Long-term deep brain stimulation in a patient with essential tremor: clinical response and postmortem correlation with stimulator termination sites in ventral thalamus

Case report


Departments of Neurosurgery, Neurology, and Pathology and Laboratory Medicine, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania

Essential tremor can be suppressed with chronic, bilateral deep brain stimulation (DBS) of the ventralis intermedius nucleus (Vim), the cerebellar receiving area of the motor thalamus. The goal in this study was to correlate the location of the electrodes with the clinical efficacy of DBS in a patient with essential tremor. The authors report on a woman with essential tremor in whom chronic bilateral DBS directed to the ventral thalamus produced adequate tremor suppression until her death from unrelated causes 16 months after placement of the electrodes. Neuropathological postmortem studies of the brain in this patient demonstrated that both stimulators terminated in the Vim region of the thalamus, and that chronic DBS elicited minor reactive changes confined to the immediate vicinity of the electrode tracks. Although the authors could not identify neuropathological abnormalities specific to essential tremor, they believe that suppression of essential tremor by chronic DBS correlates with bilateral termination of the stimulators in the Vim region of the thalamus.

KEY WORDS • deep brain stimulation • essential tremor • thalamus

I mproved understanding of the pathophysiological basis of movement disorders, as well as improved neurosurgical techniques, have led to a resurgence in stereotactic interventions for the treatment of motor impairments in PD and other movement disorders. For example, chronic DBS directed to thalamic nuclei has been used for several decades to treat parkinsonian tremor, essential tremor, and other tremors. The clinical efficacy of DBS has improved with the progressive refinement of this intervention, which has several advantages over thalamotomy (for example, reversibility and modulation of DBS over time). However, despite the fact that the neuroanatomical locus of the DBS electrodes is a critical determinant of therapy efficacy, there is little information correlating the clinical efficacy of DBS in patients with essential tremor with the location of the stimulating electrodes in the brain postmortem. For this reason, we report neuropathological postmortem studies of the brain in a woman in whom essential tremor was suppressed by bilateral thalamic DBS. These studies show that both stimulating electrodes terminated in the region of the thalamic Vim and that chronic DBS induced only minor reactive changes that were confined to the electrode tracks.

Case Report

History of Tremor

This 47-year-old right-handed woman presented with a history of depression and essential tremor. Her symptoms involved both hands, were worse on the left than the right, and began 11 years before admission. She had not benefited from medical therapy. Although antidepressants may have worsened her trembling, the tremor had been present before the medication was started. The patient also suffered from severe mouth tremor, which had resulted in dental damage and swallowing difficulty.

Operation and Postoperative Course

The patient underwent bilateral implantation of DBS electrodes directed to the thalamic Vim as described previously. The stimulators (Medtronic, Inc., Minneapolis, MN) are made of platinum/iridium conductor wires and electrodes with a polyurethane/polytetrafluoroethyl-
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ene insulation. The lead length was 10 to 50 cm and 1.27 mm in diameter, with four stimulation ports spaced 1.5 mm apart at the tip of the electrode. The left thalamic electrode was implanted first to address the patient’s dominant hand tremor, and the right electrode was placed 6 months later. The parameters of stimulation were as follows: stimulator frequency on the right side was 130 Hz, voltage was 4.3 V, and the pulse width was 150 μsec; stimulator frequency on the left side was 130 Hz, voltage was 2.6 V, and pulse width was 90 μsec. Both electrodes produced tremor suppression. The patient did well immediately postoperatively with no complications. However, 10 months after placement of the second electrode she underwent an elective septoplasty and turbinoplasty, after which she experienced significant bleeding from one or more surgical sites postoperatively, with aspiration of blood into her lungs. The patient died 66 hours after the rhinological surgery and 10 and 16 months after the right and left thalamic electrodes were placed, respectively. Neuropathological postmortem studies of the patient’s brain are reported here.

Pathological Findings

Macroscopic and microscopic findings were as follows: after immersion fixation in 10% formalin, the brain was examined macroscopically and paraffin sections cut from the amygdala, hippocampal formation, neocortical regions, and subcortical regions, as well as serial sections cut through the right and left thalamus, were stained with hematoxylin and eosin, thioflavin S, cresyl violet, Gomori iron stain, and the Klüver-Barrera method. Immunohistochemical studies were performed as described earlier on similar paraffin sections by using rat monoclonal antibody (2.2B10) to GFAP (diluted 1:10,000) as well as the rabbit polyclonal antiserum (17026) to anti-tau protein (diluted 1:5000) to identify neurofibrillary tangles and related filamentous tau disease processes. In addition, selected sections were stained with LB509, a monoclonal antibody specific for α-synuclein (1:500 antibody dilution) to detect Lewy bodies and other lesions formed by aggregated α-synuclein. As shown in Fig. 1A, the electrode tracks were inconspicuous on macroscopic examination of 1- to 2-cm-thick coronal slabs of whole brain, but both tracks were demonstrated clearly on light microscopic examination of paraffin sections stained with hematoxylin and eosin, cresyl violet, and the Klüver-Barrera method as well as in immunohistochemical studies in which the anti-GFAP antibody was used (Fig. 1B–G).

