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Regular Article

Pilot study of deep brain stimulation in refractory obsessive–compulsive disorder ethnic Chinese patients

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Aims: Deep brain stimulation (DBS) of the ventral capsule/ventral striatum (VC/VS) is a promising alternative to ablative surgery in treatment of refractory obsessive–compulsive disorder (OCD). A pilot study was conducted to assess 15-month outcomes of DBS in patients with refractory OCD in Taiwan.

Methods: Four adult patients with a 3-year or more history of refractory OCD (Yale–Brown Obsessive–Compulsive Scale [Y-BOCS] score of at least 28) met the criteria for DBS surgery. DBS electrodes were implanted bilaterally in the VC/VS. Stimulation was adjusted for therapeutic benefit and absence of adverse effects. Psychiatric evaluation was conducted preoperatively, postoperatively, and at follow up at every 3 months for 15 months. Primary outcome measure was Y-BOCS. Secondary outcomes included the Hamilton Depression Rating Scale (HAM-D), and the Global Assessment of Function Scale.

Results: Mean severity of OCD was a Y-BOCS score of 36.3 ± 2.1. At the end of 15 months' follow up, there was a 33.06% decrease in OCD severity ($P = 0.001$). Similar findings were seen for HAM-D (32.51% reduction, $P = 0.005$), and Global Assessment of Function Scale (31.03% increase, $P = 0.026$). In terms of adverse effects, two patients suffered from hypomania episodes after several weeks of DBS stimulation, and one had transient hypomania-like syndrome during DBS initial programming. One patient (Case 1) had an allergic reaction to implantation of the pulse generator in the chest, and another patient (Case 3) exhibited vertigo.

Conclusions: We confirm that DBS of the VC/VS appears to be beneficial for improvements in function and mood among patients with treatment-resistant OCD. Compared to previous studies examining the therapeutic effects of DBS, no serious adverse effects were observed.

Key words: deep brain stimulation, refractory obsessive–compulsive disorder, treatment outcome.

OBSESSIVE–COMPULSIVE DISORDER (OCD) is a chronic and disabling neuropsychiatric disorder characterized by recurrent obsessive thoughts that dictate repetitive ritualized behaviors (compulsions). OCD is notorious for its chronicity and resistance to behavioral and pharmacological treatment. Up to 10–20% of patients may be unable to obtain relief following first-line treatments.[1] Therapeutic options for this subset of patients include ablative procedures, such as anterior capsulotomy or anterior cingulotomy.[2]

DBS was approved by the US Food and Drug Administration in 1997 for the treatment of tremor in essential tremor (ET) and Parkinson's disease (PD),

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and has since been widely accepted as an alternative to ablative procedures for refractory PD and movement disorders.[3] Following the case series on the use of DBS in refractory OCD by Nuttin *et al.*,[4,5] anecdotal reports,[6,7] and a sham-controlled stimulation study,[8] an open-label case series with 3-year treatment outcomes,[9] and a blinded, staggered-onset study with six patients with intractable OCD[10] have documented the promising effects of DBS in OCD. Even though this therapeutic approach has been validated for the treatment of OCD, the paucity of studies using this technique have yet to establish a standard stimulation protocol or optimized brain region. DBS of the ventral capsule/ventral striatum (VC/VS) putatively mimics the effects of tissue lesioning of this region,[11] with the added benefit of allowing clinicians to reversibly manipulate both the amplitude of the stimulation and the site of the stimulation.

We conducted an independent pilot study of DBS in four patients with refractory OCD who were referred to us for neurosurgery. To our knowledge, this study is the first to describe the effects of DBS in patients with refractory OCD in Asia.

METHODS

Patients

Patients who fulfilled DSM-IV criteria for OCD, and who suffered from a history of severe, disabling OCD were eligible to participate in this study. All patients were referred to Tzu-Chi General Hospital for neurosurgery. A thorough independent assessment of family history, present history, and past evaluations/treatments was conducted at our institution, and suitability for neurosurgery was determined using previously published criteria and guidelines.[4,5,9,12] The index diagnosis of OCD was confirmed by using a structured clinical interview for DSM-IV and a review of clinical data. The severity of OCD symptoms was quantified by using the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS).[13] The severity of depressive symptoms was quantified by using the Hamilton Depression Rating Scale (HAM-D).[14] The eligible patients had a history of refractory OCD for at least 3 years, and a minimal Y-BOCS score of 28. Treatment resistance was defined as failure to obtain improvements following multiple trials of pharmacotherapy at maximally tolerated doses, and one or more adequate trials of cognitive behavioral therapy. Additional exclusion criteria included: (i) a clinical history of severe personality disorders, body dysmorphic disorders, or other serious psychiatric symptoms, such as delusions, and hallucination; (ii) patients who posed an immediate suicidal risk; (iii) a history of substance abuse; (iv) inability to provide written informed consent or adhere to operational requirements; and (v) congenital or acquired organic brain diseases. This study was approved by both institutional review boards of the Buddhist Tzu-Chi Hospital and the Department of Health, Taiwan. All patients provided written informed consent and were apprised of the alternatives to DBS, and possible risks associated with DBS surgery.

