Psychiatric Complications of Deep Brain Stimulation for Parkinson's Disease

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Background: The purpose of this article is to review the current literature regarding deep brain stimulation (DBS) of the subthalamic nucleus as a treatment for Parkinson's disease and to bring to the attention of the psychiatric community the possible psychiatric complications of this treatment.

Method: A MEDLINE search of English-language publications was conducted using PubMed in July 2003. The search term used was *deep brain stimulation*. In addition, pertinent references were obtained from the retrieved articles. Reports and studies of psychiatric complications of DBS patients were reviewed and are discussed. A case report is presented of a man who developed hypomanic symptoms shortly after beginning DBS treatment for Parkinson's disease.

Results: There have been an increasing number of reports of postprocedure psychiatric complications, including depression, mania, aggression, and deficits in language. Improvement in symptoms of severe obsessive-compulsive disorder and depression has also been reported.

Conclusion: As information continues to emerge, psychiatrists will play vital roles in the assessment and continuing care of patients who receive DBS. These findings may also provide the framework to determine which patients are at psychiatric risk from DBS. Symptoms of refractory obsessive-compulsive disorder have been noted to improve with DBS, which has led researchers to begin studying its effectiveness for this condition.

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Over the past decade, deep brain stimulation (DBS) has become an effective treatment for severe Parkinson's disease.[1,2] In 1997, the U.S. Food and Drug Administration (FDA) approved the unilateral use of a deep brain stimulator to help control tremors in Parkinson's disease and essential tremor. In 2002, the indication was expanded to bilateral use for Parkinson's disease not adequately controlled with medication. Currently, surgeons are targeting 3 sites for DBS: thalamic, pallidal, and subthalamic.[3] Of the 3 sites, stimulation of the subthalamic site is most likely to enable patients to reduce the amount of dopaminergic medication. Globus pallidus stimulation may be most useful for dystonias and drug-induced dyskinesias. Thalamic stimulation has proven most effective for the treatment of tremor.[4]

The procedure consists of stereotactic placement of either unilateral or bilateral electrodes (usually bilateral) in the appropriate brain region (most commonly the subthalamic nucleus) with wires connected to pulse generators implanted under the skin of the chest. Advantages of DBS versus other invasive treatments for Parkinson's disease include fewer complications than lesioning the brain, the ability to adjust stimulation for the individual patient, and relatively low, although far from negligible, overall risk.[3,5]

DBS of the subthalamic nucleus has improved motor symptoms, reduced motor fluctuations, decreased the need for dopaminergic agents, and improved quality of life for many Parkinson's patients. However, there have been an increasing number of reports, particularly with bilateral stimulation, of postprocedure psychiatric complications, including depression, mania, aggression, and deficits in language. Improvement of symptoms of severe obsessive-compulsive disorder (OCD) and depression has also been reported (vide infra).

CASE REPORT

Mr. A, a 64-year-old man with a more than 40-year history of DSM-IV bipolar disorder who had been euthymic on lithium therapy since the mid-1970s, was diagnosed with Parkinson's disease in 1984. The patient's medical team concluded that it was unlikely that the Parkinson's disease was related to lithium therapy. A progressive decline in renal function resulted in the dis-

continuation of lithium in February 2001. Due to progression of Parkinson's disease with severe dyskinesias, electrodes were implanted bilaterally in the subthalamic nucleus in June 2002. Post-implantation magnetic resonance imaging showed the electrodes extending through the subthalamic nuclei and entering into the substantia nigra near the cerebral peduncles bilaterally. Generators were then implanted in November 2002, their placement having been delayed due to an intervening episode of pneumonia and atrial fibrillation. The initial voltage was 1.0 volts bilaterally, with increases in December 2002, first to 2.1 volts bilaterally and then to 2.3 volts right and 2.5 volts left.

Approximately 6 weeks after DBS was initiated, Mr. A presented to the emergency department with altered mental status characterized by agitation, increased irritability, increased goal-directed activity, odd thinking, expansive statements, and sexually inappropriate behavior that had begun 2 weeks earlier. He was experiencing initial insomnia and expressed generally vague suicidal ideation, although he stated once, "I have never had a stronger sense of suicide." He described "terrible anger" and reported that he was "wild with [his] money." He also expressed thoughts of harming his daughter. He was diagnosed as having hypomanic symptoms, but did not meet all criteria for a hypomanic episode. Prior to this time, his mood had been euthymic, despite his not receiving psychiatric medications for almost 2 years. Subsequently, he was treated successfully with 5 mg of olanzapine daily. No change was made in electrode voltage to manage the patient's hypomania, although a later increase was made to combat tremor.

