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Dorsal Subthalamotomy for Parkinson's Disease

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Abstract: We report our experience of unilateral subthalamotomy in patients with Parkinson's disease (PD). Eleven patients were included in a pilot, open-labeled study to assess the effect of unilateral lesion of the subthalamic nucleus (STN) with a minimum of 12 months of follow-up. The guidelines of CAPIT (Core Assessment Program for Intracerebral Transplantation) were followed for recruitment into the study and follow-up assessment. Levodopa equivalents daily intake (mean 967 mg) were unchanged during the first 12 months in all but one patient who stopped medication. The sensorimotor region of the STN was defined by semimicrorecording and stimulation and a thermolytic lesion was placed accordingly. There was a significant reduction in both UPDRS parts II and III in the "off" state at 1-, 6-, and 12-month follow-up. This effect was maintained in four patients up to 24 months. The dyskinesia score did not change postoperatively. Lesion-induced dyskinesias were not a management problem except in one patient who developed a large infarction several days postsurgery. This initial study indicates that a lesion of the STN is not generally associated with hemiballismus in PD. Subthalamotomy may induce considerable motor benefit and could become another surgical option under specific circumstances.

Key words: subthalamic nucleus; subthalamotomy; Parkinson's disease; hemiballismus. Mov. Disord. 16:72–78, 2001.

Levodopa maintains its position as the mainstay treatment of Parkinson's disease (PD). Chronic treatment, however, is associated with motor and psychiatric complications that lead to high levels of disability; hence the need for alternative approaches. Surgery for PD has been revitalised in recent years[1] in part because of the lack of efficacious pharmacological treatments to combat the long-term complications, but also due to the development of safer and more accurate stereotactic neurosurgical techniques and more importantly, as a result of a better understanding of the basal ganglia mechanisms underlying the parkinsonian state.[2,3]

Hyperactivity of the subthalamic nucleus (STN) is now considered a hallmark of the parkinsonian state as demonstrated in animal models of PD.[2,4] Increased activity of the STN leads, through its glutamatergic excitatory effect, to increased neuronal activity in the globus pallidus pars interna (GPi) and substantia nigra reticulata (SNr) which, in turn, overinhibit the thalamo-cortical projections and the brainstem.[2,5] In monkeys intoxicated with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), lesioning the STN was associated with a marked amelioration of the parkinsonian motor signs[6,7] and reversal of the increased neuronal activity in the GPi and SNr.[8,9] In keeping with this, surgical treatment with pallidotomy and deep brain stimulation (DBS) of the STN or GPi are capable of producing a marked clinical improvement even in advanced parkinsonian patients.[10,11,12,13] DBS is rapidly gaining favor in the medical community due to its reversibility and the reduced

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chance of permanent side effects compared with ablative surgery of the basal ganglia. However, there are some drawbacks associated with DBS for PD, such as the need for intensive and specialized medical assistance to obtain optimal clinical benefit as well as periodic surveillance to guarantee the correct functioning of the system. More importantly, at present DBS is not available throughout the world due to a number of practical limitations.

The experience in parkinsonian monkeys[6,7,8] has strongly suggested that a lesion of the STN could produce marked clinical benefit without inducing hemiballismus. There are a few anecdotal instances of parkinsonian patients with vascular lesions of the STN having experienced motor improvement without severe dyskinesias.[14,15] In addition, a review of the incidence of complications following stereotactic surgery in the 1960s and 1970s reveals a very low occurrence of hemichoreaballism even when the STN was unintentionally lesioned. We therefore argued that subthalamotomy could be performed in patients with PD without inducing disabling hemiballism.[16]

Following are the results of a pilot study including 11 patients with a unilateral lesion of the STN followed up for 12–24 months.

