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ORIGINAL COMMUNICATION

Bilateral subthalamic nucleus stimulation in advanced Parkinson's disease: Five year follow-up

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Abstract *Objective* To assess the long-term efficacy and safety of bilateral subthalamic nucleus (STN) stimulation in patients with advanced Parkinson's disease (PD). *Methods* 42 consecutive patients with idiopathic PD treated with bilateral STN stimulation were enrolled. Parkinsonian status, medication intake and neuropsychological evaluation were assessed preoperatively and at 1 and 5 years postoperatively in on and off medication/on and off stimulation conditions. *Results* 23 patients could be followed-up 5 years after surgery. In the remaining cases, 5 died, 1 could not be assessed because of device removal for infection, 1 decided not to be stimulated, and 11 were lost of follow-up (one because of a liver carcinoma and the others because they refused the formal four conditions of assessment). STN stimulation reduced the UPDRS motor score by 55 % compared to baseline in the off-medication conditions. Tremor, rigidity, bradykinesia, postural stability, and gait improved by 74 %, 66 %, 59 %, 17 % and 37 %, respectively. UPDRS part II scores were reduced by 38 %. The dopaminergic treatment daily dose was reduced by 54.4 % after surgery. Axial dopa-unresponsive signs worsened in some patients. Among the 42 initial patients we observed the following: 2 brain hemorrhages, 3 infections of the device, 2 phlebitis and 1 pulmonary embolism. In addition, 2 patients needed a repositioning of the electrode. Among the 23 patients followed at 5 years, long lasting side effects consisted in dysarthria (56 %), depression (39 %), eyelid opening apraxia (30.4 %) and apathy (4.3 %). *Conclusions* Our data confirm that bilateral STN stimulation is beneficial in the long-term for PD patients but does not prevent disease progression and the occurence of axial levodopa unresponsive signs in some patients.

Key words Parkinson's disease · subthalamic nucleus · deep brain stimulation · long term

Introduction

Since the mid-1990s numerous studies have demonstrated that bilateral subthalamic nucleus (STN) stimulation can dramatically improve parkinsonian motor symptoms and levodopa-induced motor complications and reduce drugs intake in patients with advanced PD, with a low risk [2, 24, 30]. Most of these studies describe the short-term outcome (between 6 and 12 months postoperatively) [1, 4, 7, 9, 11, 12, 15, 21, 27, 29–34, 37, 43–45, 48, 51]. On the other hand, few data are available concerning the long-term (more than 2 years) outcome of this procedure [5, 18, 20, 26, 28, 35, 36, 38, 39, 41, 49, 50,

52]. Among these studies only three reported 5-year follow-up of PD patients operated with bilateral STN stimulation [26, 41, 52]. Following our previous published experience [18, 45], we report the results obtained 5 years postoperatively in a cohort of 42 consecutive patients with advanced PD who underwent chronic bilateral STN stimulation.

Material and methods

Patients

Between November 1998 and June 2002, 42 patients with idiopathic PD underwent a surgical procedure for bilateral STN stimulation at our institution. All patients had a good levodopa responsiveness (mean reduction of the UPDRS motor score by levodopa : 66 ± 14 %) and severe motor complications. The exclusion criteria were age ≥ 70 years old because of poor outcome of this kind of surgery in these patients [10, 40]; cognitive decline (score < 130 on the Mattis Dementia Rating Scale), major depression on the Beck Depression Inventory (score > 20), abnormal brain magnetic resonance imaging (MRI), and concomitant severe medical pathologies.

Surgery

The surgical procedure has been detailed previously [18, 45]. Briefly STN was located by MRI and ventriculography. Then, leads implantation was performed under local anesthesia and guided by microrecordings (Axon Instruments Guideline System 3000a, Foster City, CA) and macrostimulation in order to determine the best trajectory among the three tested on average for each side (Radionics, Inc., Burlington, MA). Then definitive electrodes were implanted bilaterally (Model 3389-28, Medtronic, Minneapolis, MN). Brain MRI was performed postoperatively to check the final electrode placement and eliminate surgical complications. Three to five days later a subcutaneous programmable pulse generator (Itrell II or Kinetra, Medtronic, Minneapolis, MN) was implanted under general anesthesia and connected to the electrodes. The adjustment of the stimulation parameters and of the medications was done progressively as previously reported [46].

