Subthalamic nucleus stimulation for Parkinson disease with severe medication-induced hallucinations or delusions

Clinical article

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Object. Subthalamic nucleus deep brain stimulation (STN DBS) improves cardinal motor symptoms of Parkinson disease (PD) and reduces antiparkinsonian medication. Therefore, STN DBS seems to be well indicated for patients suffering from medication-induced psychotic symptoms. However, there are few available data dealing with the effect of STN DBS in this kind of patient. The authors studied the effect of STN DBS in patients with PD and severe medication-induced hallucinations or delusions.

Methods. The authors retrospectively reviewed the clinical course of 10 patients who suffered from severe medication-induced hallucinations or delusions and underwent bilateral STN DBS. Patients whose preoperative thought disorder score (Unified Parkinson’s Disease Rating Scale Part I, item 2) was 3 or more were enrolled in this study. All patients underwent cognitive function examination and brain perfusion SPECT preoperatively to exclude dementia with Lewy bodies.

Results. Subthalamic nucleus DBS yielded significant improvement of motor function in all patients. In 8 patients, psychotic symptoms completely disappeared with significant reduction of dopaminergic medication. In 2 patients, hallucinations and delusions deteriorated immediately after surgery despite complete withdrawal of antiparkinsonian medication. However, these psychotic symptoms completely disappeared after a few months with administration of antipsychotics, and no recurrence was observed afterward in either patient.

Conclusions. Subthalamic nucleus DBS is a good treatment option for patients with PD who are suffering severe medication-induced hallucinations or delusions. However, vigilance is needed, because temporary deterioration of psychotic symptoms may occur after surgery. (DOI: 10.3171/2011.2.JNS101261)

Key Words • Parkinson disease • deep brain stimulation • subthalamic nucleus • medication-induced psychosis • hallucination • delusion
significant motor complications from levodopa such as fluctuation and dyskinesia. Among these patients, some had severe medication-induced hallucinations or delusions. The degree of hallucinations or delusions were evaluated according to the thought disorder (item 2) of UPDRS Part I, that is, 0, none; 1, vivid dreaming; 2, “benign hallucinations” with insight retained; 3, occasional to frequent hallucinations or delusions without insight, could interfere with daily activities; and 4, persistent hallucinations, delusions, or florid psychosis, not able to care for self. Ten patients (3 men and 7 women) whose preoperative thought disorder score was 3 or more were enrolled in this study. We retrospectively reviewed the clinical course of these 10 patients.

The diagnosis “medication-induced” was made by referring neurologists for all patients. Most patients did not undergo sufficient treatment with antipsychotic medication to avoid deterioration of PD symptoms. All patients underwent cognitive function examination and brain perfusion SPECT preoperatively to exclude DLB before surgery. In short, cases of obvious cognitive decline with typical hypoperfusion in the occipital lobe were excluded as candidates for STN DBS.

Surgical Procedure

Quadrupolar DBS electrodes (Activa 3389, Medtronic) were implanted into the STN bilaterally stereotactically with MR imaging guidance under local anesthesia. The target localization was based on the Schaltenbrand-Wahren atlas and on direct visualization on the MR image using surgical planning software (Frame Link, Medtronic). The target was refined physiologically by intraoperative microelectrode recording. The DBS lead was placed as the most distant contact (contact 0) placed at the bottom of the STN. Subsequently, internal pulse generators (Soletra, Medtronic) were placed in infraclavicular pockets and subcutaneously connected to the DBS leads under general anesthesia. The duration of general anesthesia was about 1 hour.

Adjusting Stimulation Parameters and Medication

Electrical stimulation began a few days after surgery. Stimulation parameters were adjusted to produce maximal clinical benefit for cardinal PD symptoms without side effects. Preferably, a monopolar electrode setting was used, unless stimulus-inducer side effects required a more focal bipolar stimulation paradigm. In most cases, stimulation parameters were 90 msec of pulse width, 130 Hz of pulse rate, and 2–3 V of amplitude. After surgery, dopaminergic medication was initially reduced by approximately 50% and then further reduced based on stimulation-induced improvements of PD symptoms.

