Deep Brain Stimulation in Benign Tremulous Parkinsonism

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Background: Benign tremulous parkinsonism (BTP) is characterized by prominent resting plus action tremor, mild parkinsonism with limited disability or progression apart from tremor, and a less-robust response to levodopa therapy. This disorder has an uncertain pathophysiologic relationship to idiopathic Parkinson disease. Deep brain stimulation (DBS) should be efficacious for this condition, but there is no previously published experience.

Objectives: To assess the clinical outcomes and surgical complications of patients with BTP who underwent DBS.

Design: Retrospective case series.

Setting: Tertiary care medical center.

Patients: Twelve men and 3 women with BTP who underwent DBS for levodopa-refractory tremor.

Main Outcome Measures: Tremor status after DBS, preoperative vs postoperative scores on the Fahn-Tolosa-Marin tremor scale, and the presence of adverse events.

Results: Of the 15 patients, 8 underwent unilateral thalamic nucleus ventralis intermedius (VIM), 4 bilateral VIM, and 3 bilateral subthalamic nucleus DBS. At last follow-up at a median of 4 years post-DBS, 7 patients were tremor free, 6 had only trace tremor, and 2 were definitely improved but with residual tremor. The median preoperative Fahn-Tolosa-Marin tremor scale score was 17 (range, 11-21); the tremor scale score at the last videotaped follow-up was 1 (range, 0-6). Median time between the 2 videotapes was 11.5 months (range, 3-14 months). No patients experienced adverse events after the surgical procedure.

Conclusions: These findings support the efficacy of DBS, with VIM and STN targets, in medically refractory BTP-related tremor. Further studies are needed to explore the long-term durability of response and to better compare the surgical targets.

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Deep brain stimulation (DBS) is efficacious and is approved by the US Food and Drug Administration for the treatment of advanced, levodopa-responsive Parkinson disease (PD) and medically refractory essential tremor. Although there is increasing knowledge regarding the long-term outcome of DBS for PD, little has been published about the use of DBS for other parkinsonian conditions.

Benign tremulous parkinsonism (BTP) is a condition in the phenotypic spectrum of parkinsonism but with an uncertain pathophysiologic relationship to PD. In the few existing publications that focus on BTP, the reported clinical characteristics are generally consistent: prominent resting plus action tremor, mild generalized parkinsonism apart from tremor but sparing gait (except for reduced arm swing or stooped posture), only mild progression or disability apart from tremor, and lack of a robust response to levodopa.

Although DBS targeting the globus pallidus pars interna, subthalamic nucleus (STN), or thalamic nucleus ventralis intermedius (VIM) has been shown to be effective for the levodopa-responsive resting tremor of PD, to our knowledge, no published series has specifically focused on the effect of DBS on BTP. In addition, it is not clear from the literature which of the 3 targets would be most appropriate for this subset of patients. For these reasons, we performed a retrospective review of all patients with BTP who have been treated with DBS at the Mayo Clinic, Rochester, Minnesota.

METHODS

This retrospective study was approved by the Mayo Clinic Institutional Review Board. To identify all appropriate cases, we searched the Mayo Clinic Rochester medical linkage system for patients undergoing DBS between January 1, 1996, and July 31, 2010. The resulting records were then subjected to a text-based search for the keywords benign tremulous parkinsonism and benign tremulous Parkinson’s disease plus the broader search terms tremor predominant parkinsonism and tremor predominant Parkinsonism.
Parkinson’s disease. These are the same search terms previously used to define the clinical characteristics of BTP. All 24 patients flagged by the search strategy had been evaluated by a senior movement disorders specialist (J.Y.M. or J.E.A.) at the time of the original diagnosis. The complete medical record for each patient was retrospectively reviewed by a third movement disorders specialist (R.S.) to ensure inclusion of only those fulfilling previously published clinical criteria for BTP: (1) prominent resting tremor as one of the first and most predominant symptoms; (2) parkinsonism that remains mild, apart from tremor; (3) absence of gait disorder apart from reduced arm swing or mild stooping; (4) no more than mild progression, except for tremor; and (5) absence of disability apart from tremor alone. Onset was defined as the year in which a sign of BTP was first noted by the patient, family, or care provider (as recorded in the medical record).

