dopamine transporter scan. Other medications included a group of drugs that did not change during treatment: lithium carbonate 100 mg, lorazepam 1 mg, flunitrazepam 1.5 mg, fluvoxamine 100 mg, clonazepam 1 mg, and brotizolam 0.25 mg (daily doses). Dates are given for events that can be confirmed after the first visit to our University Hospital. Black arrowheads on Home Exercise timeline indicate outpatient rehabilitation after discharge.

noted for rehabilitation intervention.

CASE

A 53-year-old man was receiving long-term treatment for depression with a regimen of neuropsychiatric drugs that included lithium carbonate (Limas®, Taisho Pharmaceutical, Japan), lorazepam (Wypax®, Pfizer Japan, Japan), flunitrazepam (Silece®, Eisai, Japan), fluvoxamine (Luvox®, Astellas Pharma, Japan), clonazepam (Landsen®, Sumitomo Pharma, Japan), and brotizolam (Lendormin®, Boehringer Ingelheim, Germany). Approximately 6 months after increasing the daily dose of ARP from 3 mg to 6 mg, he complained of trouble walking on planar floors and soon after of difficulties when pushing off the ground (**Fig. 1**). The patient visited the Department of Neurosurgery of our hospital on March 25, 2019 (**Fig. 1**). He had no history of perinatal or developmental disorders, general medical disease, head injury, drug abuse, or preceding abnormal involuntary movements. The patient was able to walk and perform daily activities independently. He was also able to commute to work and had no history of falls. Brain magnetic resonance imaging (MRI; Ingenia Provida 1.5T, Philips, USA) indicated a right sphenoid ridge meningioma. He was admitted to our hospital on April 16, 2019. The brain tumor (BT) was removed by neurosurgery on April 17, 2019 (**Fig. 2A,B**).

Despite complete removal of the BT, the disturbance of ankle movement during walking persisted. The day after BT removal, the patient was referred to the Rehabilitation Department. During the stance phase, he showed difficulties of right ankle inversion, plantar flexion, and dorsiflexion (**Fig. 3A**). This disturbance of ankle movement appeared only during gait. He could move his ankle without any difficulties while sitting, pedaling, and even during backward walking. At the start of rehabilitation on April 18, 2019 (**Fig. 1**), the muscle strength of the bilateral iliopsoas quadriceps, tibialis anterior, and gastrocnemius was almost 4 with manual muscle testing. Trunk balance was within normal limits, with a standing retention time of more than 10 s on each side in the tandem limb position with open eyes. He was prescribed a regimen of physical therapy for 40 min a day. Blood pressure during orthostatic movements was stable,

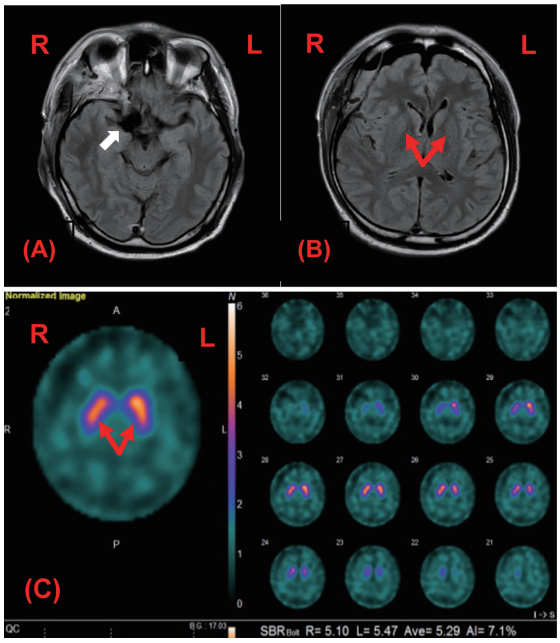

Fig. 2. Postsurgical brain MRI scans included axial FLAIR sequences. (A) Brain MRI scan showing the low-intensity area in the right sphenoid ridge, and the arrow indicates the location of the tumor after removal. (B) Bidirectional arrows indicate asymmetry in the shape of the basal ganglia. (C) ^{123}I-FP-CIT SPECT shows visually distorted tracer accumulation in right posterior putamen despite functionally normal binding capacity [SBR: right (R)=5.10, left (L)=5.47, average (Ave)=5.29, asymmetry index (AI)=7.10%]. These findings indicate that there is no loss of dopaminergic nerve terminals because the quantitative SBR is normal without a decrease in dopamine transporter density in the striatum.

