Movement Disorders
CLINICAL PRACTICE
CASE SERIES

Malignant Subthalamic Nucleus-Deep Brain Stimulation Withdrawal Syndrome in Parkinson's Disease

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Abstract: Abrupt cessation of STN-DBS is an under-recognized cause of life-threatening akinetic crisis in Parkinson's disease (PD) and can present as a movement disorder emergency. We report on 2 patients who survived severe and prolonged akinetic crisis after abrupt cessation of STN stimulation for PD (malignant STN-DBS withdrawal syndrome). We discuss the clinical similarities and possible differences in pathophysiology from the akinetic crisis in medically-treated PD. Although early implantable pulse generator (IPG) replacement is the definitive treatment, medical and economic considerations may preclude early surgery and strategies for medical management assume importance. We reflect upon the socioeconomic concerns surrounding DBS in countries lacking health care coverage and the need for user-independent monitors and indicators of low IPG battery status.

Deep Brain Stimulation (DBS) is the standard of care for Parkinson's disease (PD) patients with severe motor complications. The lack of alarms to alert the end-of-battery life in older models and delays in implantable pulse generator (IPG) replacement can result in fatal complications in patients who do not regularly monitor battery status.[1] Accidental cessation of STN stimulation may result in a rebound of parkinsonian symptoms.[2] At the far end of the spectrum is the rapid development of a life-threatening withdrawal syndrome reported also in patients who require hardware removal postinfection.[3] We report on 2 survivors of IPG depletion-related malignant DBS withdrawal syndrome and discuss the possible mechanisms and the treatments used.

Case 1

A 51-year-old gentleman with PD for 11 years underwent bilateral STN-DBS in 2008 (Kinetra; Medtronic, Minneapolis, MN), which led to substantial improvement in his motor symptoms (UPDRS, part III [0–108]: presurgery, drug *off*: 35; last visit postsurgery stimulation [Stim] ON drug *off*: 14; pacemaker settings: right STN: contact 7 (−)/case (+), 2.5 V/60 μs/130 Hz; left STN: contact 2 (−)/case (+), 2.5 V/60 μs/130 Hz) and drug reduction by 80% (levodopa equivalent daily dose presurgery: 1,820 mg; postsurgery: 310 mg). He was lost to follow-up after the initial yearly visits. He reported to us 7 years after DBS with a history of abrupt-onset immobility and difficulty speaking and swallowing. On examination, he had severe rigidity, bradykinesia, dysphagia, and anarthria. His IPG had reached "end-of-life" status and an urgent IPG replacement was planned. Unfortunately, he had no insurance coverage and finances could not be arranged immediately. During this time, intensive medical management was initiated with liquid preparation of L-dopa/carbidopa (1,500 mg/day), pramipexole (4.5 mg/day), amantadine (200 mg/day), and domperidone (30 mg/day) through Ryle's tube. He continued to remain in an akinetic state and, by day 4, developed fluctuating blood pressure (100–190 mm Hg systolic and 60–100 mm Hg diastolic) followed by serial elevation of creatine phosphokinase (CPK up to 4,380 μ/L; normal range: 21–232 μ/L) without myoglobinuria. On day 9, the axillary temperature rose to 104°F, which was treated with external cool-

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ing, intravenous paracetamol, and hydration. Repeated cultures of urine, blood, and sputum grew no organisms, but intravenous antibiotics were started for a positive throat swab culture of *Staphylococcus aureus*. On day 10, there was deterioration in the sensorium, for which no obvious cause could be identified. On day 11, the IPG was replaced under local anesthesia. Neurostimulation was initiated in the immediate postoperative period (right STN: contact 7 (−)/case (+), 3.0 V/60 μs/130 Hz; left STN: contact 2 (−)/case (+), 3.0 V/60 μs/130 Hz), and it resulted in a rapid improvement of parkinsonism. By day 3, his speech and swallowing normalized and he became ambulant (UPDRS III score before reimplantation = 71; day 3 postimplantation = 33). Two weeks later, his medications were substantially reduced and he was independent in all activities (UPDRS III score = 19) and experienced only minimal dyskinesias. Three months after restoration of neurostimulation, he continues to do well without motor fluctuations or disabling dyskinesias.