REVIEW OF LITERATURE

A MEDLINE search of English-language publications was conducted using PubMed in July 2003. The search term used was *deep brain stimulation*. In addition, pertinent references were obtained from the retrieved articles.

Possible Causes of Psychiatric Complications With Deep Brain Stimulation

Many theories have been postulated as to why some DBS patients suffer psychiatric complications. These can be simplified into three: (1) electrode placement, (2) neurotransmitter changes, and (3) primary psychiatric disorder progression. Most of the literature has focused on aberrant electrode placement as the etiology for psychiatric complications.

Electrode placement. The subthalamic nucleus is thought to regulate not only motor circuits but also associative and limbic cortico-subcortical circuits.[6] Cells adjacent to the subthalamic nucleus project to the anterior cingulate, ventral striatal, and frontal regions.[7,8] Mood disturbances induced by subthalamic nucleus stimulation could be the result of altering nonmotor circuits within the subthalamic nucleus or could be due to electrode misplacement resulting in stimulation of adjacent areas.

Neurotransmission. Stimulation of the subthalamic nucleus and/or surrounding structures may result in the perturbation of neurotransmitters known to play pivotal roles in psychopathology.[5,9] For example, an imbalance could be created between the γ-aminobutyric acid (GABA)-ergic inhibitory axons from the globus pallidus and excitatory glutaminergic outflow from the subthalamic nucleus. That no simple explanation is likely to be forthcoming is illustrated by the following statement: "An increasingly complex picture of neurotransmitter distribution, interaction, and function in the basal ganglia has emerged involving dopamine, serotonin, acetylcholine, excitatory amino acids, GABA, nitric oxide, neuropeptides, and adenosine, and it is likely that much more remains to be clarified."[10(p13)]

Progression of psychiatric disorder. Some clinicians postulate that subclinical psychiatric disorders may become more apparent after DBS as a result of simple progression or treatment-related unmasking.[3] Parkinson's disease itself is commonly associated with depressive and anxiety disorders and dementia, as well as dopaminergic drug-induced hypomania, mania, and psychoses.[10] Others believe that if the procedure is not as successful as anticipated, patients may react with depressive or anxiety symptoms.[11]

Mania

Kulisevsky et al.[12] described 3 DBS patients (among the first 15 they had treated) with no prior psychiatric history who became manic after receiving stimulation at the lowest contact of quadripolar electrodes implanted bilaterally in the subthalamic nucleus. The patients' symptoms developed within 48 hours after stimulation was begun and satisfied DSM-IV criteria for mania due to a general medical condition. After stimulation was changed to higher electrode contacts, the manic symptoms resolved gradually over the next 2 weeks. It was suggested that the lowest electrode contacts may have been stimulating neurons at the level of the midbrain, caudal to the subthalamic nucleus, where fibers from the ventral tegmental area or anterior cingulate cortical circuits may have been involved.

Tröster et al.[13] described 9 patients who underwent unilateral globus pallidus stimulation for Parkinson's disease as experiencing increased energy, reduced anxiety, and a trend toward fewer depressive symptoms. Schneider et al.[8] studied the effects of DBS of the subthalamic nucleus in 12 Parkinson's disease patients who had no prior psychiatric history. During stimulation, mood was enhanced and "improved processing of emotionally laden information and enhanced self-reported well-being"[8(p301)] were noted. Krack et al.[14] mentioned transient postoperative

hypomania in 4 of 49 patients, none of whom had "major ongoing psychiatric illness."

Houeto et al.[11] described a 61-year-old man with a history of depression who developed aggressiveness, irritability, exhibitionism, excessive gambling, and mood swings from depression to exaltation following subthalamic DBS. Because a hypomanic episode had occurred 10 years previously, it was thought that DBS had activated the patient's mood disorder. Treatment with lithium and later clozapine was unsuccessful.

