ORIGINAL PAPER/*ARTYKUŁ ORYGINALNY*

Bilateral subthalamic nucleus stimulation in the treatment of advanced Parkinson's disease. Five years' personal experience

Obustronna głęboka stymulacja jądra niskowzgórzowego w leczeniu zaawansowanej choroby Parkinsona. Doświadczenia własne w obserwacji pięcioletniej

Mirosław Ząbek, Michał Sobstyl, Henryk Koziara, Bartosz Kądziołka, Zbigniew Mossakowski, Sebastian Dierzęcki

Klinika Neurochirurgii, Centrum Medycznego Kształcenia Podyplomowego w Warszawie

Neurologia i Neurochirurgia Polska 2010; 44, 1: 3–12

Abstract

Background and purpose: The objective of the study was to assess bilateral subthalamic nucleus (STN) deep brain stimulation (DBS) for patients with advanced Parkinson disease (PD).

Material and methods: The study population included 5 patients with bilateral STN DBS who completed a 5-year postoperative follow-up period. In all patients electrodes (Model 3387 or 3389) were stereotactically bilaterally inserted into the STN using a Leksell stereotactic G frame. The clinical rating tests included Unified Parkinson's Disease Rating Scale (UPDRS) and two motor-timed tests derived from CAPIT (rapid movements between two points and stand-walk-sit test). All patients were assessed in off and on condition before implantation and 1, 3 and 5 years in medication on and off condition and stimulation on condition and stimulation off condition. To compare preoperative to postoperative UPDRS scores, only mean values and standard deviations are presented because of the small study population.

Results: The stimulation effect was noted in the off state, resulting in a 59% improvement in motor scores of UPDRS at 5-year follow-up, when compared to preoperative scores. In the on state the stimulation improved motor scores by 17%. At 5-year follow-up, reduction of daily levodopa dose was 50%.

Streszczenie

Wstęp i cel pracy: Celem pracy była ocena skuteczności obustronnej głębokiej stymulacji jądra niskowzgórzowego (*subthalamic nucleus* – STN) w leczeniu zaawansowanej postaci choroby Parkinsona (ChP).

Materiał i metody: Badany materiał kliniczny stanowiła grupa 5 chorych poddanych obustronnej stymulacji STN, u których czas pooperacyjnej obserwacji wynosił co najmniej 5 lat. U wszystkich chorych wszczepiono obustronnie elektrody do głębokiej stymulacji STN (Model 3387 lub 3389) z zastosowaniem ramy stereotaktycznej Leksell G. Kliniczną ocenę stanu chorych przeprowadzono za pomocą Ujednoliconej Skali Oceny Choroby Parkinsona (UPDRS) i dwóch testów ruchowych CAPIT (szybkie ruchy pomiędzy dwoma punktami oraz test chodu). Pacjentów oceniono w fazie *off* i *on* przed operacją oraz po upływie roku, 3 i 5 lat w fazie *off* i *on* w czasie stymulacji i przy włączeniu generatorów impulsów. Do oceny różnic pomiędzy pomiarami przedoperacyjnymi i pomiarami pooperacyjnymi według UPDRS podano wartości średnie i odchylenia standardowe ze względu na niewielką liczbę badanych chorych.

Wyniki: Wpływ stymulacji odnotowano w fazie *off*, co spowodowało zmniejszenie nasilenia objawów ruchowych o 59% w 5-letnim okresie pooperacyjnym w porównaniu z wartościami przedoperacyjnymi. W fazie *on* efekt stymulacji przy-

Correspondence address: dr Michał Sobstyl, Klinika Neurochirurgii, Centrum Medycznego Kształcenia Podyplomowego, ul. Marymoncka 99, 01-813 Warszawa, e-mail: mrsob@op.pl
Received: 29.06.2008; accepted: 11.01.2010

Conclusions: Bilateral STN DBS is an effective and safe treatment for patients with advanced PD. Bilateral STN DBS contributes to improvement of parkinsonian symptoms in the off state and levodopa-induced dyskinesia. This can be correlated with a 50% reduction of daily levodopa dose 5 years postoperatively.

Key words: deep brain stimulation, subthalamic nucleus, Parkinson disease.

Wnioski: Obustronna stymulacja STN jest najbezpieczniejszą i najskuteczniejszą metodą leczenia chorych z zaawansowaną ChP. Obustronna stymulacja STN przyczynia się do ustąpienia objawów fazy *off* i dyskinez pląsawiczych, co związane jest z 50-procentowym zmniejszeniem dobowej dawki lewodopy w obserwacji 5-letniej.

Słowa kluczowe: głęboka stymulacja mózgu, jądro niskowzgórzowe, choroba Parkinsona.

Introduction

Deep brain stimulation (DBS), especially deep brain stimulation of the subthalamic nucleus (STN DBS), is an established procedure in the treatment of advanced Parkinson disease (PD) complicated by levodopa-induced dyskinesia. Many reports confirm the efficacy of bilateral STN DBS in short-term as well as long-term follow-up [1-24]. The advantage of STN DBS is the possibility to perform the procedure simultaneously, which ameliorates parkinsonian symptoms on both sides of the body [7,21,24]. Moreover, bilateral STN DBS efficiently controls axial symptoms and tremor affecting axial musculature. The DBS is a safer procedure than ablative surgery because of its reversibility and adjustability. The stimulation-induced side effects may be accomplished by switching between monopolar and bipolar stimulation modes. The introduction of the DBS lead into the stereotactic target avoids ablative radiofrequency thermocoagulation in progressive neurodegenerative disorders such as PD. In the ablative procedure, despite the good control of ablative parameters such as temperature and time of thermoablation, there is no possibility to predict exactly the volume of thermocoagulated brain tissue and accompanying brain oedema. Moreover, the ablative procedures of the STN itself can cause postoperative disabling hemiballism [25,26].