and no discomfort or dizziness was noted during sitting, standing, or walking. At the start of gait training, his physical therapist noted an abnormal gait with the involvement of both LE. Dystonia was suspected by the physiatrist because an abnormal muscle tone in the LE was induced only during walking. Abnormal muscle tone in the LE did not appear in backward or lateral gait. However, there was a risk of tripping and falling because of decreased stability during walking, probably caused by the combined effects of bedrest after surgery and the abnormal gait. Therefore, consideration was given to rehabilitation aimed at restoring LE muscle strength and improving coordinated movements of the LE, especially the ankle joint, without inducing TSD. At the same time, the ward nurses were instructed to assist the patient in walking by grasping the ipsilateral axilla with the unilateral upper limb to prevent the ankle joints from crossing during walking.

Rehabilitation specifically for TSD confined to the LE has not yet been established. Therefore, we attempted to understand the characteristics of the patient's motor abilities to avoid TSD in this case, considering the task specificity of forward walking, and to find sensory motor reorganization, such as finding sensory tricks, based on a study of a small number of cases of spasticity and spastic dystonia in the past.[1,2] In this case, TSD was not induced by lateral or backward walking, nor by supine bicycle pedaling, and these were actively employed. In addition, stretching and isometric strength training did not induce TSD, and these were performed in parallel. Given that sensory tricks may be effective in treating dystonia, we tested measures that included the use of shoe soles with fine uneven special marks to stimulate the plantar area, binding of the LE, and application of vibration to the front part of the LE. However, we were unable to find a specific tactile stimulus that was effective for his dystonia. On April 26, 2019 (the last day of rehabilitation), the patient had a Barthel Index (BI) of 95 points, 5 of which were for bathing, and, although the TSD remained, the patient improved to the point where he was able to receive home care (**Fig. 1**). This improvement was attributed to a short but continuous rehabilitation program that avoided TSD.

Upon discharge from hospital, the patient was instructed in home exercises. The home exercises included lifting the hips in the supine position and standing on tiptoe while supporting the body with one hand in the standing position, thereby maintaining the range of motion and muscle strength in the LE without inducing TSD. The patient was also instructed to perform stretching exercises in a sitting position with towels placed over both ankle joints to extend the knees and back in a forward bending position, and balance exercises in a standing position with both upper limbs supporting the trunk and holding the posture while extending the bilateral Achilles tendons. Imaging of the dopamine transporter by ^{123}I-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) tropane single-photon emission computed tomography (^{123}I-FP-CIT-SPECT; Symbia S, Siemens Medical Solutions, USA) on May 9, 2019, showed that dopamine transporter binding capacity was functionally normal (specific binding ratio, SBR: right=5.10, left=5.47; **Fig. 2C**). Surface electromyography (EMG; Trigno Avanti Platform; Delsys, Natick, MA, USA) showed the findings of dystonia in his LE (**Fig. 4**).

At the first post-discharge rehabilitation outpatient visit on June 29, 2019, approximately 2 months after cessation

