Deep brain stimulation has been established as a safe and efficacious treatment for various movement disorders. 3,12,20–23,30,35 While the STN has been established as the major target in PD, 1,2,24,30 the GPi is currently the favored structure for chronic stimulation in dystonia. 5,22,35 Nevertheless, controversy remains about whether alternative targets might not be more beneficial in individual patients. 12,32 Only recently has the concept of multifocal DBS been introduced. 4,13,15,17,19,31,33 Thus far, few reports have demonstrated the added value of combined multifocal DBS in the same or different targets in patients with movement disorders. 13,15,19,31

Here, we report on a young patient with atypical levodopa-responsive dystonia-parkinsonism who benefited from combined chronic STN and GPi DBS.

Case report

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Multifocal deep brain stimulation (DBS) is a new technique that has been introduced recently. A 39-year-old man with dystonia-parkinsonism underwent the simultaneous implantation of subthalamic nucleus (STN) and globus pallidus internus (GPi) DBS electrodes.

While bilateral STN DBS controlled the parkinsonian symptoms well and allowed for a reduction in levodopa, the improvement of dystonia was only temporary. Additional GPi DBS also alleviated dystonic symptoms. Formal assessment at the 1-year follow-up showed that both the parkinsonian symptoms and the dystonia were markedly improved via continuous bilateral combined STN and GPi stimulation. Sustained benefit was achieved at 3 years postoperatively. (DOI: 10.3171/2011.8.JNS101552)

Key Words • pallidum • subthalamic nucleus • deep brain stimulation • dystonia-parkinsonism • functional neurosurgery

Deep brain stimulation has been established as a safe and efficacious treatment for various movement disorders. 3,12,20–23,30,35 While the STN has been established as the major target in PD, 1,2,24,30 the GPi is currently the favored structure for chronic stimulation in dystonia. 5,22,35 Nevertheless, controversy remains about whether alternative targets might not be more beneficial in individual patients. 12,32 Only recently has the concept of multifocal DBS been introduced. 4,13,15,17,19,31,33 Thus far, few reports have demonstrated the added value of combined multifocal DBS in the same or different targets in patients with movement disorders. 13,15,19,31

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Case Report

History and Examination. Dystonia developed within a fortnight in this 33-year-old man. He had involuntary inward rotation, supination, and plantar flexion of the right foot followed by retrocollis and laterocollis to the left. His family history was negative for movement disorders. Magnetic resonance imaging of the head, neck, and lumbar spine were normal. Blood laboratory tests, urinary copper excretion, and CSF analysis were normal.

Within the next 6 months, he demonstrated hyperlordosis of the trunk, hypomimia, and rigidity in the right arm more pronounced than in the right leg with bradykinesia and action tremor of the right hand. A PARK2 mutation analysis was negative. Reduced decarboxylase activity was revealed in the left anterior and posterior striatum by using 18F-dopa PET. Moreover, 11C-raclopride PET showed an increased D2-receptor density more pronounced in the left than in the right putamen with a rostrocaudal gradient. The FDG-PET studies of the basal ganglia were normal; however, there was a decrease in metabolic activity of the frontobasal cortex bilaterally. These findings were partially consistent with early-onset idiopathic PD, although the FDG-PET indicated a more widespread disorder. With regard to the development of the movement disorder and the phenomenology, a diagnosis of atypical dystonia-parkinsonism was made. Since more exclusive genetic testing was not available, the movement disorder was not further classified. Initial therapy included biperiden (5 mg/day), tiapride (100 mg/day), trihexyphenidyl (30 mg/day), clonazepam (3 mg/day), olan-
zapine (10 mg/day), and paravertebral botulinum toxin injections (maximum 1500 units Dysport) without lasting positive effects. Levodopa (maximum 600 mg/day) moderately reduced the rigidity and akinesia with inconsistent improvement in the dystonia. After 5 years, marked motor fluctuations occurred. Ropinirole (15 mg/day) was not tolerated because of the sleepiness it induced.

