Motor Cortical Stimulation for Parkinsonism in Multiple System Atrophy

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Background: Functional neuroimaging studies have demonstrated disturbances in the activity of premotor and motor cortices in Parkinson disease and in animal models of parkinsonism that improve in response to effective basal ganglia surgical therapy. Techniques that directly alter the function of these cortical areas, such as transcranial magnetic stimulation, have been applied in patients with Parkinson disease, with transient improvement in their bradykinesia and gait dysfunction. Recently, a patient with refractory Parkinson disease was claimed to have obtained a marked bilateral clinical benefit from extradural unilateral motor cortical stimulation. We hypothesized that direct cortical stimulation could alleviate the disability of the treatment-refractory parkinsonian symptoms commonly present in MSA.

Objective: To evaluate the efficacy of motor cortical stimulation in patients with refractory parkinsonism due to multiple system atrophy (MSA)

Methods: Five patients with a diagnosis of MSA with predominant parkinsonism underwent surgery for subdural motor cortical stimulation.

Main Outcome Measures: Changes in activities of daily living and motor subscores on the Unified Parkinson’s Disease Rating Scale 12 hours after medication withdrawal. Scores at baseline and 3 to 6 months following surgery were compared.

Results: All patients had a decline in motor scores at the follow-up evaluations despite the application of a variety of adjustments. The activities of daily living score mildly worsened by 9.7% (95% confidence interval, 32.3 to –13.0; P = .37) and the motor score worsened by 25.6% (95% confidence interval, 58.7 to –7.5; P = .06). Despite objective worsening over time and no deterioration when stimulation was immediately turned off, 3 patients still claimed subjective benefit and requested continued stimulation. No patients suffered adverse effects from the surgery or long-term stimulation, although 1 patient had a stimulation-induced seizure during the initial programming. The range of settings for 4 patients with bipolar configuration and 1 patient with monopolar configuration were as follows: amplitude, 3 to 3.6 V; pulse width, 40 to 90 milliseconds; and pulse rate, 145 to 185 Hz.

Conclusions: Our data suggest that motor cortical stimulation using these parameters fails to improve the motor disability in MSA. Worsening of motor scores was likely a function of disease progression.

Arch Neurol. 2003;60:1554-1558

MULTIPLE SYSTEM atrophy (MSA) is a progressive neurodegenerative illness that consists of autonomic and pyramidal dysfunction, with either a predominance of parkinsonism or cerebellar symptoms or a variable combination of these. The clinical phenotype depends on the distribution of neuronal loss, gliosis, and glial cytoplasmic inclusions (GCIs), the hallmark pathologic feature of the condition. Parkinsonian features in MSA include tremor (more often postural and action tremor than typical rest tremor), rigidity, bradykinesia, and postural instability, all of which are usually poorly or only transiently responsive to levodopa. The natural history of this condition is one of rapidly progressive disability over a few years, typically with loss of the ability to ambulate, complete dependence, and eventual death from the complications of an immobile bed-bound state. The median survival from diagnosis is estimated to be between 5 to 6 years, with early and more prominent autonomic symptoms thought to shorten survival. Basal ganglia surgery, including pallidotomy and striatal fetal dopaminergic cell transplantation, have been ineffective in improving the symptoms or altering the natural history of the disease.

Little is known about the underlying pathogenesis of parkinsonian fea-
tures in MSA given the lack of animal models and limited functional imaging studies. The importance of cerebral cortex dysfunction in generating signs of parkinsonism comes from studies in animal models of Parkinson disease (PD) as well as in humans with PD. There is recent evidence in N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine lesioned monkeys that excessive motor cortical synchronization may underlie muscle rigidity by causing a persistent cocontraction of antagonistic muscles.10

Firing rates in M1 neurons were unchanged compared with those in normal monkeys; however, the M1 neurons discharged in abnormally long synchronized bursts that did not elicit movement. Furthermore, the synchronized bursts were not present in the internal segment of the globus pallidus (Gpi), which suggests that the motor cortex synchrony arises independently of basal ganglia function or dysfunction. As such, direct disruption of the abnormal M1 neuronal firing might be expected to ameliorate symptoms.