Ablative procedures are less predictable regarding their volume and often exceed the boundaries of the targeted nucleus. To confine the ablative lesion only to the dorsolateral (sensorimotor) part of a small nucleus such as the STN is challenging and sometimes impossible without the lesion encroaching on the surrounding structures such as the thalamic fasciculus or zona incerta. Paradoxically, the ablative destruction of these surrounding structures can prevent the occurrence of postoperative hemiballism [26]. It was observed that in patients with lesions restricted to the STN itself the incidence of postoperative hemiballism was higher than in patients with lesions encroaching on the surrounding structures [26]. The above-mentioned considerations contribute to the fact that unilateral or bilateral ablative procedures in the subthalamic nucleus or subthalamic region are performed rarely.

The STN is a small structure and the dimensions of this nucleus are $5 \times 9 \times 7$ mm in coronal, sagittal and axial planes, respectively. This small nucleus can also be regarded as an ideal stereotactic target for DBS because the stimulating voltage used for functional reversible inhibition remains relatively low [27]. The dimensions of the STN require very precise stereotactic targeting to achieve the best therapeutic effects. Neuronavigation and the fusion of computed tomography with resonance magnetic imaging allow very precise localization of an individual anterior-posterior commissural line and indirect targeting of deep brain nuclei according to the midpoint of the intercommissural line. Moreover, the STN can be directly visualized in coronal and axial T2-weighted MR images [28-30]. Some authors use the red nucleus to target directly the STN [31-33]. The above-mentioned techniques define the anatomical boundaries of a targeted nucleus and require intraoperative electrophysiological mapping of the target by macrostimulation or microelectrode recording [34,35]. Most authors conclude that intraoperative microrecording is mandatory to optimally place the DBS lead in the sensorimotor part of the STN [36]. All authors use macrostimulation to assess the intraoperative effect of stimulation on parkinsonian motor symptoms and to elicit stimulation-induced side

effects from surrounding structures. According to some authors, microrecording verifies the stereotactic target in about 80% of procedures [37]. Some authors claim that additional microelectrode passes increase the incidence of intracerebral haemorrhage and the occurrence of surgery-related side effects such as postoperative confusion [38]. According to them, only macrostimulation is a reliable method to place the DBS lead.

In some countries bilateral STN DBS has completely replaced ablative functional neurosurgery because of its reversibility and adjustability. Because of the high costs of the DBS equipment, this method is still not easily available. The DBS procedure was introduced in Poland at the Neurosurgical Department of the Postgraduate Medical Centre in Warsaw in 1999 in the treatment of tremor-dominant PD targeting the ventralis intermedius nucleus of the thalamus and in the treatment of akinetic-rigid Parkinson's disease complicated by levodopa-induced dyskinesia in the on state targeting the STN [22,23].

The aim of this study was to assess the long-term efficacy of bilateral STN DBS in our first 5 patients with at least 5-year postoperative follow-up.

Material and methods

Between July 1999 and December 2005, 15 patients with advanced PD underwent STN DBS at the Neurosurgical Department of the Postgraduate Medical Centre in Warsaw. According to the clinical symptoms, the DBS leads were implanted bilaterally in 8 patients and in 7 patients the DBS leads were implanted unilaterally. The study received the institutional review board approval of the Postgraduate Medical Centre in Warsaw. All patients signed a written informed consent form. Moreover, patients were cleared about the possible surgical complications associated with stereotactic surgery and functional mapping of the stereotactic target.

The patients referred for STN surgery had a minimum of 5-year history of idiopathic PD. The patients also had improvement of over 33% of parkinsonian motor signs according to part III of the Unified Parkinson's Disease Rating Scale (UPDRS) after administration of a standard levodopa dose when compared to the off state. All patients exhibited motor fluctuations and levodopa-induced dyskinesia during the on state. The contraindications were as follows: psychiatric disorders, negative levodopa test, Mini-Mental State Examination less than 24 points. Severe coagulopathies were also treated as a contraindication for stereotactic surgery. All aspirin-containing medications were withheld 10 days before surgery.

The population study included the first 5 patients treated at our institution with a minimum 5-year postoperative follow-up. The study group comprised 2 women and 3 men. The mean age at the time of PD diagnosis was 52.1 $\pm$ 6.2 years, and the mean age at the time of the operation was 61.2 $\pm$ 5.9 years.

Over the 6-year period, the stereotactic technique of bilateral DBS lead implantation at our institution has considerably changed. In the first 4 patients the bilateral lead implantation procedure was staged with a minimum 3-month interval between procedures. With the gained and accumulated experience, the procedure was simultaneous in the last (fifth) patient. The Leksell G stereotactic frame (Stereotactic Instruments, Elekta, Stockholm, Sweden) was used in all patients. Fixation of the frame to the patient's head was done under local anaesthesia. The skin and the periosteum were infiltrated copiously with 1% lidocaine. The stereotactic frame was fixed to the patient's head as parallel as possible to the Frankfurter line. The stereotactic CT images were performed. The coordinates of the anterior and posterior commissures were directly calculated from the CT stereotactic images. The STN stereotactic coordinates were then obtained according to the mid-commissural point. The STN target was defined as 12 mm lateral to the AC-PC line, 4 mm inferior to AC-PC plane, and 3 mm posterior to the mid-commissural point. In the first 5 patients treated in our institution, the above described radiological technique of deriving the STN coordinates was used. In the following patients the stereotactic procedures were planned according to neuronavigation system Stealthstation Treon 3. After calculating the stereotactic STN coordinates, the patients were transferred to the operating room. The patients were placed in a comfortable semi-sitting position. The burr-hole was located in the uppermost position, which prevented excessive leakage of cerebrospinal fluid and also development of pneumocephalus during the stereotactic procedure. The operations were performed in local anaesthesia without sedation. All patients were operated on in the medication off state (after withdrawal of antiparkinsonian medication for at least 12 hours). The 14-mm burr-holes were made 1 cm before the coronal suture and 3 to 4 cm lateral to the midline. The dura

mater was extensively coagulated and sharply incised in a crucial manner. The brain surface over the gyrus was coagulated and the DBS lead was introduced to the stereotactic target (DBS lead Model Medtronic 3387 or 3389 Minneapolis, MN).