Surgical procedure

All four patients received implantation of quadripolar electrodes (model 3387; Medtronic Inc, Minneapolis, MN, USA) at our institution. Each electrode was 1.27 mm in diameter with four electrode contacts 1.5 mm in length and spaced 1.5 mm apart. Contacts were named according to convention: 0 being most distal and 3 being most proximal. Electrodes were implanted according to a set of anatomical landmarks – anterior commissure (AC) and posterior commissure (PC), AC–PC plane, and the anterior limb of the internal capsule – using a Leksell stereotactic frame under general anesthesia. The two stimulating distal contacts 0 and 1 were placed next to or in the anterior limb of the internal capsule through the anterior commissure and into the VS. All implants were bilateral. Programmable, battery-operated pulse generators were implanted in the chest wall, and were connected to electrodes by means of subcutaneous tunneled wires, which were implanted under general anesthesia on the same day.

Initial DBS stimulation protocol

At about 2 weeks or 1 month following implantation, patients underwent a stimulation protocol to ensure that the DBS system was operational, to evaluate acute effects, and to optimize stimulation parameters (frequency, amplitude, pulse width, and stimulation mode) of active contacts (Table 1). Stimulation settings were slightly modified from those used in a previous study.[15] We fixed the pulse width at 210 μs, the stimulation frequency at 130 Hz, and used a monopolar mode. The initial voltage was applied at 2V steps to reach 0, 2, 4, 6, or 8 V. This

Table 1. Coordinates and variables of active contacts[†]

	Length of AC–PC line	Coordinate[‡]						Active contact	Amplitude (Voltage)	Pulse width	Frequency
		Left side			Right side						
		X	Y	Z	X	Y	Z				
Case 1	24.7 mm	9.6 mm	17.5 mm	−0.1 mm	9.9 mm	17.3 mm	−0.2 mm	2-	3–6	210 μs	130 Hz
Case 2	28 mm	8.6 mm	18.3 mm	−4.9 mm	8.9 mm	18.3 mm	−3.7 mm	0-	4–5	210 μs	130 Hz
Case 3	24.4 mm	7.1 mm	13.4 mm	−2.3 mm	6.0 mm	12.8 mm	−3.6 mm	0-	2–4	210 μs	130 Hz
Case 4	27 mm	7.6 mm	16 mm	0.6 mm	10.2 mm	16.8 mm	−1.2 mm	1-	2–3	210 μs	130 Hz

[†]There were four contacts designated as 0, 1, 2, 3. During the study we used the mono-polar mode, in which one contact was set as the cathode that was selected as the active contact.
[‡]Coordinate, the coordinate of the particular lead was presented as the distance lateral to the midline, the distance anterior to the mid-commissural point, and the distance inferior to the AC–PC plane.
AC–PC, anterior commissure-posterior commissure.

applied voltage was later optimized according to patient responses. We instructed the patients to choose a number from 0 to 10 that best described their current euphoria and obsession: 0 would mean 'No euphoria/No obsession', and 10 would mean 'Best possible euphoria/Worst obsession'. This stimulation protocol was videotaped and conducted in a double-blinded method (i.e., investigators and patients were blinded to the parameter settings). Patients were asked to share any emotional, perceptual, or somatic experiences. DBS was given as adjunctive treatment to pharmacotherapy. According to the study design, no additional drugs were to be given during the study period to manage OCD symptoms; however, the Case 4 patient was hospitalized due to emotional changes 6 weeks after DBS stimulation and the dosage of valproate for this patient was increased from 250 mg/day to 500 mg/day. For all patients, the amplitude and combination of contacts were empirically adjusted at every follow-up visit.

