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Tremor and Other Hyperkinetic Movements

Case Reports

Orthostatic Tremor is Responsive to Bilateral Thalamic Deep Brain Stimulation: Report of Two Cases Performed Asleep

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Abstract

Background: Orthostatic tremor (OT) is a hyperkinetic movement disorder characterized by rapid tremor in the lower extremities or trunk upon standing.

Case Report: We report two patients presenting with OT, whose symptoms improved markedly following asleep bilateral thalamic deep brain stimulation (DBS) surgery.

Discussion: Medically refractory OT can respond favorably to asleep bilateral DBS surgery similar to awake surgery, and may have the advantages of less psychological trauma to the patient, shorter procedure times, and less exposure to anesthesia.

Keywords: Orthostatic tremor, deep brain stimulation, asleep, shaky legs syndrome

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Introduction

First reported in 1984, orthostatic tremor (OT) is a rare progressive hyperkinetic movement disorder characterized by imbalance and unsteadiness due to high-frequency leg and body tremors that occur only when standing.[1] Although early neurophysiological studies described the tremor to be of 13–18 Hz frequency, subsequent studies showed tremor outside that range.[2] Tremors attenuate when sitting, walking, or leaning on an object or person. Early or mild OT may respond to benzodiazepines (most commonly clonazepam), beta-blockers (most commonly propranolol), and antiepileptic drugs (most commonly gabapentin).[2,3] For patients with moderate to severe disease, oral medications have proved to be ineffective or are associated with intolerable side effects. We have previously reported a case of medically refractory OT that responded well to bilateral awake deep brain stimulation (DBS) of the ventralis intermedius (VIM) nucleus of the thalamus.[4] Additionally, there have been 17 other cases of OT reported in the literature that have undergone thalamic VIM awake DBS surgery.[5–12] We report on two patients with OT who responded favorably to bilateral thalamic asleep DBS.

Case reports

The two OT patients presented herein were implanted with bilateral Medtronic quadripolar 3387 DBS electrodes, and a Medtronic Activa™ PC implantable pulse generator. Our intraoperative asleep procedures and targeting for VIM DBS have been summarized in an earlier publication.[13] Briefly, the VIM was targeted indirectly relative to the midcommissural point using preoperative stereotactic imaging, and final electrode placement was determined via intraoperative computed tomography scans. The stereotactic coordinates of contact 1 were compared with target coordinates to verify that the vector error was less than 2 mm.

Case 1

R.B. is a 73-year-old male who first presented at age 60 with tremors of the legs when standing. With time, the tremors involved the trunk

Video 1. **Case 1.** Pre deep brain stimulation (DBS). The patient had almost immediate onset of orthostatic leg tremors on standing and had extreme difficulty standing without holding on to the table or walls. Post DBS (10 months). The patient demonstrates no visible tremor on standing, and has no difficulty at all standing in place without support.

while standing, and the hands during action or posture holding. Because of the leg tremors, he felt unsteady. By age 73, he claimed he could only stand in place for 15 seconds at a time. The leg tremors made him anxious, and proved resistant to several medications at maximum tolerated doses, including gabapentin (1,200 mg per day), clonazepam (1 mg per day), primidone (75 mg per day), and carbidopa/levodopa (25/100 0.5 mg tablet three times a day). His initial neurological evaluation revealed intact strength in all four limbs, reduced vibration sense and temperature sense in the distal upper and lower limbs, symmetric breakdown of rapid alternating movements, wide base upon standing but normal base when walking, moderate cautious gait, mild resting tremor in both hands, moderate action/postural tremor in both hands, mild tremor in either leg upon raising the leg while seated, moderate to severe bilateral leg tremors that were evident immediately upon standing in place, and no rigidity. During his initial examination, he could only stand for 7 seconds at most with feet wide apart before needing to lean or sit (Video 1). His blood tests were normal, including thyroid stimulating harmone (TSH), T3, and T4 levels. A brain DaTscan using ioflupane I-123 was unremarkable. Surface electromyography (EMG) recordings showed 10–14 Hz tremors of both lower limbs proximally and distally that were noted when standing but not when seated, as well as 6–7 Hz hand tremors on posture holding or action.

