Chronic bilateral thalamic stimulation: a new therapeutic approach in intractable Tourette syndrome

Report of three cases

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Based on the results of thalamotomies described by Hassler in 1970, the authors performed bilateral thalamic high-frequency stimulation (HFS) in three patients with intractable Tourette syndrome (TS). In this report they describe the long-term effects.

Three male patients (42, 28, and 45 years of age) had manifested motor and vocal tics since early childhood. The diagnosis of TS was made according to the criteria of the Tourette Syndrome Classification Study Group. Any drug or alternative treatment had been either ineffective or only temporarily effective in all three patients. There was no serious comorbidity. The target for stimulation was chosen at the level of the centromedian nucleus, substantia periventricularis, and nucleus ventrooralis internus. After 2 weeks of test stimulation, the pulse generators were implanted. After a follow-up period of 5 years in the patient in Case 1, 1 year in the patient in Case 2, and 8 months in the patient in Case 3, all major motor and vocal tics had disappeared and no serious complications had occurred. When stimulation was applied at the voltage necessary to achieve an optimal result on the tics, a slight sedative effect was noted in all three patients. In the patients in Cases 1 and 3 there were stimulation-induced changes in sexual behavior.

Chronic thalamic HFS may be an effective and safe treatment for medically intractable TS in adult patients. Unwanted stimulation-induced side effects may occur.

KEY WORDS • deep brain stimulation • thalamus • Tourette syndrome • high-frequency stimulation

Tourette Syndrome is a chronic neurological disorder with an onset in early childhood that is characterized by tics. These tics are defined as sudden, brief, intermittent, involuntary, or semivoluntary movements (motor tics) or sounds (phonic or vocal tics). They may be abrupt in onset, fast and brief (clonic), or slow and sustained (dystonic or tonic). Once considered to be a rare and bizarre syndrome, TS is now recognized as a relatively common, biological, genetic disorder with a spectrum of neurobehavioral manifestations that characteristically wax and wane during its natural course. In addition to motor and vocal tics, patients with TS often have a variety of behavioral symptoms, particularly those associated with attention deficit–hyperactivity disorder and obsessive–compulsive disorder.

Drug treatment of TS consists of neuroleptics and other agents interacting with the dopaminergic system. Side effects such as depression, drowsiness, weight gain, and extrapyramidal symptoms are a major drawback for their prolonged use, however. Frequently, TS is found to be a self-limiting disorder as the patient reaches adulthood, whereas in a small proportion of patients the tics continue into adult life and require long-term medication. Behavioral therapy has not been proven to be effective long term.

Surgery has rarely been performed in patients with TS. Hassler and Dieckmann performed bilateral coagulations of the medial and intralaminar thalamic nuclei in three patients with TS in 1970. In this report they describe the long-term effects. In 1997 we performed stereotactic bilateral HFS of the thalamic nuclei targeted by Hassler in a patient with intractable TS. In the present study, we report on the long-term effects of bilateral HFS of the thalamus in three patients with TS. In the patients in Cases 1 and 3 there were stimulation-induced changes in sexual behavior.

Clinical Material and Methods

Patient Characteristics

Three patients were selected on the basis of intractable
TS with absent comorbidity. The diagnosis was made according to the criteria of the Tourette Syndrome Classification Study Group.\(^\text{15}\) Characteristics of tics with their frequencies per patient and per tic are shown in Table 1. The impact of thesetics as determined by each patient is presented in Table 2. All three patients suffered from compulsive behavior. None of the patients or their partners reported obsessions (such as sexual obsessions). Psychotherapy had failed in all patients, and medication, including various dopamine-depleting or dopamine receptor blocking agents and clonidine, either had no effect or had to be withdrawn after prolonged use because of unbearable side-effects, depression being the most important.

In all patients blood chemistry, electroencephalography, and MR images were normal. Neuropsychological evaluations were performed in the patients in Cases 1 and 3.

**Evaluation of Tics**

One week postoperatively the patients were evaluated by a blinded examiner while the neurosurgeon manipulated the pulse generator. In all patients an assessment of the acute effects of bipolar (poles 0 and 1 negative, 2 and 3 positive) stimulation with a frequency of 125 Hz and a pulse width of 210 μsec was performed. Randomly, the amplitudes of both installed stimulators were set between 0 V and the maximum voltage, which was defined as the voltage above which the patient felt an unpleasant sensation of dizziness (Case 1, 6 V bilaterally; Case 2, 4 or 5 V for the left and 4 V for the right; and Case 3, 5 V for the left and 3 V for the right). Each evaluation was performed 15 minutes after manipulation of the stimulus intensity. Each session contained two periods during which both stimulators were switched off, and installed at the maximum voltage.

