Movement Disorders
CLINICAL PRACTICE
CASE SERIES

Resolution of Othello Syndrome After Subthalamic Nucleus Deep Brain Stimulation in 3 Patients with Parkinson's Disease

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Abstract: Psychiatric symptoms are historically thought a relative contraindication to DBS for advanced Parkinson's disease (PD). However, in the case of drug-induced mental illness, DBS may provide an acceptable alternative for the treatment of motor symptoms. This allows reduction of pharmacological dopaminergic therapy that might otherwise cause negative psychiatric consequences. For example, DBS is increasingly used to ameliorate specific complications of PD *treatment*, such as impulse control disorders. We present a series of 3 cases of young male patients who developed Othello syndrome (OS) during treatment with dopamine agonists. In each case, the OS resolved with withdrawal of the offending drug. Subsequent treatment with bilateral STN DBS improved motor symptoms and allowed reduction in their dopaminergic drug regimen. We therefore propose that drug-induced psychopathology may be an indication (rather than a contraindication) for DBS in selected cases.

"Othello syndrome" (OS) is an uncommon, but potentially dangerous, complication of neurological illness including Parkinson's disease (PD).[1–3] It is comprised of the combination of morbid jealousy and delusional thoughts of infidelity regarding the patient's partner. Unfortunately, OS can have catastrophic consequences for patients and their families, including reported homicide.[4] OS may be provoked in PD by treatment with dopamine agonists[5,6] or amantadine.[7] In such cases, withdrawal of the provoking agent is often effective in remedying the delusional disorder,[2,5,6] but treatment withdrawal leaves a therapeutic gap in treatment of the motor symptoms. Evidence is accumulating in support of the use of DBS to replace drugs that have induced neuropsychiatric symptoms in patients with PD—for example, impulse control disorders (ICDs)—though reported outcomes are highly variable.[8–10]

We report on 3 young male patients who developed OS after treatment of PD with a dopamine agonist. In each case, the morbid jealousy was successfully treated by withdrawal of the drug. Motor symptoms were successfully ameliorated by STN DBS without re-emergence of the psychiatric symptoms. We therefore propose that surgical therapy should be considered in the management of drug-induced morbid jealousy in PD.

Case 1

At the age of 28, this man developed exercise-induced foot dystonia. He was diagnosed with PD at the age of 30. DaTSCAN revealed reduced right putaminal uptake. He was initially responsive to dopaminergic therapies and maintained good gait and motor function. Unfortunately, he later developed moderate dyskinesia and had persistent dystonia of the left foot. With regard to premorbid psychiatric history, at age 34 he had presented with a brief episode of psychosis in the context of recreational drug use, a major psychological stress, and a breakdown in his relationship with his partner. He suffered with both mild depression and anxiety. He was a former "social smoker" who did not drink to excess, though admitted to some binge drinking during his twenties. He had developed mild paranoid ideation and some hallucinations secondary to the addition of entacapone, so this was withdrawn. At age 41, while on treat-

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ment with cabergoline (total levodopa equivalent dose [LED[11]]: 1,567 mg/day), he developed prolonged morbid jealousy: He falsely accused his wife of entertaining other men in the house. He undertook covert audio and video surveillance, which he believed confirmed the infidelity; however, his treating doctors could not interpret any meaningful sounds when this evidence was given to them. He was admitted to hospital and cabergoline was withdrawn with complete resolution of his psychiatric symptoms over the subsequent few weeks. Unfortunately, this led to worsening of his motor function and increasing doses of L-dopa (LED, 1,750 mg/day), which were associated with motor fluctuations.

He was subsequently assessed as otherwise suitable for DBS surgery after comprehensive neurological, psychiatric, and neuropsychological evaluations. After bilateral STN DBS surgery, later the same year, the patient experienced the abolition of motor fluctuations and is now able to use a simplified medication regimen of L-dopa/carbidopa and benzhexol (total LED: 600 mg/day), in addition to stimulation (see Table 1). With 24-month follow-up, there has been no recurrence of psychotic symptoms and he has returned to playing recreational sport. He has not tolerated attempts at reducing benzhexol.

Case 2

A 38-year-old man was diagnosed with sporadic early-onset PD. Two years later, he was troubled by motor fluctuations: His eating was disrupted by dyskinesia and he complained of severe "off" periods. He denied any previous mental health issues. A dopamine agonist, cabergoline, was therefore added to L-dopa/carbidopa (total treatment LED: 467 mg/day), when he was 39 years old. He subsequently became acutely psychiatrically unwell for several months with morbid jealousy, becoming suspicious of his wife and her friendships with other men. He also exhibited hypomania, hypersexuality, some auditory hallucinations, and began compulsive shopping. Withdrawal of the agonist ameliorated the psychiatric symptoms, except for residual anxiety. Prolonged attempts to manage his motor fluctuations with adjuvant entacapone and rasagiline were partially successful, but only temporarily effective (at an LED of 1,197 mg/day), and the patient therefore elected to undergo DBS surgery. At age 44, he was treated with bilateral STN DBS surgery with consequent improvement in motor symptoms and reduction in L-dopa requirement. He is maintained postoperatively with lower doses of L-dopa and rasagiline, but no entacapone (LED, 500 mg/day), in addition to the stimulation (see Table 1). The delusional symptoms and associated ICD have not recurred in the 12 months since surgery.

