Extradural motor cortex stimulation for advanced Parkinson disease

Report of two cases

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Motor cortex stimulation is a minimally invasive surgical procedure used for pain control. The authors report their results treating two patients with typical Parkinson disease. Unilateral motor cortex stimulation proved to be beneficial bilaterally. Motor cortex stimulation may represent a cost-effective alternative to deep brain stimulation.

STNS, which resulted in dramatic improvement.3 We report the long-term benefit in that first patient as well as in an additional patient.

Case Reports

Case 1

History. This 75-year-old woman, in whom the gradual development of typical PD was diagnosed in 1976, presented in 1998. At presentation she scored IV–V on the Hoehn and Yahr Scale and showed moderate-to-severe PD-associated dementia.

Examination and Initial Treatment. A CT scan revealed marked cerebral atrophy. She scored 44 on Part III (motor) of the UPDRS while receiving levodopa.3 Left unilateral extradural MCS was performed and improvement in her symptoms was dramatic (Fig. 1).

Choreiform dyskinesias and painful focal dystonias of the right foot seen preoperatively were absent and she could walk independently. The best stimulation parameters were 3 V , 180 msec, 25 Hz, and a 3+ /11001/ setting; stimulation did not take place during sleep. Five months after stimulator implantation, a direct injury resulted in wound dehiscence, local infection, and system failure. Clinical worsening started approximately 4 days later with a slow worsening of gait and postural stability over a 2-week period. The infection was successfully treated. In April 1999, a new system (ITREL III; Medtronic, Minneapolis, MN) was implanted when the prestimulation level was almost present. Benefit was as for the first implantation and levodopa was reduced to 80%. In particular, she could walk independently and lift a glass without spilling the contents. By April 2002, the results of her neuropsychological examination revealed absence of rigidity, tremor, and akathisia.

Abbreviations used in this paper: CT = computerized tomography; ECD = ethyl cysteinate dimer; GABA = gamma-aminobutyric acid; IBZM = iodine-123 iodobenzamide; MCS = motor cortex stimulation; MR = magnetic resonance; PD = Parkinson disease; PMC = primary motor cortex; SPECT = single-photon emission CT; STNS = subthalamic nucleus stimulation; UPDRS = Unified PD Rating Scale.

In the early decades of the 20th century, Bucy relieved PD symptoms by surgical ablation of the PMC,14 although this was done at the expense of severe motor deficits. In 1979, Woolsey and coworkers17 relieved both tremor and rigidity in two patients with PD during acute intraoperative stimulation of the PMC. In 1991, extradural MCS was reported by Tsubokawa, et al.:15 MCS is a minimally invasive technique for pain control with no reported mortality, minimal morbidity, and no serious adverse effects.3

Starting from these published observations, we performed chronic unilateral stimulation of the PMC in a patient with PD who did not meet the inclusion criteria for STNS, which resulted in dramatic improvement.3 We report the long-term benefit in that first patient as well as in an additional patient.

Abbreviations used in this paper: CT = computerized tomography; ECD = ethyl cysteinate dimer; GABA = gamma-aminobutyric acid; IBZM = iodine-123 iodobenzamide; MCS = motor cortex stimulation; MR = magnetic resonance; PD = Parkinson disease; PMC = primary motor cortex; SPECT = single-photon emission CT; STNS = subthalamic nucleus stimulation; UPDRS = Unified PD Rating Scale.
Extradural motor cortex stimulation for Parkinson disease

V. 150 msec, and 31 Hz. She scored 10 of 30 on the Mini-Mental State Examination.

Case 2

History. This 65-year-old woman first experienced tremor of the right hand in 1992, with contralateral involvement occurring a few months later. Her condition slowly worsened with severe hypobradykinesia, marked postural instability and diffuse rigidity to all four limbs. Administration of levodopa and selegiline produced marked improvement, particularly in bradykinesia and spastic hypertonia. After 4 years, increasing tolerance to levodopa, halting speech and gait, marked on–off phenomena—but not dyskinesias—appeared. There was short-term memory impairment with normal semantic and procedural memory; slow, monotonous, and hypophonic speech; shuffling; fasiculating; short-stepping gait in a camptocormic attitude; difficulty in initiating gait; marked facial hypomimia; severe bradykinesia; diffuse rigidity to all four limbs (right 3+/H11001, left 2+/H11001); small to medium range tremor in both hands (worse on the right); and feeble, monotonous voice with slight dysarthria. There was no frank psychosis, but moderate reactive depression and personality disorder were present. Ropirinole and pergolide were added to her medication regimen but the patient did not improve with severely compromised gait and unpredictable on–off phenomena, even at the maximum tolerated levodopa dosage.

