Treatment of Resistant Obsessive-Compulsive Disorder With Ventral Capsular/Ventral Striatal Gamma Capsulotomy: A Pilot Prospective Study

Antonio Carlos Lopes, M.D., M.Sc., Ph.D. Benjamin D. Greenberg, M.D., Ph.D. Georg Norén, M.D., Ph.D. Miguel Montes Canteras, M.D., M.Sc. Geraldo F. Busatto, M.D., Ph.D. Maria Eugênia de Mathis, Psy.D. Anita Taub, Psy.D., M.Sc. Carina Chaubet D'Alcante, Psy.D. Marcelo Queiroz Hoexter, M.D. Fernando Sauerbronn Gouvea, M.D. Janaína Philippi Cecconi, M.D. André F. Gentil, M.D. Ygor Arzeno Ferrão, M.D., M.Sc., Ph.D. Daniel Fuentes, Psy.D., Ph.D. Cláudio Campi de Castro, M.D., Ph.D. Cláudia C. Leite, M.D., Ph.D. João Victor Salvajoli, M.D., Ph.D. Fábio L. S. Duran, M.D., Ph.D. Steven Rasmussen, M.D. Eurípedes Constantino Miguel, M.D., Ph.D.

OCD, anxiety and depressive symptoms, and side effects pre- and postoperatively. Three patients (60%) met response criteria 48 months after surgery. Adverse effects were episodic and transient. Ventral capsular/ventral striatal gamma capsulotomy holds therapeutic promise, with few adverse effects.

(The Journal of Neuropsychiatry and Clinical Neurosciences 2009; 21:381–392)

A subgroup of obsessive-compulsive disorder (OCD) patients remains refractory to conventional treatments. For them, a new stereotactic radiosurgery has been recently developed: the ventral capsular/ventral striatal (VC/VS) gamma capsulotomy. The authors aim to report efficacy and adverse events of VC/VS gamma capsulotomy. Five refractory OCD patients were selected. The authors assessed

reatment of most cases of obsessive-compulsive disorder (OCD) includes serotonin reuptake inhibitors (SRI), alone or in combination with other medications, and cognitive behavior therapy (CBT). However, unresponsiveness to available treatments may reach up to 30% to 40% of patients.^{1–4} For them, different neurosurgical techniques have been employed.⁵ Some of these interventions aim at the ventral anterior internal capsule and ventral striatum (VC/VS) to disrupt the frontal-basal ganglia-thalamic circuit, implicated in the pathogenesis of OCD. This can be achieved with ablative procedures such as thermocoagulation and Gamma Knife radiosurgery or with deep brain stimulation. Radiosurgery has the advantage of being noninvasive, which reduces possible complications related to neurosurgery. Studies with Gamma Knife anterior capsulotomy, with various response criteria, have suggested improvements in 55% to 70% of patients.^{6,7}

A smaller double-shot, bilateral gamma knife anterior capsulotomy lesion has been recently proposed at Brown University, with few side effects and good efficacy profile, named (VC/VS) gamma capsulotomy.⁸ Preliminary data indicated that clinical response (at least 35% reduction in Yale-Brown Obsessive Compulsive Scale [Y-BOCS] scores) was obtained in 13 out of 22 patients (59%) after 1 year and in 15 patients (69%) after 2 years of follow-up.⁸

In this article we report preliminary findings from five patients who underwent VC/VS gamma capsulotomy for refractory OCD with a minimum follow-up period of 36 months. The aims of this study were to report preliminary findings of efficacy of the technique and to assess the safety of this procedure, including

Copyright © 2009 American Psychiatric Publishing, Inc.

general medical and neurological adverse events/complications.

MATERIALS AND METHODS

Ethical Issues

This study complies with the guidelines for neurosurgery of severe psychiatric disorders in Brazil⁹ and was approved by the Brazilian National Commission of Research Ethics (CONEP). Approval was also granted by local Ethics Committees at the University of São Paulo Medical School and Santa Paula Hospital, respectively, the institutions where the patients were clinically assessed and submitted to radiosurgery.

Written informed consent was obtained, with a member from the Brazilian OCD Patients Foundation present to ensure adequate protocol understanding from all patients. An independent panel composed of two psychiatrists appointed by the Regional Medical Council of São Paulo and the president of the Brazilian OCD Patients Foundation reviewed video-taped interviews confirming the patients' adequate knowledge of benefits and risks related to gamma radiosurgery.

The research team will provide all patients with systematic assessments of adverse events and complications for a minimum follow-up period of 5 years.

