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Clinical predictive factors of subthalamic stimulation in Parkinson's disease

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Summary

High-frequency stimulation of the subthalamic nucleus (STN) constitutes one of the most effective treatments for advanced forms of Parkinson's disease. The cost and potential risks of this procedure encourage the determination of clinical characteristics of patients that will have the best postoperative outcome. Forty-one Parkinson's disease patients underwent surgery for bilateral STN stimulation. The selection criteria were severe parkinsonian motor disability, clear response of symptoms to levodopa, occurrence of disabling levodopa-related motor complications and the absence of dementia and significant abnormalities on brain MRI. Clinical evaluation was performed 1 month before and 6 months after surgery. The improvement in the activities of daily living subscale of the Unified Parkinson's Disease Rating Scale, Part II (UPDRS II) and parkinsonian motor disability (UPDRS III) was greater when the preoperative scores for activities of daily living and parkinsonian motor disability, in particular axial symptoms, such as gait disorders and postural instability assessed at the time of maximal clinical improvement (on drug), were lower. Age and disease duration were not predictive, but parkinsonian motor disability tended to be more improved in patients with younger age and shorter disease duration. The severity of levodopa-related motor complications was not a predictive factor. The outcome of STN stimulation was excellent in levodopa-responsive forms of Parkinson's disease, i.e. in patients with selective brain dopaminergic lesions, and moderate in patients with axial motor symptoms and cognitive impairment known to be less responsive or unresponsive to levodopa treatment, i.e. when brain non-dopaminergic lesions develop in addition to the degeneration of the nigrostriatal dopaminergic system. The results are consistent with the classical inclusion criteria for STN stimulation, but imply that the decision to operate on the oldest patients and/or patients with gait and postural disorders, who are poorly responsive to levodopa, should be weighed carefully.

Keywords: Parkinson's disease; high-frequency stimulation; subthalamic nucleus; predictive factors

Abbreviations: ADL = activities of daily living; MADRS = Montgomery–Åsberg Depression Rating Scale; STN = subthalamic nucleus; UPDRS = Unified Parkinson's Disease Rating Scale

Introduction

Although substitutive treatment with levodopa and dopaminergic agonists remains the most effective treatment for Parkinson's disease (Lang and Lozano, 1998), long-term clinical benefit for patients is fraught with disabling adverse reactions, including motor and psychic complications. Continuous bilateral high-frequency stimulation of the subthalamic nucleus (STN) is an increasingly popular neurosurgical technique that decreases the severity of parkinsonian motor disability and levodopa-induced motor complications by 60–80% and the daily dose of levodopa required by 40–80% (Limousin *et al*., 1998; Moro *et al*., 1999; Houeto *et al*., 2000; Molinuevo *et al*., 2000). Bilateral high-frequency STN stimulation is effective in Parkinson's disease patients with a levodopa-responsive form of the disease who have disabling on–off phenomena and levodopa-induced dyskinesia in the absence of contraindications (dementia, psychiatric disorders, abnormal brain MRI) (Lang, 2000). However, the inclusion criteria that are used for STN stimulation remain imprecise. In particular, the influences of age and duration of the disease (Krack

et al., 1998*a*) and the contributions of the various parkinsonian symptoms (Limousin *et al*., 1998; Bejjani *et al*., 2000*a*) have not been evaluated precisely. This study was undertaken to identify which preoperative clinical variables were predictive of the best postoperative clinical improvement in Parkinson's disease patients treated by bilateral STN stimulation.

