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Effect of subthalamic nucleus stimulation on levodopa-induced dyskinesia in Parkinson's disease

Article abstract—The authors studied the effect of bilateral subthalamic nucleus stimulation on levodopa-induced dyskinesias in 24 consecutive parkinsonian patients with disabling dyskinesias. The improvement in the three subtypes of levodopa-induced dyskinesias was significant from the third post-operative month and was mainly due to the decrease in the daily dose of levodopa allowed by the stimulation-induced improvement in the motor score.

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A few years after beginning levodopa treatment, many patients with idiopathic PD develop motor fluctuations and levodopa-induced dyskinesias (LID), which may be more disabling than parkinsonism, especially in patients with young-onset PD. Chronic stimulation of the subthalamic nucleus (STN) is effective in treating parkinsonian motor symptoms and can be suggested to patients with severe motor fluctuations.¹ Operating on the STN might theoretically be harmful to LID. Hemiballism can be induced by spontaneous lesions of the STN and by experimental high frequency stimulation of the STN in patients with PD as well.² We investigated the effect of STN stimulation on different types of LID in parkinsonian patients.

Patients and methods. Twenty-four consecutive patients—12 men and 12 women—with severe PD and motor complications were bilaterally operated. The characteristics of these patients are summarized in table 1. The neurosurgical procedure has been described.¹ Clinical evaluation was based on the Core Assessment Program for Intracerebral Transplantation (CAPIT) protocol and was performed after a 12-hour withdrawal of antiparkinsonian drugs.³ Patients were assessed twice before surgery and 3 and 12 months after the operation in “off”-drug and “on”-drug conditions, using Unified PD Rating Scale (UPDRS) motor scores and the dyskinesia duration and disability items of the UPDRS part IV. Levodopa-induced dyskinesias were evaluated during a levodopa challenge using the same suprathreshold dose as preoperatively.⁴ “Off”-period dystonia, onset-of-dose, and peak-dose dyskinesias were assessed separately using three scales encompassing the face, neck, and the four limbs, each scored from zero to four proportionally to severity.⁵ The conditions of evaluation were not randomized and onset-of-dose dyskinesia was evaluated in “off”-stimulation condition at least 30

minutes after the neurostimulator was switched off. The patients were blinded but not the examiner. Results are presented as mean $\pm$ SD values. The data were analyzed by analysis of variance for repeated measures, and by the paired *t*-test and the Wilcoxon signed-rank test when required.

Results. Results are presented in table 2 and the figure. STN stimulation significantly reduced the UPDRS motor score. In the “off”-drug condition, the UPDRS motor scores decreased from 54.4 ± 13.1 before surgery to 45.8 ± 19.7 and 49.3 ± 17.9 in the “off”-stimulation condition and to 18.3 ± 12.3 and 18.2 ± 8.8 in the “on”-stimulation condition at 3- and 12-month follow-ups, respectively. In the “on”-drug condition the UPDRS motor scores changed from 13.3 ± 6.8 before surgery to 14.1 ± 9.7 and 17.5 ± 9.9 in the “off”-stimulation condition and to 9.8 ± 6.7 and 11.2 ± 7.7 in the “on”-stimulation condition at 3- and 12-month follow-ups. The mean duration and disability of LID decreased from the 3-month follow-up. Sixteen of 24 patients (60%) no longer had dyskinesia 3 months after the operation, increasing to 18 at 12-month follow-up. The “off”-period dystonia score significantly decreased at 3- and 12-month follow-ups in the “on”-stimulation condition. When the stimulators were switched off, dystonic postures immediately reappeared. During the levodopa challenge, onset-of-dose and peak-dose dyskinesias significantly improved from the 3-month follow-up. The levodopa daily dose significantly decreased from 952 ± 509 mg to 223 ± 169 mg at 3-month follow-up and 184 ± 190 mg at 12-month follow-up. Five of the 24 patients had stopped levodopa within the 4 weeks following the operation, increasing to eight 1 year after the operation.