Baseline factors and postsurgical outcomes were determined for patients fulfilling the inclusion criteria. Because no single clinical rating scale had been uniformly applied in all cases, we devised a 5-point outcome scale into which information from available rating scales, clinical histories, and descriptive examinations was incorporated: 0, no improvement in tremor; 1, equivocal improvement; 2, definite improvement but with at least moderate residual tremor; 3, only slight residual tremor; and 4, tremor free. In addition, a movement disorders specialist (R.S.) who was blinded to stimulation status reviewed the operative videotape. The median preoperative Fahn-Tolosa-Marin tremor scale score was 17 (range, 11-21), whereas only slight tremor, and 2 (13%) had a moderate degree of disability.

Fifteen of the 24 patients identified by the text-based search met the inclusion criteria (Table). The remaining 9 patients had been flagged under the search term tremor-predominant Parkinson’s disease or tremor predominant parkinsonism but did not fulfill the criteria for BTP, most often on the basis of disabling parkinsonism beyond tremor alone. There were 12 (80%) men and 3 (20%) women with BTP. Median age at the onset of BTP was 61 years (range, 44-77 years), with the median time from clinical disease onset to DBS surgery being 5 years (range, 1-13 years). Six of the 15 patients (40%) reported a positive family history of tremor or PD.

Mild bradykinesia was present in 5 patients (33%) and mild rigidity in 7 (47%). Five of the 15 patients (33%) presented with symmetrical disease, 5 (33%) with left-sided predominant symptoms, and 5 (33%) with right-sided predominant symptoms. All 15 patients underwent a levodopa titration trial to doses of 900 mg/d (300 mg 3 times daily) or greater. An initial, although insufficient, response of tremor to levodopa therapy was present in 9 patients (47%), whereas the remainder (53%) had no benefit. Among patients continuing levodopa therapy at the time of surgery, the median maintenance daily dose was 900 mg (range, 600-1200 mg). Dopamine agonists were used in 7 patients (47%), but in none did the agonist significantly improve tremor.

For all 15 patients, the indication for surgery was inadequate control of the tremor with levodopa; none of the patients had prominent motor fluctuations or dyskinesia. The VIM was targeted in 12 patients (8 unilateral and 4 bilateral). The STN was targeted in 3 patients, all bilateral implants.

Median follow-up after surgery was 4 years (range, 1-7 years). At last follow-up, all 15 patients sustained definite improvement in tremor above their preoperative levels. Seven patients (47%) were tremor free, 6 (40%) had only slight tremor, and 2 (13%) had a moderate degree of residual tremor.

Eight patients had a preoperative and at least 1 postoperative videotape. The median preoperative Fahn-Tolosa-Marin tremor scale score was 17 (range, 11-21), whereas

<table>
<thead>
<tr>
<th>Patient No./Sex/Age at Onset, y</th>
<th>Years to Surgerya</th>
<th>Family Historyb</th>
<th>Bradykinesia</th>
<th>Rigidity</th>
<th>Symmetry</th>
<th>Levodopa Response</th>
<th>Surgical Site</th>
<th>Tremor Outcome Rating Scorec</th>
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<td>Yes</td>
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<td>No</td>
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Meanwhile, stimulation targeting the STN seems to have resulted in parkinsonian features, and the adverse-effect profiles. Although this study suggests that DBS targeting either the VIM or the STN is beneficial in BTP, the limited number of patients precludes comparison of outcomes between groups. In this series, target selection was not randomized but rather was based on shifting practice patterns and specific patient characteristics; this further complicates attempts at comparison. Even if both targets are ultimately found to be equally effective against BTP-related tremor in the short term, they may be dissimilar regarding the durability of response, the effects on other parkinsonian features, and the adverse-effect profiles.

In the present analysis, outcomes were determined retrospectively, and no single clinical rating scale had been consistently applied across all the patients. However, we found that the outcome rating system we devised allowed us to use existing scales, descriptive examinations, and histories to easily classify each patient unambiguously. The 13 patients (87%) with no, or only slight, tremor after DBS would be considered to have an excellent outcome regardless of the specific scale used to measure this effect. Moreover, the availability of archived videotapes for a subset of patients allowed the application of a quantitative tremor scale; the reduction in Fahn-Tolosa-Marin tremor scale scores showed striking improvement, consistent with the subjective rating scale we applied to the entire cohort.

