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Thalamic deep brain stimulation for management of essential tremor

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Object. Deep brain stimulation (DBS) of the thalamus is used for the treatment of patients with medically refractory essential tremor (ET). The authors evaluated patient outcomes after DBS surgery.

Methods. Clinical outcomes were evaluated in 19 patients who had undergone DBS surgery by using the Fahn-Tolosa-Marin clinical tremor rating scale. All adverse outcomes were also systematically recorded during follow-up outpatient visits.

Eighteen DBS systems were implanted. The median follow-up period after surgery was 27 months (range 10–75 months). The preoperative mean Fahn-Tolosa-Marin action tremor score was 3.3 $\pm$ 0.5, and the postoperative mean score with the DBS system activated was 0.8 $\pm$ 0.4. The mean preoperative writing score was 2.8 $\pm$ 0.9, and the postoperative mean writing score with the DBS system activated was 1 $\pm$ 0.6. (Wilcoxon rank-sum test, $p < 0.005$). Fourteen patients were treated with bipolar stimulation, and four eventually required monopolar stimulation. Complications included lead breakage (one patient); temporary erythema of the incision through which the pulse generator had been implanted, which required oral antibiotics (one patient); electrode migration, which required surgery (one patient); and mild hand tingling during stimulation (three patients). Twelve of 18 patients with implanted systems experienced no morbid condition.

Conclusions. Thalamic DBS is safe and effective for medically refractory ET. Stimulator adjustments can frequently occur in some patients, and tremor may worsen despite a readjustment in the system.

KEY WORDS • essential tremor • deep brain stimulation • thalamus

ESSENTIAL tremor is the most common movement disorder.[20] In patients who remain refractory to medical therapy, one surgical option is placement of a DBS system in the VIM. Although many investigators have documented the safety and efficacy of DBS for ET, many of the studies on which these findings are based have been conducted at a variety of institutions by several surgeons.[10,12,18,27] We thus reviewed a series of 19 patients who underwent placement of bilateral DBS electrodes for the treatment of ET at a single institution by a single surgeon.

Clinical Material and Methods

Nineteen patients underwent placement of a thalamic Activa Tremor DBS system (Medtronic Inc., Minneapolis, MN) for management of ET between May 1997 and November 2003. All patients gave informed consent for the surgery. This study was conducted according to the Health Insurance Portability and Accountability Act and the University of Pittsburgh Internal Review Board guidelines. In all of these patients medical management of tremor, consisting of propranolol or Mysoline therapy, had failed and severe tremor was present, causing major disability in activities of daily living.

We reviewed the medical and neuroimaging records of all 19 patients. The mean patient age was 60 years (range 35–82). Twelve patients were men and seven were women. Tremor was present for an average of 23 years prior to surgical intervention (range 2–60 years). All patients had tremor in the upper extremities. Nine patients had associated head tremor, and only one patient had lower-extremity tremor as well.

Surgery to place the DBS system was performed after the patient had received a local anesthetic, by using the Leksell stereotactic system (Elekta Instruments, Atlanta, GA). Briefly, after frame application the patient underwent contrast-enhanced magnetic resonance imaging, which involved a volume-acquisition short-relaxation-time sequence to identify deep brain structures. The locations of the AC and PC were noted. Fast–inversion recovery sequences in the axial and coronal planes were used to identify the location of the internal capsule and to help select a safe trajectory from the cortical surface of the precoronal frontal lobe down into the thalamus. The standard site of the thalamic target was one quarter of the length of the AC–PC line plus 1 mm, anterior to the PC; one half the width of the third ventricle plus 11 mm, lateral to the thalamus; and the depth was at the AC–PC line. The lateral target was adjusted to avoid the medial edge of the internal capsule. A 14-mm burr hole was created and either an Activa burr-hole cap or, later, a Navigus burr-hole cap (Image Guided Neurologics, Inc., Melbourne, FL) was placed into the opening in the bone. The DBS electrode lead was then inserted into the thalamus for stimulation testing. Different electrode contacts were used for stimulation so that we could test the following parameters: 170 to 185 Hz, a 90-μsec pulse width, and 0 to 3 V. If stimulation led to tremor cessation without side effects, the electrode was kept in place. The algorithm for readjustment of the lead position based on macrostimulation was based on anatomical inference alone. No microelectrode re-

Abbreviations used in this paper: AC = anterior commissure; DBS = deep brain stimulation; ET = essential tremor; PC = posterior commissure; VIM = ventralis intermedius nucleus of the thalamus.