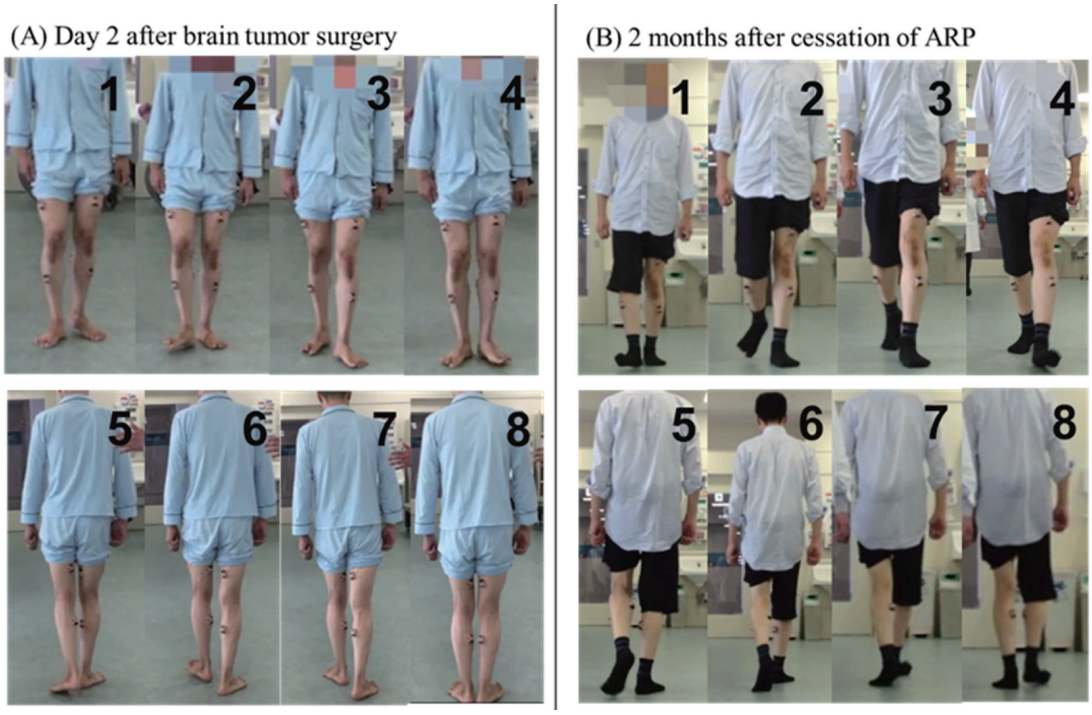

Fig. 3. TSD during forward walking after brain tumor surgery and after cessation of ARP. Forward gait transition observed from both frontal (1, 2, 3, 4) and posterior (5, 6, 7, 8) views, on the second postoperative day (A) and after cessation of ARP administration (B). The forward walking transition is shown in the order 1 to 4 and 5 to 8. Bilateral lower extremity dystonia is visible during forward gait, with both knees in extension during the swing phase of the gait cycle, and poor leg kicking. Bilateral dorsiflexion and toe extension are also observed, and the patient appears to have difficulty pushing off the ground or walking on tiptoe. Although not recorded, dystonia did not appear during backward walking or bicycle pedaling. Two months after ARP was discontinued following discharge from the hospital, the abnormal limb position associated with dystonia seen in (A) improved during walking (B). Although the gait appeared to be spastic, a diagnosis of dystonia was made based on findings from neurological examination and surface electromyography (**Fig. 4**).

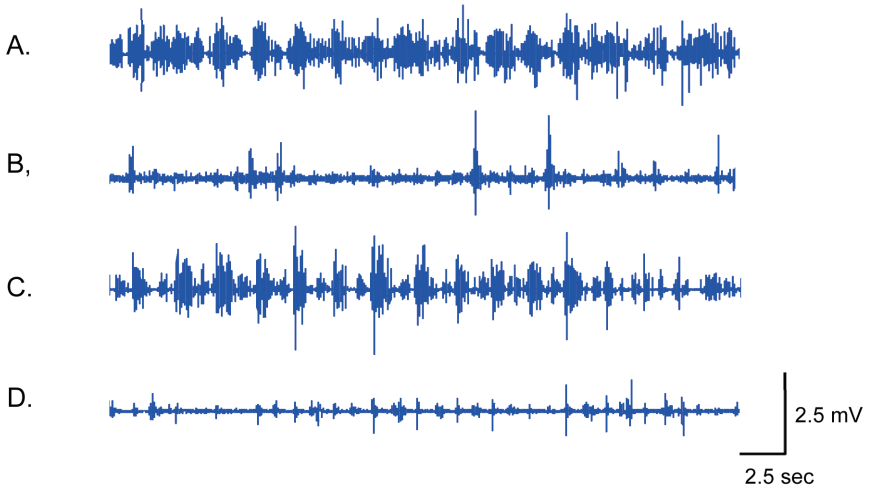

Fig. 4. Dynamic multichannel recordings of surface EMG during forward walking. Surface EMG results reflected either phasic or tonic co-contraction of agonist and antagonist muscles in the lower extremities. These were seen only during ambulation and not while sitting at rest, consistent with (but not diagnostic of) TSD. Bilateral asymmetric dystonic muscle activity was observed in the tibialis anterior and gastrocnemius muscles. Different traces (from top to bottom) refer to (A) right tibialis anterior, (B) right gastrocnemius, (C) left tibialis anterior, and (D) left gastrocnemius.