In the first 4 patients the stereotactic target was confirmed only by macrostimulation through the implanted DBS lead. The stereotactically implanted lead was connected intraoperatively to the external Medtronic Screener (Medtronic Screener Model 3625; Medtronic, Inc., Minneapolis, MN). The intraoperative stimulation parameters were as follows: frequency 130 Hz, pulse width 60 μs, voltage up to 10 V. If macrostimulation below 4 V was effective in ameliorating the contralateral rigidity, bradykinesia and tremor without causing unacceptable stimulation-induced side effects, the lead was left in place. In the last (fifth) patient the microrecording was used to guide the DBS lead placement. The hydraulic microdrive was attached to the stereotactic arc (Microdrive; Medtronic, Inc., Minneapolis, MN). The recording of extracellular single potentials was performed 15 mm above the calculated stereotactic STN target and continued 5 mm deeper. For intraoperative microrecording platinum-iridium microelectrodes were used (resistance between 0.1 and 1 MΩ, frequency 1000 Hz). Five microrecording trajectories were performed to spatially map the boundaries of the right STN. Three microelectrode trajectories were utilized to confirm the left STN. The final DBS lead (DBS lead Model 3397 or 3389; Medtronic, Inc., Minneapolis, MN) was introduced through the trajectory with the longest recording of the STN cells. During the cup placement over the burr-hole ring, the possible displacement of the DBS lead was monitored by intraoperative fluoroscopic guidance. All patients had postoperative computed tomography on postoperative day 1 or 2 to exclude any clinically silent intracerebral bleeding. In the first 4 patients, the internal pulse generator type Itrel II (Medtronic, Inc., Minneapolis, MN) was implanted in general anaesthesia after initial external stimulation of 7 to 10 days. In the last, fifth patient the internal pulse generator type Kinetra was implanted just after simultaneous DBS leads' placement under general anaesthesia. The pulse generators were activated on the third day after implantation.

The clinical assessment was performed according to the UPDRS and two motor timed tests (rapid movements between two points and stand-walk-sit test) according to the Core Assessment Program for Intracerebral Transplantation [38]. The patients were evaluated in the off and on state before surgery. The patients in the off state were evaluated after 12 hours of dopaminergic treatment withdrawal. The evaluations in the on state were performed approximately 1 hour after intake of 1 Madopar tablet (250 mg).

In the postoperative follow-up period, the patients were assessed in four states: stimulation on/medication off; stimulation on/medication on; stimulation off/medication off; and stimulation off/medication on. The patients were evaluated at 1, 3, and 5 years after bilateral STN DBS. The postoperative assessment in the stimulation off state was performed at least 4 hours after switching off the internal pulse generators to allow the reoccurrence of parkinsonian motor symptoms. It should be noted that not all patients tolerated that long time period without chronic bilateral STN DBS. In the postoperative period 2 patients could not withstand being in the medication off and stimulation off state for 4 hours until assessment. The reason for this was rapid reappearance of a very severe akinetic-rigid state with breathing problems attributable to increased rigidity of thoracic and abdominal muscles as well as fear of being off stimulation and off medication for a longer period. One patient was assessed after 15 minutes of being stimulation off and medication off at all postoperative follow-up visits and another was evaluated after 2 hours at 3- and 5-year follow-up visits. The remaining 3 patients were assessed after 4 hours of being stimulation as well as medication off during each postoperative visit. The motor time tests according to CAPIT were performed before surgery in the on and off state. The preoperative daily levodopa dosage was compared to the postoperative daily levodopa dosage at 1, 3 and 5 years after surgery. The clinical assessment of the patients was performed by Z.M., H.K., M.S. and B.K. The surgeries, including stereotactic implantation of the DBS leads, IPGs, reimplantation of the malfunctioning part of the DBS system and postoperative patient care, like adjustment of stimulating parameters and pharmacological therapy, were done by M.Z., Z.M., H.K., M.S., B.K. and S.D.

Results

All 5 operated patients benefited from the bilateral STN DBS. In the postoperative period, the patients were assessed clinically in 4 states as described previously, which allowed the effect of the stimulation as well as the medication on parkinsonian motor symptoms to be

Table 1. Clinical assessments before and after surgery – during on stimulation/off medication period (stimulation on/off state). Values are means ± standard deviations

Off state	UPDRS items	Score range	Baseline	One-year follow-up	Three-year follow-up	Five-year follow-up
UPDRS II	5-17	0-52	28.7 ± 9.4	17.3 ± 7.2	18.5 ± 6.5	19.5 ± 6.5
UPDRS III	18-31	0-108	55.4 ± 12.7	20.7 ± 7.9	21.1 ± 8.1	22.7 ± 7.8
Tremor score	20-21	0-12	8.2 ± 2.4	2.1 ± 1.0	2.0 ± 1.1	1.9 ± 1.2
Rigidity score	22	0-8	8.9 ± 2.8	3.8 ± 2.6	3.6 ± 2.1	3.7 ± 1.4
Bradykinesia score	23-26	0-16	18.4 ± 7.2	5.5 ± 2.1	8.5 ± 3.1	9.8 ± 4.1
Postural instability/ gait disorder score	13, 14, 15, 29, 30	0-20	14.9 ± 4.8	5.6 ± 2.7	5.8 ± 3.1	5.1 ± 3.2