Patients and methods

Patients

We studied 41 Parkinson's disease patients (26 men and 15 women) who underwent surgery for the bilateral placement of stimulating electrodes within the STN between January 1996 and February 2000. The inclusion criteria for surgery were as follows: (i) age under 70 years at the time of surgery (mean age 56.4 ± 8.6 years), except for two women aged 71 and 74 years; (ii) advanced form of the disease [mean Hoehn and Yahr 'off' score (Hoehn and Yahr, 1967) 4.3 ± 0.8] with a disease duration <25 years (mean 16 ± 5 years); (iii) >40% response of motor symptoms to levodopa treatment (mean improvement 72 ± 15%); (iv) occurrence of severe levodopa-related motor complications despite optimal adjustment of antiparkinsonian medication (mean daily dose of levodopa equivalent 1459 ± 600 mg/day) (Lozano *et al*., 1995); (v) absence of severe cognitive impairment [mean Mattis Dementia Rating Scale (Mattis, 1988) 137 ± 9, mean 'frontal' score (Pillon *et al*., 2000) 40.7 ± 10.7]; (vi) absence of depression [assessed in only 36 patients: mean Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) 10 ± 6]; and (vii) absence of corticosubcortical lesions such as severe atrophy, leucoencephalopathy and multiple lacunae on brain MRI. All patients gave informed written consent according to the Declaration of Helsinki and the protocol was approved by the local ethical committee of the Groupe Hospitalier Pitié-Salpêtrière.

Neurosurgical procedure

The neurosurgical procedure was performed as described previously (Bejjani *et al*., 2000*b*). The electrodes were implanted under local anaesthesia during a single operative session, using a combined approach of intraoperative recording and stimulation. The definitive quadripolar electrodes (model 3389-28; Medtronic, Minneapolis, Minn., USA) were implanted bilaterally and connected to a subcutaneous programmable pulse generator (Itrel II, $n = 37$; Kinetra, $n = 4$; Medtronic) in the subclavicular area. Electrical parameters (pulse width, frequency and voltage) were adjusted progressively using an electromagnetic programmer (7532 neurological programmer; Medtronic).

Clinical evaluation

Evaluation of patients was performed 1 month before and 6 months after surgery. Activities of daily living [ADL; Unified Parkinson's Disease Rating Scale (UPDRS) Part II] (Fahn *et al*., 1987) were scored during an interview evaluating the state of patients in the 'off' and 'on' drug conditions. The percentage improvement in ADL was determined in respect of the preoperative ADL 'off' drug condition. Before surgery, evaluation of the motor disability score (UPDRS Part III) (Fahn *et al*., 1987) was performed in the 'off' state as defined by the Core Assessment Program for Surgical Interventional Therapy (CAPIT) in Parkinson's disease (Langston *et al*., 1992), i.e. after an interruption of at least 12 h in antiparkinsonian medication, and in the best 'on' drug condition ('residual' motor disability score) after the administration of a single suprathreshold dose of levodopa (50 mg higher than the usual effective dose taken in the morning). The 'axial' score was defined as the sum of the following motor subscores: speech, gait, posture, postural stability (items 18, 28, 29 and 30 of the UPDRS Part III). The axial score was assessed in the same 'off' and 'on' drug conditions. After surgery, the parkinsonian motor disability score (UPDRS Part III) was evaluated in four conditions: (i) 'off' stimulation and 'off' drug after a night without drug treatment and after stimulation had been switched off for 12 h (first 27 patients) or for at least 1.5 h (14 patients); (ii) 'on' stimulation and 'off' drug, after stimulation had been switched on for at least 1 h; (iii) 'off' stimulation and 'on' drug after stimulation had been switched off for at least 1 h and after the administration of a suprathreshold dose of levodopa (equivalent to the preoperative dose); (iv) 'on' stimulation and 'on' drug after stimulation had been switched on using the chronic stimulation parameters. For each condition, evaluation was performed the same day and in the same order in all patients. The percentage improvement in motor disability was determined in respect of the preoperative 'off' drug condition. Levodopa-related complications were evaluated using the UPDRS Part IV (Fahn *et al*., 1987), including the duration of motor fluctuations (item 39) and levodopa-induced dyskinesias (item 32).