At the long-term follow up (5 years for Case 1, 1 year for Case 2, and 8 months for Case 3), each patient was recorded on videotape for 20 minutes while chronic bilateral stimulation was applied and for 20 minutes after both stimulators had been switched off for 12 hours. The number of tics displayed on the videotapes was counted by two independent, blinded investigators (Y.T. and G.H.) during a period
planted infraclavicularly at a second stage. A Kinetra pulse generator (model 7428; Medtronic) was im-

of 10 consecutive minutes, which showed the greatest variety of tics on the videotape. For tonic tics, the duration was counted in seconds.

Illustrative Cases

Case 1. This man was 42 years of age at the time of surgery, which was performed by V.V.V. The first tics had appeared at the age of 5 years and had consisted mainly of eye blinking and grimaces. As a child, he used to hurt himself by cutting his arms with a knife. From the age of 17 years, the most frequent tics consisted of licking objects, including his own shoulders, and making turning movements with his neck. Vocal tics consisted of throat clearing, uttering meaningless sounds, and blowing. Frequently he could not sit still on a chair and made adduction movements of the knees. He suffered from checking compulsions such as inspecting doors and lights. The patient and his partner confirmed that the tics had a greater impact on their lives than the compulsive behavior.

During surgery, the stereotactic frame (Leksell G frame; Elekta, Linköping, Sweden) was fixed while the patient was sedated with propofol delivered through a laryngeal mask. After defining the target on the CT scan by using the aforementioned coordinates (5 mm lateral to the AC–PC line, 4 mm posterior to the middle of the AC–PC line, and at the AC–PC plane), sedation was tapered and the laryngeal mask was removed. At that time, the patient did not display any tics and was sufficiently cooperative for test stimulation to be performed. We started at his left side because we thought that the dominant hemisphere might have a greater impact on the tics than the nondominant one. A burr hole was made and the test stimulation initiated. At target minus 6 and target minus 4, there was no effect following the application of 3 V. At target minus 2, the patient reported a pleasant feeling at 1.75 volts. At target, this pleasant feeling was very intense, and the patient compared it with a feeling of euphoria elicited by drugs and felt that it would have a positive effect on his tics. At target plus 2, this pleasant feeling returned at 2.25 V, albeit less intense. The test electrode was replaced by the final quadripolar electrode with pole 1 (the second deepest pole) installed at the target.

On his right side we started stimulation at the same point. During stimulation of the target, however, the patient reported an intense stimulation of fear and begged us to stop. The test stimulation electrode was reinstalled at a location 2 mm more medially, and here, at target, the patient again experienced a pleasant feeling of euphoria. The quadripolar electrode was installed at this site, with pole 1 at target.

On the 1st postoperative day, the patient progressively raised the voltages on his right and left sides, to intensify the pleasant feeling. He increased them very suddenly to 6 V bilaterally, after which he experienced a sudden intense rebound of tics accompanied by dizziness. We set the voltages at 2 V bilaterally and instructed the patient not to raise stimulation to more than 3.5 V, after which there was an important reduction of tics.

Case 2. This man was 28 years of age at the time of surgery, which was performed by H.C. His first tics had appeared as grimaces at the age of 8 years. At the time of surgery, the patient’s most disabling tics consisted of screaming, head shaking, and obscene finger gestures. He performed automutilation by burning his eyelashes with cigarettes. Because of his tics and the compulsion to touch people, he became completely socially isolated and lived with his parents.

