Ineffective subthalamic nucleus stimulation in levodopa-resistant postischemic parkinsonism

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Article abstract—The authors report a patient with postischemic parkinsonism who responded neither to levodopa nor to bilateral subthalamic nucleus (STN) stimulation. MRI revealed bilateral lesions of the substantia nigra, the striatum, the external pallidum, and part of the internal pallidum. PET showed reduced striatal dopa-decarboxylase activity, D_2 receptor binding, and glucose metabolism. Perioperative microrecording showed low-frequency activity of STN cells. This case suggests that parkinsonian patients who do not have a good response to levodopa or in whom a postsynaptic dopaminergic lesion can be shown may not be good candidates for STN surgery. **Key words:** Subthalamic nucleus—Deep brain stimulation—Postischemic parkinsonism.

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Pallidal surgery and subthalamic nucleus (STN) high-frequency stimulation are highly beneficial in patients with advanced PD. The response of akinesia to an L-dopa challenge predicts the benefit of bilateral STN stimulation and pallidotomy.[1] Little is known about the effect of surgery in levodopa-resistant parkinsonism. No benefit was maintained after pallidotomy in single cases with striatonigral degeneration, olivopontocerebellar atrophy, or corticobasal degeneration.[2,3] A single case report indicates a positive effect of pallidotomy in a patient with postischemic parkinsonism, in whom the lesions involved the putamen and the globus pallidus externus bilaterally but spared the globus pallidus internus.[4] Another patient with levodopa-resistant parkinsonism with a normal preoperative MRI and mildly reduced ^{18}F-fluorodopa PET improved after pallidotomy.[5] We report the case of a patient with a postischemic akineto-rigid parkinsonian syndrome, unresponsive to L-dopa, who showed only a minor response to bilateral STN stimulation.

Case report. A 63-year-old man experienced syncope. He was immediately diagnosed with cardiac arrest and received cardiac massage and mouth-to-mouth respiration. Ventricular fibrillation was diagnosed on arrival at the hospital 25 minutes later. Electrical defibrillation restored a sinus rhythm. He regained consciousness, but had generalized tonic-clonic seizures, which were treated with high doses of barbiturates. A barbiturate coma was maintained over 10 days and ventilation was prolonged because of pulmonary infection. Although cognitive functions were quickly recovered, he was left with a severe postischemic akinetic-rigid syndrome that was stable over time. There was no subjective or objective improvement under levodopa (600 mg + decarboxylase inhibitor per day) for 18 months and no deterioration when levodopa was stopped. Administration of subcutaneous apomorphine up to 8 mg as a bolus did not induce any change in the motor state. Before surgery, the parkinsonian syndrome was rated 65/108 on the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS). He had severe generalized akinesia and rigidity, mild action tremor of the upper limbs, severe hypophonic speech, frequent choking when swallowing liquids, and loss of postural reflexes. He was able to get out of a chair and walk unassisted, but gait was greatly impaired by initiation difficulties, festination, and freezing. There were no motor fluctuations or dyskinesias. There was no dementia, but neuropsychological examination revealed mild difficulties in tests sensitive to frontal lobe scoring. No definite signs of pyramidal, sensory, or cerebellar involvement were found. MRI revealed bilateral lesions of the basal ganglia with a hypointense signal on T2- and a hyperintense signal on T1-weighted sequences, mainly of the putamen and caudate but also involving the globus pallidus, sparing its most internal part. Mild hyperintense signals were also seen lateral to the interpeduncular cistern in the substantia nigra (figure). Striatal measurements of dopa-decarboxylase activity (fluorodopa PET), D_2 receptor binding (raclopride PET), and metabolism (fluorodeoxyglucose PET) were all markedly decreased. The mean ratios for the putamen (left and right averaged) compared with age-matched control subjects ($\pm$1 SD) were as follows: fluorodopa 1.69 (2.24 $\pm$ 0.14), raclopride 1.24 (3.45 $\pm$ 0.58), and fluorodeoxyglucose 0.75 (1.21 $\pm$ 0.09). The data for the caudate were of a similar magnitude, whereas there was no decrease in the thalamic fluorodeoxyglucose ratio. Stereotaxic surgery was performed in 1995, 3 years after the cardiac arrest, using a technique described elsewhere.[6] Perioperative recording of STN neuronal activity showed a low mean firing frequency (15 $\pm$ 6 Hz, n = 8). Neuronal firing was not modified by passive limb displacement or voluntary movements and there was no oscillatory activity. Perioperative stimulation led to a mild improvement in contralateral upper limb rigidity. Permanent electrodes were implanted into the STN on both sides. Postoperative

