Efficacy of deep brain stimulation of the subthalamic nucleus in Parkinson's disease 4 years after surgery: double blind and open label evaluation

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Objective: To evaluate the long term (4 years) efficacy of deep brain stimulation (DBS) of the subthalamic nucleus (STN) in advanced Parkinson's disease.

Methods: We performed a double blind crossover evaluation of the efficacy of DBS of the STN in the "off" medication condition in 10 patients with Parkinson's disease. Assessments included the Unified Parkinson's Disease Rating Scale (UPDRS) part III (motor) and two timed tests (arm tapping and walking). Open evaluation of the effect of stimulation in the off and on drug states preoperatively and at 1 and 4 years postoperatively was also conducted. The latter assessment included the UPDRS parts II (activities of daily living) and III (dyskinesia scale and global assessment) as judged by the patient and examiner. The mean amount of levodopa daily dose at base line, 1 year, and 4 years after surgery was compared.

Results: A significant ($p < 0.04$) effect of stimulation was observed in the overall group regarding both the UPDRS motor and the timed tests. Open evaluation also showed a significant benefit of STN DBS with respect to preoperative assessment in both the motor and activities of daily living scales, dyskinesia scale, and in global assessment. Levodopa daily dose was reduced by 48% and 50% at 1 and 4 years, respectively. There was no difference between the 1 and 4 years evaluations in any of the parameters evaluated. Complications due to stimulation were minor.

Conclusions: DBS of the STN provides a significant and persistent anti-parkinsonian effect in advanced Parkinson's disease 4 years after surgery.

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) or globus pallidus pars interna has been shown to convey marked motor benefit in patients with advanced Parkinson's disease.^{1–2} Long term evaluations have been limited to 2–3 years postoperatively under open conditions.^{1–3–8} Double blind evaluations have been conducted in three studies at 3 and 6 months postoperatively.^{2–9–10} One particularly important aspect to properly evaluate the efficacy of an invasive and costly treatment,¹¹ like DBS, is the long term evolution. We report a double blind assessment of the effects of bilateral DBS of the STN 4 years after surgery and openly compared the results obtained at 1 and 4 years, respectively.

METHODS

Subjects

Ten patients (8 men and 2 women) with ages ranging 53–73 years (mean 62) operated on between 1996 and 1999 were recruited for assessment. Five of these patients are part of a current protocol for long term evaluation of DBS, sponsored by Medtronic Inc. They were also included in the initial multicentre study reporting results at 3 and 6 months postoperatively.²

All patients had clinical features, disease evolution, and response to levodopa typical of Parkinson's disease and were not adequately controlled with the available pharmacological therapy. They were evaluated with the same protocol before and after surgery^{2–12} and gave informed consent for the study. The surgical technique has been described in detail previously.^{2–12–13}

Procedures

Patients were admitted to hospital for evaluation between 2001 and 2003. They were not selected for having experienced

an especially good response to DBS (positive bias) but represented a consecutive series of patients regularly assessed at our centre. The evaluations were prospectively planned before recruitment with the open evaluation on the first day and the double blind assessment on the second day.

Double blind evaluations were undertaken in the "off" medication state only. Stimulators were turned off at 6 am and evaluations were started at 9 am. Medication was stopped overnight. Patients were randomly assigned to one of two treatment sequences (fig 1): sequence 1, the first evaluation was performed when the patient had been without stimulation for an additional 2 h and the second evaluation after stimulation had been reinitiated for another 2 h; sequence 2, the order was reversed. Neither the neurologist assessing the motor state (MCR) nor the patients were informed when the stimulation had been turned on or off. Once the study was finished, patients and investigators were asked to guess which of the assessments was performed with the stimulation on, and patients to describe any symptoms that may have resulted in breaking the blind evaluation. Evaluations included the Unified Parkinson's Disease Rating Scale (UPDRS, motor part-III) and two timed tests—the walking test, which measures the time spent to walk 4.5 m and return to the starting position, and the arm tapping test measuring the number of times that subjects could alternately tap two points 30 cm apart in 60 sec. Separate scoring of the cardinal features of Parkinson's disease were carried out adding the items related to one particular sign in the UPDRS-III as follows: tremor (items 20