General anesthesia was maintained throughout the ste-
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TABLE 3
Stimulation characteristics at 2-month and long-term follow up in three patients with TS who received bilateral thalamic stimulation

<table>
<thead>
<tr>
<th>Case No.</th>
<th>2-Mo FU</th>
<th>LT FU</th>
<th>Frequency†</th>
<th>2-Mo FU</th>
<th>LT FU</th>
<th>Pulse Width (μsec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lt</td>
<td>Rt</td>
<td>Lt</td>
<td>Rt</td>
<td>Lt</td>
<td>Rt</td>
<td>Lt</td>
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<td>0–1,–1/2,+,3+</td>
<td>0–1,–1/2,+,3+</td>
<td>75</td>
<td>100</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>2</td>
<td>7–/case+</td>
<td>2–,–/case+</td>
<td>65</td>
<td>65</td>
<td>2.7</td>
<td>2.7</td>
</tr>
<tr>
<td>3</td>
<td>4–,–5/–case+</td>
<td>0–,–1/–case+</td>
<td>130</td>
<td>100</td>
<td>2.0</td>
<td>2.4</td>
</tr>
</tbody>
</table>

† Each electrode has 4 poles, with 0 being the most ventral and 3 the most dorsal, or 4 being the most ventral and 7 the most dorsal.
‡ In all patients the frequency and pulse width are the same for the left and right side at the 2-month follow up and at the long-term follow up.

Results

Effect on Tics

One week postoperatively there was a tic reduction of 82.5% in the patient in Case 1 (from 422 tics/10 minutes to 42 tics/10 minutes), 53.6% in the patient in Case 2 (from 196 tics/10 minutes to 91/10 minutes), and 55.3% in the patient in Case 3 (from 196 tics/10 minutes to 91/10 minutes).

Neuropsychological Effects

The general intelligence level in both tested patients (Cases 1 and 3) was average to above average (intelligence quotient 108 and 114, respectively). Preoperatively, these patients showed borderline to low results on verbal memory testing, and the patient in Case 3 performed below average on facial recognition testing. Postoperatively, the patient in Case 1 showed little or no change on the same tests performed preoperatively. In the patient in Case 3 the results on most timed tasks were lower, including visual reaction time and word fluency, which, seeming vulnerable preoperatively, now fell below average in four of five categories. Verbal memory and facial recognition scores increased, indicating a possible retest effect.

Stimulation Parameters

The stimulation parameters for each patient at 2 months and at the long-term follow up are shown in Table 3.
symptoms was due to the natural evolution of the disease. We consider it highly unlikely that these patients with TS, which had been refractory to any kind of conservative treatment, would have such a spontaneous reduction in symptoms without presenting new ones. Only in the patient in Case 1 did eye-blinking become apparent after switching the stimulator off.

All three patients suffered from compulsions preoperatively. Compulsions consist of repetitive, seemingly purposeful types of behaviors that are performed to certain rules or in a stereotyped fashion. Obsessive-compulsive and self-injurious behaviors completely disappeared in all patients (Table 2), even when both stimulators were switched off.

In the past, many different lesioning procedures have been performed in patients with TS. Frontal lobe operations have included prefrontal lobotomies,37,42 and bimedial frontotemporal leukotomies.3,27 The limbic system was targeted during limbic leukotomy,12,14 and cingulotomy10,21,24 with or without hypothalamotomy. Thalamic operations have included lesions of the medial, intralaminar, and ventrolateral thalamic nuclei.1,5,10,16–18 Infrahinal lesions were created at the level of Forel’s field (camptotony), the zona incerta, and the red nucleus.2,3,8 Cerebellar surgery has included dentatorubral-pallido-luysian atrophy.3,6,22 The majority of the reports lack any specification of the tic reduction or any rationale for choosing a specific target. Hassler and Dieckmann,16,17 however, presented a detailed report of the successful results achieved by creating lesions in the midline and intralaminar thalamic nuclei as a treatment for TS in nine patients. In patients with facial tics, they created lesions of the nucleus ventrooralis internus. Based on these positive results and actual knowledge of the pathophysiological features of TS,25–26 we decided to target the same thalamic nuclei in patients with intractable TS. Rather than lesioning these nuclei, however, we applied high-frequency stimulation. In the course of the neurosurgical treatment of Parkinson disease and tremor, HFS has been shown to have effects on symptoms similar to those of lesioning. Note, however, that HFS is safer and has the advantage that its effects can be modulated in accordance with the patient’s needs.

