Clinical review of DBS for Tourette syndrome

Jonathan W. Mink

1Departments of Neurology, Neurobiology & Anatomy, Brain and Cognitive Sciences, and Pediatrics, University of Rochester School of Medicine and Dentistry, 601 Elmwood Ave., Box 631, Rochester, NY 14642

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1. ABSTRACT

Deep brain stimulation for Tourette Syndrome is an emerging therapy for patients with severe, disabling tics. The complexity of symptoms associated with TS present challenges for electrode target selection and evaluation of outcome that distinguish it from other disorders for which DBS has been studied. Accumulating data have been sufficiently promising to justify further study. Yet, many questions remain. Systematic, controlled, collaborative studies are required to answer the many questions that remain.

2. INTRODUCTION

Tourette Syndrome (TS) is a complex neurobiological disorder that is defined by the chronic presence of motor and phonic (vocal) tics (1). Motor tics are stereotyped repetitive involuntary movements that typically involve the face, head, and upper body. Phonic (vocal) tics are sounds such as sniffing, grunting, or throat clearing that are associated with muscle contractions of the oropharynx and diaphragm. The severity of tics depends on multiple factors including frequency, intensity, and complexity of movements and sounds and can range from simple and infrequent to complex, intense and nearly continuous. A typical feature of tics is that they change their anatomical location, pattern, severity and complexity over time. Tics are influenced by environmental factors; stressful or exciting activities are associated with transient increases in tic severity; relaxation or calm, focused concentration may be associated with transient reduction of tic severity. Tics most often begin in the first decade of life, usually between ages 5 and 7 years. They wax and wane, but typically have maximum severity during early adolescence and then decrease in severity into adulthood (2, 3). Remission of tics may occur in the third decade of life in up to 50% of patients. However, a small percentage of patients have severe, disabling tics refractory to standard medical treatment that continue or even increase in adulthood.

Although tics are the defining symptom in TS, many individuals with TS have other neuropsychiatric symptoms (4). Up to 50% of patients with TS have obsessive-compulsive behaviors (OCBs). Similarly, up to 50% of people with TS have attention deficit hyperactivity disorder (ADHD). Smaller, but significant, percentages have anxiety, depression, or other affective symptoms. Identification of these co-morbid symptoms is critical as...
they are often more impairing than the tics themselves. The diversity of these co-morbid symptoms, and their potentially aggravating effects on tic severity and overall disability, complicates the determination of “best” treatment strategies and also complicates the interpretation of treatment trials.

A large body of data suggests abnormal function of cortico-basal ganglia-thalamocortical circuits in TS, but it is not known specifically which components are responsible for tics or comorbid symptoms (5, 6). Theoretically, DBS at any of several nodes in the circuit could provide clinical benefit for tics or comorbid symptoms. The medical literature contains several reports of stereotactic lesions for treatment of tics (7). Unfortunately, there are scant outcome data and only approximate lesion location data in many cases. Based on review of the older lesion reports, the best outcomes appeared to result from ablations in the region of the centromedian-parafascicular complex (CM-PF) of the thalamus (7). Thus, the first DBS target to be reported in TS was the region of CM-PF (8). However, based on experience with other targets in other movement disorders and with obsessive compulsive disorder (OCD), the internal segment of the globus pallidus (GPi) and the anterior limb of the internal capsule (AIC) have been targeted in some TS patients. Results from each of these targets will be reviewed in the following sections.