Discussion. In this study STN stimulation was effective on all the subtypes of dyskinesias. Dyskinesia duration and disability in daily living were significantly reduced from the third month follow-up. The use of a suprathreshold dose of levodopa facilitated the distinction between the two subtypes of “on”-period dyskinesias by maximizing the peak-dose effect that was associated with minimal parkinsonism. The scores of the three subtypes of LID were also significantly reduced during the levodopa challenge at 3- and 12-month follow-ups compared with the preoperative scores, with a trend to a greater improvement over time. However, this was only signifi-

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Table 1 Characteristics of patients before surgery (n = 24)

Characteristics	Mean $\pm$ SD
Age at surgery, y	55.7 $\pm$ 7.3
Age at onset of PD, y	39.4 $\pm$ 7.7
Duration of PD, y	16.3 $\pm$ 5.4
Duration of levodopa therapy, y	14.4 $\pm$ 5.9
Levodopa daily dose, mg	952 $\pm$ 509
Levodopa equivalent daily dose, mg	1265 $\pm$ 540
Hoehn & Yahr stage (0 to 5)	
"Off" condition	4.5 $\pm$ 0.5
"On" condition	2.5 $\pm$ 0.3
Schwab & England scale, %	
"Off" condition	33 $\pm$ 16
"On" condition	81 $\pm$ 7

icant for onset-of-dose dyskinesia. The improvement in motor symptoms allowed a dramatic decrease in the daily dose of levodopa from the third month. We have already reported the effects of chronic bilateral STN stimulation in a previous series of 20 other consecutive patients¹ but the improvement in motor symptoms and the decrease in dyskinesia scores were greater in the current study and similar to more recent reports.^{6,7} The differences between the two studies of our group might be assigned to many causes. The patients were younger in the current study; the levodopa daily dose was reduced just after surgery, which was not the case in the previous study; and, finally, we have improved our expertise in the global management of patients with bilateral STN stimulation. This might contribute to the satisfactory outcome of STN surgery. The improvement in LID with chronic STN stimulation is probably multifactorial. STN stimulation might have a direct effect

on "off"-period dystonia.⁸ When the stimulators were switched off in the "off"-drug condition, parkinsonism soon reappeared, but so did "off"-period dystonia. This suggests that the pathophysiologic mechanisms of "off"-period dystonia might be similar to those of parkinsonism. The improvement in "on"-period dyskinesias might be mainly due to the decrease in the levodopa daily dose. After several weeks of levodopa withdrawal or dramatic decrease we could still induce some dyskinesias after a supratherapeutic dose of levodopa, which might mean that a hypersensitivity of the neuronal structures to levodopa persisted. However, the improvement in the "on"-period dyskinesia scores showed that the adverse motor effects of levodopa might be partly reversible over time. A significant improvement in LID has been already reported in young-onset but also in older parkinsonian patients, but with a lesser decrease in the levodopa daily dose and a shorter follow-up.^{4,6} Besides, we might assume that the dyskinesia threshold was modified by the continuous high frequency stimulation of the STN supposed to chronically inhibit this structure.⁹ Similarly to spontaneous or experimental lesions of the STN, acute high frequency stimulation can induce biphasic-like dyskinesia while increasing the voltage.² The improvement in dyskinesias after surgery might suggest that continuous inhibition of the STN along with the decrease in levodopa daily dose could induce plastic changes of the neuronal sensitivity of the pallidothalamocortical circuitry.¹⁰ Because the results of this study mainly concern young-onset patients with PD, we cannot extend them to the majority of parkinsonian patients with severe LID.

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Table 2 Dyskinesia duration (Unified PD Rating Scale [UPDRS] item 32) and disability (UPDRS item 33) and dyskinesia scores during the levodopa challenge before and after surgery (mean $\pm$ SD)