Clinical Assessments

Patients included in the study were submitted to a detailed psychiatric history, as well as physical, neurological, and psychiatric examinations. Psychiatric axis I and axis II comorbidities were further assessed by the Structured Clinical Interview for DSM-IV (SCID) and the Structured Interview for DSM-IV Personality Disorders (SIDP-IV).^{10,11}

Sample Selection

Thirteen severe OCD patients from various States in Brazil were initially screened as candidates for surgery. Only five patients (38.5%) fulfilled our inclusion and refractoriness criteria (see details in Table 1). The main reasons for exclusion were lack of adequate medication/CBT trials (four patients), a history of full treatment response after the introduction of a previous medication (one patient) and other main axis I/II diagnosis (three patients), namely factitious disorder, severe bipolar disorder and one case of prominent paranoid personality disorder.

Received March 11, 2008; revised June 29 and August 29, 2008; accepted September 22, 2008. Drs. Lopes, Busatto, Mathis, Taub, D'Alcante, Gouvea, Cecconi, Gentil, Ferrão, Fuentes, Duran, and Miguel are affiliated with the Department and Institute of Psychiatry, University of São Paulo School of Medicine (FMUSP), São Paulo, Brazil; Drs. Greenberg, Norén and Rasmussen are affiliated with the Department of Psychiatry and Human Behavior and Department of Clinical Neurosciences - Neurosurgery, The Warren Alpert Medical School of Brown University; Providence, R.I.; Drs. Canteras and Salvajoli are affiliated with the Institute of Neurological Radiosurgery-Hospital Santa Paula, São Paulo; Dr. Hoexter is affiliated with the Department of Psychiatry, Federal University of São Paulo, UNIFESP, São Paulo; Dr. de Castro is affiliated with the Heart Institute (INCOR), FMUSP, São Paulo; Dr. Leite is affiliated with the Department of Radiology, FMUSP, São Paulo. Address correspondence to Antonio Carlos Lopes, Obsessive Compulsive Spectrum Disorders Program (PROTOC), Department of Psychiatry, University of São Paulo School of Medicine, R. Dr. Ovídio Pires de Campos, 785, 3° andar, sala 9, São Paulo, SP, Brazil 01060-970; antonioclopesmd@gmail.com (e-mail).

The five patients included (two men, three women, mean age 35.0 ± 11.0 years, mostly single) had a median of 18 years of severe, disabling OCD symptoms and considerable psychosocial impairment. Three patients (A, C, E) were unable to complete their University degrees. Only one patient (D) was working regularly at the time of surgery (Table 2).

All patients reported early onset of their obsessivecompulsive symptoms (before 10 years of age). Compulsions appeared first (median age for first compulsions was 8 years) (Table 3). Obsessive-compulsive symptoms important enough to interfere with daily living activities were present, on average, by the age of 18. Major depressive and panic disorders were the most prevalent axis I comorbidities (Table 3). Cluster C personality disorders such as dependent and avoidant personality disorders (patients B and C) and obsessivecompulsive personality disorder (patient E) were common (Table 3). There were no comorbid tic disorders.

Specific treatments were usually sought at a median age of 20.5 years, or 2.5 median years after full-blown OCD. The mean number of previous medication trials was 14.6—more specifically, 5.4 different SRI trials, one of which was with clomipramine (Table 4). All patients had received adequate CBT treatment, except for patient E, who tolerated only very few sessions. Patients

TABLE 1. Inclusion, Refractoriness and Exclusion Criteria for the "(VC/VS) Gamma Capsulotomy Obsessive-Compulsive Disorder Study"

- 2. Age range between 18 and 55 years old.
- 3. At least 5 years of OCD symptoms.
- 4. Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) scores greater than 26 (or greater than 13, for isolated obsessions or compulsions). 5. Refractoriness criteria fulfilled.
- 6. To be accepted by the "best estimate" method as a treatment refractory patient. It consists of the careful examination of each patient's history by two OCD specialists, so as to confirm his refractoriness status.
- Refractoriness Criteria For Previous Treatments
- 1. At least 3 serotonin reuptake inhibitors have been tried (selective or not). One of these trials must have included clomipramine. All drugs were used for a minimum of 12 weeks, at the maximum doses or the maximally tolerated doses.
- 2. Previous participation in a cognitive behavior therapy program, for a minimum of 20 hours' time; or participation for some time, without subsequent adherence, due to severe OCD symptoms, and acceptance by an independent review board.
- 3. Reduction in Y-BOCS scores after adequate drug therapy and psychotherapy not better than 25 %.
- 4. By the end of adequately conducted pharmacological trials, "Clinical Global Impression" (CGI) scores not better than minimal improvement.
- 5. Previous use of at least two augmentation strategies (such as the association of a typical or atypical neuroleptic, a benzodiazepine, or another SRI), in adequate doses for a sufficient period of time, without satisfactory responses. Exclusion Criteria
- 1. Younger than 18 or older than 55 years old.
- 2. Past history of head injury, with posttraumatic amnesia.
- Past manifested neurological or general medical condition, or history of physiological effects of a substance, as determinants of psychopathological symptoms.
- 4. Pregnancy or lactation.
- 5. Refusal to radiosurgical procedures.
- 6. Refusal to sign the Patient Information and Consent Form, or refusal to take part in this study.
- 7. History of mental retardation and/or being unable to understand the Patient Information and Consent Form, confirmed by poor performance on neuropsychological tests.