Six years after disease onset, the patient was referred for DBS surgery because of increasing motor fluctuations. On admission, he was on levodopa, 600 mg/day; clonazepam, 3 mg/day; and trihexyphenidyl, 6 mg/day. He had marked hypomimia, dysarthric hypophonia, and reduced blinking. He displayed torticollis to the left, laterocollis to the right, and hyperlordosis of the trunk. Dystonic posturing of the right hand along with finger adduction, wrist flexion, and radial deviation was accompanied by intermittent resting tremor. Mild action tremor was present in all 4 limbs. Diadochokinesia was disturbed in the right more than the left hand. Dystonic supination, inward rotation, and plantar flexion of the right foot were more prominent while walking than while running.

Preoperatively, the patient was evaluated while on his regular medication (M-On) and in a practically defined off-medication (M-Off) state after drug discontinuation for ≥12 hours overnight. The protocol included the UDRS, the BFM dystonia movement scale, the GDS, and the UPDRS as well as a standard video protocol. The patient improved on the UPDRS part III by 58% while on the levodopa as compared with the M-Off state (Table 1). However, improvement was accompanied by marked dyskinesias of the head, neck, and limbs.

Operation. The patient gave written informed consent for multifocal DBS including periprocedural follow-up. Because of the combined parkinsonian symptoms and severe dystonia, 4 DBS electrodes, that is, 2 STN and 2 GPi, were implanted with guidance via CT-stereotactic surgery and microelectrode recording. Concepts and techniques of the surgical procedure for DBS have been described in detail elsewhere.18 Quadrupolar electrodes were implanted in the posteroventral lateral GPi (Medtronic, Inc.) and the dorsolateral STN (Medtronic, Inc.). Electrodes were externalized for a period of test stimulation. There were no intraoperative adverse effects. Postoperative MR imaging demonstrated appropriate electrode placement (Fig. 1).

During STN stimulation, the patient improved on the UPDRS part III by 67%, on the BFM scale motor by 69%, and on the UDRS motor by 57% as compared with the M-Off state. The improvement of dystonia via GPi stimulation was 76% on the BFM scale motor and 74% on the UPDRS motor; the reduction on the UPDRS part III remained at 65%. With GPi DBS, resting tremor of the right arm and leg persisted. Subsequently, STN electrodes were connected to an implantable pulse generator (Kinetra, Medtronic, Inc.), and the GPi electrodes were left in situ but not connected. Although rating scales improved slightly more with GPi stimulation, we decided to use the STN electrodes for chronic stimulation with regard to the possible option of reducing dopaminergic drugs.

Postoperative Course. After 2 months, control of tremor and bradykinesia was still excellent, but the dystonia had recurred. Multiple trials of adjusting the stimulator settings were unsuccessful. A particular problem was that levodopa markedly increased the dystonia at that time. Thus, we decided to implant a second pulse generator for additional chronic stimulation of the GPi. Subsequently, the dystonia improved substantially. At the 12-month follow-up of bilateral bifocal stimulation of the STN and GPi, there was persistent improvement in both the parkinsonism and the dystonia (Table 1). The following stimulation settings were used: GPi, bipolar stimulation (Contacts 1 and 5 negative, Contacts 2 and 6 positive), pulse width 210 μsec, frequency 130 Hz, voltage 3.0 V; STN, monopolar stimulation (Contact 2 negative, case positive), pulse width 60 μsec, frequency 130 Hz, voltage 2.8 V. There were no stimulation-induced side effects. Medication included levodopa, 300 mg/day; clonazepam, 1.5 mg/day; and trihexyphenidyl, 6 mg/day.

Three years postoperatively, the patient still benefited markedly from bilateral bifocal stimulation. At that time, the most disturbing symptom was truncal hyperextension, which was increased on walking. Voltage had been slightly increased from 3.0 to 3.2 V for pallidal stimulation and from 2.8 to 3.0 V for STN stimulation. Levodopa had been increased to 600 mg/day.

Discussion

Multifocal DBS is an emerging technology for treating complex movement disorders. It can be used to select the optimal target in patients with movement disorders, such as tremulous dystonia or secondary dystonia—either the GPi or the ventral intermediate nucleus of the thalamus.5,19,33 Another possibility is to combine the effect of chronic stimulation via multiple electrodes.

