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## Tremor Induced by Thalamic Deep Brain Stimulation in Patients With Complex Regional Facial Pain

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**Abstract:** We report on two patients who developed a new postural and action tremor after chronic stimulation of the contralateral thalamus (VPM nucleus) during treatment of a complex regional facial pain syndrome. The tremor was only present during deep brain stimulation (DBS) and was suppressed with adjustment of the stimulation parameters. Tremor was seen only with low frequency stimulation (50 Hz or lower) and disappeared with higher stimulation frequencies. In addition to being an unusual side effect of thalamic DBS, we believe that this phenomenon affords insight into one possible mechanism underlying essential tremor (ET). A central oscillatory mechanism involving the olivocerebellar complex and the thalamus, which is a part of the cerebro-cerebello-cerebral circuit, is thought to play an important role in the genesis of ET. Induction of a tremor resembling ET in our patients indicates an active role for low frequency stimulation. A plausible explanation for this is that low frequency stimulation in the thalamic area enhances the output of the tremor-producing network. This leads credence to the concept of central oscillations in a “tremor circuit,” of which the thalamus is a part, as being important in ET. © 2004 Movement Disorder Society

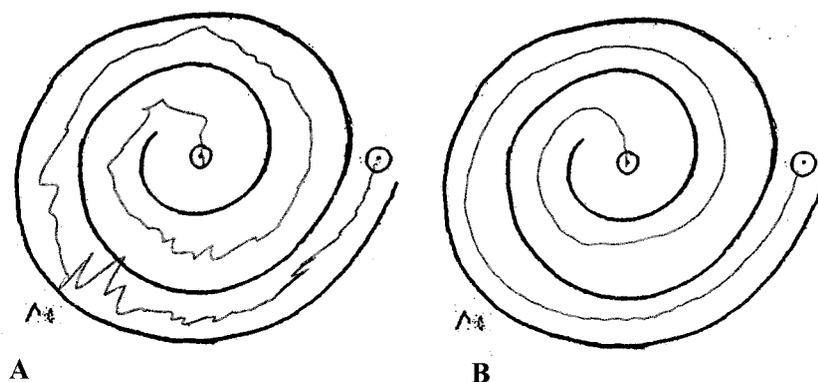
**Key words:** tremor; deep brain stimulation (DBS); pain; thalamus

A videotape accompanies this article.

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**FIG. 1.** Archimedes spirals. Patient 1 drawing an Archimedes spiral with the DBS turned on (A) and off (B).

Deep brain stimulation (DBS) for the treatment of medically intractable pain has been in use for nearly 50 years. The first attempts to modulate pain by targeting deep brain structures were reported by Heath and associates in 1954 and by Pool and colleagues in 1956.<sup>1,2</sup> Several authors have confirmed that electrical stimulation of the periaqueductal gray matter, the thalamic sensory nuclei, or the internal capsule produces pain relief with acceptable long-term effectiveness.<sup>3-7</sup> Over the last 30 years, over 1000 patients have undergone DBS for the relief of chronic pain.<sup>8</sup> Most complications are transient and amenable to therapy. The authors report stimulation-induced tremor in two patients with thalamic DBS for complex regional facial pain. This unusual side effect may provide an insight into one possible mechanism underlying essential tremor (ET).

#### PATIENT 1

A 52-year-old man underwent left thalamic DBS surgery for treatment of right-sided complex regional facial pain. He presented with a 10-year history of right-sided facial pain that developed several years after accidental trauma. The trauma was associated with multiple facial fractures including the anterior wall of the frontal sinuses, the nasal bones, the right infraorbital wall, and the lateral wall of the maxillary antrum on the right. In the following years he noticed discomfort below the right eye that he described as burning. This was centered in the upper jaw and below his right eye and radiated toward the ear and forehead. Medication did not provide relief and he underwent two nerve blocks of the infraorbital nerve, which relieved the pain only temporarily.

The patient underwent left thalamic DBS, with a lead (model 3389-40; Medtronic Inc., Minneapolis, MN) placed in the thalamic sensory nucleus (VPM). The patient had excellent pain control during an externalization trial and proceeded to implantation of an Itrel 3 (Medtronic) pulse generator. Maximum pain relief was

obtained with an amplitude of 1 to 1.3 V, using 50 Hz stimulation and a pulse width of 450  $\mu$ sec (parameters for often used for pain). At this voltage, the patient felt paresthesia in the face corresponding to the previous region of pain. The patient had no difficulty for 4 months but then noticed a tremor in his right arm that only stopped completely when the stimulator was turned off. There was no history of the tremor before this and there was no family history of tremor.

Neurological examination with the stimulator turned on showed a large amplitude postural tremor of 8 to 10 Hz frequency in the right upper limb that was exacerbated by action. The neurological examination was normal when the stimulator was turned off. Figure 1 shows his Archimedes spirals with the stimulator on and off.

Readjustment of the stimulator parameters was carried out to eliminate tremor. Using a bipolar setting with stimulation frequency >100 Hz (with the first contact as anode and third contact as cathode) the tremor was suppressed and facial pain was relieved. With both monopolar and bipolar settings there was an increase in tremor with low (<50 Hz) stimulation frequencies. Tremor suppression was less profound with high stimulation amplitudes or pulse widths.

#### PATIENT 2

A 40-year-old woman underwent right thalamic DBS surgery for treatment of left-sided complex regional facial pain. Her pain began after a dental procedure and was most severe in the right upper jaw. She described the pain as burning. The burning pain continued for 6 years and was refractory to all medications. Seven years ago, she had a right thalamic stimulator implanted in the VPM nucleus, and this helped relieve her discomfort. The patient recently noticed a tremor in her left arm that ceased completely only when the stimulator was turned off. The tremor was not alcohol responsive. There was

no previous history of tremor. No family history of tremor was forthcoming.