Case 2

A 54-year-old woman with PD for 11 years underwent bilateral STN-DBS in 2004. She did well (UPDRS, part III: presurgery, drug *off*: 45; last visit postsurgery Stim ON drug *off*: 23; pacemaker settings: right STN: contact 5 (−)/case (+), 4.0 V/60 μs/130 Hz; left STN: contact 1 (−)/case (+), 3.4 V/60 μs/130 Hz) and her medications could be reduced by 60%. After 6 years, she had her first elective IPG replacement (Kinetra; Medtronic). In early 2015, elective IPG replacement was advised within 1 to 2 months, based on the low IPG battery status detected at her yearly follow-up visit. She could not arrange finances within this time and, 3 months later (after 11 years of continuous STN stimulation), developed an abrupt worsening of parkinsonism. She was confined to bed overnight and had difficulty swallowing and was rushed to our center. On evaluation, she had severe rigidity, bradykinesia, and dysphagia (UPDRS III score = 68). IPG had reached end of life, and she was admitted for emergency replacement, but it had to be delayed while finances were arranged. She was started on liquid L-dopa (1,200 mg/day), pramipexole (3 mg/day), and amantadine (300 mg/day). On day 2, she developed aspiration pneumonia and type II respiratory failure. Intravenous antibiotics and intermittent positive pressure ventilation were initiated. There was serial elevation of serum CPK (up to 606 μ/L) and hyponatremia resulting from antidiuretic hormone overactivity, but no autonomic dysfunction. She remained in an akinetic state until day 8 when IPG could be replaced. The postoperative period was uneventful and parkinsonism improved dramatically upon initiation of neurostimulation (right STN: contact 5 (−)/case (+), 4.0 V/60 μs/130 Hz; left STN: contact 1 (−)/case (+), 4.0 V/60 μs/130 Hz). Ryle's tube was removed 2 days later, and at discharge 1 week later, she was ambulant (UPDRS III score = 19) and had no disabling dyskinesias on the reduced dose of drugs. Two months later, she continues to do well without and disabling motor fluctuations or dyskinesias.

Discussion

Abrupt worsening of motor status in PD patients who had successful motor outcomes after STN-DBS is known to follow aggressive reduction of medications or temporary cessation of stimulation in order to treat side effects of DBS.[4,5] A fatal outcome in a case of malignant DBS withdrawal syndrome was reported, despite replacement of a depleted IPG for STN stimulation.[1] Of 15 patients who required explantation of DBS hardware because of infection, 3 developed a malignant withdrawal syndrome during the stimulation holiday, among whom 2 succumbed and only 1 survived until neurostimulation could be restarted.[3] We report on 2 survivors of malignant STN-DBS withdrawal syndrome resulting from lack of early detection of low IPG status and delay in replacement.

An operational definition for acute akinesia (parkinsonism-hyperpyrexia syndrome) in PD is a sudden worsening in UPDRS scores by ≥20 points along with transient lack of response to dopaminergic medications at the usual doses or rescue medications for ≥3 days.[6] Both our patients met these criteria, though the inciting event was DBS withdrawal. The annual incidence of akinetic crisis in medically treated PD is around 0.3% and occurs in the setting of infections, surgery, stress, and so on.[6] It is debatable whether acute STN-DBS withdrawal syndrome is the same as akinetic crisis in PD (Table 1). In both situations, the clinical picture mimics neuroleptic malignant syndrome (NMS) with the common features of muscular rigidity, bradykinesia, autonomic dysfunction, and hyperthermia.[7] Full-fledged akinetic crisis can also cause total akinesia, dysphagia, and elevated muscle enzymes. In less severe cases there may be only a sudden worsening of parkinsonian symptoms and milder autonomic involvement.[8] Classical NMS is attributed to blockade of dopamine (especially D2) and acetylcholine (M2) receptors in the striatum and the anterolateral hypothalamic area. Akinetic crisis in PD follows the sudden withdrawal of exogenous dopamine in a patient with presynaptic dopaminergic neuronal degeneration who was on chronic exogenous dopamine replacement. (^{123}I) beta-carboxymethyoxy-3-beta-(4-iodophenyl) tropane/single-photon emission computed tomography studies have found markedly reduced dopamine active transporter (DAT) activity in PD patients with akinetic crisis.[9,10] A combination of reduced DAT expression in response to sudden reduction in striatal dopamine levels and mitochondrial dysfunction are implicated in the markedly depressed nigrostriatal dysfunction observed in akinetic crisis.[9]

In contrast, the malignant STN-DBS withdrawal syndrome cannot be attributed to striatal dopamine reduction because STN-DBS does not increase striatal dopamine.[11] It is more likely that cessation of neurostimulation unravels a severely hypodopaminergic state resulting both from large reduction in dopaminergic drugs (50–70%) after STN-DBS for many years and advanced nigrostriatal degeneration. STN-DBS has no proven effect on disease progression, and striatal dopamine reduction persists in patients tested after 1 year.[12] Presynaptic DAT