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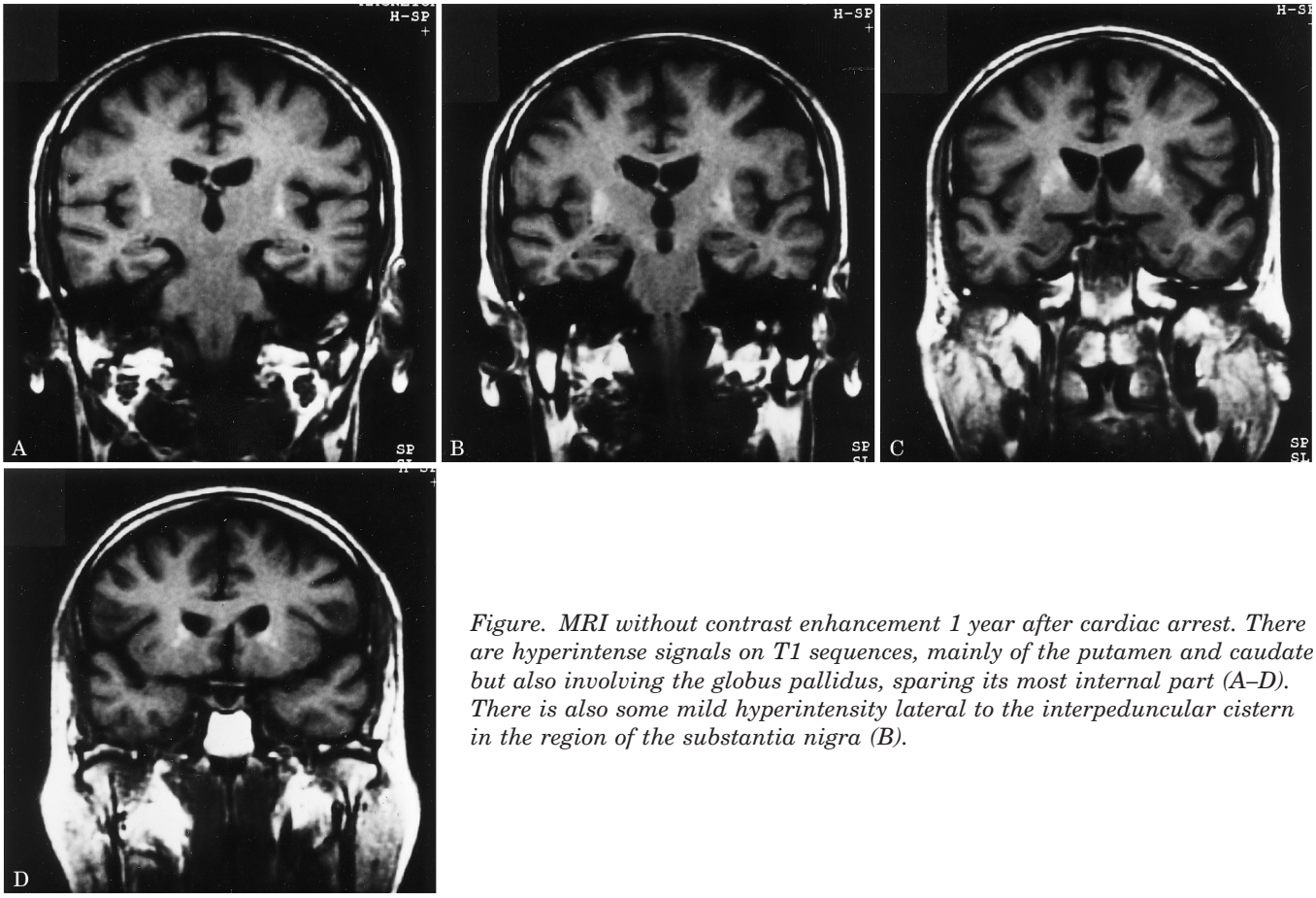

Figure. MRI without contrast enhancement 1 year after cardiac arrest. There are hyperintense signals on T1 sequences, mainly of the putamen and caudate but also involving the globus pallidus, sparing its most internal part (A–D). There is also some mild hyperintensity lateral to the interpeduncular cistern in the region of the substantia nigra (B).