Clinical evaluation

A clinical evaluation was performed one week before surgery, and at one and five years postoperatively with the Unified Parkinson's Disease Rating Scale (UPDRS), Mattis Dementia Rating Scale and the Beck Depression Inventory [13]. UPDRS part III rated the motor symptoms, UPDRS II the activity of daily living (ADL), UPDRS I the mood and behavior, and UPDRS IV the motor complications (motor fluctuations and dyskinesias). These assessments were performed before surgery in on (i.e after intake of a supraliminar dose of levodopa equal to 150 % of the usual first morning dose) and off medication (i.e after at least 12 hours antiparkinsonian medication withdrawal). Postoperative evaluation was conducted in four conditions: on-stimulation and off-medication for at least 12 hours; off-stimulation for at least 30 minutes and off-medication; on-medication (after a levodopa challenge) and off-stimulation; on-medication and on-stimulation for at least 30 minutes. Scores at the UPDRS parts I, II and IV were also determined pre- and postoperatively.

Statistical analysis

Results are expressed as means ± SD. A $p < 0.01$ was considered as significant using the Wilcoxon Rank Sum test or the Kruskal-Wallis test.

Results

Patients

A total of 42 PD patients were operated consecutively with bilateral STN implantation. One patient died due to pneumonia unrelated to surgery within the first year after the surgery. For this patient we cannot obviously exclude a direct link with PD as all these advanced patients have dysphagia. One patient died 2 years after the surgery in a context of dementia. This patient had a normal MATTIS scale (score 132/144) at baseline but we cannot completely rule out the presence of mild cognitive impairment which could have been found using more extensive cognitive tests. One patient committed suicide 6 months after the surgery. This patient had no past history of depression or suicide attempt; before surgery his BDI score was of 14. However the surgery was complicated in the immediate post-operative period by atrial fibrillation and pneumonia complicated by cardiac failure. He then never fully recovered to his preoperative neurological status and presented severe postural instability and gait disturbances although the brain CT scan did not show any stroke. He then developed depression, but did not tell to his family he was about to commit suicide. For this patient we do not think, although this cannot be completely ruled out, that the suicide was directly due to the stimulation but rather to indirect complications of the surgery. One patient died in the context of severe rheumatoid arthritis, and a fifth patient died from myocardial infarction. One patient was lost of follow-up because of a liver carcinoma. One patient chose not to be stimulated because of stimulation-induced dysarthria. Ten patients were lost of follow-up because they lived far away from the hospital and refused to be hospitalized for formal assessments. One patient was excluded because of a skin infection over the electrodes, which had to be removed during the first post-operative year. Another patient presented intracerebral hemorrhage during surgery, with persistent aphasia. He subsequently developed dementia, and was lost of follow-up.

Finally, 23 patients (17 males, 6 females) could be assessed at both 1 year and 5 years after surgery. We present the formal results of the 23 patients at the five years follow-up. Their clinical characteristics are detailed in Table 1.

In order to compare the two populations of patients (those who were followed-up and the other those who did not), the clinical characteristics of the 19 patients,

Table 1 Preoperative characteristics of the 23 patients who completed the 5 year follow-up

No. of patients	23
sex	17 M/6 F
age at time of surgery (years)	
range/mean ± SD	42–65/55.1 ± 7.2
age at disease onset (years)	
range/mean ± SD	30.2–57/42.1 ± 7.5
disease duration (years)	
range/mean ± SD	7.9–19/12.9 ± 3.2
dose of levodopa equivalent medication (mg/D)	
range/mean ± SD	300–2050/1188 ± 465

Table 2 Preoperative characteristics of the 19 patients who did not fulfill the 5 year follow-up