Statistical analysis

The effects of continuous bilateral STN stimulation on parkinsonian symptoms were evaluated using a paired Student's *t*-test to compare scores obtained before and after surgery. To determine the effects of age and disease duration on the postoperative clinical outcome, we chose the mean age and mean disease duration as cut-off points for the population and we assessed the postoperative clinical improvement using a non-parametric test, the Mann–Whitney test. To determine which preoperative clinical characteristics (age, disease duration, neuropsychological evaluation, ADL and motor disability and axial scores) were predictive of the clinical outcome after surgery, we first performed a univariate

Table 1 *Effects of continuous bilateral high-frequency stimulation of the STN in 41 patients with Parkinson's disease*

	Before surgery		After surgery			
	Off drug	On drug	Off stimulation		On stimulation	
			Off drug	On drug	Off drug	On drug
Hoehn and Yahr score	4.3 ± 0.8	2.3 ± 1.1* (48)	NA	NA	1.7 ± 1.2*† (61)	1.0 ± 1.2*†‡(77)
UPDRS II	29 ± 8.8	10.4 ± 8.3* (66)	NA	NA	11.1 ± 7.4* (61)	6.6 ± 5.8*†‡(77)
UPDRS III	51.4 ± 18.6	14.7 ± 10.5* (72)	45.4 ± 18*	18.1 ± 13.1* (64)	18.5 ± 14.5* (65)	10.6 ± 10.3*†‡(80)
Axial score	12 ± 4.2	4.1 ± 2.5* (68)	7.5 ± 3.2*	3.5 ± 3.1* (73)	3.7 ± 3.2* (72)	2.3 ± 2.4*†‡(83)
Levodopa equivalent (mg/day)	–	1459 ± 600		–	–	480 ± 435†(68)
Motor fluctuations	–	2.1 ± 0.8		–	–	0.2 ± 0.4†(87)
Levodopa-induced dyskinesias	–	2.1 ± 0.9		–	–	0.5 ± 0.6†(69)
UPDRS IV	–	12.3 ± 2.9		–	–	2.5 ± 2.3†(78)

Values are mean ± standard deviation. Values in parentheses are percentage improvement compared with the 'off' drug condition before surgery. NA = not available. *$P < 0.05$ compared with the 'off' drug condition before surgery; †$P < 0.05$ compared with the 'on' drug condition before surgery; ‡$P < 0.05$ compared with the 'on' stimulation, 'off' drug condition after surgery.

analysis Pearson correlation test with a threshold of 0.0023 to prevent false positive results (Bonferroni correction). Variables relating to improvement after surgery were included in stepwise multiple linear regression with the same threshold. Statistical analysis was performed with the SAS statistical software package, version 6.12 (SAS Institute, Cary, NC, USA).

Results

Effects of continuous bilateral stimulation of the STN on parkinsonian motor disability (Table 1)

Before surgery, antiparkinsonian drug treatment improved the ADL score (UPDRS II) by 66%. Six months after surgery, the ADL score was improved by 61% when patients were under continuous STN stimulation without drug treatment ('on' stimulation, 'off' drug). The combination of STN stimulation and levodopa treatment ('on' stimulation, 'on' drug) induced a greater improvement in the ADL score (+77%) than that obtained preoperatively with the medical treatment (Table 1). Before surgery, there was a 72% improvement in parkinsonian motor disability (UPDRS III) at the time of maximal clinical improvement following the administration of levodopa. Six months after surgery, the motor disability score was improved by 64% following the administration of levodopa alone ('off' stimulation, 'on' drug condition) and by 65% under STN stimulation alone ('on' stimulation, 'off' drug condition). The combination of STN stimulation with levodopa administration induced a greater motor improvement (+80%) than that obtained with levodopa alone, either preoperatively or postoperatively, or with stimulation alone. Before surgery, there was a 68% levodopa-induced improvement in the axial motor score. After surgery, the axial score was improved by 73% when the patient was in the 'off' stimulation, 'on' drug condition. The combination of STN stimulation and levodopa administration induced a greater improvement of the axial score (+83%). Following STN stimulation, the levodopa-equivalent doses were decreased by 68%, whereas the scores for the duration of motor fluctuations, levodopa-induced dyskinesias and UPDRS IV were improved by 87, 69 and 78%, respectively.