Outcome measures

Psychiatric evaluations were conducted preoperatively, postoperatively, and at follow-up visits every 3 months for 15 months. Semi-structured interviews with family members were conducted. The primary efficacy end-point of this study was the mean change of Y-BOCS score from baseline. An investigator blinded to the present study administered the questionnaires at each follow up. Secondary outcomes included the HAM-D and the Global Assessment of Function (GAF) Scale.[16] To assess adverse events, patients were asked to report if any changes in physical or mental state had occurred. These accounts were corroborated by family members, which were then confirmed by a physician.

Neuroimaging studies

All four OCD patients received fluorodeoxyglucose positron emission tomography (FDG-PET) brain scan studies at two time-points: before the DBS surgery and at a mean of 3 months after the DBS surgery. The patients fasted for at least 4 h before the PET studies, and then received an intravenous injection of 370 MBq of F-18 FDG. During the 45-min uptake period, patients were kept in a dim quiet room, and were instructed to close their eyes. The PET studies were performed with a GE Discovery ST PET-CT scanner (GE Healthcare, Milwaukee, WI, USA). The system produced 47 contiguous slices, 3.27-mm thick PET images, and had an axial resolution of 2.14 mm full width at half maximum (FWHM) in the center of the field of view. The raw data were reconstructed into a 128×128 matrix with use of built-in algorithms of a 3-D interactive reconstruction method. The emission images were attenuation-corrected with computed tomography (CT)-based translation.

The PET images from four OCD patients were compared to those of ten normal healthy subjects on a voxel-by-voxel basis by using statistical parametric mapping (SPM) (version 2; Wellcome Department of Imaging Neuroscience, London, UK). The PET images were spatially normalized using nonlinear warping with 16 iterations, with a voxel size of $2 \times 2 \times 2$ mm after normalization. Smoothing was performed with an isotropic kernel of 12 mm. Proportional scaling

and analysis threshold were set to values of 50% and 80%, respectively. To evaluate significant differences, the *P*-values were set at less than 0.001 of the uncorrected level. The results were converted to the Talairach coordinates by a Montreal Neurological Institute (MNI)-to-Talairach conversion tool.[17,18]

Statistical analysis

Data are presented as mean ± standard deviation (SD). Repeated measurements analysis was carried out to assess the effect of time of the study period. To compare the metabolic difference between the OCD patients and the healthy volunteers, a two-sample *t*-test was performed. To evaluate the treatment effect of DBS, a paired *t*-test was used. All statistical assessments were two-sided and evaluated at the 0.05 level of significance. Statistical analyses were performed using SPSS 15.0 statistics software (SPSS, Chicago, IL, USA).

RESULTS

Patients

Of the 30 patients referred to our institution, four patients met the study criteria and received DBS surgery. All four patients were men; their mean age was 25.5 ± 5.2 years and mean duration of OCD was 8.3 years. All patients had suffered from major depressive disorder for at least 1 year previous to DBS surgery, which was confirmed by their HAM-D score and clinical diagnosis. Table 2 describes the clinical demographic characteristics of these four patients.

FDG-PET findings

Compared to healthy individuals, the OCD patients preoperatively showed hypermetabolic activity in the limbic system: left parahippocampal region (Brodmann area 28 [BA 28]; peak MNI coordinates, x, y, z = −16, −6, −26; $P < 0.001$, uncorrected), right parahippocampal region (amygdala; peak MNI coordinates, x, y, z = 26, 0, −24; $P < 0.001$, uncorrected), right inferior frontal lobe (BA 47; peak MNI coordinates, x, y, z = 28, 14, −20; $P < 0.001$, uncorrected), and bilateral cerebellum ($P < 0.001$) (Fig. 1a). In contrast, DBS at a mean of 3 months after surgery caused diminished metabolic activity in the bilateral parahippocampal regions ($P < 0.001$), left anterior cingulate gyrus (BA 24; peak MNI coordinates, x, y, z = −16, −4, 44; $P < 0.001$) and left cerebellum ($P < 0.001$) (Fig. 1b). Also noted after DBS was elevated metabolic activity at the electrode sites of the bilateral ventral striatum ($P < 0.001$) and right midbrain (substantia nigra; peak MNI coordinates, x, y, z = 14, −20, −4; $P < 0.001$).