The LEDD calculations were adapted as follows: 100 mg levodopa with a dopa carboxylase inhibitor = 1 mg pergolide = 1.5 mg pramipexole = 9 mg ropinirole = 4 mg cabergoline.

Results

The demographic details for all patients are shown in Tables 1 and 2. The mean age of the patients at the time of surgery was 61.1 years (range 41–72 years), and the mean duration of the disease was 13.4 years (range 7–20 years). The mean LEDD before surgery was 536 mg. All patients showed severe psychotic symptoms at the time of surgery although some patients (Cases 1, 6, and 9) had been forced to reduce their medication. As for details of psychotic symptoms, all patients had visual hallucinations such as bugs, animals, or someone’s face in the room. Six patients had firm delusions of persecution or jealousy. All patients had a preoperative thought disorder score of 3. Three patients (Cases 5, 6, and 8) were judged as having mild dementia by a preoperative MMSE. However, their dementia was diagnosed as non-DLB from SPECT findings.

Table 1 shows outcomes of motor function and medication. Subthalamic nucleus DBS yielded marked improvement in the UPDRS III motor score and UPDRS IV dyskinesia/fluctuation score, and reduced the need for dopaminergic medication in all patients.

Table 2 shows outcomes of psychotic symptoms. In 8 patients, psychotic symptoms completely disappeared with significant reduction of dopaminergic medication after STN DBS. In 2 patients, hallucinations and delusions deteriorated immediately after surgery despite complete withdrawal of antiparkinsonian medication. However, these psychotic symptoms completely disappeared in a few months with antipsychotic medication, and no recurrence was observed afterward in either patient. Details of these 2 patients are provided below.

Illustrative Cases

Case 2

This 72-year-old woman with a 12-year history of PD developed motor fluctuation and psychotic symptoms with increased antiparkinsonian medication. For 1 year, she often saw bugs or animals and had delusions of being robbed. She underwent bilateral STN DBS. Immediately after recovery from general anesthesia, she became restless, and this was thought to be postoperative delirium. However, delusions of persecution continued, such as attempted murder with poison gas. We administered quetiapine, gradually discontinued antiparkinsonian medication in 7 days, and started STN stimulation. Although motor symptoms significantly improved, psychotic symptoms continued even with administration of risperidone. Abnormal behavior necessitated admission to the psychiatric ward. We temporarily turned off DBS for a few days. Her motor function deteriorated markedly; however, delusions were unchanged. Psychotic symptoms gradually improved with antipsychotics over 3 months with DBS turned on, and the patient returned home 5 months after surgery. Motor symptoms have been well controlled, and independent living has been possible for 4 years without antiparkinsonian medication. No relapse of psychotic symptoms has been reported.

Case 6

This 53-year-old woman with a 20-year history of PD developed motor fluctuation and severe dyskinesia and was referred for surgical treatment. She had visual
and auditory hallucinations and had the delusion that someone was setting fire to her. Her delusion was particularly prominent when she showed severe levodopa-induced dyskinesia. She underwent bilateral STN DBS. We soon started stimulation and reduced her antiparkinsonian medication. Stimulation significantly improved her motor symptoms. She showed delusional speech and abnormal behavior again several days after surgery. We administered quetiapine and stopped her antiparkinsonian medication. However, she had to be placed in isolation in the psychiatric ward due to deteriorating psychotic symptoms. The symptoms gradually improved with additional administration of olanzapine in 2 months with DBS turned on, and she returned home 3 months after surgery. Her motor symptoms have been well controlled without antiparkinsonian medication for 19 months, with no relapse of psychotic symptoms.

**Discussion**

Psychotic symptoms such as hallucinations and delusions are seen in patients with PD, generally as a side effect of dopaminergic medication. Cognitive impairment, increased age, disease duration and severity, depression, and sleep disorders have been consistently identified as independent risk factors for their development. Therefore, medication-induced hallucinations or delusions seem to be rather prevalent in patients with advanced PD who are candidates for STN DBS. Voon et al. revealed a preoperative history of hallucinations or delusions in 35% of patients who presented for assessment prior to STN DBS. However, they did not describe whether these medication-induced symptoms might improve following surgery.