TABLE 1

Grades of tremor and handwriting before surgery and after placement of the DBS system when maximal therapeutic stimulation is applied

Grades*	Clinical Assessment	No. of Patients	
		Preop	Postop†
tremor			
0	no tremor	0	4
1	slight tremor—barely perceivable, may be intermittent	0	14
2	moderate tremor—amplitude <2 cm, may be intermittent	0	0
3	marked tremor—amplitude 2–4 cm	12	0
4	severe tremor—amplitude >4 cm	6	0
handwriting			
0	normal	0	4
1	mildly abnormal—slightly untidy, tremulous	1	10
2	moderately abnormal—legible, but w/ considerable tremor	5	4
3	markedly abnormal—illegible	8	0
4	severely abnormal—patient unable to keep pencil or pen on paper w/o holding writing hand down w/ other hand	4	0

* Grades developed by Fahn, et al.

† Postoperative scores represent latest scores at the last follow-up visit.

cording was performed. For example, if a patient described a weak arm or leg or increased muscle tone, the lead was moved medially by 1.5 mm. If numbness or tingling was persistent, the lead was moved 2 mm anterior. If little or no tremor response was found on initial lead placement, the lead was moved 1 to 2 mm posterior. The initial target proved to be the final target in 17 of 18 implanted systems. In only one patient did the lead need to be repositioned 2 mm posteriorly because of the lack of initial tremor cessation with macrostimulation.

After lead placement, the stereotactic frame was removed and a general endotracheal anesthetic agent was administered. The pulse generator was placed in the upper chest and the cable was tunneled from a separate small parietal scalp incision down into the chest. The frontal incision was opened and the lead tunneled to the parietal exposure for attachment to the cable. All patients were discharged from the hospital the day after surgery. The device was turned on while the patient was still in the hospital or 2 weeks later when the patient was examined in the clinic.

Neurological improvements in tremor were tested by the operating surgeon (D.K.) by using selected items from the Fahn-Tolosa-Marin clinical tremor rating scale.[4] Important elements included tremor and handwriting and drawing capabilities (Table 1). Tremor was objectively assessed by requiring patients to hold out their hands and also to hold a cup of water. Tremor was graded on a scale from zero to four. For the handwriting test, only the dominant hand was tested. The severity of the tremor was judged by asking patients to write a sentence as well as their names. Drawing was assessed by asking patients to copy an Archimedes spiral in an unsupported freehand manner. These clinical measures of tremor were tested at every outpatient visit, and the postoperative results seen in Table 1, which were also used for statistical analysis, are the results obtained at the most recent follow-up clinical examination.

Results

Eighteen of 19 patients underwent implantation of the DBS system. One patient only underwent temporary placement of the electrode lead, which eliminated her tremor. She complained of headache and arm heaviness in the operating room, and the electrode was removed several minutes later to ascertain whether an intracerebral hemorrhage had occurred. No hemorrhage was found and her symptoms resolved. Two years later she remains without tremor. This patient was not included in the statistical analysis. A second patient displayed an excellent tremor response but his electrode lead fractured 2 months later (the connector had been placed in the upper neck rather than under the scalp). The lead was replaced and the position of the lead was confirmed on a computerized tomography scan. Several months later, the system was removed because it failed to control the patient's worsening tremor. This patient was included in the statistical analysis.