No. of patients	19
sex	7 M/12 F
age at time of surgery (years)	
range/mean ± SD	40–69/57.8 ± 9.2
age at disease onset (years)	
range/mean ± SD	28–60/45.6 ± 9.4
disease duration (years)	
range/mean ± SD	4–23/12.2 ± 4.2
Baseline (n = 19)	
UPDRS III Off (/108)	44.5 ± 13.1
UPDRS III On (/108)	15.3 ± 6.7
UPDRS II Off (/52)	27.3 ± 7.1
UPDRS II On (/52)	6.2 ± 4.1
UPDRS I (/16)	2.3 ± 1.9
UPDRS IV (/23)	10.2 ± 3.6
dose of levodopa equivalent medication (mg/d)	
range/mean ± SD	625–3000/1133 ± 590
5 years (n = 10)	
UPDRS II Off (/52)	15.1 ± 6.1
UPDRS II On (/52)	12.3 ± 5.4
dose of levodopa equivalent medication (mg/d)	
range/mean ± SD	0–2300/678.6 ± 618.8

who could not or did not want to be undergo a formal evaluation at 5 years are presented in Table 2. As expected as the selection criteria were the same, both populations did not differ for the main clinical characteristics. In addition it is of great importance to note that all of the 10 patients (23.8 % of the total number of patients) who denied the formal four conditions for assessment are presently still stimulated with a substantial clinical benefit. In these patients the mean reduction of dopaminergic drugs was 40.2 % at 5 years. Finally we administered by phone call the UPDRS part II scale in off medication condition to compare it to the preoperative off UPDRS II score. This showed a 44 % reduction of this score compared to the baseline ($p = 0.0001$), which confirms the efficacy of the stimulation in this population. This is of great importance to avoid a major bias (i.e. the loss of follow-up of some patients) in the interpretation of the results presented below.

Clinical effects

Off-medication conditions

In the off-medication conditions, compared with preoperative off scores, STN stimulation reduced the total UPDRS motor score by 61 % and 55 %, respectively, at one and 5 years ($p = 0.0001$). The degree of improvement was not statistically different between the score at 1 and at 5 years ($p = 0.503$). This improvement was observed for all the UPDRS III subscores, except speech, at one year, and for some subscores at five years, with respect to baseline: for tremor (improvement: 82 % at 1 year ($p = 0.0002$); 74 % at 5 years ($p = 0.001$)); rigidity (improvement: 61 % at 1 year ($p < 0.0001$); 66 % at 5 years ($p < 0.0001$)), bradykinesia (improvement: 61 % at 1 year ($p = 0.0002$); 59 % at 5 years ($p < 0.0001$)), postural stability (improvement: 76 % at 1 year ($p = 0.0002$); 17 % at 5 years ($p = 0.48$)) and gait (improvement: 71 % at 1 year ($p = 0.0001$); 37 % at 5 years ($p = 0.003$). No significant improvement was noted for speech between baseline and 1 year ($p = 0.171$). Moreover speech worsened between 1 and 5 years ($p = 0.016$). Postural stability and gait were initially improved but worsened progressively from 1 year to 5 years after surgery (respectively, $p = 0.002$ for postural stability and $p = 0.006$ for gait). When stimulation was off, there was no difference between the preoperative UPDRS III score (43.11 ± 14.04) and the one at 1 (41.5 ± 9.5) ($p = 0.23$), and 5 years after surgery (45.9 ± 10.8) ($p = 0.43$).

As compared to baseline, STN stimulation induced a reduction of the UPDRS part II score (activities of daily living) of 57 % at 1 year ($p < 0.0001$) and of 38 % at 5 years ($p = 0.0001$). These results are presented in Table 3 and Figs. 1 and 2.

On-medication conditions

No difference was noted for the UPDRS III scores between the preoperative on medication condition and the postoperative on medication/on stimulation conditions ($p = 0.09$ at 1 year, and $p = 0.819$ at 5 years).