When STN DBS is considered for patients with medication-induced hallucinations or delusions, the physician must subsequently distinguish the diagnosis of PD from DLB, which is a contraindication for DBS. Visual hallucination is a core symptom of DLB and occurs more frequently in patients with DLB than in those with PD. Close observation by the neurologists in charge seems to be the

### TABLE 1: Clinical features and outcomes of motor function and medication

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Duration of Disease (yrs)</th>
<th>Follow-Up Period (mos)</th>
<th>UPDRS III Pre-DBS (on meds)</th>
<th>UPDRS III Pre-DBS (off meds)</th>
<th>UPDRS III Post-DBS</th>
<th>LEDD (mg) Pre-DBS</th>
<th>LEDD (mg) Post-DBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66, F</td>
<td>19</td>
<td>63</td>
<td>42</td>
<td>81</td>
<td>17</td>
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<td>1</td>
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<td>2</td>
<td>72, F</td>
<td>12</td>
<td>54</td>
<td>14</td>
<td>21</td>
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</tr>
<tr>
<td>3</td>
<td>41, M</td>
<td>10</td>
<td>35</td>
<td>1</td>
<td>26</td>
<td>4</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>63, F</td>
<td>20</td>
<td>28</td>
<td>20</td>
<td>40</td>
<td>23</td>
<td>6</td>
<td>3</td>
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<td>5</td>
<td>72, F</td>
<td>14</td>
<td>21</td>
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<td>49</td>
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<td>20</td>
<td>19</td>
<td>16</td>
<td>46</td>
<td>18</td>
<td>6</td>
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<tr>
<td>7</td>
<td>67, F</td>
<td>12</td>
<td>19</td>
<td>17</td>
<td>42</td>
<td>7</td>
<td>3</td>
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<tr>
<td>8</td>
<td>60, M</td>
<td>10</td>
<td>15</td>
<td>13</td>
<td>48</td>
<td>4</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>65, F</td>
<td>7</td>
<td>12</td>
<td>31</td>
<td>36</td>
<td>6</td>
<td>5</td>
<td>0</td>
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<tr>
<td>10</td>
<td>52, M</td>
<td>10</td>
<td>12</td>
<td>2</td>
<td>22</td>
<td>0</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>mean</td>
<td>61.1</td>
<td>13.4</td>
<td>27.8</td>
<td>18.4</td>
<td>41.1</td>
<td>11.1</td>
<td>5.6</td>
<td>0.5</td>
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</table>

### TABLE 2: Clinical details and outcomes of psychotic symptoms

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Details of Psychiatric Symptoms</th>
<th>UPDRS I Item 2 Score Pre-DBS</th>
<th>MMSE Score Pre-DBS</th>
<th>UPDRS I Item 2 Score 1 Mo Post-DBS</th>
<th>MMSE Score 1 Mo Post-DBS</th>
<th>UPDRS I Item 2 Score At Final Follow-Up</th>
<th>MMSE Score At Final Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>visual hallucinations, nightmare, depression, suicide attempt</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>30</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>visual hallucinations, delusions (someone stealing her money)</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>24</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>visual hallucinations, delusions of persecution (someone attacking or slandering him)</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>29</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>visual hallucinations, delusions (brandishing a knife toward her family)</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>24</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>visual hallucinations (someone or small animal at her bed side)</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>21</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>visual hallucinations, delusions of persecution (someone setting fire to her)</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>23</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>visual hallucinations, nightmare, depression, panic attack</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>27</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>visual hallucinations, delusion of persecution (violence to his family)</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>23</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>visual hallucinations, delusion of jealousy (infidelity)</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>28</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>visual hallucinations, auditory hallucinations (someone is standing &amp; talking to him)</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>30</td>
<td>27</td>
<td>0</td>
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</table>
most important basis for diagnosing medication-induced psychosis. In addition, preoperative cognitive screening is important for excluding DLB. As for imaging study, brain perfusion SPECT and \[\text{I-metaiodobenzylguanidine (MIBG)}\] myocardial scintigraphy are useful in the diagnosis of DLB.\(^{11,13}\) \[\text{I-metaiodobenzylguanidine scintigraphy is sensitive to Lewy body disease and useful in differentiating other parkinsonian syndromes. However, this modality cannot differentiate DLB from PD in patients with medication-induced psychosis. Some experts recommend excluding patients on the basis of an MMSE cutoff score of 23 or 24.}^{8}\] In our series, some patients were diagnosed with dementia by MMSE. However, they subsequently received STN DBS because perfusion SPECT ruled out DLB. These patients finally obtained a good outcome in both motor and psychological function. There is also a possibility that preoperative hallucinations or delusions might affect the MMSE score. On the other hand, brain perfusion SPECT, which we used, is certainly not definitive, although it is useful. These patients might be early cases of DLB and require prolonged antipsychosy.