TABLE 2. Preoperative Sociodemographic Characteristics of Five Obsessive Compulsive Patients Submitted to (VC/VS) Gamma Capsulotomy

Patient	Age	Gender	Race	Marital status	Level of education	Job status
A	23	Male	Caucasian	Single	College, incomplete	Never worked
В	42	Female	Caucasian	Divorced	University	Adapted job
С	49	Female	Mixed-race	Married	Primary school	Housewife, disabled
D	36	Female	Caucasian	Single	University	Regular job
Е	25	Male	Caucasian	Single	High school, incomplete	Unemployed
Median	36			0.1	8, 1	I
Mean	35					
SD	11.07					

^{1.} A DSM-IV diagnosis of OCD as the main diagnostic entity. If comorbid axis I or II disorders are present, OCD symptoms are the most troublesome and precede other disorders.

were told to maintain their medications unchanged after surgery. However, prescription modifications were necessary in two patients (C and E), and one of the responders independently reduced his dosage (A).

Follow-up Assessments

Clinical global changes were prospectively assessed by the Clinical Global Impression (CGI) Scale and Global Assessment of Functioning (GAF) Scale.^{12,13} The presence and severity of OC symptoms and tics were respectively determined by the Y-BOCS and the Yale Global Tic Severity Scale.^{14–16} The Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI) were administered to all patients.^{17,18} All inventories were applied before surgery and at every subsequent follow-up visit. Patients who missed their follow-up appointments were interviewed by phone to minimize loss of data collection.

Sleep and cognitive, emotional and/or physical adverse events were prospectively assessed by a detailed questionnaire (SAFTEE Event List and Interview).¹⁹

Postoperative follow-up visits were scheduled at 2 weeks, 1 month, 2 months, and subsequently at 3, 6, 9, 12, 24, and 36 months after surgery. At 48 months of

TABLE	TABLE 3. Psychopathological Features in Five Obsessive Compulsive Patients Submitted To (VC/VS) Gamma Capsulotomy									
Patient	Age	Age first obsessions	Age first compulsions	Age first obsessive compulsive symptoms (discomfort)	Age of obsessive compulsive symptoms interference	Age of OCD	Age first treatment	Y- BOCS scores	Lifetime comorbid axis I diagnosis	Comorbid axis II diagnosis
A	23	13	8	8	18	18	18	30	Alcohol abuse; cyclothymic disorder	Borderline personality disorder
В	42	6	6	6	18	18	23	32	Major depressive disorder, recurrent; social phobia; skin picking	Dependent personality disorder; avoidant personality disorder
С	49	10	10	10	20	20	?	33	Major depressive disorder, single episode; panic disorder with agoraphobia	Dependent personality disorder; avoidant personality disorder
D	36	10	10	12	19	20	25	34	Major depressive disorder, single episode; panic disorder without agoraphobia	-
Е	25	14	8	8	12	12	15	32	0.1	Obsessive compulsive
Mediar Mean SD	36 35 11.07	10 10.6 3.13	8 8.4 1.67	8 8.8 2.28	18 17.4 3.13	18 17.6 3.29	20.5 20.25 4.57	32 32.2 1.48		personality disorder

OCD=obsessive compulsive disorder; Y-BOCS=Yale-Brown Obsessive Compulsive Scale

TABLE 4. Preoperative History of Previous Treatment Trials of Five Obsessive Compulsive Patients Submitted To (VC/VS) Gamma Capsulotomy

Patient	Previous medications	Previous SRI trials	Previous CBT trials	Previous other psychotherapies	Hospitalizations
A	21	7	1	1	4
В	14	6	1	2	1
С	14	4	1	0	9
D	12	6	1	0	0
Е	12	4	1	0	1
Median	14	6	1	0	1
Mean	14.6	5.4	1	0.6	3
SD	3.71	1.34	0	0.89	3.67

SRI=serotonin reuptake inhibitor; CBT=cognitive-behavior therapy.

follow-up, two patients (B and D) completed a full follow-up visit, whereas three patients (A, C, and E) were interviewed by telephone.

Clinical Response Criteria

Response criteria were defined as a minimum of 35% reduction in Y-BOCS scores and an "improved" or "much improved" score on the CGI.

Operative Technique

A preoperative stereotactic MRI was obtained, and determination of dose planning and target selection was performed using a dedicated software (Leksell GammaPlan, 5.32, 2002).