PATIENTS AND METHODS

Patients and Assessment

Eleven patients with a diagnosis of PD were included in this study. The trial consisted of an open-label prospective evaluation of the effect of unilateral subthalamotomy with a minimum follow-up period of 12 months. The main clinical characteristics of the patients are summarized in Table 1. Patients were selected by the predominance of axial motor manifestations and absent or mild levodopa-induced dyskinesias. They were all consecutively recruited and represent the initial experience of the surgical team with this approach. All patients were receiving levodopa plus benserazide; five had additional treatment with bromocriptine (mean daily dose 17.5 mg), and two received trihexyphenidyl (2–3 mg daily).

Patients were admitted to the hospital for evaluation for 1–3 weeks before surgery and at 1, 3, 6, 9, 12, 18, and 24 months postoperatively. The guidelines of CAPIT (Core Assessment Program for Intracerebral Transplantation)[17] were followed for recruitment into the study and assessment. The latter includes the UPDRS, parts II (activities of daily living) and III (motor scale), the dyskinesia scale (0 = absent abnormal movements to 4 = generalized, severely disabling movements), the Hoehn and Yahr scale (stages I–V), and timed tests (pronation-supination of the hand). In addition, the time taken to turn around in bed (once), blinking rate, and the sit-and-walk test were recorded. Patients were scored in the "off" state (minimum 12 hours without medication) and in the "on" state following oral administration of levodopa/carbidopa (250/25 mg) at 9 a.m. in the fasting state ("levodopa test"-CAPIT). The duration of the "on" state and severity of dyskinesias were scored during the levodopa test. During the recruitment period and admission pre-operatively, patients and relatives were trained to recognize the duration of "on-off" periods and to complete home diaries. They were asked to ascertain the proportion of waking hours spent in the "on" state at baseline and during the follow-up. Patients were videotaped pre-operatively and during follow up in the "off" and "on" states while wearing a hat. Videotapes were

TABLE 1. *Dorsal subthalamotomy for PD. General characteristics of the patients*

Patients	Age (years)	Disease duration (years)	Hoehn & Yahr	UPDRS motor		Time spent in off (%)	Dyskinesias	L-Dopa equivalents (mg/daily)
				Off	On			
1	54	10	IV	58	26	50	Chorea (1/4) DD (1/4)	1000
2	57	17	III	61	28	19	NONE	600
3	58	11	IV	66	20	43	Chorea (2/4)	1800
4	57	10	IV	52	16	39	Chorea (2/4) DD (2/4)	1000
5	69	14	IV	73	27	47	Chorea (2/4)	950
6	59	8	IV	70	26	56	Chorea (2/4) DD (2/4)	1250
7	53	10	IV	62	26	50	Chorea (2/4)	900
8	56	16	IV	42	21	43	NONE	1150
9	61	6	III	69	20	62	Chorea (2/4)	800
10	66	8	III	47	30	59	Chorea (1/4)	1000
11	66	8	III	66	25	48	NONE	800
MEAN	59,5	11,2	7/IV–4/III	61,8	25.5	47,3		967

DD: Diphasic Dyskinesia.

used subsequently for blind assessment by a neurologist who had not been directly involved either in the management of the patients or in the surgical procedure. Different video segments were randomized to avoid any clue about the preoperative and postoperative period and the "on" or "off" drug conditions. Part III of the UPDRS, excluding rigidity, was used. The levodopa daily dose was to be kept constant during the first 12 months of evaluation. One patient (No.3) developed a severe hemichorea on day 5 after surgery. He was excluded from the statistical analysis.