The ventralmost depths of the left and right thalamic DBS electrode tracks were traced to the region of the ventral thalamic nuclear groups, including Vim and ventralis posterior medius nucleus of the thalamus, in which DBS has been shown to have some therapeutic benefits for tremor of diverse origins.3,5 Although we found mild gliosis largely confined to the immediate vicinity of the electrode tracks and occasional Gomori-stained iron deposits within the tracks, there was no discernible neuron loss in thalamic nuclei around or adjacent to the electrode tracks. Representative light photomicrographs illustrating these findings include Fig. 1B to G. Finally, additional studies with histochemical stains (for example, thioflavin S) and antibodies (for example, LB509 and anti-tau antiserum 17026) did not reveal the presence of neurofibrillary tangles, senile plaques, Lewy bodies, or other tau or synuclein disease processes. Indeed, there were no neuropathological findings diagnostic for a specific nervous system disorder or to account for the essential tremor in this patient.

Discussion

Essential tremor is a postural disability that is inherited in an autosomal dominant pattern in approximately two thirds of cases, and the age at onset is most commonly in young adulthood. The tremor frequency is 4 to 12 Hz, and it usually resolves with limb support and at complete rest.1,12 The upper extremity is affected in 90% of cases, the head in 40%, and the voice in 30%. Alcohol and β-adrenergic receptor antagonists often adequately suppress essential tremor.1,12 Although the pathogenesis of this disorder is unknown, the olivocerebellorubral loop and the cerebellum are believed to be critical in the development of essential tremor.1,2

For the last several decades, stereotactic surgery has been applied to the thalamus for alleviation of essential tremor. Since the 1950s, the neurosurgical treatment of choice for disabling, medically intractable essential tremor had been thalamotomy, especially of the thalamic Vim.1,2 However, in the last two decades, chronic thalamic DBS has supplanted thalamotomy for the treatment of parkinsonian and essential tremor because of its reversibility and adaptability.1,2,12,15 Benabid, et al.,1 reported that tremor suppression by stimulation directed to the Vim was maintained over the long term (> 2 years) and that such stimulation induced fewer adverse effects such as dysarthria, disequilibrium, limb ataxia, dystonia, and paresthesias. Control of these side effects is easily accomplished by reducing the intensity of the stimulator or stopping stimulation altogether.1,12,15

The physiological basis for Vim stimulation remains speculative, but the cerebellothalamic pathways may play a significant role in the development of essential tremors.1 Autonomous neuronal activities have been recorded in the Vim and these “tremor” cells were found to have a bursting discharge pattern, with the burst frequency equal to the patient’s tremor frequency.15 The Vim is considered to be a convergence point for both pallidal and cerebellar afferent pathways.2 The therapeutic mechanism of thalamic DBS may involve an alteration or functional ablation of the firing center of the Vim or a desynchronization of overactive neurons seen in essential tremor.2,12,15 Stimulation could directly activate cells or axons by depolarization, but it could also inactivate cells or axons by depolarization blockade.12 Activation of cells could also have effects similar to inactivation by increasing the release of inhibitory neurotransmitters such as γ-aminobutyric acid, or by overriding abnormally patterned burst activity. Based on the data presented here, which show that the ventralmost depths of both the left and the right thalamic DBS electrodes were traced to the ventral thalamic nuclear groups including the Vim, we infer that the successful therapeutic response seen in our patient reflects correct placement of these electrodes in the vicinity of the Vim bilaterally.
Fig. 1. A: Macroscopic view of a coronal section of brain obtained at autopsy and cut through the electrode track (arrow) in the anterior thalamus of the right hemisphere. B–G: Photomicrographs. B: Myelin-stained (Klüver-Barrera method) paraffin sections of the right thalamus stained at the termination site (black dot) of the electrode track. Original magnification × 3.13. C: Section of left thalamus (prepared as in B) obtained at the termination site (black dot) of the electrode track. Original magnification × 3.13. D: Section of left thalamus (prepared as in B) obtained at the termination site (black dot) of the electrode track. Original magnification × 3.13. E: Section of left thalamus (prepared as in B) obtained at the termination site (black dot) of the electrode track. Original magnification × 3.13. F: Section of left thalamus (prepared as in B) obtained at the termination site (black dot) of the electrode track. Original magnification × 3.13. G: Section of left thalamus (prepared as in B) obtained at the termination site (black dot) of the electrode track. Original magnification × 3.13.
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The impact of the electrode or of the stimulation on the central nervous system is not clearly defined. Using cat brains and stainless steel electrodes, Schultz and Willey and Collias and Manuelidis showed that even unstimulated electrodes induced neurocytological changes, including giant cell formation, enlargement of astrocytes, stacking of endoplasmic reticulum, and vascular proliferation. Stock, et al., concluded that histological examination of stimulated tissue revealed only a fibrillary gliosis caused by trauma from insertion of the electrodes. They found no definite signs of late tissue damage caused by chronic electrical stimulation at different frequencies.

