Stimulation of the Subthalamic Nucleus in a Patient With Parkinson Disease and Essential Tremor

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Background: The preferred surgical target for the treatment of Parkinson disease (PD) is either the internal globus pallidus or the subthalamic nucleus (STN); the target for treatment of essential tremor (ET) is the thalamic subnucleus ventralis intermedius (Vim). Some patients with PD have coexistent ET, and the identification of a single surgical target to treat both parkinsonian motor symptoms and ET would be of practical importance.

Objective: To describe the use of the STN target in deep brain stimulator (DBS) surgery to treat PD motor symptoms and the action-postural tremor of ET.

Design: Case report.

Patient: A 62-year-old man had a greater than 30-year history of action-postural tremor in both hands, well controlled with β-blockers for more than 20 years. He developed resting tremor, bradykinesia, and rigidity on his right side that progressed to his left side during the past 10 years. Dopaminergic medication improved his rigidity and bradykinesia, with only mild improvement of his resting tremor and no effect on his action-postural tremor.

Interventions: Left pallidotomy followed by placement of a left DBS in the Vim and subsequent placement of a right STN DBS.

Main Outcome Measures: Control of symptoms of PD and ET.

Results: The left pallidotomy controlled the patient’s parkinsonian motor symptoms on the right side of his body, but did not affect the action-postural component of his tremor. The symptoms on the left side of the body, including both an action-postural and a resting tremor (as well as the rigidity and bradykinesia), improved after placement of a single right STN DBS.

Conclusion: Placement of an STN DBS should be considered as the procedure of choice for surgical treatment of patients with a combination of PD and ET.

Arch Neurol. 2005;62:141-143

TREMOR IS AN INVOLUNTARY movement characterized by a rhythmic oscillation about a fixed point or trajectory.1 Tremor that occurs in humans can be divided into resting, postural, and action-intention tremor. Resting tremor is the hallmark of Parkinson disease (PD) and action-postural tremor is the typical manifestation of essential tremor (ET). There may be overlap in these categories of tremors, with severe resting and action-postural tremor occurring in the same patient, making it difficult to determine the predominant cause of tremor in patients with both parkinsonian tremor and ET.2,3

The thalamic ventralis intermedius (Vim) nucleus has been the primary target for the surgical treatment of ET, with both thalamotomy and placement of a thalamic deep brain stimulator (DBS) proving effective.4-6 Patients with PD have 3 potential targets for the surgical treatment of tremor: Vim, internal globus pallidus (GPI), and subthalamic nucleus (STN). Surgical ablation and placement of a DBS in the Vim, while effective in the treatment of both parkinsonian tremor and ET, do not improve bradykinesia and may be associated with a worsening of gait in patients with PD. Ablation or placement of a DBS in the sensorimotor portion of the GPI or the STN improves the cardinal motor symptoms of PD, and these have become the targets of choice for patients with PD with or without tremor.7,8 On the basis of our observations, however, STN may be a better target for patients with both resting and action-postural tremors.

REPORT OF A CASE

A 62-year-old, right-handed man who had had ET for more than 30 years and PD for 10 years presented for consideration for surgical therapy. He had a history of moderate to severe action and postural tremor of his upper extremities that had been well controlled with β-blockers for more than 2 decades. The patient did not have a family history of tremor, but described dramatic im-
provement of his tremor with the use of alcohol. He had difficulty eating, drinking, and performing his job as a maintenance technician. The action and postural components of his tremor had become more disabling in recent years, and medical therapy with different combinations of propranolol hydrochloride, primidone, and clonazepam had not been effective during the past years. Ten years before the current examination, the patient had developed resting tremor, bradykinesia, and rigidity on the right side of the body that progressed to the left side. By the age of 59 years, the resting, action, and postural tremors were significantly worse and had become incapacitating for the patient. Medical therapy with different combinations of propranolol, primidone, and clonazepam was not effective. The addition of levodopa, trihexyphenidyl hydrochloride, pergolide mesylate, and amantadine hydrochloride improved his rigidity, bradykinesias, and postural stability, but only mildly improved his testing tremor and left his action and postural tremor unchanged.

The patient underwent a left GPi pallidotomy, with complete resolution of the resting tremor in his right upper extremity as well as improvement of the rigidity and bradykinesias. The action and postural components of his right arm tremor were not affected by this procedure, and there was no improvement of ipsilateral symptoms. One year later, a left Vim thalamic DBS was placed, resulting in complete suppression of the action and postural tremor in his right arm.

The symptoms in the left side of the body continued to worsen during the next 2 years, including the action-postural and resting tremor, rigidity and bradykinesia. Again, no clinical benefit was achieved with multiple combinations of medical therapy. A right STN stimulator was placed, resulting in resolution of left-sided resting and action-postural tremor and improvement in bradykinesia and rigidity. This procedure allowed reduction of the dose of pergolide and primidone and discontinuation of amantadine, trihexyphenidyl, propranolol, and clonazepam. The patient continued taking levodopa and a low dose of pergolide and primidone.

