Deep Brain Stimulation for Refractory Obsessive–Compulsive Disorder

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Background: *Neurosurgery (anterior capsulotomy) has been beneficial to many patients with debilitating, refractory obsessive–compulsive disorder (OCD), but the irreversibility of the procedure is an important limitation to its use. Nondestructive, electrical stimulation (deep brain stimulation; DBS) has proven an effective alternative to ablative surgery for neurological indications, suggesting potential utility in place of capsulotomy for OCD.*

Methods: *The effects of DBS for OCD were examined in four patients in a short-term, blinded, on–off design and long-term, open follow-up. The patients had incapacitating illness, refractory to standard treatments. Hardware developed for movement disorder treatment was surgically implanted, with leads placed bilaterally in the anterior limbs of their internal capsules. Patients received stimulation in a randomized "on–off" sequence of four 3-week blocks. Ongoing, open stimulation was continued in consenting patients after the controlled trial.*

Results: *Patients tolerated DBS well. Dramatic benefits to mood, anxiety, and OCD symptoms were seen in one patient during blinded study and open, long-term follow-up. A second patient showed moderate benefit during open follow-up.*

Conclusions: *It appears that DBS has potential value for treating refractory psychiatric disorders, but additional development work is needed before the procedure is utilized outside of carefully controlled research protocols.*

Key Words: Deep brain stimulation, neurosurgery, obsessive–compulsive disorder

Obsessive–compulsive disorder (OCD) is a common psychiatric disorder that is often chronic, severe, and extremely debilitating (Skoog and Skoog 1999; Stein et al 1997). It also is often refractory even to optimal treatments, with a substantial proportion of patients failing to respond or obtaining only partial relief (Hollander et al 2002; Rasmussen and Eisen 1997). In severe, refractory cases, stereotaxically applied neurosurgical lesions in the anterior limb of the internal capsules (anterior capsulotomy) have been utilized as a "last resort" treatment (Jenike 1998). Extensive case reporting suggests substantial benefit (Bingley et al 1977; Greenberg et al 2003; Mindus and Jenike 1992), but controlled study has been difficult.

Ethical ramifications of surgical lesioning for psychiatric conditions have slowed development and study of this approach (Fins 2003), and the potential for permanent neurological or psychiatric morbidity has limited its use. Many severely ill patients with refractory OCD have nevertheless been willing to pursue this option, but alternatives might have more appeal if they could avoid the permanent nature of capsulotomy lesions and their potential to undermine the effectiveness of new interventions that may be developed in the future.

The observation that lesion effects can be simulated by electrical currents delivered at levels that are too low to produce tissue destruction has led to the development of implantable stimulation systems to treat neurologic disorders for which lesions have proven effective as last resort treatments, but for which safety concerns hampered widespread use. Studies of deep brain stimulation (DBS) in the treatment of essential tremor and Parkinson disease have demonstrated efficacy comparable to lesioning, together with a favorable safety profile (Krack et al 2003; Rehncrona et al 2003). Because DBS consists of the delivery of a high-frequency current that reduces and desynchronizes output from the stimulated region while resulting in no neuronal injury, it has been much more widely accepted and clinically applied (Benabid 2003). Based on this experience, a number of research centers have initiated studies of DBS in the anterior limb of the internal capsule as a substitute for anterior capsulotomy in refractory OCD. Case reports have appeared describing successful DBS treatment of a small number of OCD patients (Anderson and Ahmed 2003; Gabriels et al 2003; Nuttin et al 1999, 2003b). Blinded, controlled data have been slower to appear, although the technology is amenable to controlled study. One recent report, covering some of the same patients previously described in case studies, documented benefit in a blinded, crossover design (Nuttin et al 2003a) with four patients. We now report preliminary data from our own pilot study of four treatment-refractory OCD patients, studied in a short-term, blinded, on–off design and an unblinded, long-term follow-up.

Methods and Materials

Entry Criteria and Measures

This study was reviewed and approved by the University of Michigan Institutional Review Board. In addition, the protocol was granted an Investigational Device Exemption by the U.S. Food and Drug Administration. Entry criteria included Yale–Brown Obsessive Compulsive Scale (Y-BOCS; Goodman et al 1989a, 1989b) score of at least 25; Global Assessment of Function (GAF; Endicott et al 1976) score of no more than 44; multiple unsuccessful attempts at treatment with antiobsessional medication at adequate dosing and duration and behavior therapy. Four consecutive patients applying to our traditional capsulotomy program and meeting DBS entry criteria were offered and accepted enrollment. All had received medication trials on at least four antiobsessional medications with proven efficacy (three selective serotonin reuptake inhibitors [SSRI] and clomi-

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Received May 25, 2004; revised October 25, 2004; accepted November 30, 2004.

0006-3223/05/$30.00
doi:10.1016/j.biopsych.2004.11.042

pramine). All had received trials of at least 12 weeks' duration at maximum tolerated or approved doses, and all had been exposed to medication combinations or augmentation (e.g., SSRI plus clomipramine or serotonergic agent plus antipsychotic). All received at least 12 weeks of cognitive–behavioral therapy (CBT) for OCD (exposure with response prevention) without meaningful benefit. All but one received intensive, residential or inpatient CBT trials. Two psychiatrists (members of the research team) independently assessed each patient. Enrollment required their full agreement on diagnosis, refractoriness, disability, and capacity to provide consent. All patients provided written informed consent after extensive discussion that included both the patient and family members. All subjects were offered capsulotomies as an alternative to protocol participation. All had been on stable medication regimens for at least 6 weeks before surgery, and no medication changes were permitted during the blinded phase of study. They had no history of psychosis, no current substance abuse, and were in good general health. Our procedures and processes were consistent with the published recommendations of an OCD-DBS Collaborative Group (Nuttin et al 2002) concerned with the safe and ethical conduct of this type of research.

