Internal Pallidal and Thalamic Stimulation in Patients With Tourette Syndrome

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Background: Tourette syndrome (TS) is thought to result from dysfunction of the associative-limbic territories of the basal ganglia, and patients with severe symptoms of TS respond poorly to medication. High-frequency stimulation has recently been applied to patients with TS in open studies using the centromedian-parafascicular complex (CM-Pf) of the thalamus, the internal globus pallidus (GPi), or the anterior limb of the internal capsule as the principal target.

Objective: To report the effect of high-frequency stimulation of the CM-Pf and/or the GPi, 2 associative-limbic relays of the basal ganglia, in patients with TS.

Design: Controlled, double-blind, randomized crossover study.

Setting: Medical research.

Patients: Three patients with severe and medically refractory TS.

Intervention: Bilateral placement of stimulating electrodes in the CM-Pf (associative-limbic part of the thalamus) and the GPi (ventromedial part).

Main Outcome Measures: Effects of thalamic, pallidal, simultaneous thalamic and pallidal, and sham stimulation on neurologic, neuropsychological, and psychiatric symptoms.

Results: A dramatic improvement on the Yale Global Tic Severity Scale was obtained with bilateral stimulation of the GPi (reduction in tic severity of 65%, 96%, and 74% in patients 1, 2, and 3, respectively). Bilateral stimulation of the CM-Pf produced a 64%, 30%, and 40% reduction in tic severity, respectively. The association of thalamic and pallidal stimulation showed no further reduction in tic severity (60%, 43%, and 76%), whereas motor symptoms recurred during the sham condition. No neuropsychological, psychiatric, or other long-term adverse effect was observed.

Conclusions: High-frequency stimulation of the associative-limbic relay within the basal ganglia circuitry may be an effective treatment of patients with TS, thus heightening the hypothesis of a dysfunction in these structures in the pathophysiologic mechanism of the disorder.

Trial Registration: clinicaltrials.gov Identifier: NCT00139308

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TOURETTE SYNDROME (TS) IS characterized by motor and vocal tics associated with various psychiatric manifestations, which can cause major familial and social disability.[1] In patients with severe and debilitating tics, the best available drug therapy is often ineffective and has serious potential adverse effects.[2,3] Several attempts at neurosurgical creation of lesions have yielded disappointing results and severe adverse effects.[4,5] In sparse case reports, high-frequency stimulation of the centromedian-parafascicular complex (CM-Pf) of the thalamus,[6] the internal part of the globus pallidus (GPi),[7-9] and the anterior limb of the internal capsule[10] has been tested, with a positive but variable effect on tics. Recently, bilateral stimulation of the CM-Pf and/or the ventro-oralis nucleus of the thalamus was applied in 18 patients with TS, resulting in a 65% improvement in tics.[11] However, these results were obtained at various postoperative delays through an open-label evaluation. Given the proposed dysfunction of

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Table 1. Preoperative Clinical Characteristics of 3 Patients With Tourette Syndrome

	Patient No., Sex		
	1, F	2, M	3, F
Age, y			
At onset of tics	7	6	13
At time of surgery	36	30	30
Tourette syndrome symptoms			
Tics			
Motor	Eyes, mouth and arms, shoulder shrugs, touching, copropraxia	Eyes, face and arms, head jerks, shoulder shrugs, knee flexion	Eyes, face and arms, head and abdominal jerks
Phonic	Throat clearing, shouting, coprolalia	Throat clearing, shouting, animal noises	Coughing, throat clearing, grunting, animal noises
Self-injurious behaviors	Self-inflicted eye lesions, severe lip biting, hair tearing, burning	Jaw biting	None
Associated behavioral disorders	Borderline personality	Arithmomania (mental counting)	None
Treatments			
Neuroleptic, mg/d	Loxapine succinate, 700; Pimozide, 18	Pimozide, 6; Tiapride, 300	Risperidone, 3; Loxapine succinate, 25
Others, mg/d	Venlafaxine hydrochloride, 300; Clonazepam, 16	Fluoxetine hydrochloride, 60; Diazepam, 20	Venlafaxine hydrochloride, 37.5
Global functioning			
Familial	Married, living alone, 4-year-old son placed with grandparents	Unmarried, living with mother	Divorced, living alone with 3-year-old daughter
Socioprofessional	Unemployed for 10 mo (secretary), hospitalized in neurologic unit for 10 mo	Unemployed for 19 mo (waiter)	Unemployed for 4 mo (checkout assistant)