Score (maximal value)	Before surgery		3-mo follow-up		12-mo follow-up		p Value
	"Off" drug	"On" drug	"Off" stim	"On" stim	"Off" stim	"On" stim	
Dyskinesia duration (4)	NA	1.8 $\pm$ 0.7	NA	0.4 $\pm$ 0.7	NA	0.4 $\pm$ 0.8	0.001*
Dyskinesia disability (4)	NA	2.7 $\pm$ 1.1	NA	0.6 $\pm$ 1.0	NA	0.2 $\pm$ 0.7	0.001*
"Off"-period dystonia (28)	3.7 $\pm$ 2.9	NA	2.3 $\pm$ 1.8	1.4 $\pm$ 1.5	2.8 $\pm$ 2.9	1.3 $\pm$ 1.5	0.035†; 0.011§; 0.03¶
Onset-of-dose dyskinesia (28)	NA	11.7 $\pm$ 4.8	6.1 $\pm$ 3.6	ND	3.6 $\pm$ 2.7	ND	0.001†; 0.002‡
Peak-dose dyskinesia (28)	NA	10.9 $\pm$ 4.6	4.5 $\pm$ 2.9	5.6 $\pm$ 4.5	3.2 $\pm$ 2.4	2.9 $\pm$ 2.3	0.001†; 0.06‡; 0.229¶

* p Value for the comparison between the preoperative score and the scores after surgery.

† p Value for the comparison between the preoperative score and the "off"-stimulation condition at 3 and 12 months follow-up.

‡ p Value for the comparison between the 3-month and the 12-month scores.

§ p Value for the comparison between the preoperative score and the "on"-stimulation condition at 3 and 12 months follow-up.

¶ p Value for the comparison between the "off"-stimulation condition and the "on"-stimulation condition.

NA = not applicable; ND = not done.

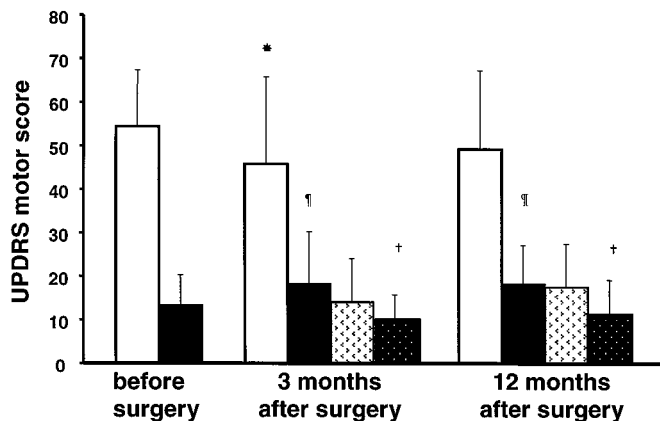


Figure. Mean $\pm$ SD motor examination score (Unified PD Rating Scale [UPDRS] part III) in the "off"-medication and "on"-medication conditions before and 3 and 12 months after surgery. After surgery, the UPDRS motor score was also evaluated in the "off"-stimulation and "on"-stimulation conditions. * $p < 0.004$ For the comparison with the "off"-medication condition before surgery; † $p < 0.001$ for the comparison with the "off"-stimulation and "on"-medication condition; ‡ $p < 0.001$ for the comparison with the "off"-stimulation and "off"-medication condition. □ = "off"-medication, "off"-stimulation; ■ = "on"-medication, "off"-stimulation; ▨ = "off"-medication, "on"-stimulation; ▩ = "on"-medication, "on"-stimulation.

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Hypotensive akathisia: Autonomic failure associated with leg fidgeting while sitting

Article abstract—The author describes a distinct clinical syndrome in six patients with autonomic failure who manifested habitual, voluntary, transiently suppressible, yet irresistible leg movements occurring only in the sitting position. Keeping the legs still brought on vague symptoms of fatigue, lightheadedness, or apprehension. Repetitive leg crossing, muscle tensing, foot twirling or wiggling, or heel or toe floor tapping while sitting may have compensated for orthostatic hypotension and raised systolic blood pressure by a mean of 28 mm Hg and diastolic pressure by a mean of 11 mm Hg.

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Manifestations of orthostatic hypotension (OH) in the sitting position have received little attention. Although the comparatively shorter vertical height of the vascular system renders sitting a lesser orthostatic stress than standing, the longer time spent

sitting can permit subtle hypotensive symptoms to occur.¹

One mechanism countering gravitational displacement of blood volume into the lower extremities is the exercise of leg muscles used in standing and walking. Skeletal muscle contraction squeezes pooled blood from venous capacitance vessels and augments venous return to the heart, thereby increasing cardiac filling pressure and cardiac output. In the sitting position, in contrast, the legs are usually relaxed.

Six patients with autonomic failure who had de-

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