Y-BOCS, HAM-D, GAF outcome

Mean severity of OCD was a Y-BOCS score of 36.3 ± 2.1. At the end of 15 months follow up, there was a 33.06% decrease in OCD severity (Y-BOC score 24.3 ± 9.1, $P = 0.001$) (Fig. 2a). Similar findings were seen for HAM-D, and GAF. Baseline HAM-D score was 36.3 ± 6.3. At 15-month follow up, there was a 32.51% decrease in severity of depression (HAM-D score = 24.5 ± 11.1, $P = 0.005$) (Fig. 2b). Baseline GAF score was 43.5 ± 12.6. At 15-month follow up, there was a 31.03% increase in global functional status (GAF score = 57.0 ± 17.5, $P = 0.026$) (Fig. 2c).

Table 2. Patient demographics and characteristics

Patient	Age (years)	Sex	Age at OCD onset (years)	OCD duration (years)	Months after surgery	Baseline Y-BOCS	MDD	Adverse event
Case 1	30	M	11	9	21	36	Yes	Hypomania, anxiety, allergy due to battery
Case 2	30	M	16	11	20	36	No[†]	
Case 3	21	M	15	5	15	34	Yes	Vertigo, olfactory hallucination
Case 4	21	M	10	8	15	39	Yes	Hypomania
Mean	25.5		13.0	8.3	17.8	36.3		
SD	5.2		2.9	2.5	3.2	2.1		

[†]Case 2 was a case of bipolar 1 disorder.
MDD, major depressive disorder; OCD, obsessive–compulsive disorder; Y-BOCS, Yale–Brown Obsessive Compulsive Scale.