The patient underwent bilateral thalamic VIM asleep DBS surgery. The Talairach coordinates were (±14.25, –6.35, 0). Per protocol, contact 1 was targeted (Figure 1A). For both sides, the routine impedance check was normal and macrostimulation was unremarkable up to 8 V. The vector errors were 1.1 mm for both sides (Euclidean errors were also 1.1 mm bilaterally). Five days after surgery, initial programming was performed. The left VIM electrode settings were case(+), 0 and 2(–); amplitude 0.5 volt; pulse width 60 μs; and frequency 185 Hz. The right VIM electrode settings were case(+); contacts 8 and 10(–); amplitude 0.5 volt; pulse width 60 μs; and frequency 185 Hz. The double monopolar settings were chosen to target both his hand and leg areas, with transient paresthesias noted in the upper and lower

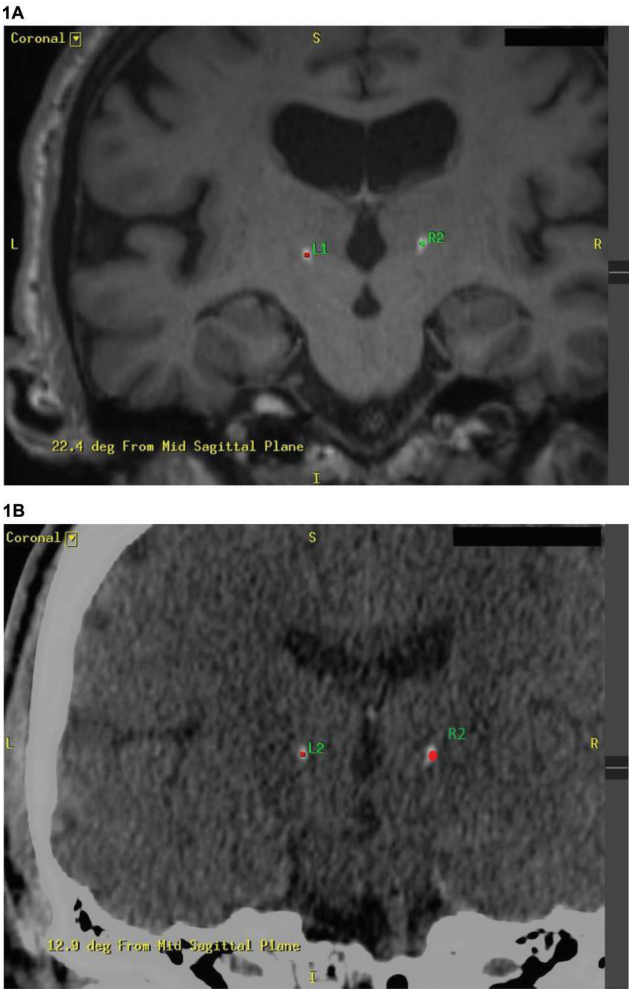

Figure 1. **Imaging of Lead Placement.** (A) Case 1. Preoperative magnetic resonance imaging and post-lead intraoperative computed tomography (CT) scan are co-registered using Medtronic FrameLink software. Targeted contacts are contact 1 on the left (L1) and contact 9 on the right (R2). On the left, the stereotactic error of contact 1 is 1.1 mm from the intended target (–14.25, 6.35, 0). On the right, the stereotactic error of contact 9 is 1.1 mm from the intended target (–14.25, 6.35, 0) (active contacts: left, case(+), 1–, 3–; right, 11+, 9–, 10–). (B) Case 2. Intraoperative post-lead placement CT shows the position of contact 2 on the left ventralis intermedius (VIM) lead (L2), and contact 9 on the right VIM lead (R2). Contact 2 has a radial error of 0.9 mm off of the stereotactic plan targeting (–13.5, –6.75, 0). Contact 9 has a radial error of 0.7 mm off of the stereotactic plan targeting (13.5, –6.75, 0) (active contact: left, case(+), 2–; right, 11+, 8–,10–; contact 9 is shown because it is between contacts 8 and 10.

limbs during programming. At these settings, the patient exhibited no hand tremors on action or posture holding, nor leg tremors at rest or upon raising his legs. He also had reduced tremor of the legs when standing. The patient was able to stand in place for 4 minutes before needing to sit or lean. Except for brief tingling in the extremities, no persistent side effects were noted after programming. At 1 month post-DBS surgery, the patient was able to move unassisted and stand indefinitely without any OT symptoms. At 10 months post-DBS surgery, he presented with no hand tremors or symptoms of OT (Video 1). He was able to perform any activity requiring prolonged