Hypersexuality has been induced by DBS, but since levodopa may cause hypersexuality, DBS may also reduce it if the levodopa dose can be decreased.[15,16]

Depression

The literature describes patients who have responded to DBS with improved motor function but who also developed severe depression. Again, possible explanations include alteration of nonmotor circuits within the subthalamic nucleus or in adjacent cells or fiber tracts. Some cases of mild depression have been reported that responded to selective serotonin reuptake inhibitor treatment.[17,18] In one report, a patient who had no premorbid history of depression experienced severe melancholic depression with psychosis that necessitated inpatient psychiatric hospitalization.[16]

Bejjani et al.[9] described a 65-year-old woman with severe Parkinson's disease and no history of psychiatric illness who developed severe, reversible depressive symptoms within seconds after beginning subthalamic DBS. Bilateral electrodes, each with 4 contacts, had been surgically placed, and each was subsequently evaluated to identify the position that would provide the patient with the most symptomatic relief. Stimulation of one contact located in the central substantia nigra produced suicidal ideation and profound sadness that resolved less than 90 seconds after stimulation ceased. Several minutes of mild hypomania followed. On several separate occasions, stimulation of that contact reproduced the depressive symptoms, while stimulation of other contacts located in the subthalamic nucleus improved parkinsonian symptoms without altering mood.

There are a few reports of completed or attempted suicide after DBS therapy.[7,11,18] A family history of suicide and a preexisting personal history of suicidal ideation appear to be risk factors, and these may, in the future, become contraindications to DBS treatment.

While suicidality may be a direct complication of DBS, dose reduction or discontinuation of dopaminergic drugs following effective DBS could also be an explanation. Volkmann et al.[19] reported that transient depression, fatigue, and abulia were common in patients who had received subthalamic nucleus or pallidal stimulation but concluded that dopamine withdrawal was the inciting factor. In other studies, researchers have postulated that withdrawal of levodopa after successful stimulation may have produced a dopaminergic discontinuation syndrome that was responsible for depressive symptoms, especially since increasing the dose of levodopa improved the symptoms.[7,8,11,16]

As reported by Doshi et al.,[7] depression has also been noted to improve in some patients after DBS. Schneider et al.[8] reported enhanced mood and improved emotional memory with DBS, although the patients "exhibited no clinically relevant psychiatric symptoms" prior to stimulation. The results obtained with stimulation alone were similar to those experienced with optimal doses of levodopa in the absence of stimulation.

Funkiewiez et al.[20] found that the mood response to DBS or levodopa treatment closely resembled the euphoria that can be induced with amphetamines or cocaine.

Neuropsychiatric Complications

As reviewed by Moretti et al.,[21] deficits in focal attention attributed to disruption of the frontostriatal circuit, as well as decreased linguistic output, have been noted in some patients following DBS. In addition, lack of initiation, apathy, and social withdrawal have been noted.[7] Saint-Cyr et al.[22] evaluated 11 patients with Parkinson's disease for neuropsychiatric complications following subthalamic DBS. They discovered significant declines in speed of mental processing, working memory, phonemic fluency, encoding of visuospatial material, and long-term consolidation of verbal material. Three of the 6 patients over 69 years of age were noted by their caregivers to have frontal behavioral dyscontrol without insight. Tröster et al.[13] evaluated 9 Parkinson's disease patients with a neuropsychiatric battery and found that 5 had significant declines in visuoconstructional test scores and semantic verbal fluency after unilateral pallidal stimulation. The patients were not aware of these changes, however, which led the authors to conclude that the cognitive changes were subtle and subclinical.

On the other hand, Alegret et al.[23] studied 15 patients before and 3 months after subthalamic nucleus DBS and found no "clinically relevant neuropsychological deterioration." They did, however, find "moderate deterioration in verbal memory and prefrontal and visuospatial functions."

Other Psychiatric Complications

Houeto et al.[11] retrospectively evaluated 24 Parkinson's patients who had received effective subthalamic DBS therapy and found worsening of agoraphobia in 2 of 4 patients and accentuation of generalized anxiety in the majority, while scores on the IOWA scales of personality changes showed no change in 7 patients, improvement in 8, and worsening in 8 (scores reported for 23 patients).

Another factor to consider when deciding which patients may benefit from DBS is the fact that some may

have difficulty adjusting socially once their physical function and independence have improved. Patients may experience conflict with family members regarding their newly found independence after years of requiring assistance.