In off stimulation condition, the UPDRS III scores on medication progressively worsened between baseline (14.8 ± 9.8), 1 year (21.93 ± 13) and 5 years postoperative (26.2 ± 12). This increase was statistically significant between baseline and respectively 1 and 5 years (respec-

Table 3 Evolution of the UPDRS scores in Off medication condition

	Baseline	On-Stimulation Off-Medication	
	OFF Medication	1 year	5 year
UPDRS III (/108)	43.11 ± 14.04	16.93 ± 8.29	19.52 ± 7.17
tremor (/28)	4.61 ± 5.11	0.83 ± 1.34	1.22 ± 1.38
rigidity (/20)	10.26 ± 3.44	4.00 ± 2.24	3.48 ± 2.45
bradykinesia (/32)	15.74 ± 6.17	6.09 ± 3.65	6.43 ± 3.36
speech (/4)	1.30 ± 0.56	1.17 ± 0.78	1.65 ± 0.71
postural stability (/4)	1.26 ± 1.14	0.30 ± 0.56	1.04 ± 0.82
gait (/4)	2.00 ± 1.13	0.52 ± 0.59	1.26 ± 0.92
UPDRS II (/52)	21.65 ± 7.59	9.22 ± 4.99	13.40 ± 4.91

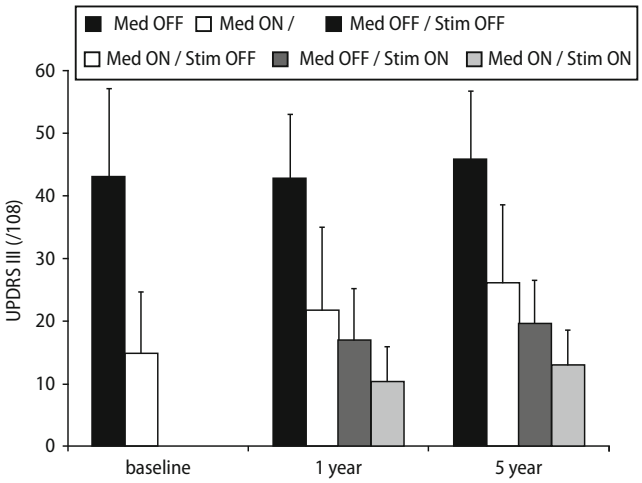

Fig. 1 Graph showing the evolution of the UPDRS motor score preoperatively and at 1 and 5 years postoperatively under different conditions (medication On or Off, stimulation On or Off). *Med On and Off* medication On and Off; *Stim On and Off* stimulation On and Off

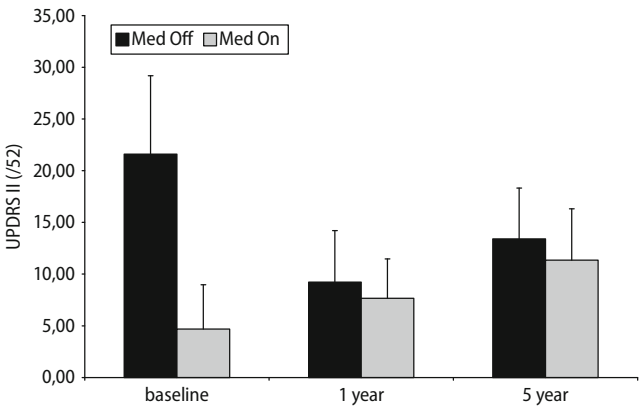

Fig. 2 Off-medication and on-medication UPDRS part II scores at baseline, and at 1 and 5 years after surgery. *Med On and Off* medication On and Off

tively p = 0.0003 and 0.0004) but also between 1 and 5 years (p = 0.0004). There was no significant change for rigidity subscore (p = 0.613), in contrary to that for tremor (0.71 ± 2.19 at baseline to 1.81 ± 2.89 at 5 years, p = 0.008), bradykinesia (4.86 ± 4.49 at baseline to 11.14 ± 6.31 at 5 years, p = 0.001), postural stability (0.33 ± 0.58 at baseline to 0.95 ± 0.8 at 5 years, p = 0.002), speech (0.70 ± 0.47 at baseline to 1.62 ± 0.67 at 5 years, p = 0.0009) and gait subscores (0.10 ± 0.30 at baseline to 0.95 ± 0.8 at 5 years, p = 0.001), which progressively worsened between baseline and five years.