The beneficial effects of DBS on tremor in levodopa-responsive idiopathic PD and essential tremor are well known, and Food and Drug Administration–approved devices are available for these indications. Although patients with early BTP may present similarly to those with PD, the natural histories of the conditions soon diverge in important ways. Those with BTP tend not to develop significant symptoms or disability beyond that imparted by tremor itself. Furthermore, the motor fluctuations and dyskinesia associated with advancing disease and long-term levodopa therapy in PD generally are not features of BTP. Even in early disease there is an important phenotypic difference between these conditions: whereas the response of tremor to dopaminergic therapy is typically robust in PD, it is suboptimal in BTP. Therefore, medically intractable tremor is often a source of significant disability relatively early in the course of BTP. For these reasons, patients with BTP may be candidates for DBS at an earlier stage of disease compared with patients with PD complicated by motor fluctuations or dyskinesia. Given that DBS targeting the STN is approved in PD specifically as an adjunctive therapy in levodopa-responsive disease, it remains open to interpretation whether DBS for patients with BTP represents a Food and Drug Administration–approved indication for DBS or is an “off-label” use of the DBS system.

Several studies have evaluated the differential effects of the thalamic nucleus VIM vs STN DBS targets in PD. The thalamic nucleus VIM seems to be an excellent target for the treatment of tremor secondary to either PD or essential tremor, with most studies reporting excellent tremor outcomes. On the other hand, DBS targeting the VIM does not provide substantial benefit to the rigidity or bradykinesia that often accompanies tremor in PD. In addition, bilateral VIM stimulation may be associated with adverse events, such as speech disturbance, bulbar dysfunction, and balance impairment. Moreover, tolerance to VIM stimulation has been reported in a subset of patients with essential tremor. Meanwhile, stimulation targeting the STN seems to have a good effect on the cardinal symptoms of PD in addition to tremor. However, there seems to be a mildly increased risk of cognitive and psychiatric adverse events with STN DBS. Given the limited progression of non-tremor parkinsonism in BTP, it is unclear whether, on balance, the STN should be targeted. In the present series, no significant adverse effects were encountered with either target, which may be the result of the small sample size; it is also possible that patients with BTP are simply less prone to the cognitive and psychiatric adverse effects of DBS than are those with typical PD.

In this cohort of patients with BTP who underwent DBS, we found a consistently beneficial response to thalamic nucleus VIM or STN stimulation, with 7 of 15 patients (47%) experiencing complete resolution of tremor and another 6 patients (40%) having only slight tremor at last follow-up. To our knowledge, there are no previous studies of the long-term effects of DBS in a rigorously selected BTP population.

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In conclusion, we found excellent tremor outcomes after VIM and STN DBS in a rigorously selected cohort of patients with BTP (using the same criteria and patient population previously used to define the clinical characteristics of BTP). Prospective studies with larger sample sizes and using randomized target selection are necessary to determine the relative efficacy, durability, and adverse events occurring with VIM vs STN DBS in this patient population.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Savica, Josephs, Ahlskog, and Klassen. Acquisition of data: Savica, Matsumoto, Ahlskog, Stead, Lee, and Klassen. Drafting of the manuscript: Savica. Critical revision of the manuscript for important intellectual content: Matsumoto, Josephs, Ahlskog, Stead, Lee, and Klassen. Statistical analysis: Savica. Study supervision: Savica, Matsumoto, Josephs, Ahlskog, Stead, Lee, and Klassen. Financial Disclosure: None reported.
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REFERENCES

Announcement
Trial Registration Required. As a member of the International Committee of Medical Journal Editors (ICMJE), Archives of Neurology will require, as a condition of publication, registration of all trials in a public trials registry (such as http://ClinicalTrials.gov). Trials must be registered at or before the onset of patient enrollment. The trial registration number should be supplied at the time of submission.
For details about this new policy, and for information on how the ICMJE defines a clinical trial, see the editorials by DeAngelis et al in the September 8, 2004 (2004;292:1363-1364) and June 15, 2005 (2005;293:2927-2929) issues of JAMA. Also see the Instructions to Authors on our Web site: www.archneurol.com.