Surgical Technique

All procedures were performed by the same surgical team. Levodopa and other antiparkinsonian drugs were withdrawn the night before. A unilateral lesion of the STN was performed under local anaesthesia on the hemisphere contralateral to the most-affected body side. A Leksell's stereotactic frame (model G) was used and a series of axial parallel slices were obtained by computerized tomography (CT) of the brain. Coordinates chosen for targeting the STN were 2–3 mm behind the middle intercommissural point (Y coordinate), 12 mm lateral (X coordinate), and 5–6 mm (Z coordinate) below the AC-PC line. Targeting was undertaken with the aid of a computerized program that contains a digitized version of the Shaltenbrand-Wahren atlas for stereotaxy of the human brain, enabling definition of the theoretical coordinates of the STN and the trajectory of the track from the frontal burr hole to the target. Semi-microrecording of multi-unit action potentials and the area obtained by the integration of the number of spikes and their amplitude at every recording site was used to identify the nucleus and to define its boundaries.[18] This procedure allows quantitative estimation of the level of neuronal activity throughout the trajectory of the electrode for each track. Entrance into the STN was defined by an abrupt and large increment in the integrated activity. This was clearly differentiated from the low level of activity recorded above the target. There was usually 4–5 mm of high electrical activity within the STN. The sensorimotor region of the STN was localized by finding neuronal responses to passive limb displacement and active movements. This area was found in the dorsal half of the nucleus and 11–13 mm lateral to the mid-line. The ventral border of the STN was defined by a return to the baseline level of activity, which ocurred 1–3 mm before entering the region of the substantia nigra pars reticulata (SNpr), where activity arose again.[18,19] Neurons in the SNpr were also distinguishable because of their more tonic pattern, higher frecuency rate,[19] and reduced incidence of sensorimotor responses, which when present, were almost always in response to stimulation of the axial musculature. Stimulation (60–180 Hz, 0.1–5 mA, 0.3 ms pulse width) with the recording electrode was used to look for therapeutic effects, possible induction of dyskinesias and sensory or motor responses. A mean of 8.6 (range 5–14) recording tracks per patient was needed to fully define the coordinates for lesioning. A thermolytic lesion (60°C for periods of 30 seconds) of 4 mm in diameter was produced with a needle of 1.1 mm diameter and a 3-mm tip (Elektra Instruments AB, Sweden). In all but the three initial patients two lesions were carried out with different X and Y coordinates but allowing some overlapping between them. This was intended to lesion mainly the dorsolateral region of the STN, sparing the medioventral zone. Patients remained under intensive surveillance in the neurosurgical unit for 24 hours and in the hospital for 7–12 days. A control CT brain scan was made within 24–48 hours postoperatively in all patients and a magnetic resonance image (MRI, 1.5 Teslas) of the brain was obtained in three patients, 11 months after surgery. In two of these same patients, a T1 weighted image obtained in a 4.1 Tesla magnetic resonance spectrometer (MRI) (Prototype Phillips -UAB) (Fig. 1) was also undertaken. In all cases the lesion appeared to be correctly placed in the region of the STN with a variable 1–2 mm dorsal extension above the nucleus.

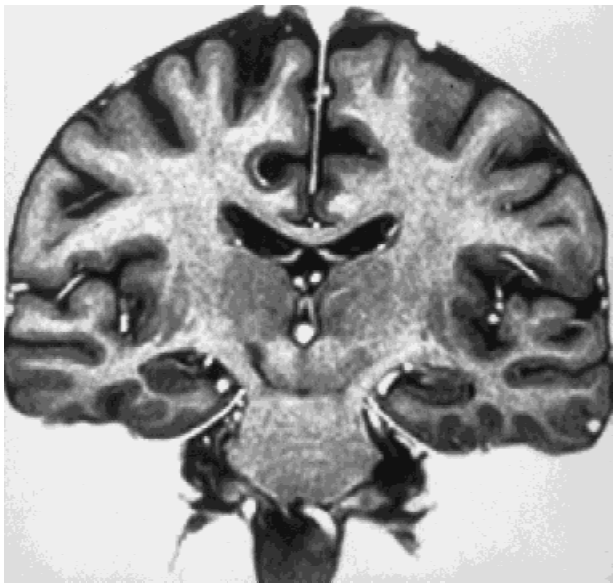

FIG. 1. Magnetic Resonance Imaging (4.1 Teslas) of the brain (coronal view) from a patient operated 11 months earlier. A lesion of about two-thirds of the right subthalamic nucleus is seen. The dorsolateral region is mainly affected by the lesion, which also extends dorsally above the nucleus.