3. CENTROMEDIAN-PARAFASCICULAR COMPLEX AND ADJACENT THALAMUS

The earliest DBS surgery for TS targeted the centromedian-parafascicular complex of the thalamus (CM-PF) and adjacent nuclei. This targeting was based on the prior lesion studies that suggested ablations in this region provided the best balance of tic benefit and side effects (7). The first case report was of a 42 year old man who had turning movements of his head, licking objects, uttering sounds, blowing, eye-blinking, and adduction of his legs (9). Postoperatively, the tics decreased from a rate of 38 per minute to zero with one year follow-up. Subsequently, the same group extended their findings to provide 5 year follow-up on the previously reported case and reported two additional cases (8). All three patients were reported to have substantial tic reduction. Tics were assessed with counts from 10 minute videotape segments. Tic reduction ranged from 72% to 90%. In all three cases, the most bothersome tic was eliminated. The effect of DBS on associated obsessive compulsive symptoms was not assessed quantitatively, but the symptoms were reported to have disappeared after surgery even with the stimulators off. Side effects included a feeling of reduced energy in all 3 patients and changes in sexual function in 2 of the 3.

In the early work from the Dutch-Belgian group (8, 9), the electrodes were targeted at 5 mm lateral to the anterior commissure – posterior commissure (AC-PC) line, 4 mm posterior to the midcommissural point, and at the AC-PC plane. Adjustments were made in two of the patients because of untoward effects of stimulation in the operating room. Post-operative programming varied across individuals, with active contacts consisting of the more distal contacts in two patients, but proximal contacts in one. Optimal voltage ranged from 2.2 to 3.0 V. Post-operative localization based on imaging was not reported.

Bajwa et al. (10) reported a 50 year old man with severe life-long tics. His most severe tic consisted of neck jerking that ultimately led to cervical cord compression and spastic paraparesis. He was assessed with Yale Global Tic Severity Scale (YGTSS) and the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) for his tic and obsessive-compulsive (OC) symptom severity, respectively. The CM-PF target was the same as described by Visser-Vandewalle (8). Post-operative imaging confirmed placement within 1 mm of the intended target. With DBS, tic severity improved by 66% with a similar improvement in OC symptoms. Stimulation voltage was 2.0 V bilaterally using the second most distal contacts (1 and 5) on each side. Higher voltages caused a sense of “worry”.

Maciunas et al recently reported a series of five cases of severe TS treated with bilateral thalamic DBS (11). Electrodes were targeted at coordinates used by Visser-Vandewalle, as above (8). Post-operative MRI was used to confirm target locations which were, on average within 1 mm of the intended target in each plane. In all but one subject, the proximal contacts were the most effective. Stimulation voltages were in the 3.5 – 3.6 Volt range. Three weeks after implantation, subjects were evaluated in a randomized, blinded manner in four conditions: both sides off, left side on, right side on, and both sides on. They were evaluated again at 3 months post-operatively. The primary outcome measure was the modified Rush Video Tic Rating Scale (12, 13). The authors determined that there was a statistically significant difference across the four conditions. However, there was no direct specific comparison of the “bilateral on” condition to the pre-operative score. Furthermore, there was no significant difference between the 3-month follow-up score and the pre-operative score. A number of secondary outcome measures were employed, including the YGTSS, that showed no significant difference. Inspection of individual results indicates that two subjects had clear benefit at 3 months, but the other three subjects had no benefit, or transient benefit at best. One subject had a psychotic episode postoperatively that was treated with haloperidol, which may have influenced the 3 month results. A variety of behavioral and quality-of-life measures showed suggestions of benefit, with no clear untoward results.

The largest series to date was published recently by Serrvello et al (14). They reported 18 subjects with severe TS who underwent bilateral thalamic DBS. They targeted the CM-PF-Voa nuclear complex. The authors did not report exact coordinates, but did employ post-operative MRI to confirm electrode location. It appears from their published images (figures 2 and 3 in (14)) that their target is somewhat anterior to that used by Visser-Vandewalle and others (8, 10, 11). The active contacts were the more distal ones and the voltage range was 2.5 – 4.0 Volts. Serrvello et al. used the YGTSS as a primary outcome measures and evaluated subjects in an open-label fashion 3
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– 18 months post-operatively. There was a significant improvement of the YGTSS at the most recent post-operative evaluation compared to pre-operative assessment. They also evaluated 9 subjects in a blinded on-off manner. The majority of subjects had subjective worsening when the stimulators were turned off, but no quantitative data were presented. The majority of subjects continued to take medication for tics, but were able to reduce medication on average by 50%. No serious adverse events were reported.