The median follow-up period after surgery was 27 months (range 10–75 months). Eleven patients participated in follow up longer than 2 years and eight patients for longer than 4 years. The tremor was measured according to the Fahn-Tolosa-Marin clinical tremor rating scale.[4] The preoperative mean Fahn-Tolosa-Marin action tremor score was 3.3 ± 0.5, and the postoperative mean score with the DBS system activated was 0.8 ± 0.4. The mean preoperative writing score was 2.8 ± 0.9, and the postoperative mean writing score with the DBS system activated was 1 ± 0.6. A Wilcoxon rank-sum test demonstrated that differences between pre- and postoperative scores were statistically significant for both the action tremor score and the writing score (Table 2; $p < 0.005$ for each).

In an effort to understand the long-term efficacy of the procedure, we reviewed the cases of 11 patients with longer than 2 years of follow up. The mean follow-up period for this subgroup of patients was 51 ± 18 months. The preoperative mean Fahn-Tolosa-Marin action tremor score was 3.3 ± 0.5, and after DBS surgery, the mean score was 0.7 ± 0.5. The mean preoperative writing score was 2.8 ± 0.8, and after DBS surgery, the mean writing score was 1.1 ± 0.8. A Wilcoxon rank-sum test for this subset of 11 patients demonstrated that differences between pre- and postoperative scores were statistically significant for both the action tremor score and the writing score ($p = 0.003$).

Approximately half of the patients did not require further adjustments in their stimulator settings, once the initial

TABLE 2.
*Statistical analysis of Fahn-Tolosa-Marin tremor scores**

Variable	Score		p Value†
	Preop	Postop	
action tremor	3.3 ± 0.5	0.8 ± 0.4	<0.005
writing assessment	2.8 ± 0.9	1.0 ± 0.6	<0.005

* Scores are expressed as mean values ± standard deviation. Postoperative scores represent latest scores at the last follow-up visit.
† Wilcoxon paired signed-rank test.

programming phase had been completed. The other half required periodic increases in voltage or pulse width to maintain tremor control. Despite these adjustments, eight patients demonstrated better tremor control immediately after surgery but then deteriorated an average of one level on the Fahn-Tolosa-Marin clinical tremor rating scale by the time of their last clinical follow-up visit. Nevertheless, all eight of these patients displayed improvement compared with their preoperative status (Table 2). In addition, all patients continued to experience significant improvement in response to stimulation, compared with their condition when the stimulator was deactivated. Fourteen patients were treated with bipolar stimulation and four eventually required monopolar stimulation.

Complications included lead breakage (one patient, noted earlier); temporary erythema of the incision through which the pulse generator was implanted, which required oral antibiotics (one patient); electrode migration (8 mm deep), which required surgery to pull back the lead (one patient); and mild hand tingling during stimulation (three patients). Twelve of 18 patients with implanted systems had no morbid condition.

Discussion

Essential tremor is the most common movement disorder.[20] It is characterized by bilateral action tremor of the hands and forearms, the head, and, less commonly, the voice, in the absence of other neurological signs.[2] The vast majority of patients with ET suffer from mild tremor, which can be treated with various medications; however, a small subset of patients suffer from significant disability. Approximately 10% of patients presenting to a movement disorder clinic suffer from severe motor disabilities, which can be practically defined as any tremor that interferes with feeding, drinking, writing, or, in the case of vocal tremor, communication.[19] Although the natural history of ET has not been systematically studied, it is widely accepted that ET is a slowly progressive disease in which major spontaneous improvements are never seen. As ET advances, the frequency of the tremor decreases and the amplitude increases. For these patients, first-line medical treatments include propanolol and primidone therapies.[11] For those in whom propanolol therapy fails, surgery is an effective option.

Two primary surgical procedures are performed in patients with ET: thalamotomy or high-frequency DBS. Both of these procedures target the VIM. The theoretical basis for targeting the VIM for the relief of tremor is not well understood. The VIM receives its major afferent projections from deep cerebellar nuclei, which then project to the motor cortex.[8] Microelectrode recording of the VIM in patients with ET identifies cells discharging in bursts that are time locked to the patient's tremor, indicating that tremor is associated with an abnormal discharge in the cerebellothalamic pathway.[17] An interruption in this pathway due to lesioning or stimulation provides some theoretical basis for the empirical observation of tremor improvement, but a more precise understanding is still unknown.