UPDRS – Unified Parkinson's Disease Rating Scale

Table 2. Clinical assessments before and after surgery – during on stimulation/on medication period (stimulation on/on state). Values are means ± standard deviations

On state	UPDRS items	Score range	Baseline	One-year follow-up	Three-year follow-up	Five-year follow-up
UPDRS II	5-17	0-52	12.8 ± 3.8	8.8 ± 3.2	11.6 ± 4.1	14.6 ± 4.4
UPDRS III	18-31	0-108	18.4 ± 6.5	14.5 ± 5.7	15.3 ± 6.1	15.4 ± 5.6
Tremor score	20-21	0-12	1.9 ± 0.5	1.5 ± 0.9	1.2 ± 0.9	1.3 ± 1.0
Rigidity score	22	0-8	7.4 ± 2.6	5.1 ± 1.8	5.2 ± 1.7	3.9 ± 1.5
Bradykinesia score	23-26	0-16	7.4 ± 2.6	5.1 ± 1.8	5.2 ± 1.7	6.8 ± 2.1
Postural instability/ gait disorder score	13, 14, 15, 29, 30	0-20	4.9 ± 2.2	3.2 ± 1.4	3.5 ± 1.6	4.0 ± 1.2
Duration of dyskinesia	32	0-4	2.3 ± 0.8	0.7 ± 0.6	0.7 ± 0.5	0.6 ± 0.4
Severity of dyskinesia	33	0-4	1.8 ± 0.6	0.5 ± 0.6	0.6 ± 0.5	0.4 ± 0.5

UPDRS – Unified Parkinson's Disease Rating Scale

documented separately. Tables 1 and 2 show the effect of the bilateral STN DBS on the activities of daily living and motor examination according to parts II and III of the UPDRS scores in the off and on state.

The stimulation effect was seen in the off state with reduction of motor scores by 63% and 62% at 1 and 3 years follow-up, respectively. Moreover, the stimulation effect in the off state was maintained 5 years postoperatively, which resulted in a 59% reduction of motor scores when compared to the preoperative motor scores in the off state. The obtained results confirm the high efficacy of bilateral STN DBS in ameliorating parkinsonian tremor, rigidity, bradykinesia and postural instability (Table 1). The effect of bilateral STN DBS on motor scores in the on state was modest. There was a 17% reduction of motor scores in the on state 5 years postoperatively when compared with the preoperative scores in the on state (Table 2). The bilateral STN DBS contributed to the reduction of the severity and duration of levodopa-induced dyskinesia (Table 2). The antidyskinetic effect could be attributable to the 50% reduction of daily levodopa dosage 5 years post-operatively. It should be noted that in the stimulation off state the scores of the activities of daily living as well as motor scores worsened in the off and on state. This could be explained by the natural progression of PD and the 50% reduction of daily levodopa dosage at 5 years of follow-up. The UPDRS scores in the off and on state during the stimulation off state are presented in Table 3.

Before the surgery, 3 patients could not manage the stand-walk-sit test in the off state. Additionally, 2 patients could not perform rapid movements between 2 points in the off state preoperatively. Five years after surgery all patients could perform the motor tests in the off state during stimulation. Before surgery the mean time to perform the stand-walk-sit test was 35 ± 15 seconds; 5 years postoperatively the mean time for performing this test was 20 ± 10 seconds. The time needed to perform the test of rapid movements between 2 points was 25 ± 17 seconds, and 5 years postoperatively it was 12 ± 9 seconds.

Bilateral STN DBS substantially decreased the daily levodopa dosage after surgery. The mean preoperative daily dose of levodopa was 1120 ± 420 mg, 1 year after surgery 780 ± 340 mg, 3 years after surgery 590 ± 255 mg, and 5 years after surgery 565 ± 310 mg.

Table 3. Clinical assessments before and after surgery – during off stimulation period in the off and on medication states (stimulation off/off state, stimulation off/on state). Values are means ± standard deviations

Stimulation off/off state	UPDRS items	Score range	Baseline	One-year follow-up	Three-year follow-up	Five-year follow-up
UPDRS II	5-17	0-52	28.7 ± 6.4	31.2 ± 13.2	32.5 ± 10.8	33.5 ± 12.1
UPDRS III	18-31	0-108	55.4 ± 12.7	55.8 ± 14.8	63.1 ± 16.8	64.7 ± 18.5
Stimulation off/on state	**UPDRS items**	**Score range**	**Baseline**	**One-year follow-up**	**Three-year follow-up**	**Five-year follow-up**
UPDRS II	5-17	0-52	12.8 ± 3.8	18.5 ± 6.7	21.4 ± 5.6	22.9 ± 8.3
UPDRS III	18-31	0-108	18.4 ± 6.5	29.5 ± 8.9	32.8 ± 11.2	36.1 ± 12.4

UPDRS – Unified Parkinson's Disease Rating Scale

Only 2 out of 5 patients received dopamine agonists before the surgery. These 2 patients took bromocriptine before surgery (1 patient 20 mg daily and another 30 mg daily). Moreover, 1 patient preoperatively took selegiline (5 mg daily) and 1 patient took entacapone (400 mg daily). Thus, 4 patients were also treated with antiparkinsonian drugs other than levodopa and 1 patient was on levodopa monotherapy before surgery. Five years after STN DBS only 1 patient took a dopamine agonists (1 patient still used 10 mg bromocriptine daily). Selegiline and entacapone were withdrawn 2 years after surgery. Thus, 5 years after STN DBS, 4 patients were on levodopa exclusively. In the 5-year follow-up period all patients experienced depletion of the internal pulse generators (IPGs). In the first 4 patients the IPGs type Itrel II were exchanged for IPGs type Soletra. The fifth patient received the new Kinetra generator. The exchange of IPGs was performed in local anaesthesia.