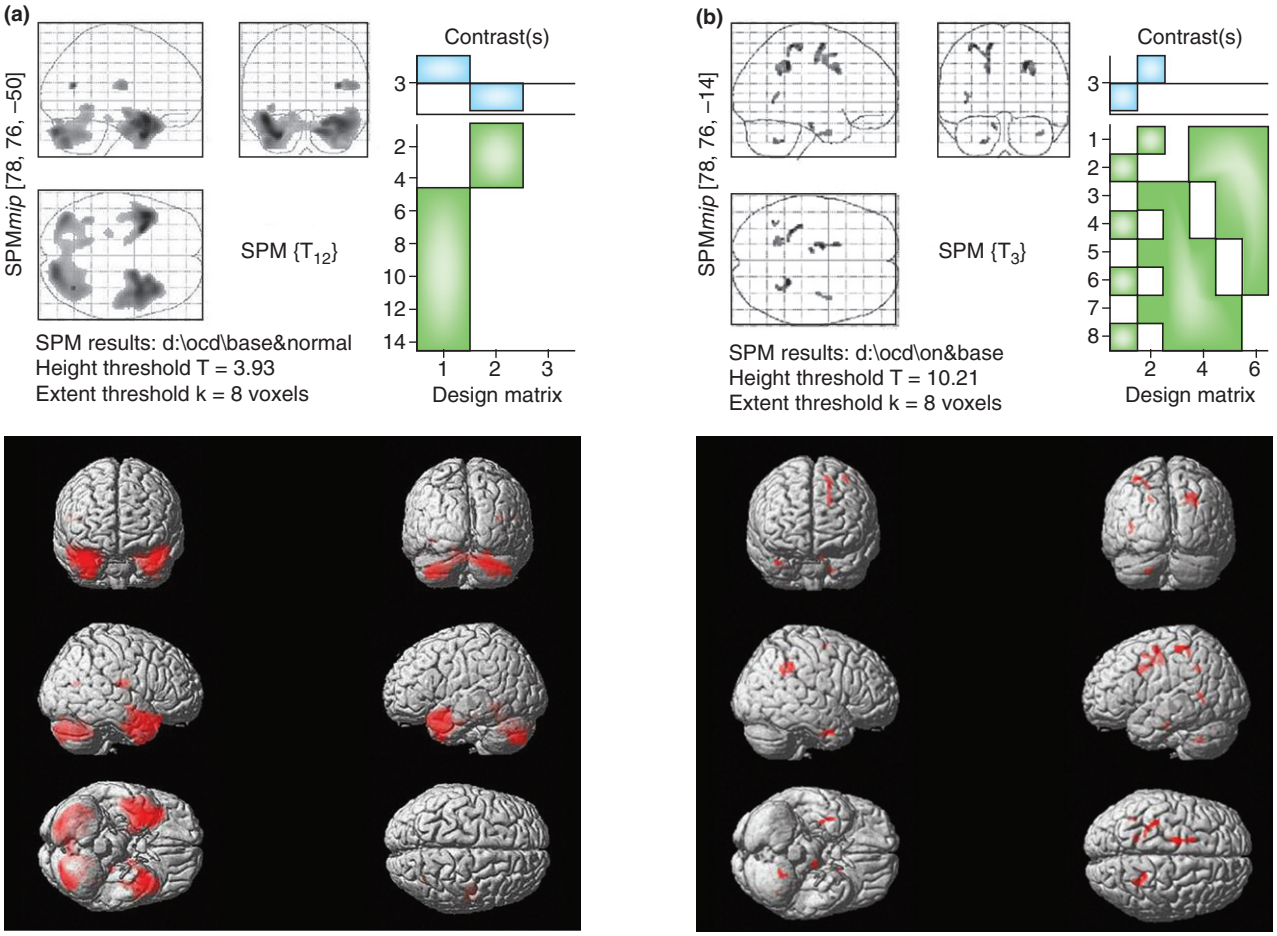

Figure 1. Statistical parametric mapping (SPM) analysis of F-18 fluorodeoxyglucose positron emission tomography. (a) Compared to the healthy control group, the obsessive–compulsive disorder patients showed hypermetabolic activity in the limbic system and in the cerebellum ($P = 0.001$, voxel threshold = 8). (b) At a mean of 3 months after surgery, deep brain stimulation resulted in diminished radioactivity in a more wide distribution pattern, including the bilateral parietal lobes, bilateral parahippocampal regions, left anterior cingulate gyrus, and the cerebellum ($P = 0.001$, voxel threshold = 8).

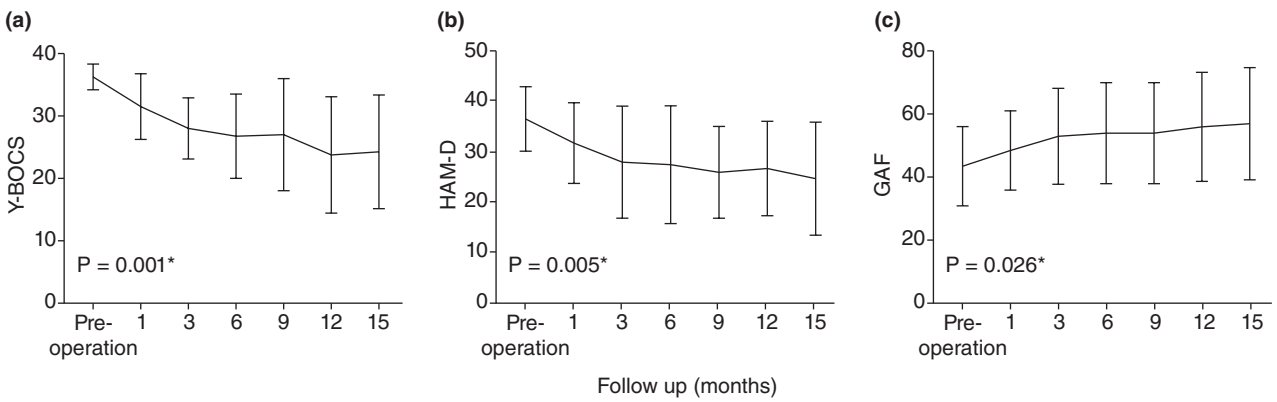

Figure 2. Primary and secondary outcomes at follow up every 3 months. (a) Mean Yale–Brown Obsessive Compulsive Scale (Y-BOCS) scores. (b) Hamilton Depression Rating Scale (HAM-D) scores. (c) Global Assessment of Functioning (GAF) scores.

Effects of initial DBS

All subjects experienced transient emotional, perceptual, gustatory, and olfactory changes during initial DBS programming trial when contacts 0 or 1 were stimulated. These emotional effects included fear, euphoria, smiling, tightness of the chest, and hotness. Frequency of euphoria appeared to be increased with higher voltages. Mean euphoria scores, which were based on a scale of 0–10 as described above, were 0, 0, 1.5, 2.5, and 3 points when contact 0 was stimulated at voltages of 0, 2, 4, 6, and 8 V, respectively, and mean euphoria scores were 0, 0, 3, 4.25, and 5.25 points when contact 1 was stimulated at voltages of 0, 2, 4, 6, and 8 volts, respectively. In terms of the effects of DBS, two patients presented with symptoms of hypomania, case 1 showed hypomania after 5-week DBS and case 4 showed hypomania after 6-week DBS. Case 2 showed hypomania-like syndrome during initial DBS stimulation. One patient (Case 1) had an allergic reaction to implantation of the pulse generator in the chest, and another patient (Case 3) exhibited vertigo.