Positron emission tomography11 and functional magnetic resonance imaging12,13 have also demonstrated disturbances of premotor and motor cortical function in patients with idiopathic PD who improve in response to dopaminergic12 and surgical therapy.14 In patients with idiopathic PD, subthreshold stimulation of the motor cortex with single-pulse transcranial magnetic stimulation15 and repetitive transcranial magnetic stimulation,16 as well as direct electrical stimulation of the motor cortex,17 have been shown to ameliorate bradykinesia and rigidity. This may also account for the recent observation of a patient with refractory PD who was claimed to have obtained a marked bilateral clinical benefit from extradural unilateral motor cortical stimulation, a technique that is used safely and effectively in patients with deafferentation pain.18 Based on this latter observation and on the experimental data suggesting that modulation of cortical circuits and disruption of pathologic synchronization of the cortex10 may relieve parkinsonism, a pilot trial of motor cortical stimulation in select MSA patients was performed.

Table 1. Characteristics of 5 Patients With Multiple System Atrophy

<table>
<thead>
<tr>
<th>Patient/Sex/ Age at Surgery, y</th>
<th>Side of Surgery</th>
<th>Disease Duration Prior to Surgery, y</th>
<th>H&amp;Y</th>
<th>Medications</th>
<th>Stimulator Settings, Pulse-Width, ms; Rate; Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/53</td>
<td>L</td>
<td>3</td>
<td>5</td>
<td>Amatine, florinef, buspirone</td>
<td>3; 0−3+; 40; 150</td>
</tr>
<tr>
<td>2/M/72</td>
<td>L</td>
<td>5</td>
<td>4</td>
<td>Levodopa/carbidopa, 250/25 qid; pramipexole, 1.25 mg qid</td>
<td>3; 0−3+; 90; 145</td>
</tr>
<tr>
<td>3/F/75</td>
<td>L</td>
<td>9</td>
<td>4</td>
<td>Levodopa/carbidopa, 100/25 tid; pramipexole, 1.25 mg tid; amantidine, 100 mg bid</td>
<td>3; 1 + 2−; 60; 85</td>
</tr>
<tr>
<td>4/M/66</td>
<td>L</td>
<td>5</td>
<td>4</td>
<td>Ropinirole, 2 mg qid; levodopa/carbidopa, 100/25 qid (CR, 200/50 qid)</td>
<td>3.6; C + 3−; 60; 185</td>
</tr>
<tr>
<td>5/F/59</td>
<td>L</td>
<td>8</td>
<td>5</td>
<td>None</td>
<td>3; 0−3+; 60; 160</td>
</tr>
</tbody>
</table>

Abbreviations: bid, twice daily; C, case; CR, controlled release; H&Y, Hoehn and Yahr stage; qid, 4 times daily; tid, 3 times daily.

Surgical Procedure

Subdural motor cortical stimulation was performed after obtaining signed informed consent and approval from the institutional review board of the Toronto Western Hospital (Toronto, Ontario). The contralateral motor cortex of the most affected side was targeted; however, in cases where symptoms were symmetrical, the dominant hemisphere was chosen. All patients underwent a left-sided procedure. A craniotomy was performed under local anesthesia using the standard procedure. A monopolar current was used to stimulate the motor cortex to identify the motor and sensory cortices. Once the motor cortex was identified, a strip (Resonue II model 3387A electrode; Medtronic Inc, Minneapolis, Minn) containing 4 electrode contacts spaced 1 cm apart was placed directly over the long axis of the motor area. Through a separate stab incision, a percutaneous connection was inserted and connected with the subdural strip. During the week following the electrode placement and prior to internalization of the pulse generator (Intell 2 single channel; Medtronic Inc), electrophysiologic testing was performed to look for optimal parameters that would reduce symptoms and determine which parameters induced adverse effects. Five to 7 days after the surgery, the cortical electrode was connected to a pulse generator that was inserted subcutaneously below the clavicle under general anesthesia. Following this, further programming was performed to define “optimal” stimulation parameters for chronic use (ie, best tolerated and, if possible, associated with perceived clinical benefit).

Statistical Analysis

Pairwise comparisons were done between baseline (preoperative) scores and postoperative scores using the Wilcoxon signed-rank test. Percent changes in scores and 95% confidence intervals were calculated, and P values were generated.