In 2001, the patient was maintained on a regimen of levodopa-benserazide (687.5 mg), pergolide (1 mg three times daily), and selegiline (5 mg). She could stand with external support. Her gait was shuffling with anteropulsion and ambulation was possible only with active assistance from another person. She suffered facial hypomimia, very marked hypobradykinesia, spastic hypertonicity of the limbs (right 4+, left 2+), severely compromised fine movements of the hands (worse on the right), dysphagia, salorrhea, medium-range tremor of the hands (worse on the right), and poorly intelligible speech with marked hypophonia. She scored IV on the Hoehn and Yahr scale. The UPDRS (version 3.0) daily living and motor scores were 25 and 42 (writing was not evaluated because the patient was illiterate).

Neuroimaging Studies. Magnetic resonance imaging revealed an enlarged cisterna magna and ischemic foci in the white matter. High-resolution IBZM SPECT scans, obtained while the patient’s medication was at a reduced level, revealed asymmetrical binding (right less than left) in the basal ganglia and ECD SPECT scans demonstrated bilateral parietotemporal hypoperfusion (Fig. 2).

The patient’s head was shaved and the location of the central sulcus was marked on the skin along Haukton–Taylor lines; a tube filled with paramagnetic liquid was secured with adhesive drapes. Motor area localization was confirmed by standard functional MR imaging sequences while the patient touched the tips of her left fingers to her thumb as fast as she could. The echoplanar multiphase acquisition in a 1-tesla MR imager consisted of a 3.31-minute sequence with 3/30 seconds of motor activation interleaved with 4/30 seconds of rest. Functional MR images were processed using dedicated software. The location of the paramagnetic marker was adjusted until there was perfect overlaying with the central sulcus (Fig. 3).

Operation and Postoperative Course. The patient received a local anesthetic and a linear incision along the projection of the right central sulcus (arm area) was made. Two burr holes were drilled in front of the projection of the central sulcus to accommodate the length of the stimulation paddle (RESUME; Medtronic) (Fig. 3). After durotomy the paddle was slid under the bone over the primary motor area and the electrocatheter was externalized behind the ear. After a 2-week stimulation test period, during which the most beneficial parameters were found, general anesthesia was induced in the patient and the pulse generator (ITREL II; Medtronic) was implanted subclavicularly and connected to the electrocatheter. The best stimulation parameters, after further adjustment, were 3 V, 90 msec, 30 Hz, and a 2+/0− setting. At 1-, 3-, and 6-month follow-up examination there was
improved cognition with correct spatiotemporal orientation and reduced response latencies. The patient could ambulate autonomously most of the time without freezing gait, although with slight camptocormia. Bradykinesia was improved, tremor was absent, spastic hypertonia was absent in the left hemisoma while it was minimal or modest contralaterally (right arm 1+/5; right leg 2+/5). Hypophonia and dysarthria were improved and the patient, who spoke in a southern dialect, was more intelligible (Fig. 4). Electroencephalographic recording at 1 month disclosed no epileptic foci. At this time, IBZM SPECT scans revealed renormalization of basal ganglia anomalies; ECD SPECT scans demonstrated fully renormalized cortical metabolism on the side of stimulation but not contralaterally (Fig. 2).

Discussion

The results in our patients illustrate the effectiveness of MCS for typical PD. Interestingly, we achieved transitory (months) motor and vegetative benefits in a patient with multisystem atrophy and parkinsonism in whom no benefit was obtained from bilateral STNS (unpublished observations). Decreased striatal D2 receptor binding seems to be a predictor of nonresponse to STN surgery.9 The patient in Case 2 showed decreased IBZM binding but nonetheless successful implantation was achieved. A detailed description of the surgical technique used in MCS and all relevant related issues have been previously reported.2