The final step of the procedure was the exposure of the targets with the patient in the Leksell Gamma Knife model B. Bilateral, double-shot capsulotomy lesions were targeted at the ventral portions of the anterior limb of the internal capsule, approximately 10 mm rostral to the anterior commissure. The target at the anterior limb of the internal capsule was covered by a 50% isodose line; maximum dose at 100% was 180 Gy. The bilateral targets were each exposed by two focus positions ("shots") from the converging sharply collimated beams of gamma radiation from 201⁶⁰Co sources, using 4 mm collimators. Sensitive structures such as the optic nerves and lenses were protected, maintaining radiation below a safe threshold in these regions. The mean total time of exposure to radiation was 480 minutes (or 240 minutes for each hemisphere). Radiation rate from the ⁶⁰Co sources was 1.788 Gy/min.

The American (BG and GN) and the Brazilian team (ACL, MC, ECM) worked together to determine optimal target localization and dose planning for all patients, either in person (cases A, B and C) or through electronic communication (cases D and E). Agreement

from all members of the team was achieved previous to each procedure.

MRI Acquisition

Structural MRI scans were acquired for all five OCD patients pre- and postoperatively (range 9 to 24 months) using a 1.5 Tesla Signa LX CVi scanner (version 9.1, 2004, General Electric, Milwaukee, Wisconsin).

Statistical Analysis

All variables were summarized using descriptive statistics (frequency, median, mean and SD). Small sample sizes and noncontinuous variables precluded parametric or nonparametric statistical analysis.

RESULTS

Assessment of Efficacy of the Procedure

Among the five patients submitted to gamma-capsulotomy, patients A and B (40%) fulfilled our response criteria after 12 months, and three patients (60%), including patient D, fulfilled criteria after 48 months of followup. Y-BOCS reductions ranged from 38% to 69% (Table 5, Figure 1, and Figure 2) among responders. Mean Y-BOCS scores changed from 32.2 ± 0.67 (standard error of mean [SEM]) to 20.6 ± 5.49 (SEM) after 48 months of follow-up. GAF improvements also reflected these changes (Figure 3). Patient C met our response criteria until 9 months of postoperative follow-up, with a subsequent relapse; she again became a responder when 36 months of follow-up was reached, but relapsed 4 years after surgery. Patient D showed only 18% reduction of the Y-BOCS at the 36th month of follow-up, but became a full responder (38% reduction of the Y-BOCS) by 48 months of follow-up. On the other hand, patient E's

TABLE 5.	Symptom Changes of Five Patients Submitted to (VC/VS) Gamma Capsulotomy, up to 48 Months of Follow-Up									
	PreOp YBOCS	PostOp YBOCS	% decrease from baseline	PreOp BDI	PostOp BDI	% decrease from baseline	PreOp BAI	PostOp BAI	% decrease from baseline	
A	30	10	66.67	18	28	-55.56	17	16	5.88	
В	32	10	68.75	35	8	77.14	45	10	77.78	
С	33	22	33.33	37	14	62.16	26	11	57.69	
D	34	21	38.24	16	1	93.75	18	2	88.89	
Е	32	40	-25.00	20	32	-60.00	32	24	25.00	
Mean	32.20	20.60		25.20	16.60		27.60	12.600		
SD	1.48	12.28		9.98	13.15		11.50	8.11		

PreOp Y-BOCS=preoperative Yale-Brown Obsessive Compulsive Scale scores; PostOp Y-BOCS=48 months of postoperative Y-BOCS scores; PreOp BDI=Preoperative Beck Depression Inventory scores; PostOp BDI=36 months of postoperative BDI scores; PreOp BAI=preoperative Beck Anxiety Inventory scores; PostOp BAI=36 months of postoperative BAI scores.

OCD symptoms deteriorated after 24 months of follow-up (25% increase on the Y-BOCS).

Beck Depression Inventory scores oscillated considerably along follow-up visits. Nevertheless, full and partial responders tended to present important reductions of the BDI scores, except for patient A, who developed a relapse of depressive symptoms at 36 months of follow-up (56% increase of scores from baseline) (Table 5, Figure 4). Patient E, a nonresponder, also showed further impairment (60% increase of BDI scores from baseline). A similar pattern was found with BAI scores, with more robust anxiety decrements (mainly with patients B, C and D) (Table 5, Figure 5).

Three patients had their medications changed during the study. Patient A did not tolerate higher dosages of antidepressants. He spontaneously changed his medication, from fluvoxamine, 100 mg/day, venlafaxine, 150 mg/day, quetiapine, 100 mg/day and clonazepam, 2 mg/day, to fluvoxamine, 50 to 100 mg/day, quetiapine, 25 mg/day, and clonazepam, 2 mg/day. For patient C, clomipramine dosage was increased from 225 mg/day to 300 mg/day, plus risperidone, 4 mg/day, and diazepam, 10 mg/day, during the study, due to depressive symptoms. By 36 months of follow-up, she was no longer taking risperidone, but OCD symptoms had improved. Patient D was initially taking citalopram, 60 mg/day, plus olanzapine, 2.5 mg/day, with no subsequent improvements on OCD. It was changed to fluoxetine, 40 mg/day, plus ziprasidone, 40 mg/day.