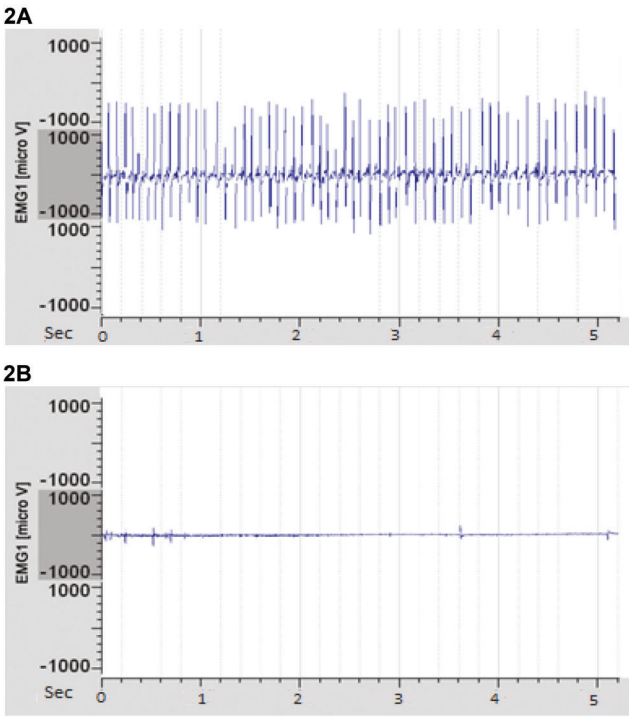

Figure 2. **Surface Electromyography (EMG) Recordings.** (A) Postoperative surface electromyography (EMG) recording of the right tibialis anterior of case 1 while standing with the deep brain stimulator off. Note the prominent high-frequency tremor of 10–13 Hz. (B) Postoperative surface EMG of the right tibialis anterior of case 1 while standing with deep brain stimulator on. Note the significant attenuation of the tremor activity in terms of frequency, amplitude, and continuity, with prolonged periods of quiescence.

standing without difficulty, reporting one occasion of remaining standing for 6 hours with no support. The programming settings at 10 months post-surgery were as follows: for the left VIM, settings were case(+), 1 and 3(–); amplitude 2.6 volts; pulse width 60 μs; and frequency 185 Hz; for the right VIM, the settings were 11(+), 9 and 10(–); amplitude 2.7 volts; pulse width 60 μs; and frequency 185 Hz. Surface EMG recordings were performed at 10 months post DBS, with marked improvement of his OT with the stimulator on compared with that when the stimulator was off (Figures 2A,B).

Case 2

R.S. is a 68-year-old male with a history of diabetic neuropathy and Meniere's disease, who first noticed bilateral hand tremors and imbalance in his forties. His tremors and gait difficulty worsened with time. Although his imbalance and gait disturbance were attributed to chronic Meniere's disease, his hand tremors were thought to result from essential tremor. The tremors were resistant to a number of medications, including topiramate (100 mg per day), zonisamide (450 mg per day), and propranolol (10 mg per day). He experienced mild relief with clonazepam (0.5 mg twice a day). Initial examination revealed intact strength in all four limbs, reduced light touch and cold perception in the distal upper and lower limbs, moderate resting tremor of the

Video 2. **Case 2.** Pre-deep brain stimulation (DBS). Note buckling of the knees and severe difficulty standing in place because of severe orthostatic leg tremors that were apparent immediately upon standing. The patient requires assistance from one person to remain standing in place and intermittently with slow ambulation. Post DBS (1 month). There is improvement of the buckling of the knees on standing with little orthostatic leg tremor noted. The patient can stand better on his own or with a cane.

hands, severe action tremor of both hands, symmetric breakdown in rapid alternating movements in all four limbs, moderate shuffling, moderately increased base on standing and walking, positive Romberg's, and no rigidity. He had buckling of the knees and a fast frequency tremor of both legs when standing, and he could only stand in place without assistance or holding on to an object for only 5 seconds or less. He also often needed assistance from another person to stand in place or to walk slowly (Video 2). Surface EMG recordings showed a 10–12 Hz tremor of the lower limbs on standing, with subharmonics of 5–6 Hz tremor noted frequently. Additionally, recordings revealed 6–8 Hz tremor of the hands on posture holding. His labs were normal, including TSH, T3, T4, B12, and folate. His DaTscan was unremarkable.