In this study, we tried to verify the validity of STN DBS for patients with PD who have severe medication-induced hallucinations or delusions. As expected, most patients showed significant improvement in motor function and complete remission of psychotic symptoms with marked reduction of dopaminergic medication immediately after surgery. On the other hand, 2 patients showed temporary deterioration of psychotic symptoms despite complete withdrawal of antiparkinsonian medication. However, these psychotic symptoms completely disappeared after a few months. Furthermore, these effects were maintained in the long-term follow-up. Our results support the validity of STN DBS in patients even with severe medication-induced psychotic symptoms. However, vigilance is needed, because temporary deterioration of psychotic symptoms may occur after surgery. As a similar condition, psychotic symptoms are rarely reported as a side effect of temporal lobectomy for medically intractable epilepsy.\(^{12}\) Although the mechanism of psychosis seems to be different from DBS surgery, antipsychotic medication is helpful in both situations.

A variety of postoperative psychotic symptoms such as transient confusion, hypomania, depression, or apathy have been reported following STN DBS.\(^{14}\) On the other hand, there are few reports concerning new-onset hallucinations or delusions. Diederich et al.\(^{1}\) reported a patient who developed new-onset visual hallucinations following STN DBS. They hypothesized that DBS may enhance various neurochemical systems such as specific or nonspecific dopaminergic stimulation and may activate serotonergic systems as well. Another possibility is that direct injury of the substantia nigra pars reticulata by insertion of the DBS lead might have induced peduncular hallucinations.\(^{9}\) Herzog et al.\(^{6}\) reported a manic episode with psychotic symptoms (delusions) induced by STN DBS in a previously psychiatrically healthy patient. With clozapine therapy, psychotic symptoms disappeared but manic symptoms remained. Yoshida et al.\(^{18}\) studied UPDRS Part I thought disorder scores in 18 patients with PD and concluded that STN DBS did not induce deterioration of preexisting hallucinations. As a general interpretation, STN DBS seems not to directly induce hallucinations and delusions. However, as we demonstrated, for patients with severe preoperative medication-induced hallucination or delusions, STN DBS could worsen these symptoms in the early period after surgery. Subthalamus nucleus DBS may lower the threshold for medication-induced psychotic symptoms. Recently, Frank et al.\(^{5}\) introduced the concept that STN DBS directly induces impulsive behavior independent of medication. This is due to interrupting the “no-go” signal delivered by the STN in high-conflict choices. Thus, patients who are impulsive preoperatively may become more impulsive postoperatively despite reduction of medication. From this point, these patients should be considered for globus pallidus internus DBS rather than STN DBS.

Conclusions

Subthalamic nucleus DBS is a good treatment option for patients with PD who suffer severe medication-induced hallucinations or delusion. However, vigilance is needed, because temporary deterioration of psychotic symptoms may occur after surgery. In that case, complete withdrawal of antiparkinsonian medications with DBS turned on and treatment with antipsychotic medication appear to be effective.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Umemura. Acquisition of data: Umemura, Oka, Okita, Matsukawa. Analysis and interpretation of data: all authors. Drafting the article: Umemura. Critically revising the article: Oka, Okita, Matsukawa, Yamada. Reviewed final version of the manuscript and approved it for submission: all authors. Administrative/technical/material support: Yamada. Study supervision: Yamada.

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