Case presentations

Case 1

Case 1 was a 30-year-old man with a 9-year history of refractory OCD. He had onset of OCD symptoms at age 11 years. The symptoms at onset were intermittent and not serious. His father had Parkinson's disease. His social and occupational functions were normal until age 21 when he had to quit college because of his illness. Although his family owned a bakery, he was unable to work there because he felt that working with flour was dirty. He had many obsessions and compulsions related to fear of contamination. He had washing rituals, compulsion to sterilize furniture, and unwillingness to touch anything previously touched by someone else. He was unable to seek employment for fear of becoming infected. Despite his problems, the patient married and had children. He sought treatment because of the stress he was experiencing. Following 1 year of treatment, he was able to occasionally work in the bakery but he was still unsatisfied with the outcome of treatment. At the time of the study, he was receiving quetiapine (300 mg/day), propranolol (30 mg/day), and triazolam (0.5 mg/day). The patient also received bupropion (300 mg/day) and venlafaxine (150 mg/day) for depressive symptoms. The patient expressed high expectations for DBS, and repeatedly requested readjustments of his voltage settings to improve his mood during the course of the study; the need for readjustments dominated his thoughts and became in essence, an obsession in itself. He showed a psychological dependence on DBS system configuration. One year following DBS surgery, the patient presented with an allergic skin reaction in the subclavicular area where the neurostimulators were implanted. He subsequently underwent wound debridement and re-implantation and recovered uneventfully. He developed DSM-IV hypomania after 5 weeks of DBS stimulation.

Case 1

Symptoms	Before surgery YBOCS 36 HAM-D 30 GAF 61	The battery of DBS had power YBOCS 25 HAM-D 25 GAF 65	The battery ran out of power YBOCS 30 HAM-D 33 GAF 65
Afraid of dirtiness, checks repeatedly	Checks furniture repeatedly, requires the furniture to be placed in order, disinfects furniture after other people touch it, mops the floor repeatedly, fears bacterial infection, experiences depression and suicide tendency	The severity of symptoms was lessened. The patient stated that he could do more things during that time period. He could work routinely at the bakery 3 to 4 times per week, for about 4 h per time, and his mood was stable	He can still go to work, but the work time cannot be fixed. Obsessive–compulsive symptoms were worse, and he experienced depression. The results of his self-assessment were poor, and the score was only half of that when the battery had power

GAF, Global Assessment of Function Scale; HAM-D, Hamilton Depression Rating Scale; YBOCS, Yale–Brown Obsessive Compulsive Scale.

Case 2

Case 2 was a 30-year-old man with an 11-year history of refractory OCD. His symptoms began at age 16. An unidentified person in his family had schizophrenia. His symptoms were severe at onset and he quit school. His obsessions included symmetry and sexual thoughts, and his compulsions included ritualized

bathing and showering, and licking his teeth to ensure uniformity. He would repeatedly check the length of his clothing to ensure that everything was even. From time to time the patient would also adjust his glasses to ensure that they were in alignment. The patient also expressed a desire for a girlfriend, and had often followed women on the street. He was unable to work. Besides having OCD he also met DSM-IV diagnostic criteria for bipolar I disorder, and had one episode of mania 4 years prior to DBS surgery. At the time of the study he was receiving zotepine (300 mg/day), lamotrigine (300 mg/day), and lorazepam (4 mg). Fluoxetine (100 mg/day) was given for depressive symptoms. On postoperative acute stimulation, he showed smiling with mirth. He demonstrated transient hypomania-like syndrome during the initial DBS programming trial after surgery. By 6 months after DBS treatment he was able to work as a part-time waiter and also was able to volunteer at a hospital.

Case 2

Symptoms	Before surgery YBOCS 36 HAM-D 36 GAF 41	The battery of DBS had power YBOCS 20 HAM-D 16 GAF 61	The battery ran out of power YBOCS 32 HAM-D 28 GAF 51
Checks repeatedly whether skin fold of the hands, nails, clothes, and teeth are symmetrical, whether the sole of his shoe is black	Obsessive–compulsive symptoms can seriously interfere with his daily life during the entire day, he could not do other things or surf the Internet, frequent occurrence	Alleviated symptoms He could do some things (worked as a volunteer / went to Church)	He could not work on anything, the frequency of checking increased again

GAF, Global Assessment of Function Scale; HAM-D, Hamilton Depression Rating Scale; YBOCS, Yale–Brown Obsessive Compulsive Scale.

