Anterior pallidal deep brain stimulation for Tourette's syndrome: a randomised, double-blind, controlled trial

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Summary

Background Deep brain stimulation (DBS) has been proposed to treat patients with severe Tourette's syndrome, and open-label trials and two small double-blind trials have tested DBS of the posterior and the anterior internal globus pallidus (aGPi). We aimed to specifically assess the efficacy of aGPi DBS for severe Tourette's syndrome.

Methods In this randomised, double-blind, controlled trial, we recruited patients aged 18–60 years with severe and medically refractory Tourette's syndrome from eight hospitals specialised in movement disorders in France. Enrolled patients received surgery to implant bilateral electrodes for aGPi DBS; 3 months later they were randomly assigned (1:1 ratio with a block size of eight; computer-generated pairwise randomisation according to order of enrolment) to receive either active or sham stimulation for the subsequent 3 months in a double-blind fashion. All patients then received open-label active stimulation for the subsequent 6 months. Patients and clinicians assessing outcomes were masked to treatment allocation; an unmasked clinician was responsible for stimulation parameter programming, with intensity set below the side-effect threshold. The primary endpoint was difference in Yale Global Tic Severity Scale (YGTSS) score between the beginning and end of the 3 month double-blind period, as assessed with a Mann-Whitney-Wilcoxon test in all randomly allocated patients who received active or sham stimulation during the double-blind period. We assessed safety in all patients who were enrolled and received surgery for aGPi DBS. This trial is registered with ClinicalTrials.gov, number NCT00478842.

Findings Between Dec 6, 2007, and Dec 13, 2012, we enrolled 19 patients. We randomly assigned 17 (89%) patients, with 16 completing blinded assessments (seven [44%] in the active stimulation group and nine [56%] in the sham stimulation group). We noted no significant difference in YGTSS score change between the beginning and the end of the 3 month double-blind period between groups (active group median YGTSS score 68·5 [IQR 34·0 to 83·5] at the beginning and 62·5 [51·5 to 72·0] at the end, median change 1·1% [IQR –23·9 to 38·1]; sham group 73·0 [69·0 to 79·0] and 79·0 [59·0 to 81·5], median change 0·0% [–10·6 to 4·8]; p=0·39). 15 serious adverse events (three in patients who withdrew before stimulation and six each in the active and sham stimulation groups) occurred in 13 patients (three who withdrew before randomisation, four in the active group, and six in the sham group), with infections in DBS hardware in four patients (two who withdrew before randomisation, one in the sham stimulation group, and one in the active stimulation group). Other serious adverse events included one electrode misplacement (active stimulation group), one episode of depressive signs (active stimulation group), and three episodes of increased tic severity and anxiety (two in the sham stimulation group and one in the active stimulation group).

Interpretation 3 months of aGPi DBS is insufficient to decrease tic severity for patients with Tourette's syndrome. Future research is needed to investigate the efficacy of aGPi DBS for patients over longer periods with optimal stimulation parameters and to identify potential predictors of the therapeutic response.

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Introduction

Tourette's syndrome is characterised by motor and vocal tics that are frequently associated with behavioural disorders, including, in particular, attention deficit hyperactivity disorder, obsessive-compulsive disorder, self-injury, anxiety, and depression.[1] It is a disabling chronic neuropsychiatric disorder and has considerable repercussions for family relationships, social life, and the ability to function at work. The recommended therapeutic options for Tourette's syndrome include antipsychotic drugs, benzodiazepines, α2 adrenoreceptor agonists, botulinum toxin injections, and cognitive behavioural therapy.[2,3] However, despite medical treatment, some patients appear to have persistent symptoms and experience lasting functional and social repercussions.[4]

The physiological basis of Tourette's syndrome is not fully understood, but dysfunction of motor and associative-limbic fronto-striato-thalamo-cortical circuits have been reported.[5] Furthermore, modulation of these circuits induce motor and behavioural signs resembling