Predictive factors for bilateral subthalamic stimulation: correlation between the characteristics of patients before and after surgery

Influence of age and disease duration on parkinsonian motor disability and ADL evaluated after surgery

No significant correlation was found between age at the time of surgery or disease duration and the postoperative clinical outcome (univariate analysis and multiple stepwise regres-

Table 2 *Effects of age and disease duration on clinical outcome after neurosurgery*

After surgery	Age (years)		Disease duration (years)	
	<56†	⩾56‡	<16§	⩾16¶
Activities of daily living (ADL = UPDRS II)				
Residual scores				
On stimulation, off drug	8.3 ± 5.9	13.3 ± 7.8*	9.6 ± 7.2	12.6 ± 7.5
On stimulation, on drug	4.7 ± 2.8	8.0 ± 7.0	4.7 ± 4.2	8.5 ± 6.6*
Improvement (%)				
On stimulation, off drug	70.6 ± 17.1	53.3 ± 27.3*	64.5 ± 23	57 ± 26.4
On stimulation, on drug	83.6 ± 8.0	72.2 ± 21.6	82.5 ± 14.9	71.7 ± 19.6*
Motor disability (UPDRS III)				
Off stimulation, off drug	42.3 ± 21.9	47.9 ± 14.4	41.4 ± 17.4	49.7 ± 18.2
Residual scores				
On stimulation, off drug	16.9 ± 17.9	19.7 ± 11.6	16.1 ± 15.7	21 ± 13.1
On stimulation, on drug	7.2 ± 8.0	13.1 ± 11.1*	6.9 ± 6	14.4 ± 12.3*
Improvement (%)				
On stimulation, off drug	70.6 ± 24.7	60.0 ± 18.0*	67.6 ± 24.4	61.6 ± 18.4
On stimulation, on drug	86.7 ± 11.8	74.8 ± 16.7*	85.9 ± 9.5	73.8 ± 18.6*
Axial score**				
Off stimulation, off drug	6.6 ± 3.5	8.2 ± 2.8	6.8 ± 3.1	8.2 ± 3.1
Residual scores				
On stimulation, off drug	2.8 ± 3.0	4.4 ± 3.3*	2.9 ± 3.2	4.5 ± 3.1
On stimulation, on drug	1.5 ± 1.7	2.9 ± 2.8	1.5 ± 1.8	3.2 ± 2.7*
Improvement (%)				
On stimulation, off drug	78.7 ± 20.5	66.4 ± 25.2	75.5 ± 24.1	68 ± 23.2
On stimulation, on drug	88.7 ± 11.6	78.3 ± 20.9	87 ± 16.1	78.3 ± 19.3

*$P < 0.05$ (Mann–Whitney analysis); †$n = 18$; mean age 48.4 ± 5 years, mean disease duration 13.6 ± 3.05 years; ‡$n = 23$; mean age 62.3 ± 4.9 years, mean disease duration 18.3 ± 5.3 years; §$n = 21$; mean age 52.9 ± 7.6 years, mean disease duration 12.2 ± 2.2 years; ¶$n = 20$; mean age 60.1 ± 8.3 years, mean disease duration 20.4 ± 3.8 years; **see Patients and methods.

sion), although there was a tendency for statistical significance for some parameters [motor disability score in the 'on' stimulation, 'on' drug condition and age or disease duration ($P < 0.005$ and $P < 0.007$, respectively)] (results not shown). This led us to separate patients aged ⩾56 years from those aged <56 years at the time of neurosurgery. Six months after surgery, the postoperative residual ADL ('on' stimulation, 'off' drug), motor disability ('on' stimulation, 'on' drug) and axial scores ('on' stimulation, 'off' drug) were lower (Table 2) and the percentage improvements in ADL ('on' stimulation, 'off' drug) and motor disability ('on' stimulation, 'off' and 'on' drug) scores were greater in young patients (Table 2). When patients were distinguished according to disease duration ⩾16 versus <16 years, we found the postoperative residual ADL, motor disability and axial scores ('on' stimulation, 'on' drug) to be significantly lower (Table 2) and the percentage improvement in ADL and motor disability ('on' stimulation, 'on' drug) scores to be significantly greater in patients with shorter disease durations (Table 2).

