Tourette’s syndrome and deep brain stimulation


In this prospective double blind randomised “N of 1” study, a patient with a severe form of Tourette’s syndrome was treated with bilateral high frequency stimulation of the centromedian-parafascicular complex (Ce-Pf) of the thalamus, the internal part of the globus pallidus (GPi), or both. Stimulation of either target improved tic severity by 70%, markedly ameliorated coprolalia, and eliminated self injures. Severe forms of Tourette’s syndrome may benefit from stimulation of neuronal circuits within the basal ganglia, thus confirming the role of the dysfunction of limbic striato-pallido-thalamo-cortical systems in this disorder.

METHODS

Patients

Between January 1999 and August 2001, five patients were selected from among the 40 who consulted for Tourette’s syndrome. Inclusion criteria were: age ≥18 years; severe form of the disease adversely affecting social integration; failure of medical treatments after a trial of at least six months; no cognitive deficits or psychosis; and ability to give informed consent. One patient refused, three asked for a period of consent. One patient refused, three asked for a period of treatment improved her tics for 14 years. She obtained a secretarial qualification but was fired several times because of professional life.1 Severe forms of the disease poorly respond to medical treatment, which has potentially serious side effects.7 Severe tics have been improved by median thalamotomy1 and hyperkinesias by pallidotomy,4 but brain lesioning can cause severe irreversible adverse reactions.3 Continuous high frequency stimulation, a reversible neurological method,7 has positive effects on tics when the median thalamus is targeted,7 and on hyperkinesias when the internal part of the globus pallidus (GPi) is stimulated.8,9 We treated a patient with a severe, intractable form of Tourette’s syndrome by stimulation of the centromedian-parafascicular complex (Ce-Pf), the internal part of which is an important associative and limbic relay of the striato-thalamo-cortical pathways,10 and the GPi, the anteromedial part of which is a limbic relay for output pathways of the basal ganglia.11

RESULTS

Before surgery

The tics were not improved by six months of treatment combining loxapine (700 mg/day), pimozide (18 mg/day), venlafaxine (300 mg/day), and clonazepam (16 mg/day). The patient (weight 81 kg, height 165 cm) was irritable, dysphoric, and anxious with cognitive slowing (impaired attention and executive functions; table 1).

Postoperative phase without stimulation

From the moment the patient awakened after the operation, there was a spectacular improvement in tic severity and self injurious behaviour. She was weaned from neuroleptics over a two month period. One month after the operation, tics and self injurious behaviour reappeared. Three months after the operation, the tics and self injuries were as severe as before implantation of the electrodes. The neuropsychological evaluations remained normal throughout the follow up (table 1).

Abbreviations: DBS, deep brain stimulation; GPi, internal part of the globus pallidus; RVBTS, Rush video based tic scale; YGTSS, Yale global tic severity scale
Bilateral thalamic stimulation

Monopolar stimulation was delivered bilaterally (1.5 V, ventral contacts 0 and 1) in the Ce-Pf (fig 1, panels A and B). Increasing the voltage induced paraesthesiae in the contralateral half of the tongue. Stimulation through the dorsal contacts (2 and 3) induced contraction of the contralateral half of the body. Three weeks later, the self-injurious behaviour disappeared and the tics improved, although intermittent coprolalia could be prompted by domestic disputes. The patient bought new undergarments, let her nails grow, and went to nightclubs, but complained of lack of affection from her relatives. She lost weight (18 kg), but endocrine examinations were normal. After two months, tic severity had decreased by 65% on the Yale global tic severity scale (YGTSS) and by 77% on the Rush video based tic scale (RVBTS). Mood, anxiety, and impulsivity were improved (table 1).

Bilateral pallidal stimulation

Monopolar stimulation was delivered bilaterally (1.5 V, ventral contacts 0) in the limbic portion of the GPi (fig 1, panels C and D). Increases in intensity provoked nausea, hypotonia, and anxiety. The tics remained under control, but coprolalia persisted although milder and intermittent. The patient asked for a divorce and wanted to go back to the job she had left two and a half years earlier. Final evaluation confirmed the improvement in tic severity (YGTSS 65%; RVBTS 67%) and the disappearance of self-injurious behaviour, although mood and impulsivity were worse than with thalamic stimulation (table 1). The patient continued to lose weight although she ate normally.

“Sham” stimulation

One month after the stimulation was stopped, the tics progressively returned, accompanied by panic attacks. Three weeks later, the tics were as severe as before the operation (“before, I was oblivious, now I am lucid and can’t stand being this way”). She stuck her finger in her eye, struck her neck causing excoriations at the site of the stimulation cables, and made several attempts to pull out the stimulators. The scores for depression, anxiety, and impulsivity showed little change (table 1).