Assessment of General Medical and Neurological Adverse Events

Table 6 describes adverse events reported by patients, according to the Systematic Assessment for Treatment Emergent Events (SAFTEE) scale. Headaches (lasting days to weeks), light-headedness/vertigo, weight changes and episodic nausea/vomiting were observed. Headaches were usually responsive to nonsteroidal anti-inflammatory drugs, except for patient C, who required steroids for a few weeks. Another patient required bladder catheterization during the surgical procedure, presenting hematuria that resolved after 1 day (patient D).

MRI Assessments

Post operative MRI scans showed that all radiosurgical targets located exactly where planned preoperatively (Figure 6). All patients, with the exception of patient E, showed postoperative bilateral double-shot anterior capsulotomy lesions, indicated by hypointense rounded volumes on T1-weighted, T2-weighted and FLAIR images, with hyperintense borders on FLAIR and T2-weighted images and peripheral ring enhancement following paramagnetic contrast media administration, adjacent to the head of the caudate nuclei. Pa-





tient E, however, showed only minimal lesions in target areas, especially in the left hemisphere, as indicated in most image series (Figure 6 and Figure 7).

DISCUSSION

Procedure Efficacy

Previous anterior capsulotomy techniques produced a relatively high incidence of side effects, possibly as a consequence of larger lesions.^{20,21} Aiming to improve



results and reduce side effects, smaller and standardized capsulotomy lesions were developed (the VC/VS gamma capsulotomy).⁸ This improved procedure is based on a more precise target definition within the internal capsule, employing smaller collimator sizes (4 mm), consequently aimed at producing smaller lesions albeit not compromising efficacy.

Our preliminary findings suggest that this procedure holds promise for selected severe and treatment resistant OCD patients. Among the five patients enrolled in this study, at the end of a 3-year follow-up period, three (60%) presented *full* response after surgery (67%, 69% and 38% reductions in Y-BOCS severity), and one had a partial response (33%). On the other hand, the one patient who was a nonresponder to surgery also developed worse OCD symptoms in the long-term followup, though maintaining his previous psychosocial impairment.

The three patients who improved the most and the partial responder showed markedly increased personal autonomy and reintegration into society, in addition to relief of persistent subjective distress.

Although comparison across studies is limited for methodological reasons (see Greenberg et al.²² for discussion), clinically significant improvement after larger capsulotomy lesions (including an earlier gamma capsulotomy technique) was previously reported in five out of nine patients (55%) and seven out of 10 patients

FIGURE 3. Global Assessment of Functioning (GAF) Scores Over 48 Months of Follow-Up for Five Patients Who Underwent Ventral Capsular/Ventral Striatal Gamma Capsulotomy



(70%).^{6,7} These rates are comparable to ours (3 out of 5 patients or 60%). However, we used more stringent response criteria. Previous studies were less rigorous regarding OC symptom amelioration and did not include measures of global improvements (such as CGI scores). Analyzing data from previous Gamma Knife techniques, but response criteria similar to ours, Rück²¹

described response rates similar to ours (five out of eight patients, 62.5%).

The delayed amelioration of symptoms observed in our study could result from multiple sources and even be unrelated to the surgery. However, the latter interpretation is less likely, since OCD in the overwhelming majority of our patients was a chronic illness (mean

FIGURE 4. Beck Depression Inventory (BDI) Scores Over 36 Months of Follow-Up for Five Patients Who Underwent Ventral Capsular/ Ventral Striatal Gamma Capsulotomy



FIGURE 5. Beck Anxiety Inventory (BAI) Scores Over 36 Months of Follow-Up for Five Patients Who Underwent Ventral Capsular/ Ventral Striatal Gamma Capsulotomy



OCD duration of 17.4 years), unresponsive to multiple conventional treatment schemes.