Influence of patients' preoperative clinical characteristics on ADL evaluated after surgery

There was no correlation between either the residual ADL score or the percentage improvement in ADL score ('on' stimulation, 'off' and 'on' drug) assessed after surgery and the following parameters evaluated before surgery: ADL score, percentage improvement in ADL score, severity of levodopa-related complications (UPDRS IV, duration of levodopa-induced dyskinesias and motor fluctuations) (not shown), the Mattis and MADRS scores and the levodopa-equivalent doses (Table 3). The residual ADL scores ('on' stimulation) assessed after surgery were positively correlated with the preoperative residual motor disability and axial scores ('on' drug) and negatively correlated with the 'frontal' score (Table 3). The percentage improvement in the ADL score under STN stimulation alone ('on' stimulation, 'off' drug) was negatively correlated with the levodopa-equivalent doses (Table 3). The percentage improvement in the ADL score under the combination of STN stimulation with drug treatment ('on' stimulation, 'on' drug) was negatively correlated with the preoperative residual motor disability score ('on' drug) (Table 3), the preoperative percentage improvement in motor disability score (not shown) and the preoperative levodopa-equivalent doses (Table 3).

Influence of patients' preoperative clinical characteristics on parkinsonian motor disability evaluated after surgery

There was no correlation between either postoperative motor disability scores (UPDRS III) ('off' stimulation, 'off' drug

Table 3 *Correlation coefficients of parkinsonian motor disability (UPDRS III), axial score and mental status evaluated before surgery with ADL and motor disability after STN stimulation*

After surgery	Before surgery								
	Motor disability		Residual axial scores on drug			Neuropsychological status		MADRS	Levodopa-equivalent dose
	Off drug	Residual on drug	Global	Gait	Postural stability	Mattis score	Frontal score		
ADL (UPDRS II)									
Residual scores									
On stimulation, off drug	0.38	**0.47***†	0.42	0.34	0.25	–0.36	–0.36	0.37	0.40
On stimulation, on drug	0.27	**0.66***†	**0.47***	0.30	0.45	–0.25	**–0.48***	0.22	0.39
Improvement (%)									
On stimulation, off drug	–0.04	–0.24	–0.23	–0.32	–0.06	0.30	0.29	–0.26	**–0.47***†
On stimulation, on drug	0.01	–0.47	–0.35	–0.30	–0.29	0.19	0.44	–0.15	**–0.47***†
Motor disability (UPDRS III)									
Off stimulation, off drug	**0.55***†	0.38	0.47	0.40	0.40	–0.35	–0.14	0.04	0.02
Residual scores									
On stimulation, off drug	**0.54***†	**0.49***	**0.47***	0.38	0.33	–0.30	–0.23	0.12	0.18
On stimulation, on drug	0.46	**0.74***†	**0.73***	**0.73***†	**0.63***	**–0.60***	**–0.59***	0.15	–0.01
Improvement (%)									
On stimulation, off drug	–0.09	–0.25	–0.36	–0.40	–0.23	0.13	0.19	–0.13	–0.25
On stimulation, on drug	–0.11	**–0.58***	**–0.69***	**–0.77***†	**–0.58***	0.40	**0.57***	–0.12	–0.02
Axial score**									
Off stimulation, off drug	0.37	0.37	**0.57***†	**0.54***	**0.48***	–0.24	–0.19	0.14	0.15
Residual scores									
On stimulation, off drug	0.44	**0.48***	**0.65***†	**0.56***	**0.54***	–0.31	–0.28	0.24	0.22
On stimulation, on drug	0.25	**0.52***	**0.63***	**0.62***†	**0.67***†	–0.43	–0.37	0.15	0.13
Improvement (%)									
On stimulation, off drug	–0.22	–0.26	**–0.55***†	–0.47	**–0.48***	0.19	0.17	–0.23	–0.30
On stimulation, on drug	–0.12	–0.34	**–0.55***	**–0.58***	**–0.61***†	0.37	0.27	–0.11	–0.12