the associative-limbic component of the basal ganglia circuitry in TS,[12-14] we evaluated the efficacy of high-frequency stimulation of 2 associative-limbic relays, the CM-Pf of the thalamus and ventromedial part of the GPi,[13,15] in a controlled, double-blind, randomized crossover study.[16]

METHODS

Three patients with severe TS were selected for bilateral implantation of quadripolar electrodes (Medtronic, Minneapolis, Minnesota) in the ventromedial part of the GPi and the CM-Pf (**Table 1**, **Figure 1**).[16] Inclusion criteria for surgery were as follows: (1) TS according to *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition)[18] (*DSM-IV*) criteria, (2) age greater than 18 years, (3) severe form of the disease adversely affecting social integration, (4) failure of best treatment by medication or intolerance after a minimum of 6 months of treatment, (5) absence of cognitive deficits or psychosis, and (6) ability to give written informed consent.[19] The protocol, agreed on and sponsored by INSERM (RBM 00-008), was approved by the local ethics committee.[16]

The 4 quadripolar electrodes were implanted stereotactically (2 within the left and right CM-Pf and 2 within the left and right GPi) and connected to 2 subclavicular implanted programmable pulse generators (Kinetra; Medtronic) with the patient under general anesthesia. The electrodes and their 4 individual contact locations were plotted on the postoperative magnetic resonance image by means of automatic alignment with a 3-dimensional digital atlas of the basal ganglia (Figure 1).[20]

Patients were examined 1 month before surgery and 2 months after surgery without stimulation. Two months after surgery, 4 stimulation conditions were individually randomly assigned in a crossover design (n of 1 design study), with both patients and investigators blinded to the condition: (1) bilateral thalamic, (2) bilateral pallidal, (3) bilateral pallidal and thalamic, and (4) no stimulation (sham). Each stimulation condition was maintained for 2 months, and patients were examined monthly (**Figure 2**). Assessments were performed, blind to the condition, every month during a 5-day hospitalization. Clinical evaluation included the following: (1) tic severity assessed by the Yale Global Tic Severity Scale (YGTSS) (primary outcome