It remains unclear how gamma capsulotomy lesions result in OCD symptom improvement. One hypothesis is that bilateral lesions of the anterior capsule could alter information flow in thalamo-orbital and thalamocingulate neuronal circuitry (particularly the subgenual cingulate), which is related to the pathophysiology of OCD, and thus be involved in the changes in OCD symptoms observed after surgery. Interestingly, functional imaging data from a small cohort of patients with severe anxiety disorders undergoing this type of neurosurgery showed reduced activity within medial orbitofrontal cortex after the intervention.^{22,23} In addition, edema and necrosis produced by gamma radiation surrounding the targets may compromise the adjacent striatum²⁴ and nucleus accumbens. Therefore, it is possible that additional cortico-striato-pallido-thalamico-cortical circuits are interrupted, especially those involving the ventral striatal-pallidal system and the extended amygdala.^{25–27}

It is unknown whether unilateral lesions would be as efficacious as bilateral targeting. One previous MRI study of anterior capsulotomy for OCD suggested that appropriate lesioning of the right anterior capsule *might be* critical to subsequent therapeutic response.⁷ It is noteworthy in our study that the only patient who did not show any clinical response to surgery had a mini-

 TABLE 6.
 Symptoms and Signs Reported Over 36 Months of Follow-up by Patients Who Underwent (VC/VS) Gamma Capsulotomy, According to SAFTEE Scale

Neurological Symptoms or Signs Episodic headaches, lasting from one day to more than 2 weeks, sometimes accompanied by nausea and photophobia (3 patients) Episodic light-headedness or vertigo (4 patients) Episodic blurred vision and photophobia (2 patients, headache-related?) Episodes of nausea/vomiting, for up to one week, sometimes accompanied by headaches (2 patients) Discrete pain and local dermatitis on the scalp, due to stereotactic frame positioning, for 2 weeks (1 patient) Left parietal paresthesia, accompanied by headache, for 2 weeks (1 patient) Discrete left lip and nose paresthesia, for months (1 patient) Dysosmia and dysgeusia for a few days, mainly in the first 2 postoperative weeks (1 patient) Tinnitus, for 2 months (1 patient) Psychiatric Symptoms or Signs Periodic insomnia (3 patients) Episodic nightmares (3 patients) Subjective feeling of sedation (3 patients) Worsening obsessive-compulsive symptoms for a few days, followed by abrupt symptom improvement (1 patient) Worsening anxiety and depressive symptoms, for a few days, followed by subsequent improvement (4 patients) Continuous anxiety symptoms, for months (4 patients) Mild subjective irritability, from 3 days to months (3 patients, anxiety-related?) Depressive mood (5 patients), lack of initiative and energy (4 patients), due to OCD/depression Discrete hypomanic symptoms, for 2 days (1 patient) Mood-related concentration and memory problems (2 patients) Subjective feeling of unquietness (4 patients) due to anxiety symptoms One episode of narrowing of consciousness (1 patient) General Medical Symptoms and Signs Postoperative throat swelling for 2 weeks, accompanied by irritability, depressive symptoms, palpitations, episodic hyperventilation, and nausea (1 patient) Weight and appetite changes: increase (1 patient, from 1 to 21 kg in 18 months of follow-up), reduction (1 patient, from 0.5 to 3 kg), and floating weight (2 patients) Blurred vision, due to previous visual problem (3 patients) Subjective "muscle weakness," occasionally, for months (3 patients, anxiety-related?) Tremors, anxiety and medication-related (2 patients) Discrete episodic hyperventilation (1 patient) Tachycardia, episodic, anxiety-related (1 patient) Discrete episodic chest pain (1 patient, anxiety-related?) Constipation/flatulence, medication-related (3 patients) One-day hematuria, due to urinary catheterization (1 patient) Signs of urinary infection, 6 months after surgery (1 patient) Menstrual changes (2 patients), sexual dysfunction (1 patient), medication-related Episodic perspiration and warm hands (2 patients) Eyebrow dermatitis (2 patients) Dry mouth, medication-related (3 patients) Sialorrhea, also present before surgery (1 patient) SAFTEE=Systematic Assessment for Treatment Emergent Events

mal left anterior capsule lesion, whereas all the other patients showed clear bilateral lesions.

It is not surprising that most of our patients also reported postoperative reductions in anxiety and depression scores. Anxiety disorders and refractory depression have been successfully treated with anterior capsulotomy by thermolesion.^{28,29} In our sample, persisting reductions in anxiety scores were more prominent than reductions in depressive symptoms (mean reduction of 15 score points or 54%, versus 8.6 score points or 34%). Patient A presented with worse scores on BDI and BAI in his last follow-up visit, and this may be attributed to his inadequate compliance with medications. He nonetheless maintained low Y-BOCS scores. Patient E, a treatment nonresponder, showed marked worsening of BDI and BAI scores, and OCD symptoms deteriorated. Therefore, it is possible that the improvement in anxiety and depressive symptoms by surgical intervention may contribute to the amelioration of OCD symptoms directly or indirectly, although not explaining the maintenance of low Y-BOCS scores in the postoperative follow-up period.

General Medical and Neurological Adverse Events

According to the SAFTEE scale, most adverse events were transient, not interfering with functioning or requiring treatment or hospitalization. Only headache, in one patient, lasted more than a few weeks. In this only case with persistent headache (around 2 weeks' duration), no evidence of brain swelling was found on MRI, although the patient was empirically treated with corticosteroids for a few weeks. None of these initial symptoms persisted 36 months after surgery. However, it is still early to draw definite conclusions regarding potential long-term adverse effects.