The UPDRS part II score increased at 1 year and at 5 years postoperatively in on medication/on stimulation condition, compared with on medication preoperatively (p = 0.003 and p = 0.0002, respectively), and also between the first and fifth year (p = 0.008) (Fig. 2).

Motor fluctuations and dyskinesias (UPDRS IV score) were dramatically reduced by 85 % (p < 0.0001), and 60 % (p = 0.0001), respectively, at 1 and 5 years postoperatively.

The UPDRS part I score increased at 1 year and 5 years postoperatively compared to baseline. This increase was not stastically significant between preoperative and 1 year postoperative scores (p = 0.24), but difference became statistically significant between preoperative and 5 years postoperative scores (p = 0.0002). These results are presented in Table 4.

Neuropsychological evaluation

There were no significant changes on the Mattis Dementia Rating Scale (p = 0.84) or on the Beck Depression Inventory (p = 0.4), 1 and 5 years after surgery compared to baseline (Table 5).

Table 4 Evolution of the UPDRS scores in On medication condition

	Baseline	On-Stimulation On-Medication	
	Med ON	1 year	5 year
UPDRS III (/108)	14.83 ± 9.80	10.34 ± 5.47	13.17 ± 5.48
UPDRS I (/16)	0.83 ± 1.03	1.48 ± 1.72	2.57 ± 2.00
UPDRS II (/52)	4.70 ± 4.27	7.65 ± 3.82	11.35 ± 4.96
UPDRS IV (/44)	8.30 ± 2.79	1.24 ± 1.30	3.26 ± 3.15

Table 5 Neuropsychological examination

	Baseline	On-Stimulation	
		1 year	5 year
Mattis Dementia Rating Scale (/144)	137.48 ± 6.01	137.62 ± 5.99	134.30 ± 16.34
Beck Depression Inventory	9.59 ± 5.89	8.74 ± 6.39	11.47 ± 6.66

Medical treatment

STN stimulation allowed a reduction of 70.5 % ± 30.7 at 1 year and of 54.4 % ± 30.4 at 5 years of the total daily dose of dopaminergic drugs expressed as levodopa-equivalent dose [47] (levodopa-equivalent daily dose: 1188 ± 465 mg at baseline; 333.7 ± 375 mg at 1 year ($p < 0.0001$), 509 ± 344 mg at 5 years ($p < 0.0001$)). The antiparkinsonian drug intake increase between 1 and 5 years postoperatively ($p = 0.0009$). Only 1 of the 23 patients was free of antiparkinsonian medication at 5 years after the surgery, while 7 patients were free of medication at 1 year.

Stimulation parameters

At 5 years, all the patients were on chronic monopolar stimulation on one contact except 5 patients who were on two contacts on one lead. The frequency of stimulation was comprised between 60 and 185 Hz and the pulse width between 60 and 90 µs. One patient was stimulated at 60 Hz because of levodopa resistant freezing of gait that occurred 4 years after the beginning of the stimulation. This low frequency stimulation improved slightly gait disorders.

The mean (± SD) stimulation parameters at 5 years were 3.85 (± 4.41) V/67.8 (± 13.32) µs/139.1 (± 23.3) Hz.

Side effects

Related to the surgical procedure

One patient presented during lead implantation a left-sided intracerebral bleeding with a slight permanent residual aphasia. This patient was not followed at 5 years.

One patient presented a right paraventricular hematoma, without any sequellae.

Three patients had a staphylococcus aureus infection at the site of the stimulator or of the connector, which led to a complete removal of the system, followed by prolonged intravenous and oral antibiotic treatment over several weeks. Then the stimulator were reimplanted without any new infectious problem at least 6 months later.

Two cases of lower limbs phlebitis were reported in the immediate postoperative period, complicated by a pulmonary embolism in one case.

Related to the device

Two patients required a repositioning of one electrode because of a lack of efficacy or capsular side effects. This was performed within the first 6 months after the intital surgery. These two patients were not evaluated at 5 years (one died, and the other one was lost of follow-up).