Much of the current literature on the histopathological effects of electrical stimulation in human brain tissue comes from studies of pain suppression with DBS. Gybels, et al., reported on five human brains in which electrical stimulation of the periventricular-periaqueductal gray matter was applied for the treatment of intractable pain. One electrode was stainless steel, and the remaining devices were made of platinum/iridium. In the brain areas in which the contacts were situated, no specific tissue damage was observed. Only mild gliosis in the vicinity of the electrode and mild chromatolysis of some thalamic neurons were seen. Boivie and Meyerson studied post-mortem five brains in patients with cancer pain who had undergone placement of platinum/iridium stimulators in the medial thalamic region. These investigators observed slight gliosis and some loss of fairly large neurons in limited segments along the electrode tracks. They noted in two patients a moderate degree of capsule formation around the electrode as well. Kuroda, et al., reported on two patients a moderate degree of capsule formation limited segments along the electrode tracks. They noted slight gliosis and some loss of fairly large neurons in the medial thalamic region. These authors found histological changes such as granuloma and gliosis within 200 μm of the chronically implanted electrodes. In two recent reports the authors assessed the condition of the brain after long-term neurostimulation for parkinsonian tremor. Haberler, et al., studied seven patients with PD who received stimulation of the Vim or the subthalamic nucleus for a median of 649 days. Mild gliosis was observed around the electrode path, and one patient had a slight foreign body reaction with multinucleated giant cells, but the authors did not otherwise see neuron loss close to the electrodes. Caparros-Lefebvre and Ruchoux reported on another case of a patient with parkinsonian tremor in whom the ventral thalamic DBS electrode caused only small areas of gliosis and spongiosis in a 1-mm perimeter around the track. They also showed an accumulation of lymphoid, macrophagic, and giant cells within 2 mm around the electrode. The autopsy results in our case confirmed that placement of an electrode and chronic thalamic stimulation for essential tremor causes minimal tissue reactivity. We observed only mild gliosis around the electrode tracks and rare iron deposits in their vicinity. There was no discernible neuron loss along the entire dorsal-to-ventral length of the electrodes.

There have been few autopsy studies in patients who have died of essential tremor, and no biological, physiological, or pharmacological marker specific for the diagnosis of the disease has been described. Rajput, et al., examined six postmortem cases and found no neuropathological lesion that might be specific for essential tremor. Despite the clinical similarity of some cases of essential tremor to PD, none of their six patients had pathological changes typical of this entity. We stained sections from regions near and remote from the electrode tracks for evidence of α-synuclein and Alzheimer disease processes, but there was no evidence of these conditions, and we did not detect any other neuropathological lesions to account for the movement disorder in the patient reported here. Thus, the enigmatic neuropathology of essential tremor remains to be elucidated.

Conclusions

We report the first autopsy study of intrathalamic DBS electrodes implanted for control of essential tremor. Anatomoclinical analysis proved that tremor suppression was achieved by stimulators that terminated in the region of the thalamic Vim. Our histopathological findings confirmed that chronic DBS for essential tremor is safe and causes only mild tissue reaction. However, the neuropathological basis of essential tremor is still unknown.

References


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Address reprint requests to: John A. Boockvar, M.D., Department of Neurosurgery, University of Pennsylvania School of Medicine, 5 Silverstein Pavilion, 3400 Spruce Street, Philadelphia, Pennsylvania 19104. email: boockvar@mail.med.upenn.edu.