Statistics

The primary outcome measures of this study were the change in the "off" drug motor UPDRS (part III) score and dyskinesia scale following unilateral subthalamotomy. Non-parametric statistical comparisons were carried out via the Wilcoxon Rank Sum test. Corrections for multiple comparisons (Bonferroni's test) were undertaken.

Secondary end-points were the blind assessment of the video tapes recorded preoperatively and at 6-month follow-up, UPDRS part II (ADL), UPDRS part III score in "on", time spent in "on," and timed tests. The effect of subthalamotomy on component items of the UPDRS was also analyzed. The Wilcoxon test was used for all of these comparisons.

RESULTS

There were no intraoperative complications and the immediate postoperative period was uneventful. Patients resumed their usual levodopa schedule on the day of surgery following the procedure. A marked amelioration of parkinsonian features was observed in all patients the day after surgery or even within the operating theater in those with tremor as a major manifestation.

Figure 2 summarizes the changes in the motor UPRDS scores in the "off" and "on" conditions throughout the follow-up period. There was a significant reduction (50%, $P < 0.01$) in the motor UPDRS scale in the "off" state at 1-, 6-, and 12-month follow-up in the 10 patients assessed over this period (Fig. 2). A similar effect was maintained in five patients up to 18 months and four patients up to 24 months. The motor UPDRS score in the "on" state (Fig. 2) was also significantly reduced (39 %, $P < 0.01$) during the 12 months of follow-up. A similar effect was observed for the ADL UPDRS scores (Fig. 3) in the "off" and "on" states.

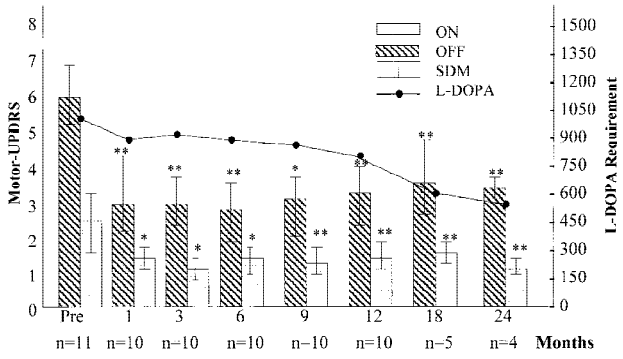

FIG. 2. Evolution of motor scores (UPDRS-part III) in the "off" and "on" medication states before surgery and during follow-up. A marked reduction in the "off" score is present from the first month postoperatively and is maintained after more than a year. There is also a significant reduction of the "on" scores. Levodopa daily dose was purposely maintained constant during the first 12 months (in all but one patient) and subsequently reduced according to the actual demand of each patient. SDM, standard deviation of the mean.

Dyskinesias were observed in the contralateral limbs during the lesioning procedure in five patients. They lasted for 1–12 hours and abated spontaneously. In another patient, chorea of the leg contralateral to the lesion developed postoperatively, lasting for 5 days before complete resolution. Dyskinesias were not a management problem at all except in one patient (No. 3) who evolved normally for the first week but developed severe right-sided hemichorea-ballism on postoperative day 7. A CT brain scan taken 48 hours after surgery revealed the typical hypodensity in the region of the left STN induced by the thermolytic lesion. Another CT brain scan on day 8 showed a large infarction extending dorsally into the anterior thalamus. Levodopa was stopped in this patient in an effort to reduce the dyskinesia, which nevertheless remained unchanged. An MRI of this patient (9 months later) showed the lesion in the left STN, extending ventrally into the substantia nigra and dorsocaudally through the zona incerta up to the anterior limb of the internal capsule. The patient maintained considerable clinical improvement of his parkinsonian state but gait, stability, and fine movements of the limbs were impaired by the hemichorea-ballism. For all these reasons, a left pallidotomy was performed 12 months after the initial STN lesion. This resulted in complete resolution of the hemiballism with no complications. In the remaining patients the mean dyskinesia score in the "on" state was 1.5 preoperatively and 1.6 at 12 months postoperatively ($P > 0.05$).