Case 3

A 34-year-old man was diagnosed with PD after 2 years of symptoms. He was initially maintained with L-dopa/benserazide, but required increasing doses and complained of motor fluctuations. Tolcapone, and later entacapone (in its place), were

TABLE 1 Medication histories in each case at the time of OS symptoms, immediately pre- and post-DBS surgery with LEDs[11] and DBS settings for each case

Case	Symptomatic Medication (Per Day)	LED (mg/day)	Preoperative Medication (Per Day)	LED (mg/day)	Postoperative Medication (Per Day)	LED (mg/day)	Lead	Contacts	Potential Difference (Range, V)	Pulse Width (μsec)	Frequency (Hz)	Impedance (Ω)	Current (mA)
1	Cabergoline 4 mg L-dopa/carbidopa 1,300/325 mg Benzhexol 8 mg	1,567	L-dopa/carbidopa 1,750/350 mg Benzhexol 8 mg	1,750	L-dopa/carbidopa 600/150 mg Benzhexol 8 mg	600	L STN1 L STN2 R STN	2-/C+ 1-/C+ 9-/C+	2.85 (1.8–3.0) 1.45 (0.4–1.6) 4.40 (3.0–5.0)	60 60 60	125 125 125	1,205 1,440 1,221	2.376 1.022 3.596
2	Cabergoline 4 mg L-dopa/carbidopa 200/50 mg Citalopram 20 mg Clonazepam 2 mg	467	L-dopa/carbidopa/ entacapone 750/187.5/ 1,200 mg L-dopa/ benserazide 100/25 mg Rasagiline 1 mg Citalopram 20 mg Clonazepam 2 mg	1,197	L-dopa/carbidopa 400/100 mg Rasagiline 1 mg Citalopram 20 mg Clonazepam 2 mg	500	L STN R STN	3-/C+ 10-/C+	1.40 (0.4–2.4) 2.30 (1.7–2.9)	60 60	130 130	1,838 1,169	0.78 1.98
3	Apomorphine 7 mg L-dopa/ benserazide 1,100/200 mg Pergolide 1 mg	1,270	Apomorphine 8 mg L-dopa/ benserazide 2,200/550 mg	2,280	L-dopa/ benserazide 400/50 mg Amantadine 200 mg	400	L STN R STN	7-/C+ 3-/C+	3.40 (2.8–3.8) 3.00 (2.4–3.4)	90 90	130 130	1,045 1,018	3.25 2.94

Postoperative imaging correlated with the intraoperative microelectrode recordings and confirmed accurate lead position in the STN bilaterally in all cases.
V, volts; Hz, Hertz; Ω, Ohms; mA, milliamperes.

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therefore added to his regimen. This was augmented by the addition of pergolide (total treatment LED: 1,270 mg/day) when he was 44. He and his wife began to report marital difficulties resulting from the patient's firm, but unfounded, belief in his wife's infidelity. He began following his wife and made concealed audiotape recordings in their home when he was not there. This led to intense arguments. He also admitted to a gambling problem, which increased in severity in concert with the morbid jealousy. He presented the "proof" of the infidelity to his psychiatrist, which contained only muffled and indiscernible noises on the cassette tapes. The agonist was withdrawn and the jealousy and gambling resolved over several weeks. The absence of the agonist and progression of disease required increasing doses of dopaminergic medication and the addition of intermittent subcutaneous apomorphine (total LED: 2,280 mg/day). There was concern over dopamine dysregulation syndrome and some recurrence of jealous ideation. He was therefore recommended for bilateral STN DBS surgery, which he received at age 45. After surgery, his motor symptoms improved and he reported increased independence. He has had no recurrence of morbid jealousy in the 8 years since DBS surgery and is maintained on lower doses of L-dopa and amantadine (postoperative LED of just 400 mg/day) in addition to the stimulation (see Table 1).

Discussion

OS is a recognized complication of PD,[1] particularly when treated with dopamine agonists.[2,5] This may relate to D_3 dopamine receptor specificity of the agonists used clinically and/or diminished frontal lobe blood flow associated with their use.[2] Male gender and early onset of PD are recognized risk factors for other psychiatric side effects, such as ICD.[8,12,13] As yet, there is insufficient evidence to conclude the same of OS in PD, but we note that our patients are similar in these respects, as were those in previously reported series,[5,14] and comorbid ICDs and/or dopamine dysregulation syndrome were present in 2 of our patients. Male gender is a risk factor for OS from all causes, according to a series of 105 cases, in which 61.9% were men.[2] In this series, mean age is higher, as one would expect when neurodegenerative and cerebrovascular causes are prevalent and are the primary cause of the syndrome. The importance of definitive management of OS is highlighted by a series of 3 cases and literature review that found a high risk of aggression, violence, and even homicide.[4] More commonly, marital disharmony and breakdown is caused, with significant knock-on negative effects upon patient outcome. This has proven to be the case in all 3 of our patients, who, with their partners, struggle with the consequences of OS even years later, despite remission of the syndrome.

Previous case reports and series reporting DBS-induced psychiatric disorder[15] have bolstered the traditional view that premorbid psychiatric symptoms are a relative contraindication to the procedure. However, there is possible publication bias in this regard.[16] Specific studies to address the effect of DBS on ICDs have been retrospective, limited in power, and used variable site and side for stimulation (e.g., as reviewed previously[8,9]). More recent literature suggests a postoperative *improvement* in suitably selected cases—particularly in the case of dopamine-agonist–induced ICD.[10] It is our experience, and that of others,[17] that DBS can provide a useful alternative for the treatment of patients who develop delusional disorders resulting from dopamine agonists.

In such cases, DBS may be advantageous, compared to other treatment modalities for advanced PD (such as subcutaneous apomorphine or intrajejunal L-dopa infusions, which might otherwise provoke or sustain psychiatric symptoms). DBS may be a reasonable alternative strategy for inadequate motor treatment resulting from withdrawal of medications when unwanted dopaminergic side effects occur and avoids increased polypharmacy, such as adding atypical neuroleptics. Our 3 cases suggest that a history of drug-induced psychiatric disorders, with resolution on drug withdrawal, is not a contraindication to STN DBS.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

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