Case 3

Case 3 was a 21-year-old man with a 5-year history of refractory OCD. He was aged 15 years when he had symptom onset. After he became ill, he quit school. He had no job or social activities and hid at home. His main obsession was intrusive sexual thoughts on sexual intercourse, which were accompanied by anxiety and guilt. The patient attempted to remove these images by hitting his eyes; he also bashed his eyes whenever he saw women's lingerie. As a result of this behavior he had a cataract and retinal detachment in both eyes. The patient would also violently stretch and pinch his scrotum whenever he had an erection, which resulted in edema and hematoma of the scrotum. At the time of the study, he was receiving clonazepam (2 mg/day) and paroxetine (80 mg/day) for his depression. He complained of vertigo at follow up. After 6 months of DBS treatment he returned to school and made new friends at school, and he no longer hurt himself because of symptoms.

Case 3

Symptoms	Before surgery YBOCS 34 HAM-D 34 GAF 41	The battery of DBS had power YBOCS 10 HAM-D 22 GAF 71	The battery still has power now
Repetitive appearance of erotic scene, invasive sexual thoughts, could not tolerate underwear ads	Social withdrawal and dropping out of school because he could not tolerate the repetitive appearance of erotic scenes and accompanied anxiety and guilty feelings. He beat his eyes in order to eliminate the erotic images, causing cataracts and retinal detachment of both eyes. Whenever he had an erection, he would continue to pinch his scrotum, resulting in scrotal swelling and hematoma	The symptoms were relieved He would not experience anxiety while watching underwear ads, and he would not hurt himself. He returned to school and went to college after graduating from high school	

GAF, Global Assessment of Function Scale; HAM-D, Hamilton Depression Rating Scale; YBOCS, Yale–Brown Obsessive Compulsive Scale.

Case 4

Case 4 was a 21-year old man with an 8-year history of refractory OCD. His age at symptom onset was 10 years. His father had OCD. There was no significant family history of bipolar disorder. The patient's symptoms were very severe after he graduated from elementary school. He was not able to go to school or work and had no social interactions. He had many obsessions and compulsions related to fear of contamination, agoraphobia, and fear of eating contaminated food. He showed ritualized washing and spitting. Although he understood that his fears were unnecessary, he routinely locked all the windows of his house from fear of being contaminated by dirty air. At the time of the study, the patient was receiving clozapine (100 mg/day), sodium valproate (250 mg/day), lorazepam (1.5 mg/day), and sertraline (100 mg/day) for depressive symptoms. After DPS treatment his symptoms remained the same. He developed DSM-IV hypomania after 6 weeks of DBS stimulation. (Case 4 did not experience significant changes so a table was not constructed.)

DISCUSSION

Fifteen months of bilateral DBS of the VC/VS appeared to result in a 100% response rate with a mean reduction of approximately 30% in Y-BOCS score and HAM-D score, and a mean improvement of 30% in GAF score. Our response rate and magnitude of improvements are in keeping with the results of Nuttin *et al.*,[5] Abelson *et al.*,[8] Greenberg *et al.*[9] and Goodman *et al.*[10] who reported that 50–60% of patients obtained a reduction of 25–35% in Y-BOCS scores. The improvement in HAM-D score may be attributable to improvement in OCD; however, an alternative explanation is that it is attributable to DBS stimulation itself, as suggested by the results of several DBS studies.[9,10] Specifically, it has been shown that DBS of the VC/VS is an effective treatment for depression.[19]

DBS was generally well-tolerated in all patients, although two patients (Cases 1 and 4) exhibited hypomania, which occurred following an adjustment of the stimulation settings from those at initial programming. One patient also exhibited an allergic reaction at the site of the implanted batteries, presumably due to chronic skin abrasion of the device from higher levels of physical activity. Other acute effects of DBS included previously described transient alterations in emotional and somatic experiences (e.g., anxiety, panic, euphoria, smiling, vertigo), and gustatory and olfactory hallucinations.[5–10] The effects of anxiety and panic are likely explained by stimulation of the amygdalofugal and hypothalamic pathways that are part of the circuitry of the VC/VS; hypothalamic and autonomic fibers in this region may also mediate autonomic changes, such as heart rate, breathing rate, heat sensation, and cold sensation.[20]