Entries shown in bold = *$P < 0.0023$ after univariate analysis (Pearson linear correlation); †$P < 0.023$ after multivariate analysis (stepwise multiple regression analysis). See Patients and methods.

Table 4 *Correlation coefficients of parkinsonian motor disability (UPDRS III), axial score and mental status evaluated before surgery with levodopa-related complications and levodopa-equivalent dose assessed after surgery*

After surgery	Before surgery								
	Motor disability		Residual axial scores on drug			Neuropsychological status		MADRS	Levodopa-equivalent dose
	Off drug	Residual on drug	Global	Gait	Postural stability	Mattis score	Frontal score		
Levodopa related complications									
Motor fluctuations									
Duration	**0.50***	0.20	0.21	0.02	0.02	–0.16	–0.15	0.41	0.28
Improvement (%)	**–0.56***	–0.23	–0.25	–0.14	–0.05	0.36	0.27	–0.44	–0.14
Levodopa-induced dyskinesias									
Duration	–0.01	–0.25	–0.22	–0.36	–0.31	0.23	0.27	0.13	0.26
Improvement (%)	0.13	0.21	0.16	0.22	0.25	–0.24	–0.28	–0.09	–0.27
UPDRS IV									
Global	0.23	0.01	0.16	–0.02	–0.01	0.13	0.08	0.40	0.43
Improvement (%)	–0.16	–0.04	–0.06	0.05	0.07	–0.17	–0.16	–0.21	–0.38
Levodopa-equivalent									
Dose per day (mg)	0.32	0.12	0.14	0.01	–0.02	0.10	0.04	0.25	**0.48***
Decrease (%)	–0.42	–0.12	–0.20	–0.15	–0.11	0.03	0.04	–0.37	–0.09

Entries shown in italics = $*P < 0.0023$ after univariate analysis (Pearson linear correlation). **See Patients and methods.

and 'on' stimulation, 'off' drug) or the percentage improvement in motor disability ('on' stimulation, 'off' and 'on' drug) and the following parameters evaluated before surgery: levodopa-related complications (UPDRS IV; not shown), MADRS score and levodopa-equivalent doses (Table 3).

The postoperative residual motor disability score under STN stimulation alone ('on' stimulation, 'off' drug) was positively correlated with the 'off' drug motor disability score (UPDRS III) and the residual motor disability and axial scores ('on' drug) assessed before surgery. The postoperative residual motor disability score under both STN stimulation and drug treatment ('on' stimulation, 'on' drug) was positively correlated with the preoperative residual ADL, motor disability, axial, posture, gait and postural stability scores ('on' drug), and negatively correlated with the Mattis and frontal scores.

No correlation was found between the percentage improvement in motor disability score under STN stimulation alone ('on' stimulation, 'off' drug) and the preoperative clinical characteristics. The percentage improvement in motor disability under the combination of STN stimulation with drug treatment ('on' stimulation, 'on' drug) was negatively correlated with the preoperative residual ADL, motor disability, axial, posture, gait and postural stability scores ('on' drug) and positively correlated with the frontal score (Table 3).

In summary, the lower the parkinsonian motor disability during the best 'on' period (in particular gait disorders) and the higher the neuropsychological status (in particular frontal aptitudes) were before surgery, the greater the improvement in parkinsonian motor disability after surgery. In other words, the efficacy of STN stimulation on parkinsonian motor disability was dependent upon the ability of levodopa treatment to improve parkinsonian motor disability and axial symptoms before surgery.