The effect of subthalamotomy on the "off" UPDRS motor scores at 6-month follow-up was confirmed by blind rating of videotaped examinations of the patients. This evaluation showed a reduction in the UPDRS motor score in the "off" state from 44.5±6.1 (mean ± SD) pre-

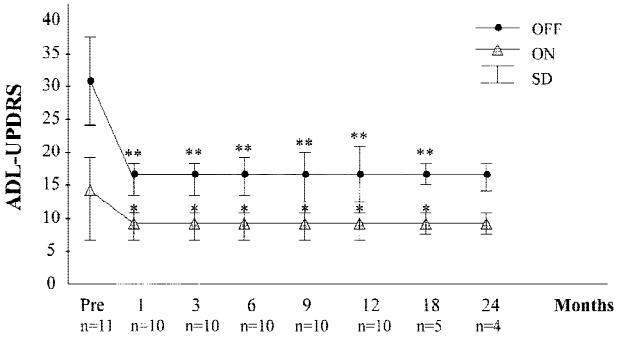

FIG. 3. Subthalamotomy produced a drastic improvement in the activities of daily living (ADL) scores of the UPDRS-Part II in both "off" and "on" medication conditions.

operatively to 26.3±8.2 postoperatively ($P < 0.01$). Values are of lesser magnitude than the total UPDRS-III scores because rigidity and speech were not assessed. Thus, the blind rating was not discordant with the open clinical evaluation.

Table 2 summarizes the effects of subthalamotomy on the major motor features of PD. A significant improvement was observed in freezing of gait, postural stability, and facial expression ($P < 0.05$). Bradykinesia and rigidity were significantly improved bilaterally (Table 2) but the effect was more pronounced on the side contralateral to the lesion, the ipsilateral benefit disappearing at 12 months of evolution. Tremor was significantly ameliorated in the whole group and eliminated in five of the eight patients in whom it was present (Table 2). This effect was limited to the contralateral limbs.

The percentage of the waking day the patients spent "on" was also significantly ($P < 0.01$) increased from 52.7% at baseline to 93.7% at 12 months of evolution. The four patients who were followed-up for 2 years maintained this response (94.8% in "on").

Table 3 shows the effect of subthalamotomy on several timed tests at 1, 6, and 12 months postoperatively. There was a very significant improvement ($P < 0.01$) in spontaneous blinking and axial tasks such as turning in bed and the sit-and-walk test. For the hand pronation/supination test the effect was bilateral with a 60% and 36% improvement for the contralateral and ipsilateral sides, respectively, at 12 months.

The levodopa daily dose was maintained unchanged during the initial 12 months of evaluation in all but one patient (Fig. 2). This particular subject realized he could perform equally well without levodopa 6 months after surgery. The five patients followed-up for more than 12 months reduced the daily levodopa requirements by 59%.

Adverse events.

Dyskinesias were severe and persistent until ameliorated by further surgical therapy in one patient as described above. There was no instance of sensory, motor, or speech deficit. Neuropsychological testing (data to be reported elsewhere) did not show any cognitive deterioration or language defect.

DISCUSSION

A dramatic improvement in motor function following unilateral subthalamotomy was observed. In most patients this effect was present immediately after completion of the lesioning procedure. The effect on the UPDRS motor and ADL scores was maintained during the follow-up period. Persistent dyskinesias were not provoked by the lesion except in one patient who developed a large infarction several days postoperatively. Thus, the two primary measures of this pilot study showed a clear-cut therapeutic benefit of subthalamotomy in this group of patients with PD. These results confirm our preliminary experience with a smaller number of patients[20] and the ongoing experience of Gill and Heywood.[21] The reduction in the "on" scores observed in our patients was an unexpected finding. Retrospective analysis of the UPDRS scores indicates that tremor in the most affected limb and freezing of gait were not completely relieved in the "on" state preoperatively but were substantially ameliorated after subthalamotomy. Interestingly, a similar finding has been encountered in patients treated with DBS of the STN or GPi.[13]