No immediate beneficial clinical changes were obtained while stimulation parameters were being adjusted. Stimulation thresholds were determined by seizure
induction, which occurred during initial programming and resolved immediately on discontinuing stimulation (1 patient) or by the induction of bothersome paresthesiae (4 patients). The stimulators were then programmed, choosing the widest electrode contact separation to facilitate the largest possible area for current spread. The settings are presented in Table 1. The stimulators were left at these settings and remained on 24 hours per day.

All patients had a decline in their motor scores at 3- to 6-month follow-up evaluations (Table 2). The UPDRS motor subscore worsened by 25.6% (95% confidence interval, 58.7 to −7.5; \( P = .06 \)), and the activities of daily living subscore worsened by 9.7% (95% confidence interval, 32.3 to −13.0; \( P = .37 \)). Two patients underwent evaluation after 12-hour medication withdrawal and then again following their usual morning dose of antiparkinsonian medications. There were no significant differences in their motor scores with or without medications. Despite objective worsening over time and no deterioration when stimulation was immediately turned off, 3 patients still claimed subjective benefit (Table 2) and requested continued stimulation. No patients experienced adverse effects from the surgery or long-term stimulation. Three patients died 6, 9, and 24 months after the completion of the study from disease-related respiratory complications (2) and after a urinary tract infection (1). These patients had continuous stimulation until the time of death. No autopsies were performed.

### Comment

In this pilot trial, motor cortical stimulation using the maximum tolerated stimulation parameters was not effective in ameliorating symptoms of parkinsonism in 5 patients with MSA. Factors that are likely to play an important role in the axonal and neuronal response to electrical stimulation include intensity, polarity (anodal vs cathodal), pulse width, frequency of stimulation, distance between the neural elements and the electric field, the duty cycle of the stimulation (how much time the stimulation is on compared with off in a given period), and the configuration of the electric field.19 Not having a strong rationale to do otherwise, we chose electrical parameters that are known to be effective in deep brain stimulation of the thalamus, Gpi and subthalamic nucleus in patients with PD.20,21 Lack of immediate feedback at the time of programming, such as is seen with the induction or abolishment of tremor in patients with PD, precluded optimization of settings at the time of programming. We chose the widest possible spacing between electrode contacts to try to increase current spread and influence a greater volume of cortex. It is not known whether alternative stimulation parameters might have provided better results. One recent report did not show a significant improvement in a patient with atypical parkinsonism following extradural motor cortical stimulation at a low frequency (25–40 Hz).22 It is also theoretically possible that the benefit could have been delayed for months and thus was not seen immediately at the time of programming or during the 3 to 6 months of follow-up. This latency of response is known to occur in patients who undergo pallidal surgery for dystonia.23 Despite a subjective benefit in 3 patients, objective measures showed a trend toward deterioration of function 3 to 6 months after the surgery compared with the preoperative baseline. It is possible that the UPDRS as the primary outcome measure was not a sensitive enough instrument to determine benefit; it may be limited owing to a ceiling effect once a certain level of disability has been attained. A recent report concluded that the UPDRS-III is a reliable but suboptimal tool with which to measure the severity of parkinsonism in MSA.24

The premise underlying this trial was that most of the pathologic characteristics in MSA (the striatonigral de-

### Table 2. Unified Parkinson’s Disease Rating Scale Scores Before and After 3 to 6 Months of Motor Cortical Stimulation in 5 Patients With Multiple System Atrophy

<table>
<thead>
<tr>
<th>Patient</th>
<th>ADL</th>
<th>Motor</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preoperative</td>
<td>Postoperative</td>
<td>Preoperative</td>
</tr>
<tr>
<td>1</td>
<td>32</td>
<td>34</td>
<td>58</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
<td>37.5</td>
<td>46.5</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>33</td>
<td>39</td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>38.5</td>
<td>27</td>
</tr>
<tr>
<td>5</td>
<td>27.5</td>
<td>24</td>
<td>64</td>
</tr>
<tr>
<td>Mean</td>
<td>30.7</td>
<td>33.4</td>
<td>46.9</td>
</tr>
</tbody>
</table>

Abbreviations: ADL, activities of daily living; UTI, urinary tract infection.