Rationale. Following the pioneering work of Bucy in the 1920s,14 the PMC was found to play a role in the pathophysiology of PD; however, at the time, there was no practical way to modulate its function. In 1972, Alberts1 found that he could initiate or augment PD tremor by direct stimulation of the motor cortex with a paddle at 60 Hz. In a seminal 1979 paper, Woolsey and colleagues17 found that acute intraoperative stimulation relieved both rigidity and tremor in two patients with PD. Direct cortical extradural stimulation was introduced at the end of the 1980s. In the 1990s, several authors reported the effect of MCS on poststroke rigidity and tremor.7,8,13 Following its introduction in 1985, repetitive transcranial magnetic cortex stimulation—a technique whereby cortical areas are focally activated by an external magnetic coil—was found to relieve PD motor signs by several, but not all, investigators.4 Direct MI modulation via the MCS was a logical option. The key role of motor cortex in parkinsonian syndromes is highlighted by the finding of a significant reduction in the N-acetylaspartate/creatine ratio in the motor cortex of patients with de novo PD.12 Moreover, modification of motor cortex metabolism contributes to the efficacy of several surgical procedures for PD, as assessed from PET imaging studies.5,15,17

Physiological Effects. The most striking finding of this report is that MCS at low frequency (20–30 Hz) relieves all three cardinal signs of PD. This is exactly the opposite of what occurs in STNS.9,10 Actually, high-frequency stimulation (> 100 Hz) produced a worsening of symptoms or never achieved the benefits found with low-frequency stimulation. Rigidity and tremor were abolished within several minutes of stimulation. The full effect on bradykinesia was appreciated only after a longer period of stimulation. In fact, the benefits achieved actually increased with time, particularly as they related to gait (days–weeks). During test stimulation, certain parameters produced a temporary burning sensation in the arm but this problem disappeared immediately after the parameters were changed. At higher voltages, headache could sometimes be provoked; this too yielded to parameter adjustments. Interestingly, unilateral MCS seems to relieve both sides: although the effect on rigidity was minimally better on the contralateral side, we observed no difference in the effect on bradykinesia. We wrote off this effect to direct corpus callosum transfer of stimulation,7 but this remains to be further explored.
Extradural motor cortex stimulation for Parkinson disease

**Mechanism of Action.** The patient in Case 2 underwent SPECT scanning, which revealed that MCS actually changes local cortical metabolism, exactly as happens for pain modulation. What could be the actual mechanism of action? Transcranial magnetic cortex stimulation studies reveal that PD is associated with excess excitability or reduced inhibition at MI levels. During production of a voluntary output, its activation is defective or inadequately modulated. One major mechanism may be a dysfunction of the interneurons mediating the level of excitation within cortical Area 4. There is a shortening of the so-called central silent period which is a complex transcranial magnetic cortex stimulation–induced inhibitory phenomenon possibly mediated by activation of GABA-B receptors. The so-called short-interval intracortical inhibition, which is possibly mediated by GABA-A receptors, is also diminished. A GABA-mediated mechanism is exactly what we hypothesize for MCS in pain conditions. In addition, MI is sensitive to dopamine modulation. We previously discussed the possible effect on plastic changes induced locally and downstream by the stimulator; SPECT data obtained in Case 2 indicate the possibility that MCS might be able to upregulate dopamine receptors in the striatum. This merits further study.

**Conclusions**

It appears that MCS relieves PD but not multisystem atrophy symptoms, and this is accomplished using unilateral implantation and stimulation, possibly reducing the cost of surgery compared with bilateral STNS. It does not require stereotactic equipment and can thus be pursued by all neurosurgeons. Targeting of the motor cortex is mandatory and is performed with functional MR imaging. If these findings can be confirmed in larger series, a new dimension will be added to the treatment of PD.

**References**


**Note Added in Press**

Ten months after stimulator implantation, the patient in Case 2 suffered depressive symptoms and hallucinations, although her symptoms of PD remained relieved. Switching off the stimulator did not improve her new symptoms and drug therapy was instituted.

A new patient with PD, a woman 74 years of age, underwent stimulator implantation on the right PMC. Treatment resulted in dramatic control of tremor and rigidity, and a modest improvement in gait at the 5-month follow-up examination. This patient had previously suffered from depressive episodes and some hallucinations. A CT scan demonstrated atrophy with ventricular enlargement and ischemic encephalopathy. Six months after implantation, she experienced severe hallucinations, which required therapy. The patient in Case 1, who underwent surgery on the left side never exhibited such behavior.

Although psychiatric symptoms and dementia frequently occur in cases of PD and these bouts could be part of the natural history of the disease, it is possible that stimulation of the right frontal lobe, which is known to process a negative affect, may have induced these symptoms in the two patients with previous psychiatric disturbances, both of whom underwent surgery on the right side. No such effect has been observed in elderly patients who have received MCS for neurogenic pain. Deep brain stimulation also may carry such a negative potential.

Until this issue is clarified, we urge surgeons to apply MCS for PD only to the left side in elderly patients with psychiatric conditions.

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