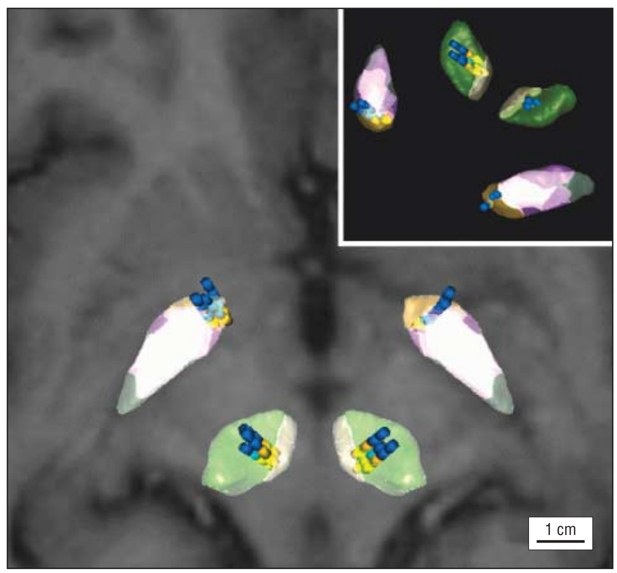

Figure 1. Axial magnetic resonance image of the 3 patients showing the 2 targets, the ventromedial part of the internal globus pallidus (GPi) and the centromedian-parafascicular complex (CM-Pf) of the thalamus, after adjustment of the 3-dimensional atlas in the image of each patient and normalization in the atlas space.[17] The CM-Pf is medial (centromedian, green; parafascicular, gray), and the ventromedial GPi target is lateral. The limbic pallidum is yellow; the associative pallidum, violet; and the sensorimotor pallidum, green. The therapeutic contacts are yellow (GPi: contact 0 in patient 1, contacts 0 and 1 in patients 2 and 3 [mean coordinates: 20 mm anterior, 12 mm lateral, 3 mm ventral to the posterior commissure point]; amplitude, 1.5-3.5 V; CM-Pf: contacts 0 and 1 [mean coordinates: 2.5 mm anterior, 6.0 mm lateral, 1.2 mm dorsal to the posterior commissure point]; amplitude,1.5-1.7 V), and the other contacts are blue. Inset, Three-dimensional representation of the same structures as seen from an anterior, dorsal, and lateral point of view. Colors are the same as in the main figure. This oblique orientation and the transparent mode of representation of the GPi and the CM-Pf improve the visibility of the therapeutic contact positions (yellow circles).

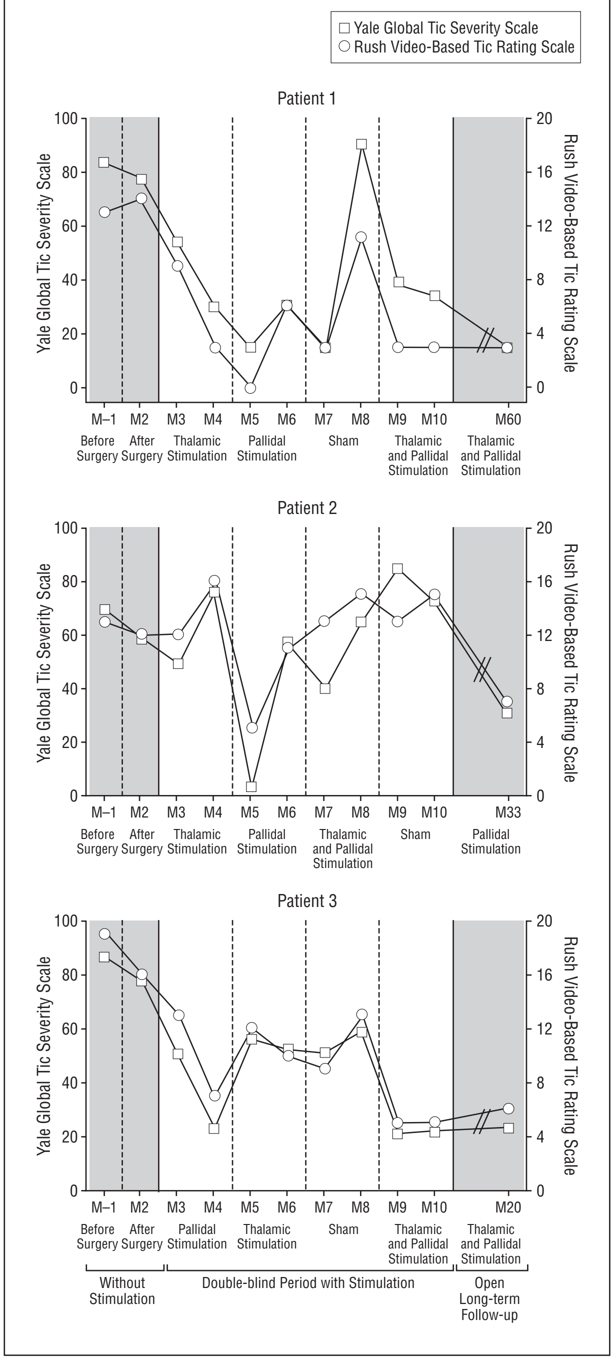

Figure 2. Effects of high-frequency stimulation of the centromedian-parafascicular complex of the thalamus and the ventromedial part of the internal globus pallidus in 3 patients with Tourette syndrome on tic severity. M indicates month.

measure), the motor and phonic tic subscore (corresponding to the YGTSS less the 50-point impairment portion), and the Rush Video-Based Tic Rating Scale; (2) psychiatric symptoms, ie, depression, anxiety, impulsiveness, and obsessive-compulsive behaviors; and (3) neuropsychological status (attention, episodic memory, working memory, and flexibility) (see Houeto et al[16] for details). With a view to maintaining the double blind for each patient, stimulation settings were adjusted for the next period as follows: after motor, psychiatric, and cognitive assessments, bilateral thalamic and pallidal stimulation was applied with intensities below the level of adverse effects during 24 to 48 hours, with a pulse width of 60 microseconds and a frequency of 130 Hz, the stimulation settings were activated for the next period.