The pulse generator was an Itrel II for the four first patients, and a Kinetra for the 19 other patients. The mean life duration of the pulse generator Kinetra was of 4.69 years and 11 stimulators had to be changed. No Itrel II was changed at 5 years. No migration of the electrode or fracture of the connector was observed.

Related to the stimulation and or the disease

Several patients experienced transient adverse effects during the setting of the electrical parameters. These side effects consisted of paresthesia (5/23), muscle contraction (5/23), ocular side effects such as conjugate eye deviation, torsional nystagmus, unilateral mydriasis and adduction (1/23). Dyskinesias could be elicited in most of the patients when stimulation intensity was increased. These adverse events could be suppressed by changing the contact of stimulation and/or by reducing the intensity of stimulation or decreasing the drugs (for dyskinesias).

One patient, as described above, without preoperative depression, committed suicide 6 months after the surgery. This patient presented the day after the surgery with pneumonia and atrial fibrillation and had never recovered his preoperative parkinsonian status.

Seven patients developed eyelid-opening apraxia and were treated by botulinum toxin injections.

Three patients experienced transient confusion or hallucination in the immediate postoperative period. They required a treatment by clozapine and recovered after 1 to 3 months.

Mood disorders occurred in 9 patients among the 23 followed at 5 years: Eight patients presented mild depression between 2 and 6 months after surgery and required antidepressant medication; 1 patient developed pure apathy that could be improved by increasing the amount of dopaminergic drug intake or by adding a dopamine agonist; 2 presented hypomania that occurred progressively within the first month after surgery and was not directly induced by the stimulation of a specific contact. This hypomania resolved progressively under clozapine that was maintained for several months after the surgery.

Three patients developed cognitive impairment and received anticholinesterase drugs. Several patients presented axial symptoms during the 5 years of follow-up. This included dysarthria ($n = 13$), freezing ($n = 9$) and imbalance ($n = 4$). Concerning the dysarthria it has to be mentioned that, among the 19 patients who were not followed-up at 5 years, one chose not to be stimulated because of STN stimulation induced dysarthria, which could not be suppressed except by using ineffective stimulation parameters.

Finally the mean weight gain was of 5 kg.

Discussion

Study limitation

Before discussing our results, we have to acknowledge that 45 % of the initial population could not be followed at 5 years. The reasons for this have been explained in the Results section. 23.8 % of the patients declined to be formally assessed either because they lived far away from the hospital, or more often because they did not want to be in Off medication/Off stimulation condition. In order to avoid a bias in the interpretation of our data we have presented the main clinical characteristics of this population of patients not followed at 5 years showing that they did not differ from the rest of the patients. In addition, these patients are still followed in our center with a significant clinical benefit of the stimulation as shown by the UPDRS part II scores obtained by phone interview.

The present study demonstrates that the beneficial effects of STN stimulation in PD are preserved 5 years after the surgery. Most of the so-called long-term studies have analyzed 2 to 3 years follow-up but only three have considered longer duration of follow-up (up to 5 years) [18, 23, 24, 26, 28, 36, 38, 39, 41, 49, 50, 52]. All these studies including the present one have demonstrated that the effects of STN stimulation are sustained over time. In the present study the mean improvement of motor symptoms off medication assessed by the UPDRS part III score was of 55 % at 5 years, which fits well with what was observed by other teams [18, 23, 24, 26, 28, 36, 38, 39, 41, 49, 50, 52]. A similar degree of improvement was found in short-term studies [1, 4, 6, 9, 12, 15, 21, 25, 27, 29–34, 37, 43–45, 51]. Overall a recent meta-analysis showed that the STN stimulation leads to a mean improvement of motor symptoms (assessed by the UPDRS III score) of 52.3 % [24]. The motor improvement concerns all the aspects of the parkinsonian triad and allowed a major reduction of dopaminergic drugs of 54 %, which in turn leads to a decrease of dyskinesias.

The reduction of the drug intake observed in the present study was comparable to the 55.9 % noted on average in other series [18, 23, 24, 26, 28, 36, 38, 39, 41, 49, 50, 52].