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TABLE 1 Comparison of neuroleptic malignant syndrome, akinetic crisis, and malignant STN-DBS withdrawal syndrome

Feature	Neuroleptic Malignant Syndrome	Akinetic Crisis	Malignant STN-DBS Withdrawal Syndrome
Underlying illness	Psychosis	PD/atypical parkinsonism	PD
Precipitating factor	Antipsychotic use, typical > atypical	Dopaminergic drug withdrawal, surgery, trauma, infection	Abrupt cessation of neurostimulation
Pathophysiology: presynaptic	Normal	Low DAT activity; near absent DAT activity in the striatum during crisis	?Low DAT activity
Synaptic dopamine	Normal	Fluctuating/high	Low
Postsynaptic	D2 blockade striatum and anterolateral hypothalamus	Slightly reduced D2 receptor binding in L-dopa-treated individuals	?Downregulation/reduced affinity of receptors; postsynaptic striatal dendritic degeneration in advanced PD
Fever	+++	+/−	+/−
Autonomic instability	++	+/−	+/−
Muscular rigidity	+++	+++	+++
Elevated muscle enzymes	+++	++	++

activity is also expected to be low, proportionate to disease progression.[12] Long-term postsynaptic changes in striatal dopamine receptor expression/affinity in the striatal neurons and striatal dendritic degeneration may account for the refractoriness to dopaminergic medications when drugs are reinstituted during this crisis.

Based on our cases, we cannot conclude that abrupt cessation of STN stimulation will invariably result in a malignant withdrawal syndrome. Early age of onset (<40 years), longer duration of illness, advanced stage, and genetic etiology are risk factors for akinetic crisis in medically treated PD.[13] Whether similar risk factors operate in STN-DBS withdrawal syndrome is not known. Genetic data were unavailable in our patients but both had early-onset PD and a long duration of illness (18 and 22 years). Longer duration of illness and longer exposure to DBS stimulation were postulated as risk factors in another recent report of DBS withdrawal syndrome.[3] Though cessation of pallidal stimulation is known to precipitate dystonic storm in primary dystonia, we suspect that such a malignant akinetic state may not follow cessation of pallidal stimulation in PD, given that these patients continue to use L-dopa.[14] Pallidal stimulation may thus be a more lenient approach in this aspect. Hardware-related risk factors also need a mention, because the current IPG devices do not have user-independent alarms to forewarn battery drainage. Akinetic crisis in PD is managed as with NMS, with increased doses of dopaminergic drugs or subcutaneous apomorphine infusion or intravenous L-dopa infusion.[15] Nonavailability of apomorphine, injectable L-dopa, and transdermal rotigotine prompted us to use liquid L-dopa to achieve more-stable plasma levels, along with pramipexole.[16,17] Though bromocriptine is traditionally used in the management of NMS, its 5HT2A agonism can be detrimental.[7] Pramipexole is a potent D3/D2 agonist with only weak 5HT2A agonist activity and its selective D3 agonism may also provide added benefits through autoreceptor activation.[18] We tried amantadine based on the putative benefits of intravenous amantadine sulphate in akinetic crisis.[17] Undoubtedly, it was IPG reimplantation that promptly reversed akinesia and autonomic instability in our patients, and there was no significant reduction in either with drugs. However, it is possible that these drugs may have contributed to their survival in the first week. Where inordinate delays are expected in restoration of neurostimulation, lesioning surgery (uni- or bilateral subthalamotomy/pallidotomy) may also considered as a desparate measure in the light of available literature and our own experience that suggests that patients do not respond to medical management alone. Though not reported in the setting of DBS withdrawal or acute akinesia, children with dystonic storm have benefited from bilateral pallidotomy.[19]

In summary, acute withdrawal of long-term subthalamic stimulation can precipitate a state similar to akinetic crisis in medically treated PD patients and can be life threatening. In countries without full health care coverage for DBS, it is of prime importance to warn potential surgical candidates on the need for repeated elective reimplantations. In spite of extensive education and printed instructions, patients may still end up presenting as medical emergencies, as in our case. Emphasizing the life-threatening consequences of abrupt cessation of neurostimulation may motivate patients in making better-informed choices and timely financial arrangements for a therapy that is greatly beneficial, but not easily affordable, to many. Intensive supportive care, liquid L-dopa, and D2/D3 agonists are helpful strategies to enable survival until IPG replacement. Alarm systems that alert patients the need for replacement well in advance can prevent this crisis.