Comorbid conditions and OCD were diagnosed using the Structured Clinical Interview for DSM-IV (SCID-IV). Primary outcome measures were the Y-BOCS and the 17-item Hamilton Depression (HAM-D) Scale. Additional outcome measures included the Hamilton Anxiety (HAM-A) Scale and Global Assessment of Functioning (GAF). Serial neurologic examinations and questionnaires were used to assess neurologic side effects. Cognitive function was assessed serially by a battery of neuropsychological tests (see Results).

Surgical Technique

Targeting of electrode placement was identical to targeting lesions for anterior capsulotomy. Guided by a preoperative magnetic resonance image (MRI), quadripolar stimulating electrodes (Model 3387 DBS™ Lead, Medtronic, Minneapolis, MN; 1.5-mm contact length, 1.5-mm contact spacing) were placed stereotaxically (using a Leksell Model G Frame) in the anterior limb of each internal capsule and connected via subcutaneous wires to implantable pulse generators (IPG Model 7424 Itrel™ II or Model 7426 Soletra™, Medtronic) placed subcutaneously in the subclavicular area. Placement strategy was based on multiplanar reformatted images acquired on the day of surgery, targeting visually the midpoint of the anterior limb of the internal capsule. The electrode tip (contact 0) was targeted at the base of the internal capsule, at its junction with the nucleus accumbens. The trajectory was planned to follow the angle of the white matter fiber tract in the coronal plane. In the sagittal plane, the trajectory was planned to lead to a burr hole just anterior to the coronal suture. In the last two subjects studied, postoperative MRI scans were obtained to verify exact lead location.

Stimulation Protocol

The study was conducted in three stages. Exploratory testing of a wide range of contact combinations and stimulation parameters was done over 3–8 days to determine tolerability and to assess acute effects. A 12-week double-blind testing stage then allowed controlled assessment of stimulation effects using an on–off design. This was followed by open-ended, open-label stimulation, with efforts to optimize results by adjusting stimulation conditions, pharmacotherapy, and behavior therapy.

Exploratory Testing. These procedures were done in a General Clinical Research Center (GCRC). Stimulation parameters were set to low levels and then systematically ramped up over a series of 2-hour stimulation blocks until side effects or benefits appeared or the safety maximum was reached. Personalized rating scales were used to look for symptom changes at the end of each block. The parameter testing ranges for subject 1 (who was tested before any other reports of DBS in the internal capsule had appeared) were 30–150 Hz for frequency, 20–60 microsec for pulse width, and 1–5 volts for amplitude. For subsequent subjects, we used a fixed frequency of 130 Hz, a pulse width of 210 microsec, and examined an amplitude range of 3.0–10.5 volts (as permitted by charge density limits). Charge density is the critical safety measure and was calculated for all stimulation configurations tried, using impedance values that were measured at amplitude of 1 volt, with all other parameters at therapy settings. Maximum allowable charge density was 30 microcoulombs/cm^2 (Medtronic product label). We also tested a limited set of lead configurations, using both bipolar (using combinations of the electrode contacts for anode and cathode) and monopolar (using electrode contacts for cathode and IPG case for anode) stimulation.

Double-Blind Testing. For the double-blind stage, stimulation conditions were chosen that either showed evidence of benefit or that provided maximal levels of undetectable stimulation. Stimulators were turned on or off for four consecutive 3-week periods (two ON and two OFF, in constrained random order). Neither the patient nor evaluating clinicians were informed of stimulator status. Clinical ratings and a brief neuropsychologic battery were completed at the end of each 3-week block.

Open Stimulation. After completing double-blind testing, the blind was broken, and patients were given the option of leaving the study or entering open treatment. Stimulation was bilateral during the exploratory and blinded testing phases. Unilateral stimulation was attempted in some patients during open-label testing.

Neuroimaging Studies. Three patients underwent positron emission tomography (PET) after implantation but before any stimulation was given and again after 3 or 6 weeks of continuous stimulation during the blinded phase. The PET scanning was conducted after the injection of 8 mCi of 18F-fluorodeoxyglucose (FDG). Sixty-three slices were obtained on a Siemens ECAT HR+ (CTI, Knoxville, Tennessee). Images were reconstructed with a final full-width half-maximum resolution of 5.1 mm, warped to the standardized, Talairach atlas space (Minoshima et al 1994) and ratio-normalized for each voxel with activity at least 15% of the global mean. To document exact probe location, two patients also underwent postoperative MRI, with a safe T2-weighted sequence (for details and important DBS-MRI safety considerations, see Rezai et al 2004).

Analysis

Our primary goal was to detect any evidence of potential efficacy, to determine whether follow-up work for more thorough testing and optimization could be supported. We were specifically interested in whether DBS could perform comparably to traditional anterior capsulotomy, for which it is a potential replacement. The literature indicates that anterior capsulotomy produces a 35% improvement in OCD symptoms in about 45% of patients who receive the operation (Mindus et al 1994). We therefore used percent improvement over baseline in OCD symptoms, as measured by the Y-BOCS, as our primary outcome measure and calculated the percent of patients achieving 35% improvement in this measure.