

## Chronic bilateral electrical stimulation of the subthalamic nucleus for the treatment of advanced Parkinson's disease

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**Abstract** Preliminary reports in patients with Parkinson's disease (PD) showed that subthalamic nucleus (STN) stimulation was able to reverse parkinsonian state. Since 1998 we evaluated the safety and the efficacy of STN stimulation in 7 patients affected by advanced PD. All patients were included using CAPIT protocol. Motor functions and quality of life were evaluated, before and after surgery, with UPDRS and PDQ38, respectively. At the 6-month follow-up, the off medication/on stimulation UPDRS motor score improved by 50.6% and the on medication/on stimulation by 20.3%. Motor fluctuations were reduced by 57.2% and dyskinesias by 73.5%. The total L-dopa equivalent daily dose was reduced by 40.7%. PDQ38 ameliorated by 49.9%. We did not observe any perioperative complication and only mild and tolerable side effects after stimulation.

Recent reports showed that hyperactivity of the subthalamic nucleus (STN) is a crucial feature in the pathophysiology of Parkinson's disease (PD) offering the STN as a putative new target for neurosurgical intervention [1-3]. We therefore investigated the therapeutic potential of bilateral chronic electrical stimulation of the STN in PD.

Seven patients (2 women and 5 men) with advanced, clinically definite PD (age  $63 \pm 8$  years, disease duration  $13 \pm 5$  years) suffering from severe, medically intractable motor fluctuations and peak dose dyskinesias, after written informed consent, underwent bilateral stereotactic implantation of quadripolar electrodes into the STN. Patients with the following features were excluded: age over 70 years; heart pace maker; unstable drug regimen; severe cognitive impairment or dementia; ongoing psychiatric problems; prior brain surgery; and unsatisfactory general condition or inability to comply with the study protocol. All patients had a strong motivation.

Clinical evaluation was based on the Core assessment program for intracerebral transplantation (CAPIT), a validat-

ed protocol for the study of surgical treatments of PD [4]. Evaluations were performed one month before surgery, the day before surgery, at months 1, 3, 6 and 12 after surgery and every 6 months thereafter. Patients were evaluated on the Unified Parkinson's disease rating scale (UPDRS) and PDQ38 for quality of life. Patients were assessed in 2 conditions before surgery (off medication and on medication) and in 4 conditions after surgery (off medication/off stimulation; off medication/on stimulation; on medication/ off stimulation; on medication/ on stimulation).

The following neuropsychological tests were performed 2 months before and 6 months after implantation: Mini-mental state evaluation, Raven standard progressive matrix, Stroop test, Paced auditory selective attention test, Wechsler intelligence and memory scale, the ten point clock, line orientation and Benton visual retention tests.

All patients received a bilateral simultaneous STN implant. Stereotactic surgery was performed in the "off" condition, with the patient under local anesthesia.

The target and trajectories for electrode implantation were calculated on stereotactic magnetic resonance images and distortion was corrected by computer software.

To identify the functional target, perioperative stimulations (pulses of 60 ms at a frequency of 185 Hz) were performed in a double-blind fashion. Current amplitude was increased or decreased in a random order until clinical efficacy or side effects were observed by the examining neurologist or patient. A target was accepted when parkinsonian signs were reversed by a current of less than 3 volts on the side contralateral to the implanted hemisphere. Following identification of functional target, the electrode was secured to the skull bone and the best position was checked by telerradiography.

For post-operative test stimulations the electrodes were connected to a percutaneous extension lead and frequency and pulse width were adjusted to keep the voltage low enough to get a good clinical effect.

Approximately one week after the test period a second magnetic resonance imaging (MRI) exam was performed and two Medtronic 7424 pulse generators were implanted in the subclavicular regions.

At the time of the last visit, the mean average stimulation amplitude was  $2.7 \pm 0.5$  V, the frequency  $150 \pm 30$  Hz and the pulse width 60 ms. STN stimulation was continuous for 24 hours a day. The average follow-up at June 2000 was  $14.5 \pm 18.2$  months.

Unipolar stimulation was more effective than bipolar. At the 6-month follow-up, the off medication/on stimulation UPDRS motor score improved by 50.6% and the on medication/on stimulation UPDRS motor score by 20.3%. Motor fluctuations were reduced by 57.2% and dyskinesias by 73.5%.

Gait freezing and off dystonia disappeared in all patients.

Disabling dyskinesias improved in three patients with L-dopa reduction while in one patient generalized dyskinesias, present with very low doses of L-dopa, completely disappeared. The total L-dopa equivalent daily dose was reduced by 40.7%.

Reduction of drugs, motor fluctuations and dyskinesias ameliorated the score on the PDQ38 rating scale for quality of life by 49.9%. Neuropsychological tests did not show significant variation after surgery.

We did not observe any perioperative complication. Side effects after stimulation were mild and tolerable. They consisted, in 6 patients, of slight transient contralateral paresthesias when switching on internal pulse generator and, in 3 patients, of diplopia which resolved changing lead contact. Speech impairment occurred in 2 patients who presented marked hypophonia during stimulation. In one patient hypophonia disappeared after a few months and in the other one it was reduced, decreasing the intensity of stimulation, but with worsening of parkinsonian symptoms.

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## Discussion

STN is considered to be the most effective target for deep brain stimulation (DBS) in advanced PD [1]. The possibility to accurately stimulate it without electrophysiologic recordings and the improvement after stimulation of all cardinal symptoms of disease are the reasons to prefer STN to internal globus pallidus (GPi) and thalamic ventral intermediate nucleus (VIM). Like STN, VIM stimulation improves parkinsonian tremor but not akinesia and rigidity so STN should be the choice target for PD patients with disabling tremor without marked rigidity and akinesia given the possibility to control these symptoms in the long run [5]. Two targets were identified in GPi: dorsal stimulation improves off condition but can worsen dyskinesias (dopaminergic effects) while posteroventral stimulation acts in the apposite side (antidopaminergic effects) [6]. GPi would be the choice target for DBS particularly in diskinctic PD patients, but electrophysiologic recordings are necessary [1].

In our 7 patients, bilateral high frequency stimulation of the STN, according to recent literature [1-3], was effective in reducing parkinsonian signs and off drug related phenomenon. Generally, after STN stimulation, dyskinesias remained unchanged and ballistic movements appeared contralaterally

above a given threshold voltage [3]. Reduction of L-dopa decreased peak dose dyskinesias, while biphasic dyskinesias improved [7], as we have seen in our patients.

Amelioration of quality of life in its globality is our most impressive result: recreative and daily living activities, general social life and interpersonal relationships benefited from an extraordinary recovery without significative side effects. One bedridden patient became completely autonomous.

In agreement with other authors [1-3], our data favor the hypothesis that STN plays a key role in the basal ganglia circuitry and that its overactivity is important in parkinsonian symptomatology. The mechanism of action of chronic electrical stimulation is unknown. As the effects induced by electrical stimulation seem to be close to those induced by a lesion, an inhibitory mechanism is possible. We cannot forget the neuroprotective effect of STN stimulation by the reduction of its glutamatergic hyperactivity [8]. In our experience, chronic electrical stimulation is a safe, efficient, reversible and non-lesional therapy for patients with advanced PD.

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## References

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