Figure 1 Localisation of the therapeutic contacts in the parafascicular nucleus of the thalamus (panels A and B) and in the pallidum (panels C and D). The thalamic and pallidal structures were delimited by three-dimensional alignment of the Schaltenbrand atlas with the axial magnetic resonance images. Hatched circles indicate the location of therapeutic contacts 0 and 1 in the thalamus (2.9 mm anterior, 6.1 mm lateral, 1.9 mm dorsal to PC point) (Schaltenbrand section: +3.5 mm) (B), and the therapeutic contact 0 in the pallidum (22.1 mm anterior, 11.2 mm lateral, 3.7 mm ventral to PC point) (Schaltenbrand section: −3.5 mm) (D). The grey circle (B) indicates the trajectory of the pallidal electrode. AC, anterior commissure; Ce, centromedian; Fx, fornix; GPe, external pallidum; GPi, internal pallidum; Gl, lateral geniculate nucleus; Gm, medial geniculate nucleus; Hb, habenula; Lpo, lateropolaris; mt, mammillothalamic tract; Pf, parafascicular nucleus; Pu, putamen; Pul, pulvinar; Ru, red nucleus; STN, subthalamic nucleus; Vc, nucleus ventrocaudalis; Vim, nucleus ventrointermedius; Voa, nucleus ventro-oralis anterior; Voi, nucleus ventro-oralis internus; Vop, nucleus ventro-oralis posterior; ZI, zona incerta.
Bilateral thalamic and pallidal stimulation

Within 12 hours after the initiation of stimulation, the patient stopped her self injurious behaviour. The tics improved although coprolalia remained moderate. The final evaluation confirmed the abolition of self injuries and the 70% reduction in tic severity (table 1), although some vociferation persisted. The patient said “my life has been transformed…I am glad I had the operation… I feel like a woman again.” Her weight stabilised. Twenty four months after the end of the protocol the tics and self injurious behaviour were still improved. The patient divorced, went back to work, and has taken steps to regain custody of her son. Follow up treatment includes regular psychotherapy and antidepressants. Her personality remains borderline, with emotional hypersensitivity, moderate anxiety, phobia, and mood fluctuations.

DISCUSSION

Continuous high frequency stimulation improved the severity and frequency of tics by about 70% and self injurious behaviour disappeared when either the thalamus, the GPi, or both were stimulated, indicating that there was no potential difference between the targets. With thalamic stimulation, the patient was less depressed and emotionally unstable than when the GPi was stimulated. Coprolalia improved, but reappeared intermittently whenever there was a loss of mental control. Neither a placebo effect nor spontaneous remission of the disease is unlikely, as the double blind protocol included two phases without stimulation (post-operative period and sham stimulation period), and the therapeutic benefit had persisted for 24 months after the operation, despite the withdrawal of neuroleptics.

The clinical improvement in the postoperative phase probably resulted from a transitory lesion caused by placement of the four electrodes, as it waned within a few weeks. This acute effect contrasted with the delay before tic improvement after thalamic stimulation and before tic worsening during sham stimulation. The reasons for these delays are not known, but they are reminiscent of the delayed effects observed in patients treated by pallidal stimulation for dystonia.

Normalisation of cognitive functions after the operation, in the absence of stimulation, can reasonably be attributed to withdrawal of neuroleptics and confirms that the neurosurgical procedure was not deleterious. The weight loss probably resulted from withdrawal of neuroleptics rather than from stimulation, as all biological test results were normal and the patient’s weight eventually stabilised.

The persistence of dysphoria, impulsivity, and difficulty with interpersonal relationships could have resulted from withdrawal of high dose neuroleptics and benzodiazepines, amplification of personality problems, difficulties with social reinsertion after 20 years of affective isolation, or deleterious effects of stimulation, although the absence of psychological change after the postoperative and placebo phases argues against this.

The limbic parts of the GPi and Ce-Pf complex of the thalamus are candidate targets for treatment of severe forms of Tourette’s syndrome by high frequency stimulation. These effects are consistent with results obtained in animal experiments on the role of the thalamus and basal ganglia in the occurrence of stereotypies and tics. According to these studies, clusters of neurones in the striatum that are important for behavioural selection would, when abnormally active, cause tic production by inhibiting target neurones in output nuclei of the basal ganglia that normally suppress unwanted movements.

High frequency stimulation holds promise for the treatment of other severe forms of Tourette’s syndrome. The best target, the thalamus (as previously suggested), or the GPi (stimulated for the first time), remains to be determined, although other limbic territories of the basal ganglia should also be explored. However, surgical treatment of neuropsychiatric diseases poses serious ethical problems, and there is always the risk of decompensating pre-existing psychiatric disorders. This form of treatment thus requires the adoption of rigorous inclusion criteria and the assurance of follow up by an experienced multidisciplinary team.

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Tourette’s syndrome and DBS

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