Abbreviations: ADL, activities of daily living; DBS, deep brain stimulation; STN, subthalamic nucleus; UPDRS, Unified Parkinson's Disease Rating Scale

Figure 1 Diagram of the double blind evaluation protocol for deep brain stimulation of the subthalamic nucleus in 10 patients. All patients remained medication free for at least 12 h and off stimulation for 3 h before starting the study. Subsequently, one group of patients ($n=6$) was assigned to sequence 1 and remained off stimulation for two additional hours. The other group ($n=4$) was assigned to sequence 2 and the stimulator turned on for 2 h. After the first evaluation (arrow), the condition of stimulation was reversed and a second evaluation (arrow) conducted 2 h later. UPDRS III, Parkinson's Disease Rating Scale, motor part III.

and 21), rigidity (items 22), bradykinesia (items 23, 24, 25, and 26), and axial features (items 18, 19, 27, 28, 29, and 30).

Open assessment of the motor state was undertaken on and off anti-parkinsonian medication (a minimum of 12 h after the last dose) before and after surgery and on and off stimulation at 1 and 4 years postoperatively. It included the UPDRS parts II and III, the CAPIT dyskinesia scale (scores severity of dyskinesias from 0 = absent to 5 = severe and generalised),¹⁴ and the global assessment of the motor state according to the patients' self-opinion and the criteria of the examiner. Global assessment was rated as follows: 0 = no improvement or worsening; 1 = less than 25% improvement; 2 = 25 to 50% improvement; 3 = between 50 and 75% improvement; and 4 = >75% benefit. A movement disorders expert neurologist (MCR) carried out all the evaluations through out the follow up. Levodopa daily consumption was calculated according to the standard equivalents.²

Statistical analysis

The Wilcoxon signed rank test was used for paired comparison in all the assessments of the double blind evaluation as it corresponds to non-parametric samples. The treatment and period effects for the motor UPDRS in the double blind evaluation were assessed by a two way analysis of variance. In this test, the between subjects and within subjects analysis reflects the treatment and period, respectively. For the open evaluations, the Friedman test was used for repeated measurements and the Bonferroni's correction for the paired wise comparisons.

RESULTS

Double blind evaluation

Stimulation was associated with a significant reduction in the UPDRS motor scores regardless of the evaluation sequence (table 1).

The effect of stimulation occurred regardless of the order in which the patients were assessed (that is, no period effect, $p=0.1$). Improvement was 38% for akinesia, 38% for rigidity, 55% for tremor, and 40% for axial symptoms. These changes were statistically significant ($p=0.04$) for the axial features only probably due to the variability provoked by the reduced number of patients. The tapping and walking tests were significantly improved by STN stimulation (see table). Four

Table 1 Double blind assessment of the effect of deep brain stimulation (DBS) of the subthalamic nucleus on the motor Unified Parkinson Disease Rating Scale (UPDRS) and timed tests in 10 patients followed up for 4 years

Assessment	Off DBS	On DBS	p Value	% change
UPDRS III				
Sequence 1 ($n=6$)	49 (58–66)	30 (13–52)		38.7
Sequence 2 ($n=4$)	31 (27–33)	18 (16–19)		41.9
Mean	43 (27–66)	26 (13–52)	0.04	39.5
Walking test	25 (18–27)	16 (14–20)	0.04	36
Tapping	114.2 (23–192)	152.4 (21–223)	0.04	33.4

patients who were unable to walk in the off stimulation condition completed the test under STN stimulation.

Only one patient experienced mild and transient paresthesias at the time of turning on the stimulator. Six patients guessed correctly the on/off sequence. The investigator made a right assertion in the same six patients who were the ones exhibiting the most dramatic motor improvement.

Open evaluation

Stimulation settings (mean and range) at the time of the study were 3.7 volts (2.3–6.6), 168 Hz (130–185), and 75 μ s pulse width (60–120). These parameters were similar to those at year 1 of assessment. Stimulation was initially programmed and remained monopolar in every patient.