Obsessive-Compulsive Disorder

Mallet et al.[24] described 2 patients with severe long-standing OCD who underwent subthalamic DBS for Parkinson's disease that resulted in marked reduction of obsessions and the disappearance of compulsions within 2 weeks of starting stimulation. The authors attributed this to the activation of serotonergic fibers in the subcortical-limbic circuitry.

DBS is currently being investigated as a treatment for severe OCD.[25,26] Nuttin et al.[27] treated 4 patients with severe OCD by stereotactic implantation of quadripolar electrodes in the anterior limbs of the internal capsules. Three of the patients improved, with 1 experiencing a 90% reduction in ritualistic behaviors. A subsequent study reported substantial improvement in 4 of 6 OCD patients.[28] A 35-year-old woman with medication-resistant OCD (Yale-Brown Obsessive Compulsive Scale [Y-BOCS] score of 34) improved dramatically after bilateral DBS of the anterior limbs of the internal capsules (3-month postoperative Y-BOCS score of 7).[29] Further studies are being conducted in the United States and Europe.[29] A plea has been made for the establishment of multidisciplinary, multicenter teams to systematically investigate DBS in OCD.[30] One patient failed to respond to internal capsule DBS, but surprisingly improved when treated with a stimulant.[31]

DISCUSSION

In the case presented here, the patient's post-DBS hypomania could represent the coincidental reemergence of his preexisting but quiescent bipolar disorder. However, the etiology is more likely to be multifactorial, with stimulation of structures adjacent to the subthalamic nucleus as a component. Indeed, in this particular patient, the reemergence of psychiatric symptoms is striking given that his mood had remained euthymic for decades prior to this procedure (and for almost 2 years with no psychiatric medication).

The current literature strongly supports the need for further investigation into the psychiatric complications of DBS and their treatment. In addition, it is clear that patients and families of patients who elect to undergo this procedure need to be counseled by clinicians who understand the possible outcomes of this treatment. Psychiatrists, psychologists, and neuropsychologists will most likely become crucial parts of the treatment team.[7,17] Neuropsychiatric testing both before and after the procedure should be considered as part of a comprehensive approach to this treatment.[32]

Finally, DBS shows promise as a novel psychiatric treatment for patients suffering from severe primary psychiatric disorders such as OCD. DBS certainly presents advantages over current invasive, tissue-destructive treatments such as cingulotomy and internal capsulotomy. While DBS is an invasive procedure, it is one for which dose and duration can be adjusted and titrated, and it is one that can be reserved should it prove unsuccessful. It is, however, not without risk (a study referred to in an FDA Talk Paper that involved 160 Parkinson's disease patients who had DBS implants found bleeding into the brain in 7.5%, infection related to the implants in 11%, weakness [paresis/asthenia] in 10%, and hemiplegia/hemiparesis in 8%).[33]

Drug names: clozapine (Clozaril and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa).