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generation type) are found in the basal ganglia. The pathologic hallmark of MSA is the GCI.14,15 These are found throughout the brain and generally in high density, especially but not exclusively in areas with the greatest cell loss and gliosis, such as the putamen in striatonigral degeneration. However, the relationship between the cell loss and GCIs is unclear with regard to causality and severity.23 as different structures show variable degrees of each with no consistent predictable relationship. The striatum is part of the corticostriatopallidothalamiccortical motor circuit, which has projections to the premotor and supplementary motor areas26 as well as the primary motor cortex.27 In a review of 203 pathologically proven cases of MSA, these same motor areas were found to have a high density of GCIs with relative sparing of neurons. There are no other known histologic alterations in the cortex of MSA28 and so it is unclear whether the GCIs in the cortex are simply a marker of disease or actually contribute to the clinical manifestations of the disease. If the former applies, then targeting the relatively spared but dysfunctional downstream motor cortex would bypass the primary site of disease and might result in a normalized cortical output. However, if the presence of cortical GCIs is causally related to the pathogenesis of symptoms of parkinsonism, then the motor cortex may be a poor candidate for surgical intervention. Finally, extrapolating from the PD model may not be justifiable because the motor cortical changes accompanying the parkinsonism of striatonigral degeneration may differ from those in PD.29 Our group has demonstrated that the neuronal firing rates in the Gpi of MSA patients undergoing pallidotomy are lower than those found in PD (Luiz C. Pereira, MD, Vanessa N. Palter, BSc, A.E.L., William D. Hutchison, PhD, Andres M. Lozano, MD, PhD, Jonathan O. Dostrovsky, PhD, unpublished data, 2003). In PD, Gpi hyperactivity is believed to result in motor cortical inhibition. The lack of this feature might predict that therapeutic modulation of motor cortical circuits, which could disrupt pathologic synchronization in PD, may not have the same clinically beneficial effect in MSA.

Canavero and Paolotti,30 who originally reported successful treatment of a medically intractable PD patient with extradural cortical stimulation, recently described a second case who failed to obtain a similar benefit. Following inadequate response to subthalamic nucleus deep brain stimulation, this patient with levodopa-resistant parkinsonism (possibly MSA) underwent unsuccessful staged bilateral extradural motor cortical stimulation. In another patient with drug-resistant parkinsonism due to a hypoxic–ischemic insult, Krack et al31 reported poor results of bilateral subthalamic nucleus surgery. It is the general consensus of centers specializing in functional surgery of movement disorders that levodopa-resistant parkinsonism in “Parkinson-plus” disorders (MSA, progressive supranuclear palsy, and corticobasal degeneration)32 fails to benefit from current surgical treatments for PD. This is in keeping with evidence that suggests that a robust presurgical levodopa response is the best predictor of a good response to basal ganglia surgery33-36; however, it remains to be determined whether this is also a prerequisite for successful motor cortex stimulation.

Further studies are required to elucidate the nature of motor cortical dysfunction in MSA and the role of GCIs in the motor cortices. It will also be necessary to study the role of corticospinal pathways in the generation of symptoms and the resistance of these symptoms to available medical and surgical therapies. This knowledge will hopefully allow the development of more effective symptomatic treatment for this severely debilitating disorder.

Accepted for publication February 11, 2002.

Author contributions: Study concept and design (Ms Sime and Drs Lozano and Lang); acquisition of data (Drs Kleiner-Fisman, Khan, Lozano, and Lang, and Ms Sime); analysis and interpretation of data (Drs Kleiner-Fisman, Fisman, Lozano, and Lang); drafting of the manuscript (Drs Kleiner-Fisman, Fisman, and Lozano and Ms Sime); critical revision of the manuscript for important intellectual content (Drs Kleiner-Fisman, Fisman, Khan, and Lozano); statistical expertise (Dr Fisman); administrative, technical, and material support (Drs Kleiner-Fisman, Khan, Lozano, and Lang and Ms Sime); study supervision (Drs Lozano and Lang).

This research was partially supported by a Center of Excellence Grant from the National Parkinson Foundation, Miami, Fla (Dr Lang), and fellowship support from Medtronic Inc.

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