UPDRS off medication score and the magnitude (off–on difference) of the response to levodopa were reduced by 62% and 77%, respectively, compared with the preoperative scores ($p<0.01$) (fig 2). The motor benefit was similar to the one obtained at 1 year after surgery (fig 2). The dyskinesia score was diminished by 53% with respect to baseline ($p<0.01$) and the levodopa daily dose from a mean of 1287.5 mg (range 300–2050) preoperatively to 641 mg (range 140–1140) at 4 years postoperatively (50%) ($p<0.01$). The UPDRS part II (activities of daily living; ALD) was improved by 61% in the off pharmacological state ($p<0.02$) and was unchanged in the on pharmacological state ($p>0.05$) with respect to baseline evaluation. There were no significant differences in the ADL scores with respect to the first year of evaluation. Global assessment by the examiner considered that stimulation induced an improvement of 71% in the motor situation at 4 years ($p<0.02$) and patients rated the improvement at 52% ($p<0.02$). There was a minor and non-significant worsening in both assessments with respect to the first year of evaluation.

New neurological manifestations, side effects, and maintenance

One patient showed signs of frank dementia with hallucinations and social misconduct that did not change when stimulators were maintained off. Two other patients showed some degree of cognitive impairment. One of them had a mini-mental score of 24 and also developed severe disequilibrium and freezing of gait and frequent urinary incontinence. The other patient had a mini-mental score of 28 and exhibited some behavioural disorders that limited his social life. He was diagnosed for moderate depression. None of these features was modified by stimulation. Another patient suffered severe dysarthria that was not aggravated by stimulation.

Figure 2 Open evaluations; UPDRS scores in the off (open bars) and on (black bars) medication (meds) state before surgery and under the effect of stimulation of the subthalamic nucleus (STN, $n = 10$) at 1 and 4 years postoperatively. With respect to baseline, deep brain stimulation (DBS) of the STN at 4 years induced a significant improvement in the off medication state ($p = 0.03$) and a significant reduction in the magnitude (difference between the off and on medication state) of the motor response to levodopa ($p = 0.03$). There was no difference in the effect of stimulation at 1 and 4 years.

One patient developed recurrent subcutaneous erosion and occasional infection of the skull 3–4 years after surgery, which required several surgical revisions.

Nineteen batteries wore out after a mean postoperative period of 46 months (36–52) and required replacement.

DISCUSSION

The value of DBS for advanced Parkinson's disease has to be judged considering its long term efficacy against the typical motor manifestations and in terms of the improvement in the quality of life.^{15–17} On the other hand the risks and complications¹⁸ associated with the procedure are also part of the therapeutic ratio. There are many publications regarding the short and mid term follow up of Parkinson's disease patients treated with DBS but there are very little data on long term evolution.

Double blind evaluation

We found that DBS of the STN conveys a significant antiparkinsonian benefit 4 years after surgery in patients with advanced Parkinson's disease. This was revealed by a significant reduction in the severity of the off medication state (that is, reduced UPDRS motor score) when the patients were on stimulation. The accuracy of double blind evaluation in patients treated with DBS may be questioned on the basis of the profound motor changes associated with the on and off stimulation states.² We rigorously maintained the assessment sequences as assigned a priori by the protocol despite obvious changes in the motor state in some patients. Thus, despite the conceptual limitations associated with a powerful therapy such as DBS, our study does provide a careful and, as far as possible, objective evaluation. The number of patients included in this study was relatively small. However, the overall effects were similar to that seen in a larger cohort but evaluated with a much shorter follow up.² Our patients were not selected by having experienced an especially good response to DBS (positive bias) but represent all of those available in our centre for the purpose of this study. The 2 h

interval for the crossover evaluations resulted in a non-significant but obvious period effect, so that patients assigned to the arm with stimulation off for 5 h showed a greater motor deterioration than those maintained off stimulation for 2 h only (table 1). However, both groups of patients exhibited a similar degree of improvement, indicating a definite antiparkinsonian effect for DBS of the STN. It has been recently indicated that the efficacy of DBS in Parkinson's disease lasts for about 3 h, with 90% of deterioration occurring after 2 h off DBS.¹⁹ This is completely in keeping with our findings.