Although the VIM is the target used for both thalamotomy and DBS, the results and side-effect profiles differ between the two therapies. Stereotactic thalamotomy for ET has been performed and patients have been studied for the past 50 years. It is effective in 73 to 93% of patients with incapacitating tremor.[5,9,16] Nevertheless, this destructive lesioning procedure is associated with permanent complications.[5,6,9,26] In addition, bilateral thalamotomy carries an even higher risk of dysarthria as well as debilitating cognitive complications and is thus no longer recommended.[21,25] Given the high rate of complications associated with bilateral thalamotomy and because of the destructive nature of the procedure, Benabid, et al.,[3] introduced high-frequency DBS using permanently implanted brain electrodes as an effective alternative in 1987. Since the initial publication of the paper by those authors, DBS has gained popularity because of its reversibility, adjustability, and lower side-effect profile.

High-frequency stimulation of the VIM has been shown to be highly effective in the suppression of tremor.[3,7,13,18,22,23] The stimulation provides tremor relief on the side contralateral to the stimulator, completely eliminating tremor in as many as 50% of patients. In the North American multicenter trial, unilateral DBS of the VIM in 29 patients provided a moderate-to-marked improvement in tremor 1 year postoperatively.[10] In a European multicenter study, 89% of 37 patients with ET demonstrated significant tremor relief 1 year after DBS surgery.[18] Recent follow-up studies for both the North American and European multicenter studies have demonstrated continued benefit at 2 and 6 years postoperatively, respectively.[13,27] The results of our study corroborate the improved patient outcome that can be seen with placement of indwelling brain stimulators.

In addition to suppression of the primary symptom of tremor, DBS has been shown to improve quality of life as measured by standardized scales.[24] Patients report a dramatic improvement in their handwriting, ability to drink liquids from a cup, and capability to follow pursuits previously abandoned such as golf and social activities. Schuurman and colleagues[24] randomized patients with ET to thalamotomy (six patients) or thalamic stimulation (seven patients). These investigators demonstrated improved functional status in the thalamic stimulation group compared with the thalamotomy group as measured using the Frenchay Activities Index. Tremor suppression was achieved in both groups at similar rates.

The side effects of thalamic stimulation include dysarthria (3–18% of patients), paresthesias (6–36%), dystonia (2–9%), balance disturbance (3–8%), ataxia (6%), and limb weakness (4–8%).[1,10,23] These side effects are mostly reversible and appear to be tolerable, given that patients prefer to keep the stimulator activated despite the side effects.[14] In addition, the neurological and cognitive complications from DBS appear to be fewer than those associated with thalamotomy. In their randomized trial of patients undergoing

thalamotomy on thalamic stimulation, Schuurman, et al.,[24] demonstrated more complications in patients randomized to thalamotomy, although one death occurred in the stimulation cohort. In addition, Troster and associates[28] used extensive and sophisticated neuropsychological methods to demonstrate that patients who receive VIM stimulation have preserved cognitive functioning. Hence, the neurological and cognitive complications of DBS appear to be fewer than those associated with lesioning methods.

Conclusions

Although DBS appears to be better tolerated than thalamotomy with respect to neurological and cognitive complications, the hardware required and the surgery-related complications can be problematic. In the present paper we report complications experienced in our series of patients; these have also been reported in a previous publication.[15] Complications included intracranial hemorrhage, both symptomatic and asymptomatic; electrode or battery failure; infection; and lead migration. Because lesioning methods do not require the permanent placement of a foreign device, thalamotomy can be considered a simpler procedure with less likelihood of hardware-related complications. These types of complications must continue to be thoroughly documented and thoughtfully considered in the decision to place a DBS system.

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