One patient developed transient confusion in the immediate postoperative period. There was 1 hardware-related complication (1 breakage of connecting cable). In the postoperative period 3 patients required frequent follow-up visits to optimize the stimulation parameters and the adjustment of the pharmacological therapy. Five years postoperatively, 3 patients had bilateral monopolar stimulation and 2 a combination of monopolar stimulation on one side and bipolar stimulation on the opposite side. In 1 case, bipolar stimulation was used to reduce persistent paraesthesia around the mouth corner and upper limb, with good control of parkinsonian motor symptoms. In the second case, bipolar stimulation was used to diminish facial twitches (mouth corner). Contact 2 was used the most often in the monopolar setting as a cathode in 6 brain hemispheres. Contact 1 was used as a cathode in 2 brain hemispheres. Bipolar stimulation used in 2 patients was as follows: contact 1 cathode and contact 3 anode. The stimulating parameters did not change significantly over the follow-up period. In the follow-up period all contacts were screened to measure the range of resistance [40]. The assessment of cathodal monopolar stimulation was used to evaluate the effect on parkinsonian motor signs and to look at possible stimulation-induced side effects. For permanent monopolar stimulation the contact was used which was the most effective in ameliorating parkinsonian motor signs. All patients with monopolar stimulation experienced transient paraesthesia after switching on the IPGs, which completely resolved after a few seconds. Bipolar unilateral stimulation was used in only 2 patients. The stimulation parameters for monopolar mode over 5-year follow-up were as follows: frequency 145 ± 30 Hz, pulse width 60 ± 30 μs, voltage 3.1 ± 0.8 V. For bipolar stimulation, the frequency and pulse width were the same as for monopolar stimulation but higher voltage was needed to achieve a comparable clinical effect. The stimulation parameters for bipolar mode were as follows: frequency 145 ± 15 Hz, pulse width 90 ± 15 μs, voltage 3.7 ± 0.7 V.

Discussion

Our results confirm the high efficacy of bilateral STN DBS in the treatment of advanced stages of PD. The stimulation effect was sustained at 5 years postoperatively, resulting in a 59% reduction of motor scores according to UPDRS part III in the off state. This observation supports the results of other investigators which reported the reduction of motor scores (UPDRS part III) between 28% and 71% after bilateral STN DBS [1,8,11,12,40-42]. The effect of bilateral STN DBS on motor scores in the on state was minimal, resulting in a 17% reduction of motor scores. The effect of bilateral STN DBS on motor scores in the on state remains controversial, in contrast to the striking reduction of motor scores in the off state under bilateral STN DBS. Some authors report that the motor scores

(UPDRS part III) deteriorated in the on state [13], did not change [11,17,45], slightly improved [12,41] or the improvement was comparable to that achieved in the off state under bilateral STN DBS [10]. These discrepancies could be attributed to complete withdrawal or different degrees of reduction of the daily levodopa dose in the postoperative period reported by these authors [10,11,13,17,41,45]. In this study the patients were assessed during switching off the IPGs for at least 4 hours. Two patients could not tolerate this period in the off state without stimulation.

The clinical assessment in the off and on state without stimulation 5 years postoperatively showed some deterioration when compared to preoperative scores in the off and on state, respectively. This deterioration could be explained by the steady progression of PD and also by the 50% reduction of daily levodopa dose 5 years postoperatively. The detailed assessment of the effect of bilateral STN DBS revealed that the stimulation was most effective in diminishing parkinsonian tremor, and, to a lesser degree, rigidity and bradykinesia. The reduction of parkinsonian tremor in the long-term follow-up according to items 20-21 of UPDRS was 77% when compared to preoperative scores. This high efficacy of STN DBS for tremor was proved by other authors [1,4-8]. Krack *et al*. reported a very good antitremor effect of STN DBS 5 years postoperatively [4]. In the experience of these authors the tremor decreased by 81% in the off state under STN DBS according to items 20-21 of the UPDRS when compared to the preoperative state. Pollak, Benabid and Krack were the first to report the high efficacy of STN DBS for tremor [7]. These authors observed near complete tremor suppression in the off state under STN DBS in 15 patients [7]. The preoperative mean tremor score in the off state decreased from 11.3 pts (maximal tremor score according to items 20-21 in UPDRS, part III is 28) to 2.2 pts in the postoperative period. This improvement in tremor control under bilateral STN DBS was nearly total. Our results in the treatment of parkinsonian tremor are comparable to the results achieved by other authors. The efficacy of STN DBS can be compared to the well-known efficacy of stimulation of the ventralis intermedius nucleus (VIM) of the thalamus in the surgical management of tremor. According to Benabid's opinion, STN DBS is also the stereotactic target of choice in tremor-dominant PD patients. Besides good control of parkinsonian tremor, STN DBS effectively ameliorates rigidity, bradykinesia and also levodopa-induced dyskinesia during the on state. The reduction of the duration and severity of levodopa-induced dyskinesia could be attributed to the significant decrease of daily levodopa dosage in the postoperative period. The most striking effect of bilateral STN DBS is visible in the off state postoperatively. In our patients the rigidity decreased by 57%, 60% and 59% at 1, 3 and 5 years after surgery, respectively. The effect on rigidity was long-lasting and did not decrease over the follow-up period. Bradykinesia decreased by 70% at 1-year follow-up. In the next postoperative years, there was some increase in bradykinesia scores. Bradykinesia was decreased by 54% and 47% 3 and 5 years after bilateral STN DBS, respectively. The efficacy of bilateral STN DBS on bradykinesia was less evident than on tremor and rigidity.