### TABLE 1: Summary of the clinical scales and scores used for STN and GPi DBS in dystonia-parkinsonism

<table>
<thead>
<tr>
<th>Subscales</th>
<th>Preop</th>
<th>Postop</th>
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<tbody>
<tr>
<td>Motor</td>
<td></td>
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<tr>
<td></td>
<td>M-On</td>
<td>test phase:</td>
</tr>
<tr>
<td></td>
<td>M-Off</td>
<td>STN-On, M-Off</td>
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<tr>
<td>Preop</td>
<td></td>
<td>2 mos STN-On, clonazepam 1.5 mg/d, trihexyphenidyl 6 mg/d</td>
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<tr>
<td>BFM</td>
<td>24</td>
<td>42.5</td>
</tr>
<tr>
<td>UDRS</td>
<td>24</td>
<td>47</td>
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<tr>
<td>UPDRS</td>
<td>18</td>
<td>43</td>
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<tr>
<td>GDS</td>
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Dystonia-parkinsonism can occur in the frame of several distinct neurodegenerative or genetic disorders. Although the time course was fairly typical in our patient, functional imaging findings did not allow us to establish the diagnosis of rapid-onset dystonia-parkinsonism. This rare familial or sporadic disorder is characterized by the presence of marked focal, segmental, or generalized dystonia associated with akinesia, rigidity, and postural imbalance. It can develop within hours or days. Genetic forms include autosomal-dominant and X-linked inheritance.

Patients with sporadic dystonia-parkinsonism have been recognized as a heterogeneous group with variable responsiveness to levodopa. In these patients, 18F-dopa PET studies have demonstrated a pattern of reduced 18F-dopa uptake in the putamen and globus pallidus similar to that in PD. Therapeutic options are limited in patients who do not have adequate improvement with medication. Dystonia-parkinsonism is distinct from early-onset idiopathic PD and can be clinically characterized by prominent dystonia early in the disease course. In the patient in our case, levodopa led to a partial improvement in the parkinsonian symptoms, but over time motor fluctuations developed and dystonia was never satisfactorily controlled.

There is very little experience with chronic DBS in dystonia-parkinsonism, and thus far mainly negative results have been published in single case reports. Deutschländer et al. described the failure of bilateral pallidal DBS in a young woman with sporadic rapid-onset dystonia-parkinsonism at 17 months after surgery. Note, however, that the interpretation of data in this study is limited since the left DBS electrode was misplaced. Symptoms were not responsive to levodopa prior to surgery. Another patient with sporadic rapid-onset dystonia-parkinsonism benefited minimally from bilateral pallidal DBS, which was more effective for dystonia than for the parkinsonian symptoms. Interestingly, marked benefits in both dystonia and parkinsonism were achieved in some patients with Lubag syndrome and were sustained at the follow-up after chronic pallidal DBS, whereas the dystonia was improved but not the parkinsonism.

With combined bilateral STN and GPi DBS, tremor, rigidity, bradykinesia, and dystonia were well controlled in our patient. Subthalamic nucleus stimulation alone reduced the parkinsonian features. But within 2 months after the operation, severe dystonia recurred and was not controlled by adjusted STN stimulation. Therefore, the initial control of dystonia could have been a temporary microlesion effect of the insertion of an electrode in the GPi. Globus pallidus internus stimulation alone reduced the dystonia, but parkinsonian symptoms were less well controlled. The role of the STN as a possible target in treating dystonia remains unclear. The STN has been suggested as a target for dystonia more recently, although well-designed comparative studies are lacking.

In our study, STN stimulation produced only short-lived improvement of dystonia. This observation concurs with previously reported findings demonstrating that M-Off state dystonia, but not generalized dystonia, in PD is improved by STN DBS. Clearly, further studies are needed in that regard.

Conclusions

Combined GPi and STN stimulation might be considered in patients with dystonia-parkinsonism, yielding additional benefit as compared with STN stimulation alone. Although combined stimulation is used only exceptionally nowadays, we think that such techniques deserve further consideration to determine their potential.

Disclosure

Dr. Krauss is a consultant for and has received honoraria for speaking from Medtronic, Inc. Dr. Capelle has received speaking fees from Medtronic, Inc.

Author contributions to the study and manuscript preparation include the following. Conception and design: Krauss, Wohrle, Blahak, Capelle, Fogel, Bätzner. Drafting the article: Krauss, Wohrle, Capelle. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Krauss. Administrative/technical/material support: Krauss, Wohrle, Blahak, Capelle, Bätzner. Study supervision: Krauss.

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