The rationale of targeting the VC/VS site is to modulate the corticobasal circuitry that is at the heart of the pathogenesis of OCD.[21] DBS targets were originally based on ablative surgery targets in OCD, but have since been based on anatomical, theoretical considerations, and direct clinical observations.[22] Greenberg *et al.*[23] have recently reported the use of a more posterior/inferior VC/VS target (the caudal nucleus accumbens) by four centers worldwide. Their 8-year, multicenter, follow-up study showed that response rates (from 30% to 70%) and global functioning improved over time, paralleling changes in device programming, surgical technique, patient management, and a systematic change of the DBS target to a more posterior VC/VS site. Their findings indicate a potential learning curve that has been seen in the use of DBS in movement disorders. To our knowledge, we are the first group to describe the use of DBS in refractory OCD patients in Asia. Our findings suggest that bilateral DBS of the VC/VS is a promising alternative to ablative surgery in refractory OCD. Although the circuit-based and cellular mechanisms underlying the therapeutic effect of DBS have not been well elucidated, they may involve neuronal suppression at the stimulated region.[24] However, the effects of stimulation settings, DBS targets, and patient management on treatment outcomes remain to be elucidated in prospective studies.

The experience of the medical team is very important for successful treatment with DBS. Patients need to be assessed before surgery, and following surgery a long-term doctor–patient relationship should be maintained so that the medical team can provide care and encouragement on a continuing basis.

The favorable findings of DBS in our study must take in to account the adverse events we observed in our four patients. Hypomania occurred in two patients (Cases 1 and 4); this has been similarly reported in four of six patients by Goodman *et al.*[10] with no significant impact on neuropsychological outcome. In addition, these hypomanic symptoms

abated with time or device settings in both our study and that of Goodman *et al*.[10] However, the occurrence of hypomania has been less frequently observed in other reports,[5–8] although the study by Greenberg *et al*. indicated that five out of ten patients exhibited transient hypomania.[9] On the basis of such a small sample size, we are unable to determine the significance of this finding, yet it may be related to the site of stimulation, which was the VC/VS in these aforementioned cases of hypomania.[9,10] In both patients in our study, hypomania occurred in the early phase of DBS treatment, after 5 weeks of stimulation in one patient and after 6 weeks of stimulation in the other patient. Case 2, a patient who had hypomania-like syndrome during DBS initial programming, 4 years previously had an episode of comorbid bipolar disorder I. Since there was no relapse of bipolar disorder during DBS treatment it appears that DBS has no effect on bipolar disorder. For the Case 1 patient, the need to optimize stimulation settings became an obsession in itself. Nevertheless, the high percentage of patients who had hypomania in our study (50%) suggests the need to emphasize this issue in the medical management of patients with OCD undergoing DBS and is a clinical concern that should be weighed against the potential benefits of DBS therapy.

In terms of adverse effects relating to hardware issues, there was only one case of allergic reaction resulting from a higher level of physical activity. Neurosurgeons should be cautioned to assess the depth at which the neurostimulators and subcutaneous tunneled wires are placed in order to accommodate younger patients who are more physically active. There were also complaints by both family members and patients over interruptions to the treatment due to batteries running out; Nuttin *et al*.[5] have also reported similar concerns. Although there was no need to replace batteries during the course of the 15 months, we have decided to substitute the current neurostimulators with rechargeable Activa RC Neurostimulators (Medtronic, Minneapolis, MN, USA) during our next follow up of these four patients. This approach will hopefully limit the number of surgical procedures and reduce patient care cost associated with DBS therapy.

Our study was not controlled, and thus we could not discriminate a placebo effect. However, the persistence of a placebo effect for 15 months does not seem to us as likely. Although DBS was used as an adjunctive therapy to ongoing pharmacotherapy, no new medications were added following initial study enrollment; our patients were also highly treatment-resistant. Due to the small sample size, we also could not account for the effects of varying pharmacotherapy regimens. We plan to use a double-blind technique to minimize possible biases in future studies.

In conclusion, the assessment and treatment of mental illness is extremely complex. Undoubtedly, DBS has pleiotropic and varying therapeutic effects, but will clearly be a valuable approach for a number of psychiatric illnesses.[25] In this study, we confirm that DBS of the VC/VS appears to be beneficial for improvements in function and mood among patients with treatment-resistant OCD.

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