Open evaluation and long term efficacy

This particular series of patients is the one with the longest follow up reported so far. The overall conclusion is that 4 years after surgery, motor severity and disability are less incapacitating than at baseline, despite the progressive and severe nature of the underlying disease process. The degree of motor improvement was the same at 1 and 4 years postoperatively, indicating a sustained beneficial effect on the patients despite maintaining a 50% reduction in daily levodopa dose with respect to baseline. The latter may be taken as an indicator of substantial benefit induced by stimulation. Interestingly, this striking levodopa sparing effect has not been encountered in patients treated with pallidal stimulation^{2,3,5} but the lack of any properly designed comparative study preclude any definitive conclusion regarding the long term efficacy of pallidal stimulation with respect to the benefit provided by STN stimulation.

The long term evolution of patients with Parkinson's disease is affected not only by the severity of the cardinal motor features (captured by the UPDRS motor scale) and levodopa related motor complications, but also, and increasingly so, by a number of other clinical problems. Among these, cognitive impairment, gait and equilibrium problems, and autonomic disturbances are major sources of disability in many patients. On this note, it is relevant to comment on the publication of Krack *et al*²⁰ (appeared after this article was submitted) reporting on a series of 42 patients with advanced Parkinson's disease treated with DBS of the STN and openly assessed 5 years after surgery. The results are essentially similar to the ones we have discussed here. Thus, they found a significant benefit in the off UPDRS motor score and in the ADL and a moderate worsening in the on medication state when comparing the 5 years and baseline evaluations. However, some motor features deteriorated over the study period, particularly speech, axial symptoms, gait, and akinesia, which are the ones especially resistant to levodopa after many years of disease progression. It is reasonable to conclude that such levodopa and DBS resistant features are likely to be related to disease progression.²¹ Nevertheless, it must be admitted that bilateral surgery of the basal ganglia can be associated with newer manifestations such as psychiatric and behavioural disorders²² and cognitive impairment that had not become clinically relevant prior to the operation. On this note, patient selection plays a crucial role.²³ It should also be considered that current results^{1,7,8} mainly represent the earliest experience with DBS of the STN for advanced Parkinson's disease. We believe that more rigorous selection of patients and technical developments could be associated with even better results. Thus, clinical features such as age at the time of surgery, presence of levodopa unresponsive motor signs, and cognitive impairment, even if mild, need to be taken into account.²³ Similarly, surgical developments may improve to shorten the duration of surgery and achieve a more accurate and reliable location of the electrodes. Certainly, the development of non-motor and atypical parkinsonian features may be a major limiting factor of any therapy for Parkinson's disease if limited only to

control the consequences of nigro-striatal dopaminergic deficiency. However, this should not be used to cast doubt²⁴ about the value of therapeutic approaches, like DBS, which can presently provide a striking relief of motor complications and reduce motor disability, thus extending the period during which the quality of life is still acceptable.^{15 16 20}