The axial symptoms (maximal axial score in items 13-15/29-30 of part II/III is 20) decreased by 66% in the off state under bilateral STN DBS 5 years postoperatively. It is worth noting that not all falls in advanced stages of Parkinson's disease are related to the off state, but can also be a consequence of impaired balance caused by severe levodopa-induced dyskinesia in the on state. Bilateral STN DBS decreased levodopa-induced dyskinesia in the on state, which decreased axial symptoms by 35%, 29% and 18% 1, 3 and 5 years after surgery, respectively. The improvement of balance in Parkinson's disease patients under STN DBS can be assessed objectively by posturography in the off as well as in the on state [43]. It is worth noting that a new emerging stereotactic target, i.e. stimulation of the pedunculopontine nucleus (PPN), can very efficiently improve the gait and axial symptoms in patients with advanced stages of PD. A preliminary report on PPN stimulation suggests that DBS of this target may be more reliable than bilateral STN DBS in the treatment of gait and axial symptoms [44].

The STN DBS studies confirmed that only STN DBS correlates with significant reduction of the daily levodopa dose and dopamine agonists in the post-operative follow-up period [1,8,11,12,22,23,40-42, 45-49]. In our patients the decrease of daily levodopa dose was 50% 5 years after bilateral STN DBS. Other authors also report the same reduction of daily levodopa dosage [1,8,48]. Molinuevo *et al*. and Houeto *et al*. noticed a 60 to 80% decrease of daily levodopa dosage in the postoperative period [17,45]. According to these authors, antiparkinsonian medication could be withdrawn in some patients completely in the post-operative period under bilateral STN DBS [45,46]. In the immediate postoperative period (3 months after

surgery), when DBS is started, the need to decrease antiparkinsonian medication could be explained by the possibility of exacerbating levodopa-induced dyskinesia. It is very important to increase the stimulation voltage slowly, especially in levodopa-sensitive patients. This approach reduces the likelihood of exacerbating levodopa-induced dyskinesia in the first weeks after starting bilateral STN DBS. Moreover, bilateral STN DBS itself can increase sensitivity to levodopa [47]. A slow increase of the voltage, which should be parallel to a slow decrease of daily levodopa dose, is suggested to achieve the best therapeutic effect of bilateral STN DBS.

Although STN DBS is an efficacious and safe stereotactic procedure, some patients may experience postoperative side effects. These side effects are related to stimulation of the surrounding brain tissue (stimulation-induced side effects), to the surgical procedure itself and to dysfunction or infection of the implanted DBS hardware [50,51]. In the immediate postoperative period, most patients experienced transient stimulation-induced paraesthesia and exacerbation of levodopa-induced dyskinesia in the on state. These side effects are transient in most patients and disappear in a few seconds after switching on the internal pulse generator. When monopolar stimulation causes permanent stimulation-induced side effects, the bipolar stimulating mode can be applied. In our patients this situation occurred in 2 cases. Other stimulation-induced side effects include hypophonia (5.8%), apraxia of eyelids (4.6%), increased libido (0.8%), increased salivation (0.9%) and memory impairment (1.1%) [51]. The most frequently encountered side effect after simultaneous bilateral STN DBS implantation is postoperative transient confusion, affecting 13.7% of operated individuals [51%]. We observed one case of transient postoperative confusion which resolved without neurological sequelae. The psychiatric side effects depression and mania affect 4.7% and 2.0% of patients, respectively, in the postoperative period [51-54]. Preoperative psychiatric assessment is mandatory to pay special attention to patients with a preoperative history of psychiatric disorders [52-55]. An active psychiatric disorder is a contraindication to STN DBS implantation. Seizures may appear in the immediate postoperative period and affect 0.9% of operated individuals [51]. The most dangerous and life-threatening consequence of all stereotactic procedures is an intracerebral haemorrhage. The prevalence of intracerebral haemorrhage in all stereotactic procedures is estimated to be 2.8% [51]. Half of these intracerebral haemorrhages are clinically asymptomatic and are discovered on postoperative computed tomography or magnetic resonance images. Permanent neurological deficits or death is estimated to affect 1% to 2% of all operated individuals [51].

Another type of side effect is related to malfunction or infection of the implanted hardware and can be encountered in up to 9% of patients [51]. The most frequent hardware complication is dislocation of the intracerebral DBS electrode, affecting 4.5% of patients. Infections occurred in 3.4% of patients but in 48% they can be managed conservatively with antibiotics. In the remaining 52% it is necessary to remove a part or parts, or, in some rare cases, all hardware. The risk of malfunction of the internal pulse generator is estimated to be 0.4% [51]. In agreement with other authors, monopolar cathodal stimulation was the most efficacious in our patients. The stimulating parameters were only minimally changed in the 5-year postoperative period. Our observations confirmed the efficacy and safety of bilateral STN DBS in 5-year follow-up.

Conclusions

1. Bilateral STN DBS is an effective treatment modality in ameliorating motor signs of advanced PD.
2. Bilateral STN DBS is the most effective method in the treatment of parkinsonian tremor, rigidity and, to a lesser degree, bradykinesia. The antiparkinsonian effect of STN DBS is maintained at 5 years postoperatively.
3. The duration and severity of dyskinesia diminished greatly. The bilateral STN DBS resulted in a 50% reduction of daily levodopa intake 5 years postoperatively.