Stimulation parameters required for tremor control during STN stimulation were: amplitude, 2.6 V; pulse width, 90 microseconds; and rate, 130 Hz, using monopolar stimulation with contact 2 anodal and the case anodal. The patient developed hemiballismus of the left arm during the next 2 days that resolved after the voltage was reduced to 1 V. Although the resting component of the tremor was controlled at this voltage, a residual action-postural tremor persisted. The voltage was gradually increased during the next several weeks, with substantial improvement in the action-postural component of his tremor without the development of hemiballismus. The patient was followed up for 3 years and maintained improvement without loss of tremor control. His most recent stimulation parameters were as follows: amplitude, 2.8 V; pulse width, 90 microseconds; rate, 185 Hz, monopolar stimulation (contact 2−; case +).

The tremor was assessed in this patient using the clinical rating scale for tremor,10 with an improvement from 56 with the right stimulator off to 27 with the stimulator on (with the left thalamic stimulator on during the testing). Comparable clinical improvement was obtained with either left pallidotomy and left Vim DBS or with right STN DBS alone (Figure). The motor part of the Unified Parkinson’s Disease Rating Scale improved from 43 with the left thalamic DBS off to 28 with it on (with the left thalamic DBS on during testing).

COMMENT

Consistent with the observations of Murata et al,11 who reported improvement in 8 patients with ET who underwent STN DBS surgery, we observed significant improvement in both essential and parkinsonian tremors in 1 patient with placement of an STN DBS. The reason for the improvement in both tremors may lie in the pathophysiologic basis underlying their development. The thalamus is considered to play a pivotal role in the genesis of tremor activity in both ET and parkinsonian tremor.12,13 The cerebellothalamic circuit is implicated in the development of tremor in patients with ET, and this has been documented by previous reports in humans with the presence of tremor-synchronous neuronal activity in the thalamus and improvement of ET after creation of focal lesions in the thalamus,14 cerebellum,15 and pons.16 The cerebellothalamic circuit has also been implicated in the development of parkinsonian tremor. In animal models of parkinsonian tremor induced by ventromedial tegmental lesions, isolated lesions of the substantia nigra were not sufficient to induce parkinsonian tremor,

Figure. Spiral and line drawings by left (L) and right (R) hands with both stimulators (right subthalamic nucleus deep brain stimulator and left thalamic deep brain stimulator) off (A) and on (B).
and it was necessary to include the cerebellothalamic pathway in these lesions to produce a resting tremor similar to that observed in parkinsonian patients.17-20 Furthermore, creating a lesion or placing a DBS in Vim, the cerebellar receiving area of the thalamus, is highly effective in alleviating parkinsonian tremor.21-23

Although the resting tremor associated with PD was completely resolved after pallidotomy in our patient, the action-postural components associated with his ET were not affected. This is likely due to sparing of the cerebellothalamic pathway, since the projections from the pallidum to the thalamus are segregated from the cerebellar projections to the thalamus.24

Improvement of both parkinsonian tremor and ET during STN DBS may be explained by a combination of effects on STN activity mediating parkinsonian motor signs and its effect on adjacent cerebellothalamic fibers mediating ET. Because both DBS and lesions in Vim, GPi, and STN produce similar effects, it has been proposed that stimulation may act by inactivating the region in which the stimulation is applied either through a mechanism called depolarization block or by activation of inhibitory afferents to the stimulated structure.25-28 An alternative hypothesis to explain the benefit of stimulation is that DBS activates the structure or fibers being stimulated.29-31 The hypothesis is that DBS may block tremor-generating activity by inhibiting rhythmic neuronal activity and preventing the transmission to the cortex, or by altering the pattern of neuronal activity, changing it from a rhythmic bursting to a more tonic pattern. This change in pattern of the neuronal activity could occur either by tonic activation of axons of the stimulated structure or by activation of fibers passing through or adjacent to the stimulated structure.32-34 The improvement of ET in our patient may be secondary to tonic activation of adjacent cerebellothalamic fibers leading to a tonic activation of Vim neurons and a disruption of tremor-synchronous activity. This hypothesis is supported by the observations of short-latency excitation of thalamic neurons during stimulation of the STN in monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (J.L.V., unpublished data).

On the basis of the results of these physiologic studies and the clinical results observed in our patient, STN DBS should be considered for patients with coexistent ET and PD. Further trials involving a larger number of patients will be necessary to corroborate these results before final conclusions and recommendations are made. However, STN DBS may represent a practical solution for the treatment of combined ET and PD with one surgical procedure.

Accepted for Publication: March 9, 2004.

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Author Contributions: Study concept, design; study supervision: Stover, Okun, Bakay, and Vitek. Acquisition of data: Stover, Okun, Evatt, Bakay, and Vitek. Analysis, interpretation of data; administrative, technical, material support: Stover, Okun, Raju, Bakay, and Vitek. Drafting of the manuscript: Stover, Okun, Vitek. Critical revision of the manuscript for important intellectual content: Stover, Okun, Evatt, Raju, Bakay, and Vitek. Obtained funding: Vitek.