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REFERENCES

- 1 Limousin P, Krack P, Pollak P, *et al*. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med* 1998;**339**:1105–11.
- 2 The Deep Brain Stimulation for Parkinson's Disease Study Group. Deep brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. *N Engl J Med* 2001;**345**:956–63.
- 3 Volkmann J, Sturm V, Weiss P, *et al*. Bilateral high-frequency stimulation of the internal globus pallidus in advanced Parkinson's disease. *Ann Neurol* 1998;**44**:953–61.
- 4 Vingerhoets FJG, Villemure JG, Temperli P, *et al*. Subthalamic DBS replaces levodopa in Parkinson's disease: two-year follow up. *Neurology* 2002;**58**:396–401.
- 5 Ghika J, Villemure JG, Fankhauser H, *et al*. Efficiency and safety of bilateral contemporaneous pallidal stimulation (deep brain stimulation) in levodopa-responsive patients with Parkinson's disease with severe motor fluctuations: a 2-year follow up review. *J Neurosurg* 1998;**89**:713–8.
- 6 Romito LM, Scerrati M, Contarino MF, *et al*. Long term follow-up of subthalamic nucleus stimulation in Parkinson's disease. *Neurology* 2002;**58**:1546–50.
- 7 Kleiner-Fisman G, Fisman DN, Sime E, *et al*. Long-term follow up of bilateral deep brain stimulation of the subthalamic nucleus in patients with advanced Parkinson's disease. *J Neurosurg* 2003;**99**:485–95.
- 8 Pahwa R, Wilkinson SB, Overman J, *et al*. Bilateral subthalamic stimulation in patients with Parkinson disease: long-term follow up. *J Neurosurg* 2003;**99**:71–7.
- 9 Kumar R, Lozano AM, Kim YJ, *et al*. Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease. *Neurology* 1998;**51**:850–5.
- 10 Katayama Y, Kasai M, Oshima H, *et al*. Double blinded evaluation of the effects of pallidal and subthalamic nucleus stimulation on daytime activity in advanced Parkinson's disease. *Parkinsonism Related Disorders* 2000;**7**:35–40.
- 11 McIntosh E, Gray A, Aziz T. Estimating the costs of surgical innovations: the case for subthalamic nucleus stimulation in the treatment of advanced Parkinson's disease. *Mov Disord* 2003;**18**:993–999.
- 12 Rodríguez-Oroz MC, Gorospe A, Ramos E, *et al*. Bilateral deep brain stimulation of the subthalamic nucleus in Parkinson's disease. *Neurology* 2000;**55**(Suppl 6):45–51.
- 13 Guridi J, Rodríguez-Oroz MC, Lozano MA, *et al*. Targeting the basal ganglia for deep brain stimulation. *Neurology* 2000;**55**(Suppl 6):21–8.
- 14 Langston JW, Widner H, Goetz CG, *et al*. Core assessment program for intracerebral transplantations (CAPIT). *Mov Disord* 1992;**7**:2–13.
- 15 Straits-Troster K, Fields JA, Wilkinson SB, *et al*. Health-related quality of life in Parkinson's disease after pallidotomy and deep brain stimulation. *Brain Cogn* 2000;**42**:399–416.
- 16 Kuehler A, Henrich G, Schroeder U, *et al*. A novel quality of life instrument for deep brain stimulation in movement disorders. *J Neurol Neurosurg Psychiatry* 2003;**74**:1023–30.
- 17 Lagrange E, Krack P, Moro E, *et al*. Bilateral subthalamic nucleus stimulation improves health-related quality of life in PD. *Neurology* 2002;**59**:1976–78.
- 18 Umemura A, Jaggi JL, Hurtig HI, *et al*. Deep brain stimulation for movement disorders: morbidity and mortality in 109 patients. *J Neurosurg* 2003;**98**:779–84.
- 19 Temperli P, Ghika J, Villemure JG, *et al*. How do parkinsonian signs return after discontinuation of subthalamic DBS? *Neurology* 2003;**60**:78–81.
- 20 Krack P, Batir A, Van Blercom N, *et al*. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med* 2003;**349**:1925–34.
- 21 Lang AE. Subthalamic stimulation for Parkinson's disease—living better electrically? *N Engl J Med* 2003;**349**:1888–91.
- 22 Houeto JL, Mesnage V, Mallet L, *et al*. Behavioural disorders, Parkinson's disease and subthalamic stimulation. *J Neurol Neurosurg Psychiatry* 2002;**72**:701–7.
- 23 Charles PD, Van Blercom N, Krack P, *et al*. Predictors of effective bilateral subthalamic nucleus stimulation for PD. *Neurology* 2002;**59**:932–4.
- 24 Linazasoro G, Houeto JL, Mesnage V, *et al*. Subthalamic deep brain stimulation for advanced Parkinson's disease: all that glitters is not gold. *J Neurol Neurosurg Psychiatry* 2003;**74**:827.