of ARP on May 11, 2019, the BI showed improvement with a full score of 100, while TSD during forward walking remained but showed improvement (**Fig. 3B**). After discharge, his dystonia still appeared crus predominant in both LE immediately after the start of forward walking. Therefore, he was prescribed 6 mg of trihexyphenidyl hydrochloride (TH) per day at a neurology outpatient clinic on September 11, 2019, after which his gait improved further, and he was able to return to work. The combination of rehabilitation and medication was effective in improving TSD as well as both muscle weakness and incoordination in LE. Written informed consent was obtained from the patient for publication of this report and the accompanying images.

DISCUSSION

The dystonia in this case appearing in the LE was activated only during walking and emerged after additional ARP administration during long-term neuropsychiatric treatment. Neuroleptics can induce movement disorders such as parkinsonism, akathisia, dyskinesia, and dystonia. The pathophysiology is usually considered to result from DA D2 receptor blockade during long-term neuroleptic exposure.

Dystonia caused by neuroleptics, termed TD, is less common than other tardive syndromes such as parkinsonism and choreic dyskinesia. Burke et al.[3] proposed criteria for the diagnosis of drug-induced dystonia and TD in 1982. According to these authors, the patient must have received neuroleptic treatment for at least 3 months. However, another report stated that one-fifth of the examined cases had been treated for less than one year, and half of the cases for more than 5 years.[4] The frequency of TD varies from 0.4% to 21.6%,[4] with a mean prevalence of 5.3%. There are only 14 reported cases worldwide of TSD localized to the LE during intense exercise, including walking.[5] However, a case of drug-induced TSD confined to the bilateral LE, as in the case reported here, has never been observed. Katz et al. reported that all seven cases of TSD localized to the LE were unilateral.[5] The prevalence of primary focal dystonia in adults, including the LE, is reported to represent only 0.7% of all adult-onset primary dystonia.[6] Therefore, cases of dystonia confined to the LE with delayed onset and task specificity appear to be extremely rare.

The patient's dystonia gradually developed after additional ARP administration; consequently, gait abnormalities improved after ARP cessation, which suggested drug-induced TD. ARP, a partial DA agonist at the DA D2 receptor, is thought to activate presynaptic DA D2 receptors to cause TD.[1] However, the pathophysiology and pathogenesis of TD remain unclear, although several hypotheses have been proposed. This pathological condition is generally thought to result from postsynaptic hypersensitivity caused by persistent inhibition of DA neurotransmission.[7] Inhibition of postsynaptic DA neurotransmission, caused by the agonistic effects of ARP on presynaptic dopaminergic nerves, may result in postsynaptic DA receptor antagonism by the usual antipsychotic agents involved in TD. We speculate that the specific effects of ARPs, which differ from those associated with common postsynaptic DA receptor antagonism by antipsychotics involved in TD, may have contributed to the development of TSD in this case. Peña et al. reported eight patients with tardive syndromes caused by ARP, with oro-bucco-lingual stereotypy being the most frequent.[2] In our case, however, the dystonia only appeared in the LE during walking. This finding is similar to isolated lower limb dystonia, which is usually associated with Parkinson's disease, peripheral trauma, and other brain lesions including cerebrovascular disease,[8] but is rarely induced by neuroleptics.[1] Schneider et al. reported a series of patients with isolated lower limb dystonia.[8] They observed isolated lower limb dystonia with plantar flexion of every toe and inversion of the foot, which were exaggerated during walking or standing, similar to our patient. None of their patients showed drug-induced dystonia.[8]