Influence of patients' preoperative clinical characteristics on parkinsonian axial motor symptoms evaluated after surgery

There was no correlation between either the postoperative axial motor scores ('off' and 'on' stimulation) or percentage improvement in axial symptoms under STN stimulation ('on' stimulation, 'off' and 'on' drug), and levodopa-related complications before surgery (not shown), MADRS, Mattis and frontal scores and the levodopa-equivalent doses before surgery (Table 3).

The postoperative residual axial score under STN stimulation alone ('on' stimulation, 'off' drug) was positively correlated with the preoperative residual ADL, motor disability, axial, posture, gait and postural stability scores ('on' drug). The postoperative residual axial score under the combination of STN stimulation with drug treatment ('on' stimulation, 'on' drug) was positively correlated with the same preoperative scores (Table 3).

The percentage improvement in the axial motor score under STN stimulation alone ('on' stimulation, 'off' drug) was negatively correlated with the preoperative residual axial and postural stability scores ('on' drug). The percentage improvement in the axial score under STN stimulation and drug treatment ('on' stimulation, 'on' drug) was negatively correlated with the preoperative residual ADL, axial, gait and postural stability scores ('on' drug) (Table 3).

In summary, the less severe the axial motor symptoms assessed under levodopa treatment before surgery (in particular gait disorders and postural instability), the greater the improvement in axial motor disability after surgery. In others words, the efficacy of STN stimulation on axial motor symptoms can be predicted from the assessment of axial motor symptoms during the best 'on' period before surgery.

Influence of patients' preoperative clinical characteristics on levodopa-related complications and levodopa treatment evaluated after surgery

There was no correlation between the severity of levodopa-related complications (motor fluctuations, levodopa-induced dyskinesias, UPDRS IV) or levodopa-equivalent doses after surgery, and ADL score, levodopa-related complications (not shown), residual axial scores, neuropsychological status and the MADRS score before surgery (Table 4).

The duration of motor fluctuations after surgery was positively correlated with the 'off' drug motor disability score before surgery. The percentage improvement in the duration of motor fluctuations was negatively correlated with the 'off' drug motor disability score before surgery.

The levodopa-equivalent doses after surgery were positively correlated with the levodopa-equivalent doses before surgery.

In summary, the efficacy of STN stimulation on levodopa-related complications was independent of the severity and duration of these motor complications evaluated before surgery.

Discussion

This study was undertaken to try to define predictive factors for the outcome of treatment for Parkinson's disease by continuous bilateral stimulation of the STN. In this group of 41 patients, who were rigorously selected on classical but empirical criteria (see Patients and methods), we found that the outcome of neurosurgery was influenced partly by the age of the patients and the duration of the disease and was markedly dependent upon whether the parkinsonian motor symptoms responded to levodopa treatment. The severity of axial motor symptoms evaluated at the time of maximal clinical improvement under levodopa treatment ('on' drug), in particular the levels of gait disorders and postural instability, was a highly

effective predictive factor, whereas the severity of levodopa-induced complications was not.

Influence of age and duration of the disease

Age tended to be significantly correlated with the effectiveness of STN stimulation ($P < 0.005$, Pearson correlation test) and older patients were less improved than younger patients (Table 2), which is in agreement with a previous report (Kumar *et al*., 1998). The conjunction of a lesser improvement after surgery with a higher risk of postoperative complications (Kumar *et al*., 1998; Saint-Cyr and Trepanier, 2000) and social maladjustment suggests that the decision to operate in such patients should be weighed carefully. There was also a tendency for patients with a longer disease duration to be less improved by surgery ($P < 0.007$, Pearson correlation test) (Table 2), suggesting that STN stimulation might be envisaged at an earlier stage of the disease. However, whether this might be worthwhile remains to be confirmed prospectively.