The patient underwent bilateral thalamic VIM asleep DBS surgery. The Talairach coordinates were (±13.25, –6.75, 0) (Figure 1B). For both sides, the impedance check was normal and macrostimulation was unremarkable up to 8 V. The vector error was 1.0 mm off plan on the left and 0.7 mm off plan on the right (Euclidean errors were 1.0 mm and 0.8 mm, respectively). Three days following surgery, initial programming was performed. The left VIM electrode settings were case(+), 2(–); amplitude 0.5 volt; pulse width 60 μs; and frequency 185 Hz. The right VIM electrode settings were 11(+), 8, and 10(–); amplitude 0.5 volts; pulse width 60 μs; and frequency 185 Hz. Although the single monopolar settings in the left electrode were sufficient to control the tremor in the right arm and leg, the double bipolar settings for the right electrode were more effective than the single bipolar or monopolar settings for controlling the tremor in the left arm and leg, with transient paresthesias noted in the upper and lower limbs during programming. One week post-DBS surgery, he had no hand tremors, though his orthostatic leg tremors were only mildly improved. Apart from temporary tingling in both the hands and legs during programming adjustments, no lingering side effects were noted. One month post-DBS surgery, his OT had improved, with much less buckling of

the knees while standing, and he needed less assistance from a person or cane while standing in place (Video 2). Six months following DBS, he had only mild orthostatic leg tremors. He was able to stand in place for at least 5 minutes at a time, which to him was clinically significant as it allowed him to be more independent and perform activities while standing. He continued to have a wide base on standing and walking, and exhibit gait difficulty, which were thought to be related to chronic Meniere's disease. At this time, the programming settings were the following: for the left VIM, settings were case(+), 1 and 0(–); amplitude 2.0 volts; pulse width 60 μs; and frequency 185 Hz; for the right VIM, settings were 10(+), 9(–); amplitude 2.8 volts; pulse width 60 μs; and frequency 130 Hz. Post DBS surgery, he was gradually weaned off clonazepam, topiramate, and propranolol, with no notable change in his hand or orthostatic leg tremors.

Discussion

Previous publications have reported the favorable response of medically refractory OT to thalamic VIM DBS surgery carried out in an awake patient, with better sustained benefit with bilateral DBS than with unilateral stimulation.[3–12] A summary of patient clinical and demographic data for 17 OT patients who underwent DBS was recently published by Merola et al.[12] in a multicenter international registry, while a summary of the target coordinates and programming parameters in 12 OT patients was recently published by Lehn et al.[11] The two cases presented herein are the first two OT cases reported to respond favorably to asleep VIM DBS. The targeting method was identical to that used when treating upper extremity tremor: 25% the distance from posterior commissure to anterior commissure, 10.5 mm lateral to the wall of the lateral ventricle at the midcommissural plane. Thus, taking microelectrode recordings (MERs) searching for the leg somatotopic location within the VIM in an awake patient may not be necessary to guarantee improvement of OT with stimulation. We have previously reported intraoperative surface EMG recordings from leg muscles with the table partly inclined and the patient stepping onto a foot board.[4] This setup may not be available in most centers, and may add significantly to the operative time. Taking MERs or intraoperative surface EMG recordings increases the duration of surgery and results in the potential exposure to more anesthesia. Thus, for OT patients who cannot tolerate awake DBS surgery with MERs, carrying out the surgery when the patient is asleep is a viable alternative. Both our cases have experienced sustained benefit from DBS of their OT at 6 and 10 months post-DBS, and their balance and ability to stand have improved, which has translated to improvement of their daily activities requiring standing.

There are certain limitations to our study. One is the small number of subjects; OT is understandably a rare disorder, and those making it to DBS are even rarer. Second is the short postoperative follow-up, though neither of the two cases has reported tolerance or waning of effect as of their last follow-up.

Although there are no studies comparing outcomes of asleep versus awake DBS in OT, asleep DBS appears to be just as effective in providing clinical improvement in OT patients who do not respond sufficiently to oral medications. Asleep DBS, especially with bilateral lead implantation, has the advantages of lessening the psychological trauma to the patient, faster procedure time, and less exposure to anesthesia.

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