An open long-term follow-up evaluation was performed on all patients in December 2006 (60, 33, and 20 months postoperatively for the 3 patients).

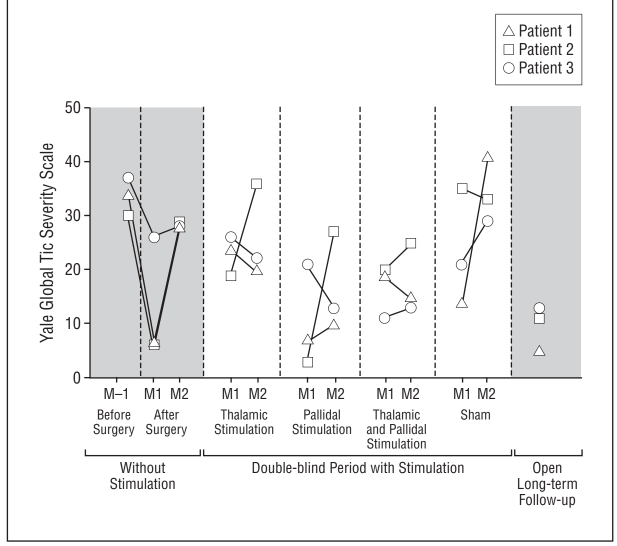

Figure 3. Effects of high-frequency stimulation of the centromedian-parafascicular complex of the thalamus and ventromedial part of the internal globus pallidus in 3 patients with Tourette syndrome on motor and phonic tic severity (Yale Global Tic Severity Scale). Each stimulation condition (thalamic, pallidal, simultaneous thalamic and pallidal, and sham stimulation) was maintained for 2 months, and patients were examined monthly. M indicates month.

RESULTS

EFFECTS OF HIGH-FREQUENCY STIMULATION ON TIC SEVERITY

A marked improvement in tic severity occurred within hours (patient 1) or days (patients 2 and 3) after the operation, which enabled us to interrupt dopamine antagonist medication in patient 1[16] and reduce dosage by 66% in patient 2. Two months after surgery and without stimulation, no significant change in tic severity was observed in any of the patients (YGTSS and Rush Video-Based Tic Rating Scale) (Figure 2 and **Figure 3**).

Thalamic and/or pallidal stimulation produced a marked improvement in tic severity in comparison with preoperative and sham assessments. Compared with preoperative assessment, the best improvement in tic severity was obtained with ventromedial GPi stimulation, with 65%, 96%, and 74% reduction in the total YGTSS in patients 1, 2, and 3, respectively (Figure 2) and 80%, 90%, and 67% reduction in motor and phonic tic subscore (Figure 3). The best effects of CM-Pf thalamic stimulation were reductions of 64%, 30%, and 40% in global tic severity (Figure 2) and 41%, 37%, and 41% in motor and phonic tic severity (Figure 3). Combined thalamic and pallidal stimulation did not improve the tic reduction (60%, 43%, and 76% in the total YGTSS, and 59%, 16%, and 70% in the motor and phonic tic subscore, respectively) (Figures 2 and 3). The

Table 2. Effects of Thalamic and/or Pallidal Stimulation on Cognitive Performance and Psychiatric Status[a]