control MRI did not show any hemorrhagic complications, and the electrodes were located in the area of the STN. The patient was in a poor general state of health. He had urinary retention, necessitating catheterization, complicated by infection. Constipation was medically treated. His diabetes mellitus decompensated. Three weeks later, the patient had recovered from his general health problems and the stimulators were implanted under general anesthesia and connected to the electrodes. Under continuous stimulation, the patient reported mild improvement of swallowing and gait. However, in a double-blinded evaluation, the motor part of the UPDRS was 61/108 in the off-stimulation condition and 62/108 in the on-stimulation condition. Only the hand-tapping test was slightly improved by stimulation, from 57 to 66/minute on the right and from 49 to 63/minute on the left. At 1-year follow-up, the subjective benefit was maintained. Both stimulators were switched off overnight, and the patient, blinded to the stimulation parameters, complained about worsening of his gait and swallowing. The motor part of the UPDRS was identical to the presurgical evaluation, with a score of 68/108. One hour after switching on the stimulators (voltage 3.6 V for the right STN and 3.0 V for the left STN, pulse width 60 microseconds, frequency 130 Hz), the UPDRS motor score was 58/108, with mild improvement in rest and action tremor of the upper limbs, neck and wrist rigidity, getting up from a chair, and gait. Finger tapping was repeated twice and increased from 58 to 67/minute on the right and 55 to 63/minute on the left side after switching on the stimulators. A standardized timed walking test (stand–walk–sit test) was repeated four times in each condition. Off-stimulation results varied from 39 to 75 seconds, with 52 to 102 steps, and on-stimulation results varied from 23 to 34 seconds, with 44 to 48 steps. Subjective improvement of swallowing was reported, but this was not assessed objectively.

Discussion. Overactivity of STN cells secondary to decreased striatal dopamine is thought to play a major role in the pathophysiology of PD. In monkeys rendered parkinsonian by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), STN lesioning was shown to reverse the parkinsonian triad.[7] STN stimulation has been shown to be effective in idiopathic PD.[6] A pure parkinsonian syndrome after anoxia is relatively rare. The cellular activity of the STN and other basal ganglia nuclei in this condition is not known. We implanted bilateral electrodes in the STN of a patient with postischemic parkinsonism unresponsive to levodopa, in whom MRI showed bilateral hyperintense lesions of the substantia nigra, the striatum, and parts of the pallidum. PET data showed decreases in striatal glucose utilization, which are not seen in typical PD. Also, striatal dopa-decarboxylase capacity and dopamine D_2 receptor binding were markedly reduced. Striatal D_2 receptor binding is either normal or moderately increased in PD. Perioperative recording did not show the typical STN neuronal activity seen in patients with PD.[8] We can-

not entirely rule out that, in addition to the nigral, striatal, and pallidal lesions visible on MRI and PET scanning, there was also an ischemic lesion of the STN itself. Compared with STN stimulation in PD, stimulation improved the parkinsonian features of our patient only very mildly. A slight improvement of gait was seen in the stand–walk–sit test. The overall improvement was very modest, as reflected by the motor scale, but was nevertheless appreciated by the patient and his family. Such a mild improvement, if it had been predictable, would not have justified the risks of stereotaxic surgery. In this case, according to the pathophysiology of the basal ganglia circuitry, the parkinsonian syndrome implies hypoactivity of the thalamofrontal pathway resulting from overactivity of the globus pallidus internus, at least the part of it thought to be intact. Inhibiting the excitatory drive of the globus pallidus internus from the STN by stimulation is expected to lead to a reduction of motor disability. This reduction was very low in our patient, with a 15% decrease in the motor score of the UPDRS. This small percentage is on the same order as placebo effects, and contrasts with a motor score decrease of over 50% in PD patients with marked motor fluctuations.[6]

These results confirm that the effect of STN stimulation can be predicted by the response to levodopa or dopamine agonists,[9,10] and suggest that patients with levodopa-resistant parkinsonism related to lesions of the nigra, putamen, or pallidum, such as postischemic parkinsonism, multisystem atrophy, or progressive supranuclear palsy (which also involves the STN), cannot expect a major benefit from STN surgery. Striatal hypometabolism or decreased striatal D_2 receptor binding also seem to predict a lack of response to STN surgery. Not all forms of parkinsonian syndromes, however, even pure ones as in our patient, may be mediated by STN hyperactivity.

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