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Research in context

Evidence before this study

We searched PubMed up to Dec 31, 2016, with the terms "Tourette's syndrome", "deep brain stimulation", "double-blind randomised trials", and "open-label trials", with no language restrictions. We identified four randomised double-blind trials. One trial assessed the efficacy of thalamic deep brain stimulation (DBS) in five patients, another assessed the efficacy of thalamic DBS in six, another assessed the efficacy of internal globus pallidus (GPi) stimulation in 15, and another assessed the efficacy of both thalamic and GPi stimulation in three. In this third study, 13 patients completed assessments, with 11 having electrodes implanted in the anterior part and two in the posterior part of the GPi. All of these studies showed a benefit from stimulation, although three (60%) of five patients showed a decrease of less than 25% in tic severity during the double-blind period in the first trial, two (33%) of six did in the second study, and 11 (85%) of 13 did in the third study. We identified 17 open-label studies, with two to 18 patients reporting significant improvements of tic severity with DBS of the thalamus, GPi, or anterior limb of the internal capsule and nucleus accumbens. The number of patients with Tourette's syndrome included in randomised clinical trials is low and evidence is still insufficient to allow DBS to be proposed for these patients.

Added value of this study

To our knowledge, this trial is the largest randomised controlled trial of patients with Tourette's syndrome assessing the efficacy of a specific pallidal target—ie, anterior GPi (aGPi)—in line with the physiological mechanisms thought to be involved in the occurrence of tics. We show that 3 months of double-blind aGPi DBS is not sufficient to decrease tic severity, but 6 months of active stimulation with optimal parameter settings was associated with some improvement in the open-label phase. Our results suggest a possible positive effect on occupational activities 11 months after surgery. The safety profile was consistent with previous reports, with a high risk of infection leading to removal of the stimulator and electrodes in this patient population.

Implications of all the available evidence

Data from the double-blind period of our trial do not support use of aGPi DBS as a treatment for Tourette's syndrome. Data from the open-label period suggest a possible benefit but the long-term effects should be investigated in larger cohorts of patients than in this study, with multidimensional approaches that also include social and psychological assessments.

Tourette's syndrome in animal models.[6] To date, deep brain stimulation (DBS) of different parts of the fronto-striato-thalamo-cortical circuits has been explored in several case reports and open-label trials.[7–10] These studies involved targeting of the centromedian-parafascicular (CM-Pf) complex or ventral anterior and ventrolateral motor parts of the thalamus or internal and external parts of the globus pallidus, nucleus accumbens, or anterior limb of the internal capsule. Stimulation of the CM-Pf complex of the thalamus has been associated with a 30–70% reduction in tic severity in large prospective open-label trials.[7] In two small randomised double-blind crossover trials, tic severity was not significantly modified with 7 days of CM-Pf thalamic active stimulation in five patients,[11] but was significantly reduced by 37% after 3 months of active stimulation in six patients.[12] However, thalamic stimulation-induced serious adverse events have been observed and some patients show no response to thalamic or other targets, despite testing of multiple stimulation sites.[7]

These results, in light of the beneficial effect of pallidal stimulation in other movement disorders,[13] led us to propose the first proof-of-concept randomised study[14] targeting both the anterior (associative-limbic) part of the internal globus pallidus (GPi) and the CM-Pf complex of the thalamus in three patients. In this study, bilateral anterior GPi (aGPi) stimulation produced a 78% improvement of motor and vocal tics, CM-Pf thalamic stimulation produced a 45% improvement, and combined aGPi and CM-Pf thalamic stimulation produced a 60% improvement, with no long-term adverse effects with combined stimulation after a median follow-up of 33 months. In subsequent open-label trials, stimulation of the aGPi produced a 40–70% reduction in tic severity, with an improvement in anxiety, depression, and quality of life.[7,10] Subsequently, stimulation of either the associative-limbic (anterior) or motor (posterior) parts of the GPi have been tested in 13 patients with a 15% reduction in tic severity during the crossover randomised double-blind phase and a 40% decrease during the open-label phase.[15] We aimed to further analyse the efficacy of aGPi stimulation in patients with severe Tourette's syndrome.

Methods

Study design and patients

In this randomised, double-blind, controlled trial, we recruited patients from eight hospitals specialised in movement disorders in France. Patients with severe and refractory Tourette's syndrome were eligible for inclusion if they were between 18 years and 60 years of age and had received a primary diagnosis of Tourette's syndrome as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision [DSM-IV-TR]),[16] a score on the Yale Global Tic Severity Scale (YGTSS)[17] of more than 45 (on a scale from 0 to 100, with lower scores indicating less severe symptoms), a score on the Social and Occupational Functional Assessment Scale[18] of less than 70 (on a scale from 1 to 100, with higher scores indicating higher levels of functioning), an