Disclosure

Authors report no conflict of interest.

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: 1105-1111.
2. Ashkan K., Wallace B., Bell B.A., et al. Deep brain stimulation of the subthalamic nucleus in Parkinson's disease 1993-2003: where are we 10 years on? *Br J Neurosurg* 2004; 18: 19-34.
3. Herzog J., Volkmann J., Krack P., et al. Two-year follow-up of subthalamic deep brain stimulation in Parkinson's disease. *Mov Disord* 2003; 18: 1332-1337.

4. 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: 1925-1934.
5. Kleiner-Fisman G., Fisman D.N., Sime E., et al. Long-term follow up of bilateral deep brain stimulation of the subthalamic nucleus in patients with advanced Parkinson disease. *J Neurosurg* 2003; 99: 489-495.
6. Rodriguez-Oroz M.C., Gorospe A., Guridi J., et al. Bilateral deep brain stimulation of the subthalamic nucleus in Parkinson's disease. *Neurology* 2000; 55: 45-51.
7. Krack P., Pollak P., Limousin P., et al. Stimulation of subthalamic nucleus alleviates tremor on Parkinson's disease. *Lancet* 1997; 350: 1675.
8. Kumar R., Lozano A.M., Kim Y.J., et al. Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease. *Neurology* 1998; 51: 850-855.
9. Limousin P., Pollak P., Benazzouz A., et al. Bilateral subthalamic nucleus stimulation for severe Parkinson's disease. *Mov Disord* 1995; 10: 672-674.
10. Ostergaard K., Sunde N., Dupont E. Effects of bilateral stimulation of the subthalamic nucleus in patients with severe Parkinson's disease and motor fluctuations. *Mov Disord* 2002; 17: 693-700.
11. Romito L.M., Sceratti M., Contarino M.F., et al. Long term follow-up of subthalamic nucleus stimulation in Parkinson's disease. *Neurology* 2002; 58: 1546-1550.
12. Pinter M.M., Alesch F., Murg M., et al. Deep brain stimulation of the subthalamic nucleus for control of extrapyramidal symptoms in advanced idiopathic Parkinson's disease: one year follow-up. *J Neural Transm* 1999; 106: 693-709.
13. Simuni T., Jaggi J.L., Mulholland H., et al. Bilateral stimulation of the subthalamic nucleus in patients with Parkinson's disease: a study of efficacy and safety. *J Neurosurg* 2002; 96: 666-672.
14. Tavella L., Bergamasco B., Bosticco E., et al. Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: long-term follow-up. *Neurol Sci* 2002; 23: 211-212.
15. Thobois S., Mertens P., Guenot M., et al. Subthalamic nucleus stimulation in Parkinson's disease. *J Neurol* 2002; 249: 529-534.
16. Vesper J., Klosterman F., Stockhammer F., et al. Results of chronic subthalamic nucleus stimulation for Parkinson's disease: a 1-year follow-up study. *Surg Neurol* 2002; 57: 306-313.
17. Houeto J.L., Damier P., Bejjani P.B., et al. Subthalamic stimulation in Parkinson's disease: a multidisciplinary approach. *Arch Neurol* 2000; 57: 461-465.
18. Deuschl G., Wenzelburger R., Kopper F., et al. Deep brain stimulation of the subthalamic nucleus for Parkinson's disease: a therapy approaching evidence-based standards. *J Neurol* 2003; 250 (Suppl 1): I43-I46.
19. Broggi G., Franzini A., Ferroli P., et al. Effect of bilateral subthalamic electrical stimulation in Parkinson's disease. *Surg Neurol* 2001; 56: 89-94.
20. Ford B., Winfield L., Pullman S.L., et al. Subthalamic nucleus stimulation in advanced Parkinson's disease: blinded assessments at one year follow up. *J Neurol Neurosurg Psychiatry* 2004; 75: 1255-1259.
21. Limousin P.L., Pollak P., Benazzouz A., et al. Effect on parkinsonian sings and symptoms of bilateral subthalamic nucleus stimulation. *Lancet* 1995; 345: 91-95.
22. Ząbek M., Sobstyl M., Koziara H. Głęboka stymulacja jądra pośredniego Vim wzgórza w leczeniu drżenia parkinsonowskiego. *Neurol Neurochir Pol* 2003; 37: 437-446.
23. Ząbek M., Sobstyl M., Koziara H. Obustronna głęboka stymulacja jądra niskowzgórzowego w operacyjnym leczeniu choroby Parkinsona. *Neurol Neurochir Pol* 2003; 37: 447-457.
24. Bejjani B.P., Gervais D., Arnulf L., et al. Axial parkinsonian symptoms can be improved: the role of levodopa and bilateral subthalamic stimulation. *J Neurol Neurosurg Psychiatry* 2000; 68: 595.
25. Vidakovic A., Dragasevic N., Kostic V.S. Hemibalism: Report of 25 cases. *J Neurol Neurosurg Psychiatry* 1994; 57: 945-949.
26. Patel N.K., Heywood P., O'Sullivan K., et al. Unilateral subthalamotomy in the treatment of Parkinon's disease. *Brain* 2003; 126: 1136-1145.
27. Lange P., Thorner G., Hopf A. Morphometric-statistical structure analysis of human striatum, pallidum and subthalamic nucleus. *J Hirnforsch* 1976; 17: 31-41.
28. Bejjani B.P., Dormont D., Pidoux B., et al. Bilateral subthalamic stimulation for Parkinson's disease by using three-dimensional stereotactic magnetic resonance imaging and electrophysiological guidance. *J Neurosurg* 2000; 92: 615-625.
29. Cuny E., Guehl D., Burbaud P., et al. Lack of agreement between direct magnetic resonance imaging and statistical determination of a subthalamic target. *J Neurosurg* 2002; 97: 591-597.
30. Starr P.A., Christine C.W., Theodosopoulos P.V., et al. Implantation of deep brain stimulators into the subthalamic nucleus: technical approach and magnetic resonance imaging-verified lead locations. *J Neurosurg* 2002; 97: 370-387.
31. Lehmann R.M. Comparison of anatomic and neurophysiological methods for subthalamic nucleus targeting. *Neurosurgery* 2001; 49: 477.
32. Zhu X.L., Hamel W., Schrader B., et al. Magnetic resonance imaging-based morphometry and landmark correlation of basal ganglia nuclei. *Acta Neurochir* (*Wien*) 2002; 144: 959-969.
33. Andrade-Souza Y.M., Schwalb J., Hamani C., et al. Comparison of three methods of targeting the subthalamic nucleus for chronic stimulation In Parkinson's disease. *Neurosurgery* 2005; 56 (Suppl 2): 360-368.
34. Benazzouz A., Breit S., Koudsie A., et al. Intraoperative microrecordings of the subthalamic nucleus in Parkinson's disease. *Mov Disord* 2002; 17 (Suppl 3): 145-149.
35. Pollak P., Krack P., Fraix V., et al. Intraoperative micro- and macrostimulation of the subthalamic nucleus in Parkinson's disease. *Mov Disord* 2002; 17 (Suppl 3): 155-161.
36. Sierens D.K., Bakay R.A.E. Is MER necessary in movement disorders surgery? The case in favor. In: Israel Z., Burchiel K.J. [eds.]. Microelectrode Recording in Movement Disorder Surgery. *Thieme Medical Publishers*, *Inc*., New York 2004, pp. 197-208.
37. Hariz M. Is MER necessary in movement disorders surgery? The case against. In: Israel Z., Burchiel K.J. [eds.]. Microelectrode recording in movement disorder surgery. *Thieme Medical Publishers*, *Inc*., New York 2004, pp. 197-208.
38. Defer G.L., Widner H., Marie R.M., et al. Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD). *Mov Disord* 1999; 14: 572-584.