On the other hand, the present study does not support a potential effect of STN stimulation on disease progression. Indeed a deterioration of UPDRS part III score On medication as well as a worsening of gait, postural stability and dysarthria were observed. In addition, some cases of cognitive decline occurred. This worsening of the on medication motor signs in the long-term follow-up has been found by other teams and probably reflects the natural evolution of PD [7, 17, 26, 35, 38, 41, 49, 52]. However one may observe that the total UPDRS motor score in off medication/off stimulation condition at 5 years was not significantly different from the preoperative off medication UPDRS motor score ($p = 0.445$), which could be interpreted as an absence of disease progression. However, this does not exclude disease progression as a "real" off state cannot be obtained after only 12 hours of antiparkinsonian withdrawal and half an hour after the stimulation has been turned off.

The side effects related to the surgical procedure or to the device were rare. However, they exist and the pros and cons aspects of the procedure have clearly to be explained to the patients before they can make a decision regarding the surgery. Among the 42 patients, 2 brain haemorrhages (4.8 %), 3 infections of the device (7.1 %) and 2 lead misplacements (4.8 %) were observed. These percentages are consistent with those reported in meta-analysis [2, 24, 53]. We did not observe any seizures, which is a rare complication of this kind of surgery [24]. The side effects directly induced by the stimulation during parameters setting were mild and easily suppressed by adjusting these parameters or changing the contact of stimulation.

Among the long lasting side effects, special interest has recently been given to the mood disorders that may occur after STN stimulation. In our series, the rate of depression, apathy, manic episodes were of 39 %, 4 % and 9 %, respectively. The percentage of depression is higher than in other series, which deserves some commentaries. Indeed in a recent meta-analysis the frequency of confusion/delirium, depression, mania and apathy were quoted as 4–8 %, 2–4 %, 0.9–1.7 %, 0.3–0.6 %, respectively [2]. Although the severity of the depression was usually mild in our series, one patient committed suicide after the surgery, which is obviously the consequence of severe depression. For this patient, depression could have been the consequence, as mentioned in the Results section, of post-operative complications leading to a loss of its preoperative motor status. In our study the cut-off of 20 for the BDI exclusionary score if higher than in some other series, which may explain at least by part our results. Another explanation is that depression can be isolated or associated with apathy and that pure apathy may have been misinterpreted as depression in the present study. However, one has to be cautious with the interpretation of the rate of depression observed in the present series, as no formal assessment of the depression was performed, this diagnosis being "only" made by a general clinical impression. In a long-term study, Funkiewiez et al. (2004) noted 1 case of permanent apathy, 1 severe depression and 5 hypomania among 77 patients followed at 3 years after the surgery. The dopaminergic drug reduction could at least partly participate to the occurrence of apathy [54]. However, other data suggest that STN stimulation by itself has a positive effect on the apathy and does not induced this change of behavior [8]. Thus it is likely that only some specific subpopulation of patients are at greater risk to develop post-operative apathy, such as those receiving

the highest dose and being addict to dopaminergic drugs. Permanent apathy can also be related to cognitive decline that occurred in three cases in our study. However strong evidence have demonstrated that the occurrence of dementia is not related to the stimulation itself, which is safe on a cognitive point of view, but rather to disease progression [2, 3, 7, 17].

Dysarthria is the second most frequent secondary side effect encountered in our study, which is in line with meta-analysis showing this side effect in 9.3 % of the patients [24]. Stimulation spreading to the internal capsule may be the explanation and a reduction of stimulation parameters can reverse this dysarthria. However, in our population one patient decided not to be stimulated because he could not tolerate the dysarthria despite clear benefits on the other motor symptoms. Interestingly this patient was not as severe as the others, which indicates that this specific side effect has to be explained before and monitored after the surgery if STN stimulation is proposed (as this is done more and more frequently) at earlier stage of the disease [42]. On the other hand the progressive worsening of dysarthria in the long term is more likely to be a sign of disease progression that cannot be modified by changes of medication or adjustment of stimulator.

The present study confirms that 1) bilateral STN stimulation remains the best alternative to medical treatment for advanced PD and 2) STN stimulation leads to a major improvement of the patients that persists in the long term even if the disease worsens.

Conflict of interest The authors declare no conflict of interest.

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