Some of the symptoms and signs assessed by the SAFTEE scale may be attributed either to the direct effects of radiation, or to the effects of anesthesia and head positioning in the Gamma Knife equipment or even be unrelated to surgery. Headaches, nausea, vertigo, weight changes, postoperative throat swelling, 1 day hematuria, local dermatitis, and discrete pain on the scalp were probably related to the surgical procedure. Even though weight changes were common in four patients, only one patient (C) developed a considerable weight gain. Most side effects were mild and lasted for only a few days. We suppose that other symptoms/signs may or may not have been related to surgery.

A less favorable profile of adverse events was reported in previous radiosurgical studies using larger targets.^{21,29} Rück²¹ reported the results of nine patients with OCD submitted to Gamma Knife capsulotomies. Three to four bilateral isocenters and 4 mm collimators were used for lesions in five patients, delivering more than 200 Gy at the center of the lesion on each side.²¹ Frontal lobe complications were evident in two patients, as well as urinary incontinence and seizures. It is unclear, however, if this was due to larger lesion volume, higher doses, and/or different targeting.

Limitations

This pilot study has several limitations. First, it included a small cohort and used an open design. Second, as patients came from regions distant to the study site, some follow-up data were obtained only by telephone





Patient A, who does not show marked lesions in this acquisition, demonstrated clear lesions on other acquisitions (see Fig. 7). This is not the case of patient E, who showed only minimal lesions on the left hemisphere in all acquisitions.

interview (especially at 48 months of follow-up). For the same reason, postoperative MRI scans schedule was different among patients (range=9 months to 24 months postsurgery). It was not possible to control for medication changes. Furthermore, patient C presented a quite variable clinical course over the 48 months of follow-up, demanding further assessment to reassure her response condition. Finally, neuropsychological and personality changes associated with this surgical procedure are not provided in this article, but they will be described in other publications.

FIGURE 7. T1-Weighted Axial and Coronal MRI Slices With Para-Magnetic Contrast (Gadolinium) Depicting Postoperative Ventral Capsular/Ventral Striatal Gamma Capsulotomy Lesions in Patients A and E



CONCLUSION

In conclusion, this pilot study supports the view that the VC/VS Gamma Knife capsulotomy for resistant OCD may hold promise for a selected group of patients who have otherwise no therapeutic options. Our findings suggest that this procedure may be effective and well-tolerated overall, particularly when compared to the previous Gamma Knife technique that employed larger lesions. These conclusions, however, must be tentative, given the limitations of the short follow-up period (4 years) and our open study design. So far, only a few pilot trials of neurosurgery for resistant OCD have used a controlled design, all of them with small sample sizes.^{30,31} Our group is currently conducting the first double-blind, randomized controlled trial on radiosurgery to address this gap in knowledge.

We thank Dr. Navid Tahamtani, Dr. George Schahin, Dr. Soraya Cecílio, Dr. Douglas Castro, Sérgio Franco, Dr. Lauro Morubaiashi, Dr. Adriana Pinto, Dr. Ademir Bonassa, Prof. Raul Marino Jr, Prof. Valentim Gentil Filho, Prof. José Alberto Del Porto, Dr. Rui Castello Branco, Dr. Carlos Longo, Cláudia Midori Yamao, Patrícia Yamashita, and Gláucia Macedo whose help was fundamental to the execution of this project.

This study received financial support in the form of grants to Dr. Miguel from Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP, Foundation for the Support of Research in the State of São Paulo; grant #1999/08560-6 and #2005/55628-08) and from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, Brazilian Council for Scientific and Technological Development; grant no. 305548/2005-0).

References

- Pallanti S, Hollander E, Bienstock C, et al: Treatment nonresponse in OCD: methodological issues and operational definitions. Int J Neuropsychopharmacol 2002; 5:181–191
- 2. Jenike MA, Rauch SL: Managing the patient with treatmentresistant obsessive compulsive disorder: current strategies. J Clin Psychiatry 1994; 55:11–17
- 3. Perse T: Obsessive-compulsive disorder: a treatment review. J Clin Psychiatry 1988; 49:48–55
- 4. Rasmussen SA, Eisen JL: Treatment strategies for chronic and refractory obsessive-compulsive disorder. J Clin Psychiatry 1997; 58(suppl 13):9–13
- Lopes AC, de Mathis ME, Canteras MM, et al: [Update on neurosurgical treatment for obsessive compulsive disorder.] Rev Bras Psiquiatr 2004; 26:62–66 (Portuguese)