39. Volkmann J., Herzog J., Kopper F., et al. Introduction to the programming of deep brain stimulators. *Mov Disord* 2002; 17 (Suppl 3): 181-187.
40. Pahwa R., Wilkinson S.B., Overman J., et al. Bilateral subthalamic stimulation in patients with Parkinson's disease. *J Neurosurg* 2003; 99: 71-77.
41. Krack P., Pollak P., Limousin P., et al. Subthalamic nucleus or internal pallidal stimulation in young onset Parkinson's disease. *Brain* 1998; 121: 451-457.
42. Lopiano L., Rizzone M., Bergamasco B., et al. Deep brain stimulation of the subthalamic nucleus: clinical effectiveness and safety. *Neurology* 2001; 56: 552-554.
43. Maurer C., Mergner T., Xie J. Effect of chronic bilateral subthalamic nucleus (STN) stimulation on postural control in Parkinson's disease. *Brain* 2003; 126: 1146-1163.
44. Mazzone P., Lozano A.M., Peppe A., et al. Combined implantation of PPN and STN improve gait akinesia and freezing in severe parkinsonian patients. XVIIth Congress of the European Society for Stereotactic and Functional Neurosurgery. Montreux, Switzerland, 4-7 October 2006. Conference materiale: S1B3.
45. Molinuevo J.L., Valldeoriola F., Tolosa E., et al. Levodopa withdrawal after bilateral subthalamic nucleus stimulation in advanced Parkinson disease. *Arch Neurol* 2000; 57: 983-988.
46. Valldeoriola F., Pilleri M., Tolosa E., et al. Bilateral subthalamic stimulation monotherapy in advanced Parkinson's disease: long-term follow-up of patients. *Mov Disord* 2002; 17: 125-132.
47. Vingerhoets F.J.G., Villemure J.G., Temperli P., et al. Subthalamic DBS replaces levodopa in Parkinson's disease. *Neurology* 2002; 58: 396-401.
48. Rodriguez-Oroz M.C., Obeso J.A., Lang A.E., et al. Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up. *Brain* 2005; 128: 2240-2249.
49. Moro E., Sceratti M., Romito L.M., et al. Chronic subthalamic nucleus stimulation reduces medication requiments in Parkinson's disease. *Neurology* 1999; 53: 85.
50. Lyons K.E., Wilkinson S.B., Overman J., et al. Surgical and hardware complications of subthalamic stimulation: a series of 160 procedures. *Neurology* 2004; 63: 612-616.
51. Hamani C., Richter E., Schwalb J.N., et al. Bilateral subthalamic nucleus stimulation for Parkinson's disease. A systematic review of the clinical literature. *Neurosurgery* 2005; 56: 1313-1324.
52. Dujardin K., Defebvre L., Krystkowiak P., et al. Influence of chronic bilateral stimulation of the subthalamic nucleus on cognitive function in Parkinson's disease. *J Neurol* 2001; 248: 603-611.
53. Saint-Cyr J.A., Trepanier L.L., Kumar R., et al. Neuro-psychological consequences of chronic bilateral stimulation of the subthalamic nucleus in Parkinson's disease. *Brain* 2000; 123: 2091-2108.
54. Pillon B. Neuropsychological assessment for management of patients with deep brain stimulation. *Mov Disord* 2002; 17 (Suppl 3): 116-122.
55. Funkiewiecz A., Ardouin C., Caputo E., et al. Long term effects of bilateral subthalamic nucleus stimulation on cognitive function, mood, and behaviour in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2004; 75: 834-839.