In the present study, the ^{123}I-FP-CIT SPECT was functionally normal, which indicated that the patient did not have Parkinson's disease. Abnormal sensorimotor plasticity and loss of cortical inhibition have been implicated in the etiology of TSD.[9,10] However, hypotheses of the condition cannot explain why these general changes appear only in certain parts of the body and not in unaffected regions.[9] A recent broad definition of TSD included loss of motor control confined to a specific motor skill; moreover, task specificity in focal dystonia may not be limited to skilled actions, with focal TSD occurring in activities that are relatively automatic.[11] An investigation using ^{11}C-raclopride positron emission tomography revealed that reduced striatum DA D2/D3 receptor levels might play important roles in TSD.[12] Therefore, ARP, a DA receptor partial agonist, may be relevant to the cause of this patient's TSD. Anticholinergic medications (AM), such as TH, are commonly used to treat dystonia.[13] AM is administered based on the speculative theory of imbalance between dopaminergic and cholinergic neurotransmission. According to this theory, imbalance results from the blockage of dopaminergic neurotransmission caused by antipsychotic drugs, which results in cholinergic

dominance in the striatum. After cessation of ARP in the patient, dystonia was alleviated, but his daily activities remained restricted. Therefore, after discharge from the hospital, TH was prescribed in the outpatient clinic of the Neurology Department of this hospital and was found to be effective (**Fig. 1**).

Although rehabilitation for focal dystonia including TSD has not been established, some findings are showing the effectiveness of drug treatment and concomitant use with botulinum toxin.[14] There is one report of ankle foot orthosis applied to a patient with TSD,[5] but this therapeutic approach was adopted because the patient presented a mild deformity of the ankle joint on the affected side that had been caused by painful dystonia. This scenario did not apply to our patient, who was able to perform walking exercises without the use of orthoses. If the patient had suffered prolonged pain, a lower limb orthosis might have been considered for safe ambulation. In the future, guidelines for orthotics in TSD should be carefully considered. Because abnormal sensorimotor reorganization for specific movements has been postulated as a pathophysiological mechanism of TSD, proposed rehabilitation methods have attempted to avoid excessive sensory input and have attempted to reorganize sensory information processing.[15] Strength training, stretching, relaxation, and postural exercises incorporated in this patient were considered potentially effective for TSD as learning-based motor-sensory exercises to reorganize sensory information processing,[16] but no effective results were obtained. Excessive muscle strength training and joint range of motion training in the affected area may cause an increase in sensory input and exacerbate dystonia. However, recovery of muscle strength in the LE and improvement of BI were obtained without aggravation of TSD, suggesting that inpatient rehabilitation was beneficial.

To date, rehabilitation guidelines for TSD have not been established, possibly because very few cases of TSD are confined to the LE and no large-scale cohort studies have been conducted. Therefore, it has been difficult to construct evidence-based rehabilitation treatment strategies for TSD. In the present case, we attempted to understand the characteristics of the patient's motor ability to avoid TSD, considering the task specificity of forward walking, and to practice walking using methods to modify plantar sensation, such as sole shape. We observed that TSD was not induced by walking laterally or backward, nor by bicycle pedaling in the supine position. Furthermore, stretch exercises and isometric strength training did not elicit TSD, and these were used for walking exercises.

Rehabilitation for dystonia has been attempted in the past, and rehabilitation using various sensory stimuli has been shown to be useful for focal dystonia, such as Musician's cramp, albeit in small studies, and positive results have been suggested.[17,18] However, in this case, the use of vibration of the LE and the use of soles that stimulate the sole did not provide any benefit for TSD of the LE during forward walking. Although the reason is not clear, a previous study of patients with writer's cramp described an intensive 8-week period during which movements and work exercises were performed to avoid movements that induce dystonia.[19] Therefore, in the present case, the hospitalization may have been too short to provide a useful rehabilitation effect. In addition, the home exercise program, which focused primarily on muscle weakness through stretching and isometric strength training, may have been inadequate for the rehabilitation of TSD. As a limitation in this study, noninvasive neuromodulation therapies such as transcranial magnetic stimulation and botulinum toxin injections, which have been reported to improve TSD by normalizing brain excitability through sensorimotor reorganization, should have been considered as rehabilitation treatment options for TSD.[16] Therefore, considering the difficulty of rehabilitating TSD and the difficulty of avoiding forward walking in daily life, it may have been beneficial for the patient to have been transferred to a convalescent hospital to continue rehabilitation for a period of 2 months or longer.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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