Author Roles

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

R.R.: 1A, 1C, 3A

S.K.: 1A, 1B, 3B

K.K.K.: 1B, 1C, 2B

A.K.: 1A, 1B, 3B

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References

1. Neuneier J, Barbe MT, Dohmen C, et al. Malignant deep brain stimulation-withdrawal syndrome in a patient with Parkinson's disease. *Mov Disord* 2013;28:1640–1641.
2. Hariz M, Johansson F. Hardware failure in Parkinsonian patients with chronic subthalamic nucleus stimulation is a medical emergency. *Mov Disord* 2001;16:166–168.
3. Reuter S, Deuschl G, Falk D, Mehdorn M, Witt K. Uncoupling of dopaminergic and subthalamic stimulation: life-threatening DBS withdrawal syndrome. *Mov Disord* 2015;30:1407–1413.
4. Urasaki E, Fukudome T, Hirose M, Nakane S, Matsuo H, Yamakawa Y. Neuroleptic malignant syndrome (parkinsonism-hyperpyrexia syndrome) after deep brain stimulation of the subthalamic nucleus. *J Clin Neurosci* 2013;20:740–741.
5. Kadowaki T, Hashimoto K, Suzuki K, Watanabe Y, Hirata K. Case report: recurrent parkinsonism-hyperpyrexia syndrome following discontinuation of subthalamic deep brain stimulation. *Mov Disord* 2011;26:1561–1562.
6. Onofrj M, Thomas A. Acute akinesia in Parkinson disease. *Neurology* 2005;64:1162–1169.
7. Gillman PK. Neuroleptic malignant syndrome: mechanisms, interactions, and causality. *Mov Disord* 2010;25:1780–1790.
8. Harada T, Mitsuoka K, Kumagai R, et al. Clinical features of malignant syndrome in Parkinson's disease and related neurological disorders. *Parkinsonism Relat Disord* 2003;9(Suppl 1):S15–S23.
9. Martino G, Capasso M, Nasuti M, Bonanni L, Onofrj M, Thomas A. Dopamine transporter single-photon emission computerized tomography supports diagnosis of akinetic crisis of parkinsonism and of neuroleptic malignant syndrome. *Medicine* 2015;94:e649.
10. Kaasinen V, Joutsa J, Noponen T, Paivarinta M. Akinetic crisis in Parkinson's disease is associated with a severe loss of striatal dopamine transporter function: a report of two cases. *Case Rep Neurol* 2014;6:275–280.
11. Hilker R, Voges J, Ghaemi M, et al. Deep brain stimulation of the subthalamic nucleus does not increase the striatal dopamine concentration in parkinsonian humans. *Mov Disord* 2003;18:41–48.
12. Hesse S, Strecker K, Winkler D, et al. Effects of subthalamic nucleus stimulation on striatal dopaminergic transmission in patients with Parkinson's disease within one-year follow-up. *J Neurol* 2008;255:1059–1066.
13. Bonanni L, Onofrj M, Valente EM, et al. Recurrent and fatal akinetic crisis in genetic-mitochondrial parkinsonisms. *Eur J Neurol* 2014;21:1242–1246.
14. Sobstyl M, Zabek M, Kmiec T, Slawek J, Budohoski KP. Status dystonicus due to internal pulse generator depletion in a patient with primary generalized dystonia. *Mov Disord* 2014;29:188–189.
15. Ikebe S, Harada T, Hashimoto T, et al. Prevention and treatment of malignant syndrome in Parkinson's disease: a consensus statement of the malignant syndrome research group. *Parkinsonism Relat Disord* 2003;9 (Suppl 1):S47–S49.
16. Dafotakis M, Sparing R, Juzek A, Block F, Kosinski CM. Transdermal dopaminergic stimulation with rotigotine in Parkinsonian akinetic crisis. *J Clin Neurosci* 2009;16:335–337.
17. Onofrj M, Bonanni L, Cossu G, Manca D, Stocchi F, Thomas A. Emergencies in parkinsonism: akinetic crisis, life-threatening dyskinesias, and polyneuropathy during L-Dopa gel treatment. *Parkinsonism Relat Disord* 2009;15(Suppl 3):S233–S236.
18. Tokunaga N, Choudhury ME, Nishikawa N, et al. Pramipexole upregulates dopamine receptor D(2) and D(3) expression in rat striatum. *J Pharmacol Sci* 2012;120:133–137.
19. Marras C, Rizzi M, Cantonetti L, et al. Pallidotomy for medically refractory status dystonicus in childhood. *Dev Med Child Neurol* 2014;56:649–656.

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