REFERENCES

1. Simuni T, Jaggi JL, Mulholland H, et al. Bilateral stimulation of the subthalamic nucleus in patients with Parkinson disease: a study of efficacy and safety. J Neurosurg 2002;96:666–672
2. Tavella A, Bergamasco B, Bosticco E, et al. Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: long-term follow-up. Neurol Sci 2002;23(suppl 2):S111–S112
3. Eskandar EN, Cosgrove GR, Shinobu LA. Surgical treatment of Parkinson disease. JAMA 2001;286:3056–3059
4. Jankovic J. New and emerging therapies for Parkinson disease. Arch Neurol 1999;56:785–790
5. Malhi GS, Sachdev P. Novel physical treatments for the management of neuropsychiatric disorders. J Psychosom Res 2002;53:709–717
6. Berney A, Vingerhoets F, Perrin A, et al. Effect on mood of subthalamic DBS for Parkinson's disease. Neurology 2002;59:1427–1429
7. Doshi PK, Chhaya N, Bhatt MH. Depression leading to attempted suicide after subthalamic nucleus stimulation for Parkinson's disease. Mov Disord 2002;17:1084–1100
8. Schneider F, Habel U, Volkmann J, et al. Deep brain stimulation of the subthalamic nucleus enhances emotional processing in Parkinson disease. Arch Gen Psychiatry 2003;60:296–302
9. Bejjani B-P, Damier P, Arnulf I, et al. Transient acute depression induced by high-frequency deep-brain stimulation. N Engl J Med 1999;340: 1476–1480
10. Ring HA, Serra-Mestres J. Neuropsychiatry of the basal ganglia. J Neurol Neurosurg Psychiatry 2002;72:12–21
11. Houeto JL, Mesnage V, Mallet L, et al. Behavioral disorders, Parkinson's disease and subthalamic stimulation. J Neurol Neurosurg Psychiatry 2002;72:701–707
12. Kulisevsky J, Berthier ML, Gironell A, et al. Mania following deep brain stimulation for Parkinson's disease. Neurology 2002;59:1421–1424
13. Tröster AI, Fields JA, Wilkinson SB, et al. Unilateral pallidal stimulation for Parkinson's disease: neurobehavioral functioning before and 3 months after electrode implantation. Neurology 1997;49:1078–1083
14. Krack P, Bagtir A, Van Blercom N, et al. Five-year follow-up of bilateral stimulation of subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 2003;349:1925–1934
15. Romito LM, Raja M, Daniele A, et al. Transient mania with hypersexuality after surgery for high-frequency stimulation of the subthalamic nucleus in Parkinson's disease. Mov Disord 2002;17:1371–1374
16. Deuschl G, Fogel W, Hahne M, et al. Deep-brain stimulation for Parkinson's disease. J Neurol 2002;249(suppl 3):36–39
17. Thobois S, Mertens P, Guenot M, et al. Subthalamic nucleus stimulation in Parkinson's disease. J Neurol 2002;249:529–534
18. Houeto JL, Damier P, Bejjani PB, et al. Subthalamic stimulation in Parkinson disease. Arch Neurol 2000;57:461–465
19. Volkmann J, Allert N, Voges J, et al. Safety and efficacy of pallidal or subthalamic nucleus stimulation in advanced Parkinson's disease.

Neurology 2002;56:548–551
20. Funkiewiez A, Ardouin C, Krack P, et al. Acute psychotropic effects of bilateral subthalamic nucleus stimulation and levodopa in Parkinson's disease. Mov Disord 2003;18:524–530
21. Moretti R, Torre P, Antonello RM, et al. Cognitive changes following subthalamic nucleus stimulation in two patients with Parkinson disease. Percept Mot Skills 2002;95:477–486
22. Saint-Cyr JA, Trépanier LL, Kumar R, et al. Neuropsychological consequences of chronic bilateral stimulation of the subthalamic nucleus in Parkinson's disease. Brain 2000;123:2091–2108
23. Alegret M, Junque C, Valldeoriola F, et al. Effects of bilateral subthalamic stimulation on cognitive function in Parkinson disease. Arch Neurol 2001;58:1223–1227
24. Mallet L, Mesnage V, Houeto J-L, et al. Compulsions, Parkinson's disease, and stimulation. Lancet 2002;360:1302–1304
25. Medina J. Neural implants and obsessive-compulsive disorder. Psychiatric Times 2003;20:43–44,46
26. George M. New methods of brain stimulation are improving research and therapy in obsessive-compulsive disorder. CNS Spectrums 2000;5 (suppl 4):12–17
27. Nuttin B, Cosyns P, Demeulemeester H, et al. Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder [letter]. Lancet 1999;354:1526
28. Nuttin BJ, Gabriëls LA, Cosyns PR, et al. Long-term electrical capsular stimulation in patients with obsessive-compulsive disorder. Neurosurgery 2003;52:1263–1274
29. Anderson D, Ahmed A. Treatment of patients with intractable obsessive-compulsive disorder with anterior capsular stimulation. J Neurosurg 2003;98:1104–1108
30. Nuttin B, Gybels J, Rasmussen S, et al. Deep brain stimulation for psychiatric disorders [letter]. Neurosurgery 2002;51:519
31. Albucher RC, Curtis GC. Adderall for obsessive-compulsive disorder [letter]. Am J Psychiatry 2001;158:818–819
32. Pillon B. Neuropsychological assessment for management of patients with deep brain stimulation. Mov Disord 2002;17(suppl 3):S116–S122
33. US Food and Drug Administration. FDA Approves Expanded Use of Brain Implant for Parkinson's Disease. Rockville, Md: National Press Office; January 14, 2002. Talk Paper T02-03. Available at: http://www.fda.gov/bbs/topics/ANSWERS/2002/ANS01130.html. Accessed June 10, 2003