Surgery for PD has consisted traditionally of thalamot-

TABLE 2. *Effect of subthalamotomy on major motor problems in 10 patients followed up to 12 months*

Motor signs(1)	Pre-op.	Post-op. 1st month	Follow up 6th months	Follow up 12th months
Axial Signs				
Facial expression	2.45 ± 0.68	1.36 ± 0.50**	1.36 ± 0.50**	1.82 ± 0.45**
Freezing (ADL)	2.00 ± 1.48	0.54 ± 0.68*	0.45 ± 0.68*	0.49 ± 0.79*
Gait disturbance	2.92 ± 0.75	1.09 ± 0.70**	0.90 ± 0.70**	1.27 ± 0.92*
Postural stability	2.65 ± 1.29	1.36 ± 0.60**	1.13 ± 0.63**	1.06 ± 0.58**
Limb signs				
Bradykinesia contra	12.08 ± 2.33	5.54 ± 1.63**	5.90 ± 1.56**	6 ± 1.34**
Bradykinesia ipsi	9.08 ± 2.00	7.27 ± 1.19*	7.26 ± 1.36*	8.18 ± 1.99
Rigidity contra	5.59 ± 1.03	1.45 ± 1.50**	1.63 ± 1.29**	1.63 ± 1.2**
Rigidity ipsi	4.43 ± 0.75	3.09 ± 0.98*	3.36 ± 0.75*	3.55 ± 1.12
Tremor contra (n = 8)	5.45 ± 3.88	0.72 ± 2.24*	0.73 ± 1.41*	0.72 ± 1.55*
Tremor ipsi (n = 8)	3.16 ± 2.92	2.63 ± 2.33	2.64 ± 2.33	3.45 ± 2.84

(1) Taken from the UPDRS-III in "off" state.
*$P < 0.03$; **$P < 0.008$.

TABLE 3. *Effect of subthalamotomy on timed tests (off state)*

	Pre-op. (mean ± SD) (n = 11)	1 month (mean ± SD) (n = 10)	6 months (mean ± SD) (n = 10)	12 months (mean ± SD) (n = 10)
Blinking (No./min)	1.45 ± 0.84	3.09 ± 0.91**	4.05 ± 0.63	3.37 ± 0.3**
Turning in bed (sec.)	16.98 ± 21.95	7.27 ± 0.64**	5.36 ± 0.67**	5.7 ± 0.36*
Sit and Walk (sec.)	34.90 ± 12.17	13.09 ± 4.73**	13.10 ± 3.75**	14.1 ± 4.25*
Pronation/Supination Test (sec.)				
Ipsilateral	38.09 ± 29.7	27.18 ± 6.70***	26.54 ± 7.77***	24 ± 5.81***
Contralateral	52.00 ± 25.74	22.90 ± 10.74**	23.00 ± 0.77**	21.18 ± 4.53***

*$P = 0.01$; **$P = 0.005$; ***$P = 0.008$

omy and pallidotomy and more recently DBS of the STN and GPi. The authors now report a marked alleviation of parkinsonian features after lesioning the STN unilaterally, which might open up another surgical option for PD. The results presented here have the methodological limitations of an open and uncontrolled pilot study. The placebo effect needs to be acknowledged as a potential source of error. The authors believe that the large-scale magnitude of improvement observed in their patients cannot be attributed to a placebo effect for several reasons. Firstly, the effect contralateral to the lesion has been well maintained over a relatively long period, while the ipsilateral improvement vanished after a year postoperatively. Secondly, the motor improvement was asymmetrical for the limbs (more in the operated side) and involved very automatic functions, such as blinking, walking, and postural stability. Thirdly, resting tremor stopped within the operating theater in some patients who were unaware of when the lesioning was occurring, and the anti-tremor effect was only contralateral to the lesion. Fourthly, the few patients followed for more than a year realized by themselves the possibility of reducing their daily intake of levodopa.