Neurological examination with the stimulator turned on showed a postural tremor in the left upper limb that was exacerbated by action. The neurological examination was normal when the stimulator was turned off.

Readjustments of stimulator parameters was attempted to eliminate tremor as in the first patient. With both monopolar and bipolar settings there was an increase in tremor with low (<50 Hz) stimulation frequencies. The tremor reduced or disappeared completely with higher stimulation frequencies. Adequate pain control with no tremor was obtained with bipolar settings (second contact as anode and third contact as cathode) using a frequency of 130 Hz and pulse width of 450  $\mu$ sec.

### DISCUSSION

Tremor induced acutely during intraoperative stimulation of the ventro-intermediate thalamic nucleus (Vim nucleus) or motor cortex has been reported.<sup>9,10</sup> Rare appearances of a new movement disorder in the form of a low-frequency proximal or ataxia has been reported after Vim DBS for tremor.<sup>11</sup> To the best of our knowledge, the postural and action tremor induced by DBS in our patients has not been reported. The manner in which these effects are mediated is unclear. This is not surprising considering that the anatomical substrates and mechanism of tremors such as essential tremor (ET), Holmes tremor, and parkinsonian tremor remain largely unknown.

Evidence from animal studies as well as functional neurosurgery in humans indicates that central oscillations in certain neural structures or circuits may play an important role in the genesis of tremors such as ET and parkinsonian tremor.<sup>12-17</sup> It has been proposed that functional disturbances in the olivocerebellar circuit may play an important role in the genesis of ET.<sup>13</sup> Other structures believed to be involved in tremor circuitry include the cerebellum, thalamus and basal ganglia.<sup>13-16,18-22</sup> It is well recognized that lesions of the cerebellum, thalamus and pons ameliorate ET.<sup>23-25</sup> It has also been suggested that reduction of parkinsonian tremor after ventrolateral thalamotomy or DBS results from either partial involvement of cerebellothalamic fibers or because of pre existing functional integration at the level of the thalamic nuclei.<sup>26-30</sup> The pathophysiology of enhanced physiological tremor (PT) is less clear. Both local reflex mechanisms<sup>31</sup> and a central oscillatory mechanism involving the olivocerebellar complex and the thalamus are thought to play a major role.<sup>12,32,33</sup> The thalamus is a prominent part of the cerebro-cerebello-cerebral circuit and lesioning or DBS of the Vim nucleus of the thalamus is accepted neurosurgical practice for treating parkinsonian

and some types of non-parkinsonian tremors.<sup>22,34,35</sup> It has been shown that Vim nucleus thalamotomy eliminates the 8 to 12 Hz supraspinal component of PT in addition to reduction of parkinsonian tremor in PD patients.<sup>19</sup> This indicates that the thalamus is a critical structure in tremor circuitry.<sup>19</sup>

Our patients had tremor that was postural and kinetic resembling ET, particularly when the DBS was turned on at low frequencies. They had never had tremor before the DBS procedure involving implantation of an electrode in the VPM nucleus and their tremor did not begin until after prolonged DBS. The delayed initiation of tremor raises the possibility of a complex plastic change within the CNS that facilitated an inducible tremor. We believe that the most plausible explanation for the induced tremor is a spread of current from the VPM nucleus to the Vim nucleus, which is just anterior and in close proximity to the VPM nucleus. Spread of current to other thalamic nuclei is unlikely as tremor was observed even with bipolar settings and low amplitudes. Onset of tremor was almost instantaneous with onset of stimulation and disappeared within seconds of the stimulator being turned off. This suggests mediation through a direct neuronal circuit, of which the thalamus is a major component, rather than due to modification of more complex circuits. Our report further buttresses the case for a dominant role of the thalamus, particularly the Vim nucleus, in genesis of ET and possibly other types of tremor.

Another interesting observation in our patients was that tremor appeared only with low frequency of stimulation (50 Hz or lower). The tremor reduced or disappeared with higher stimulation frequencies. Higher stimulation amplitudes and pulse widths also tended to diminish the tremor although this was not as sensitive as changes in stimulation frequency.

There are two inferences that may be made from this observation. First, the induction of tremor resembling ET in our patient indicates a pro-active role for low frequency stimulation. We believe that the explanation for this is that low frequency stimulation sets up reverberations in the relevant thalamic tremor circuitry artificially mimicking the condition in which ET is generated in patients with these conditions. We can hypothesize that in our patients, the output of the tremor-producing network was enhanced by additional input (DBS) in the area of the thalamus and a subclinical symptom may have become clinical and evident. This would be in keeping with studies that have proposed a central oscillatory mechanism for patients with ET.<sup>12,13,15,32,33</sup> The mechanisms that induce or perpetuate oscillations in such patients, however, are unclear.

Second, this may give an insight into one of the possible mechanisms of DBS. Through the exact mechanisms of DBS are far from clear, one widely accepted mechanism is functional lesioning produced by high stimulation frequency.<sup>36,37</sup> The induction of tremor with low frequency stimulation and disappearance with high frequency stimulation supports this view.

In summary, our cases illustrate the critical role of the thalamus in tremor circuitry as well as provide insight into one possible central mechanism of ET.

### LEGENDS TO THE VIDEO

**Segment 1.** First patient with the DBS on and then with the DBS off.

**Segment 2.** Second patient with the DBS on and then with the DBS off.

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