Various clinical, neuropathological, and neuroimaging observations indicate that a dysfunctioning of the basal ganglia and related thalamocortical circuits form, at least in part, the pathophysiological basis of TS.13,14,23,25,30,35 It is assumed that the basal ganglia play a major role in the “limiting and sequencing” of motor and behavioral programs by selecting desired and by suppressing unwanted programs to be executed.2,3,13 In this way, the basal ganglia “assist” the (pre)frontal cortex in facilitating or by suppressing behavioral or motor responses.1,13 Thus, the uncontrolled movements and vocalizations in TS might be the result of defective inhibitory mechanisms at the level of the basal ganglia, leading to the expression of simple or more complex purposeful motor or behavioral acts. The thalamic involvement in the aforementioned circuits is dual in nature. Although the medial and ventral thalamic nuclei are weigh stations within these circuits that lead back to the premotor and prefrontal cortices from which the circuits originate, the midline and intralaminar thalamic nuclei send projections to both the premotor and prefrontal cortices and the striatum. Therefore, the basal ganglia–thalamocortical circuits are strongly influenced at the level of

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Discussion

In all three patients there was clearly a positive effect on the number of tics per 10-minute period before and after chronic bilateral stimulation. The number of tics did not necessarily reflect the impact of the tics on the patient’s self-esteem and socioprofessional life. Furthermore, not all tics exhibited by the patient during the last month prior to surgery were recorded on the videotape; for example, on the preoperative video of the patient in Case 3, we did not see him pounding himself in the stomach. It is a well-investigated phenomenon that patients with TS who are video-taped at home exhibit a wider variety of tics than those who are videotaped in the clinician’s office.32 Given that we did not videotape these patients at home, we relied not only on the videotapes recorded in the hospital, but also on anamnestic and heteroanamnestic data. Moreover, the number as well as the intensity of the tics might be different, for example, in the case of the grimaces. For all these reasons, we preferred to present the impact of the tics on the patient’s life, as shown in Table 2. In all patients, the remaining symptoms only had a minimal impact on their lives.

After switching the stimulator off for 12 hours, symptoms did not return to baseline (Table 1). We considered this to be an after-effect of stimulation. One might criticize the effect of stimulation and infer that the reduction in

Side Effects and Complications

All patients described a feeling of reduced energy at the stimulus voltage necessary for the best effect on their tics. One patient (Case 1) experienced it as being very pleasant. At the long-term follow up, however, he reported that he preferred to lower the stimulation intensity during physical exercise, as did the other two patients. At the long-term follow up, the patient in Case 1 reported an increased sexual drive and the patient in Case 3 complained of reduced sexual potency and ejaculation. These functions were examined by a sexologist during stimulation-on and -off conditions (except for ejaculation) and were found to be stimulation-related.

Two patients (Cases 1 and 3) each underwent three revisions of the pulse generator and extension cable because of traction pain.

FIG. 2. Schematic representation illustrating the target of stimulation. Dotted lines represent the output, hypothetically reduced by the stimulation, toward the main output structures of the targeted nuclei. Ce = centromedian nucleus; Svp = substantia periventricularis; Voi = nucleus ventrooralis internus; III = third ventricle.
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their major input (the striatum) by excitatory thalamic input. It has been hypothesized that in this way the midline and intralaminar thalamic nuclei may strongly influence the level of activity in these circuits.1 1 The caudal intralaminar thalamic nuclei, the presumptive target of our HFS electrodes in the present study, are thought to play a major role in the level of activity in these circuits.15 The caudal intralaminar and intralaminar thalamic nuclei may strongly influence their major input (the striatum) by excitatory thalamic input. 

According to the target coordinates used in our study, we believe that the three groups of nuclei that were lesioned by Hassler and Dieckmann are affected by the stimulation used in our study in the centromedian nucleus (as part of the intralaminar thalamic nuclei), the substantia periventricularis (as part of the midline thalamic nuclei), and the nucleus ventrooralis internus (Fig. 2). Nonetheless, with the ampli-

The reversibility of the effect of stimulation is very important for these patients because of the sedative effect that accompanies the positive effects on thetics. The patient programmer enables them to control the stimulus intensity and hence the level of energy that they prefer based on the situation in which they find themselves.

The effects on sexual behavior in the patients in Cases 1 and 3 might be explained by stimulation of the caudal intralaminar thalamic nuclei.16 Thus, data from preclinical studies indicate that the posterior intralaminar thalamic nuclei are possibly involved in processing the sexual outflow from the spinothalamic pathway toward the preoptic area, temporal lobe, and frontal cortex.

Conclusions

Chronic thalamic stimulation could well be an effective and safe treatment for intractable TS. Caution with regard to unwanted stimulation-induced side effects is warranted.

Acknowledgments

We thank Brenda Vollers-King and Lieve Desbonnet for their editorial assistance.

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Manuscript received March 10, 2003.
Accepted in final form August 1, 2003.
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