Test and Patient No.	Without Stimulation		Double-blind Period With Stimulation			
	Before Surgery	After Surgery	Thalamic	Pallidal	Thalamic and Pallidal	Sham
Episodic memory (Verbal Learning; maximum 36)						
1	14	28	30	29	31	31
2	29	30	26	30	30	30
3	30	31	32	29	30	30
Working memory (Digit Ordering Test; maximum 105)						
1	67	86	85	86	89	86
2	98	100	104	102	100	100
3	98	85	100	98	102	98
Flexibility (Trail Making Test A-B)[b]						
1	96	43	28	27	30	36
2	21	3	19	22	13	14
3	27	20	27	45	23	27
Impulsivity (BIS; maximum 100)						
1	77	66	35	58	61	31
2	68	65	66	69	73	73
3	63	72	65	69	63	66
Depression (MADRS; maximum 60)						
1	25	19	10	23	17	20
2	2	0	1	1	2	3
3	13	3	2	9	4	7
Anxiety (BAS; maximum 60)						
1	7	15	8	10	15	7
2	2	0	5	4	2	7
3	19	4	4	3	0	8

Abbreviations: BAS, Brief Anxiety Scale; BIS, Brief Impulsivity Scale; MADRS, Montgomery and Asberg Depression Scale.

[a] For episodic memory, working memory, and flexibility scores, high values correspond to better performance; for impulsivity, depression, and anxiety scores, high values correspond to worse psychiatric status.

[b] The Trail Making Test A-B produces a reaction time expressed in seconds; the mean normal value is 35 ± 20 seconds.

effects of both thalamic and pallidal stimulation remained stable or increased during the 2-month period in patients 1 and 3. In patient 2, the best result was obtained after 1 month with stimulation, but the improvement decreased or disappeared after 2 months. In the sham condition, patients 1 and 2 experienced a recurrence of motor symptoms, with a severity similar to that observed before surgery. In patient 3, tic severity decreased by 32% in the sham condition (Figure 2).

ADVERSE EFFECTS

With therapeutic stimulation settings, transient cheiro-oral or arm paresthesias (lasting a few minutes) or lethargy (3-4 days) were induced under thalamic or pallidal stimulation, respectively. With increasing intensity of pallidal stimulation, 2 patients reported sensations of nausea and vertigo and 1 patient reported anxiety. A libido decrease was reported by patient 3 under thalamic stimulation.

EFFECTS OF STIMULATION ON PSYCHIATRIC, NEUROPSYCHOLOGICAL, AND SOCIAL STATUS

Before surgery, patient 1 had a major depressive disorder with severe self-injurious behaviors and impulsiveness, fulfilling the *DSM-IV* criteria for borderline personality disorder.[16] Self-injurious behaviors were dramatically reduced by pallidal and/or thalamic stimulation, but they reappeared during the sham stimulation condition. Depressive mood, emotional hypersensitivity, moderate anxiety, and impulsiveness tended to decrease with thalamic or simultaneous thalamic and pallidal stimulation but not with pallidal stimulation alone (**Table 2**). Patient 2 had no psychiatric disorder either before or after surgery (Table 2). Mild anxiety-free mental counting was present before surgery; it disappeared under both thalamic and/or pallidal stimulation but reappeared during the sham procedure. Patient 3 had a moderate generalized anxiety disorder, which was controlled at the time of surgery with venlafaxine hydrochloride therapy (37.5 mg/d). No resurgence of anxiety occurred after surgery despite discontinuation of venlafaxine therapy (Table 2). None of the 3 patients showed obsessive-compulsive symptoms either before or after surgery (not shown).

Neuropsychological status, which was normal before surgery, remained stable in all patients (Table 2).

LONG-TERM FOLLOW-UP

In patient 1, 60 months after surgery, simultaneous thalamic and pallidal stimulation induced an 82% decrease in tic severity and a dramatic reduction in self-injurious behaviors and impulsiveness (Figure 2). Two years after surgery, she went back to full-time work and began interpersonal psychotherapy, which enabled an improvement in interpersonal relationships. Four years after surgery, failure of the pallidal neurostimulator led to a reappearance of tics and self-injury, dramatically decreasing a few hours after replacement.

Patient 2 required monthly adjustment of the stimulation settings, with an increase in the intensity of stimulation and pulse width because of the resurgence of tics. A stable reduction in tic severity was obtained 27 months after surgery under noncontinuous (20 hours on followed by 4 hours off) pallidal stimulation. Because of mild and intermittent improvement in tic severity during the 17 months after the end of the protocol, patient 2 did not recover his professional activity.