- 6. Rylander G: Försök med gammakapsulotomi vid ångest-och tvångsneuroser. Lakartidningen 1978; 75:547–549
- 7. Lippitz BE, Mindus P, Meyerson BA, et al: Lesion topography and outcome after thermocapsulotomy or gamma knife capsulotomy for obsessive-compulsive disorder: relevance of the right hemisphere. Neurosurgery 1999; 44:452–458
- 8. Norén G, Lindquist C, Rasmussen SA, et al: Gamma Knife capsulotomy for obsessive-compulsive disorder. American Association of Neurological Surgeons [abstract on the Internet]. 2002. Available at http://www.aans.org//library/article.aspx?ArticleId=12171
- 9. Miguel EC, Lopes AC, Guertzenstein EZ, et al: Guidelines for neurosurgery of severe psychiatric disorders in brazil: a preliminary proposal. Rev Bras Psiquiatr 2004; 26:7–8

- 10. First MB, Spitzer RL, Gibbon M, et al: User's Guide for the Structured Clinical Interview for DSM-IV Axis I Disorders – clinician version (SCID-CV). Washington, DC, American Psychiatric Publishing, 1997
- Pfohl B, Blum N, Zimmerman M: Structured Interview for DSM-IV Personality (SIDP-IV). Washington, DC, American Psychiatric Publishing, 1997
- 12. Guy W (ed): ECDEU Assessment Manual for Psychopharmacology, Revised (publication ADM 76-338). Rockville, MD, US Department of Health, Education, and Welfare, 1976
- 13. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed, text revision. Washington, DC, American Psychiatric Association, 2000
- 14. Goodman WK, Price LH, Rasmussen SA, et al: The Yale-Brown Obsessive Compulsive Scale, I: development, use, and reliability. Arch Gen Psychiatry 1989a; 46:1006–1011
- Goodman WK, Price LH, Rasmussen SA, et al: The Yale-Brown Obsessive Compulsive Scale, II: validity. Arch Gen Psychiatry 1989; 46:1012–1016
- Leckman JF, Riddle MA, Hardin MT: The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. J Am Acad Child Adolesc Psychiatry 1989; 28:566–573
- Beck AT, Ward CH, Mendelson M, et al: An inventory for measuring depression. Arch Gen Psychiatry 1961; 41:561–571
- Beck AT, Epstein N, Brown G, et al: An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 1988; 56:893–897
- 19. Guy W, Wilson WH, Brooking B, et al: Reliability and validity of SAFTEE: preliminary analyses. Psychopharmacol Bull 1986; 22:397–401
- Kihlström L, Guo WY, Lindquist C, et al: Radiobiology of radiosurgery for refractory anxiety disorders. Neurosurgery 1995; 36:294–302
- 21. Rück C: Capsulotomy in anxiety disorders. Thesis for doctoral

degree (PhD) [Dissertation]. Stockholm, Karolinska Intitutet, 2006

- 22. Greenberg BD, Price LH, Rauch SL, et al: Neurosurgery for intractable obsessive-compulsive disorder and depression: critical issues. Neurosurg Clin N Am 2003; 14:199–212
- 23. Mindus P, Ericson K, Greitz T, et al: Regional cerebral glucose metabolism in anxiety disorders studied with positron emission tomography before and after psychosurgical intervention: a preliminary report. Acta Radiol Suppl 1986; 369:444– 448
- 24. Rauch SL: Neuroimaging and neurocircuitry models pertaining to the neurosurgical treatment of psychiatric disorders. Neurosurg Clin N Am 2003; 14:213–223
- Heimer L: A new anatomical framework for neuropsychiatric disorders and drug abuse. Am J Psychiatry 2003; 160:1726– 1739
- 26. Ribas GC: [Considerations about the nervous system phylogenetic evolution, behavior, and the emergence of consciousness.] Rev Bras Psiquiatr 2006; 28:326–338 (Portuguese)
- 27. Ribas GC: [Neuroanatomical basis of behavior: history and recent contributions.] Rev Bras Psiquiatr 2007; 29:63–71 (Portuguese)
- Hurwitz TA, Mandat T, Forster B, et al: Tract identification by novel MRI signal changes following stereotactic anterior capsulotomy. Stereotact Funct Neurosurg 2006; 84:228–235
- Rück C, Andreewitch S, Flyckt K, et al: Capsulotomy for refractory anxiety disorders: long-term follow-up of 26 patients. Am J Psychiatry 2003; 160:513–521
- 30. Fodstad H, Strandman E, Karlsson B, et al: Treatment of chronic obsessive compulsive states with stereotactic anterior capsulotomy or cingulotomy. Acta Neurochir (Wien) 1982; 62:1–23
- 31. Nuttin BJ, Gabriels LA, Cosyns PR, et al: Long-term electrical capsular stimulation in patients with obsessive-compulsive disorder. Neurosurgery 2003; 52:1263–1272