5. COMBINED TARGETS

There is a single report of combined stimulation of CM-PF thalamus and GPi. Houeto et al. (21) reported the case of a 36 year old woman with severe TS including self-injurious tics and comorbid anxiety and depression. She had electrodes implanted in region of CM-PF bilaterally and in the “limbic” portion of GPi. Initial targeting was not reported. The locations of the most effective contacts in CM-PF were 2.9 mm anterior and 1.9 mm dorsal to the mid-commissural point and 6.1 mm lateral to midline. The locations of the most effective contacts in GPi were 22.1 mm anterior and 3.7 mm inferior to the mid-commissural point and 11.2 mm lateral to midline. Stimulation intensity was 1.5 Volts at each electrode. The subject was evaluated in 5 conditions: no stimulation, CM-PF bilateral DBS, GPi bilateral DBS, combined CM-PF and GPi DBS, and “sham” stimulation when the subject did not know the stimulators were off. Outcome measures included the YGTSS and Rush Video Tic Rating Scale. She had substantial tic benefit from both CM-PF and GPi DBS. The benefit was essentially equal for the two targets. Combined stimulation of thalamus and GPi provided no additional benefit. Anxiety and depression improved with CM-PF and combined CM-PF and GPi DBS, but not with GPi DBS alone.

6. ANTERIOR LIMB OF INTERNAL CAPSULE

Two cases of bilateral DBS in the region of the anterior limb of the internal capsule and nucleus accumbens have been reported. The first was a 37 year old woman with severe TS without significant co-morbidity, who underwent placement of bilateral electrodes at the midpoint of the internal capsule, 7 mm below the anterior commissure and 12 mm lateral to midline (22). At stimulation voltage of 4.1 Volts, she had a 17% improvement of the total tic score on the YGTSS. Higher voltage or use of adjacent contacts caused substantial mood alteration including hypomania or depression.

The second case was a 26 year old man with severe TS and obsessive-compulsive disorder (23). Target coordinates were 2.5 mm anterior to the anterior commissure, 4.5 mm ventral to the anterior commissure, and 6.5 mm lateral to midline. Stimulation will all 4 contacts active and a voltage of 7 Volts provided a 41% improvement of the total tic score on the YGTSS with “clear amelioration” of obsessive-compulsive symptoms.

7. PERSPECTIVE

Since the first report of DBS for TS in 1999 (9), there have been as many questions as answers about this therapy. Although there still has been no single well-controlled large study, the cumulative experience suggests that DBS has the potential to be an effective treatment for severe TS and possibly for common co-morbid symptoms. Still, many questions remain. Although most reported subjects had bilateral DBS of the CM-PF complex, there are differences in targeted coordinates, actual electrode location, location of active contacts, and stimulation
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...voltage which suggest that the “best target” in that region of the thalamus has not yet been defined. The positive results in some cases of GPi DBS, despite very different targets, indicate that there is much more work to be done. It is also not known whether DBS for tics will have a beneficial, neutral, or deleterious effect on co-morbid symptoms. Published reports contain some anecdotal information on these symptoms, but more systematic study is required.

To make progress investigating the efficacy and appropriate role for DBS in TS, systematic study is critically important. Guidelines for patient selection, outcome measures, electrode localization, and neuropsychological evaluation have been published (24). Although those guidelines will change as additional data are gathered, it is important to pursue further study in a systematic, collaborative, controlled manner.

8. ACKNOWLEDGEMENT

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9. REFERENCES


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Key Words: Tourette Syndrome, Deep Brain Stimulation, Tics, Review

Send correspondence to: Jonathan W. Mink, Departments of Neurology, University of Rochester School of Medicine and Dentistry, 601 Elmwood Ave., Box 631, Rochester, NY 14642, Tel: 585-275-3669, Fax: 585-275-3683, E-mail: Jonathan_Mink@urmc.rochester.edu

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