In patient 3, 20 months after surgery, tic severity was reduced by 74% without medication under pallidal and thalamic stimulation. Four months after the end of the protocol, patient 3 began a professional educational retraining program.

COMMENT

An improvement in tic severity with no cognitive or psychiatric adverse effects was seen with high-frequency stimulation of the CM-Pf or ventromedial part of the GPi, which form part of the basal ganglia associative-limbic circuits. In all patients, double-blind GPi stimulation induced the greatest reduction in tic severity, with no improvement from simultaneous thalamic and pallidal stimulation (Figure 2). Nevertheless, during long-term follow-up, an overall improvement in tic severity, as well as in impulsivity and anxiety, was confirmed in 2 patients with simultaneous thalamic and pallidal stimulation without adverse effects. In 1 patient, the reduction of motor symptoms was obtained with intermittent pallidal stimulation.

The results obtained in our 3 patients are robust, for the following reasons. (1) This was a double-blind randomized protocol including a sham period during which patients experienced a reappearance of symptoms. (2) The stimulating electrodes were accurately positioned within the CM-Pf and the GPi, and the active contacts used for continuous stimulation were identically localized in the structures (Figure 1). (3) The therapeutic benefit persisted for a long period (20, 33, and 60 months after surgery), enabling a marked concomitant reduction of drug treatment. In the pallidum, in patient 2, this improvement was obtained after intermittent adjustment of the stimulation settings. We do not have any explanation for this patient's recurrences despite repeated attempts at adjustment and exclusion of neurostimulator malfunction. Similar difficulties in adjustment of stimulation settings have been reported in most patients with TS recently treated by CM-Pf and/or ventro-oralis stimulation.[11] This could result from neuronal plasticity with a decrease of the effects of electrical high-frequency stimulation on local neuronal activity.

Some limitations could affect these results. (1) The number of patients is small; however, because of ethical issues, this investigation was a pilot study, and the crossover design enabled us to evaluate the differential effect of each stimulated structure, CM-Pf of the thalamus vs ventromedial part of the GPi. (2) The duration of the stimulation effects could have led to a carryover effect. This cannot be totally excluded, but the fact that in 2 patients the effects of stimulation were maximal after 2 months of stimulation for each structure does not favor this hypothesis (Figure 3).

This controlled, double-blind, randomized crossover study confirms previous results obtained in open-label studies in patients with TS using high-frequency stimulation of the CM-Pf of the thalamus,[6,11] but it shows that stimulation of the ventromedial GPi produced a similar or greater improvement in TS symptoms (Figure 2). This result is in line with the proposal of corticostriato-pallidocortical pathway dysfunction.[19] In nonhuman primates, complex stereotyped movements resembling tics have been produced by selective modulation of the limbic (ventromedial) external part of the globus pallidus by means of microinjection of the γ-aminobutyric acid antagonist bicuculline,[13] and consequently of the ventromedial part of the GPi.[21] In our patients, stimulation of the ventromedial part of the GPi seems to be more efficient than stimulation of the CM-Pf of the thalamus. This difference could be explained by the different anatomic and functional positions of these structures within the basal ganglia circuitry. Indeed, the ventromedial part of the GPi is a key structure as the output nucleus of the main direct pathway.[17] Conversely, the CM-Pf is part of an internal loop of the basal ganglia circuitry receiving its input from the output nuclei and projecting back to the striatum.[17] It is therefore plausible that stimulation applied to the main loop, ie, the GPi, would be more efficient than that applied within an indirect internal loop, ie, the CM-Pf of the thalamus.

This study suggests that high-frequency stimulation of the ventromedial part of the GPi can produce a marked reduction in tic severity in patients with TS, which is in the process of being tested in a large patient population (STIC [Traitement de la maladie de Gilles de la Tourette par stimulation bilatérale à haute fréquence de la partie antérieure du Globus Pallidus interne] French multicenter study).

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