Another methodological problem to consider is the possibility of biased assessment by the investigators. This may partially account for the results observed in our patients. We tried to reduce the possibility of this effect by blinded rating of the videotapes pre- and postoperatively. In addition, the timed tests, which provided more objective evaluation of the motor state, were also significantly improved postoperatively. We therefore believe that lesioning the STN has a real and profound effect in relieving parkinsonian features. This conclusion is consistent with the experimental data from MPTP monkeys.[6,7,8] The STN exerts an excitatory drive on the GPi, SNr, the external globus pallidum (GPe), and pedunculopontine nucleus (PPN), all of which are primarily involved in the pathophysiology of PD.[2,4,5] The pronounced anti-parkinsonian effect described here may be mediated by the capacity of an STN lesion to reduce the abnormal and excessive inhibitory output from the main basal ganglia output nuclei.[22] By comparison, thalamotomy and pallidotomy seem to have a more restricted effect in the parkinsonian state.[1,23]

Avoiding lesioning the STN has been considered a neurosurgical dogma ever since the initial experience with surgery for basal ganglia disorders.[24] However, previous experiences lesioning the subthalamic region (campotomy) were believed to be therapeutically effective without necessarily inducing dyskinesias.[25] Moreover, a review of the literature of patients with PD in whom hemiballism was provoked during stereotactic surgery revealed only seven patients with a pathologically proven lesion.[16] Interestingly, only two of those patients had a lesion of the STN. Our results clearly indicate that lesioning the STN does not necessarily induce hemiballism in PD. In fact, dyskinesias of any type were not a problem at all in the majority of our patients. Only one patient developed hemiballism as a consequence of a large ischaemic lesion that extended far beyond the STN occurring a few days after surgery. The dissociation between a lesion of the STN and production of hemidyskinesias may have several explanations. The effective, complication-free lesion may have spread out beyond the limit of the STN dorsally to interrupt the thalamic fasciculus, which conveys the main outflow from the GPi, thus mimicking the effect of pallidotomy. The latter is well known to abolish dyskinesias both in monkeys[26] and patients.[27,28] The present experience does not allow us to rule out the possibility of a pallidotomy-like effect to explain the absence of dyskinesias, since the MRI in two of our initial patients (Fig. 1) showed part of the lesion spreading dorsally into the region of the zona incerta. In addition, the sensitivity for eliciting hemiballism may vary depending upon the functional state of the GPi. In the parkinsonian state there is increased activity of the GPi as a result of both excessive excitatory driving by the STN and reduced gamma amino butyric acid (GABA) inhibition driving from the striatum.[2,4,5] Guridi et al.[8] found that dyskinesias following a kainic acid lesion of the STN were elicited more frequently and were more severe in normal monkeys

than in MPTP-induced parkinsonian monkeys. It may be suggested that the dyskinetic threshold to induce hemiballism following STN lesions may be higher in PD than in the normal state.[29]

The results presented here are in keeping with current observations in patients treated with DBS of the STN[12,13] regarding the outstanding clinical improvement associated with a putative reduction of STN hyperactivity. There may be differences in the postsurgical management of patients treated with either approach, particularly regarding dyskinesias, but such issues will require prospective and comparative analysis. The experience reported in this article refers to our initial patients with lesions of the STN, thus explaining the high number of recording tracks needed. Our more recent experience with the facility of performing the procedure is more favorable. Nevertheless, further work is required to establish more accurately some characteristics of the lesion such as topography, volume, and the most effective intraoperative methodology to secure the best benefit-to-risk ratio. It is still premature to attempt any comparison with DBS, which will undoubtedly continue to be the preferred technique for surgical treatment of PD. However, subthalamotomy could become an additional resource for specific patients under special circumstances.

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