The reason why the efficacy of STN stimulation seems to diminish with patient age and disease duration is unknown. Assuming that the clinical benefit induced by STN stimulation is similar to that observed with levodopa treatment (Pollak *et al*., 1996; Pinter *et al*., 1999*a*, *b*), the mechanism responsible for it may be similar to the mechanism underlying the effect of levodopa treatment, which is also known to lose efficacy progressively with age (Blin *et al*., 1991) and disease duration (Bonnet *et al*., 1987).

Influence of the characteristics of parkinsonian motor symptoms and levodopa treatment

The efficacy of neurosurgery was not dependent upon the severity of parkinsonian motor disability, assessed preoperatively in the absence of levodopa treatment ('off' drug) (Table 4). The best predictive factors were a good response to levodopa, in particular when the residual motor disability score (especially gait disorders and postural instability) was low ('on' drug) (Tables 3 and 4). This confirms that bilateral STN stimulation in Parkinson's disease patients who are good responders to levodopa results in motor improvement mimicking the effects produced by levodopa (Pollak *et al*., 1996; Krack *et al*., 1998*b*; Pinter *et al*., 1999). Bilateral stimulation of the STN, therefore, seems to have the same effects downstream from the lesions of the dopaminergic nigrostriatal system as the re-establishment of normal dopaminergic transmission in the striatum of patients. The fact that the severity of the residual parkinsonian motor score in the 'on' drug condition and, especially, the axial motor score (known to be less responsive to levodopa treatment) were predictive of a poor postoperative outcome is probably explained by the presence of non-dopaminergic lesions within the basal ganglia, in addition to the characteristic degeneration of the dopaminergic nigrostriatal pathway (Agid, 1991). In line with this suggestion is the relative failure of STN stimulation in the treatment of other parkinsonian syndromes, such as multiple system atrophy (Pinter *et al*., 1999) and vascular parkinsonism (Krack *et al*., 2000), which are characterized by the presence of additional non-dopaminergic lesions in the brain. Taken together, these results stress the importance of the levodopa test, performed before surgery, for the accurate evaluation of the levodopa-responsive motor score (difference between the 'off' drug and 'on' drug parkinsonian motor scores), which reflects the severity of the degeneration of the nigrostriatal system, and the residual motor score ('on' drug), which reflects the severity of the non-dopaminergic lesions. Our data provide firm evidence in favour of excluding from neurosurgery patients with axial motor symptoms that respond poorly or not at all to levodopa, in particular gait disorders and postural instability, the severities of which are known to increase during the course of the disease (Bonnet *et al*., 1987).

Influence of dopaminergic treatment and related motor complications on the outcome of neurosurgery

The improvement of parkinsonian symptoms by STN stimulation was not related to the severity of levodopa-induced motor complications evaluated before surgery (Table 4). This indicates that, theoretically, the decision to operate should be based on the existence, rather than the severity, of levodopa-related fluctuations in motor performance and levodopa-induced dyskinesias. The severity of these motor complications is nevertheless taken into account when deciding whether to include patients for neurosurgery, as it constitutes a major factor in disability.

Patients receiving high doses of levodopa before neurosurgery also required a high daily intake of levodopa after the operation (Table 4). It is unlikely that lack of improvement in parkinsonian motor disability can explain this observation, as motor symptoms were markedly improved by STN stimulation alone (Table 1), even when the levodopa treatment was reduced (not shown). The high doses of levodopa still being taken by some patients postoperatively, despite motor improvement, might have contributed to the persistence of adverse motor reactions, causing persistent impairment in ADL (Table 3).

Conclusion

Our results confirm the efficacy of continuous bilateral high-frequency stimulation of the STN in a levodopa-responsive form of Parkinson's disease and suggest that age, long disease duration and residual axial motor symptoms that have a low level of responsiveness to levodopa treatment, in particular

gait disorders and postural instability, are factors contributing to an unfavourable motor outcome of neurosurgery. Other factors may contribute to the outcome of neurosurgery, and the issue of quality of life, which was not evaluated in the present study, remains to be addressed.

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