J Neurol (2015) 262:2780–2782
DOI 10.1007/s00415-015-7956-4

LETTER TO THE EDITORS

Parkinsonism–hyperpyrexia syndrome and deep brain stimulation

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Received: 12 September 2015 / Revised: 22 October 2015 / Accepted: 23 October 2015 / Published online: 3 November 2015

Keywords Parkinson's disease · Deep brain stimulation · Subthalamic nucleus · Parkinsonism · Hyperpyrexia

Dear Sirs,

Parkinsonism–hyperpyrexia syndrome (PHS) is a life-threatening disorder that shares many similarities with neuroleptic malignant syndrome, namely rigidity, hyperpyrexia, impaired consciousness and elevated creatine phosphokinase (CPK) in serum [1]. Patients with Parkinson's disease (PD) may develop PHS after the acute withdrawal of dopaminergic therapies, and cases of PHS have been reported in the perioperative phase of deep brain stimulation (DBS), when dopaminergic therapies are markedly reduced [2]. However, the mechanism of DBS-related PHS may be more complex than previously envisioned.

A 63-year-old man with an 18-year history of PD, and stable on 900 mg/day of levodopa for 5 years after bilateral subthalamic nucleus (STN)-DBS (UPDRS-III score at the last evaluation = 24) was admitted to the hospital a day after the abrupt onset of an akinetic state (UPDRS-III score at the hospital admission = 77) accompanied by dyspnea, tachycardia, hypertension and fever (38.5 °C), associated with increased CPK (2.820 U/L; reference value <190 U/L) and C-reactive protein (CRP) (50.1 mg/L; reference values <3 mg/L). There had been no changes to the dose of levodopa or recent administration of any other medications. A prior evaluation of the DBS impulse generator (IPG-Kinetra, Medtronic®- left STN: 3.4 V, 60 μs, 180 Hz [contact 3-]; right STN: 3.4 V, 60 μs, 180 Hz [contact 5-]) had revealed low battery, while a complete cessation of IPG battery life was confirmed at the time of hospital admission. ECG and chest X-ray were normal and no signs or symptoms of infection were revealed. The patient received intravenous hydration, clonazepam, paracetamol, and levodopa was increased to 1300 mg/day. It was only after IPG (Activa-PC, Medtronic®) replacement, 4 days after symptom onset, that he began his recovery, accompanied by gradual normalization of CPK and CRP serum values and sustained control of motor symptoms (UPDRS-III score at the 6-month follow-up evaluation = 28).

Anecdotal PHS cases were associated with acute DBS withdrawal (Table 1). Kadowaki et al. [3] described a patient with a 17-year history of PD in whom several attempts at discontinuing STN-DBS to improve psychiatric complications (manic symptoms) resulted in recurrent PHS. Neuneier et al. [4] reported a patient with an 18-year history of PD, who developed PHS a few days after battery depletion. IPG replacement was postponed because of concomitant antiplatelet therapy and the patient died of multi-organ failure and disseminated intravascular coagulation. Three additional cases were reported after the removal of DBS implant because of hardware-related infection, whereby dopaminergic dose increases or subcutaneous apomorphine, which may represent a possible therapeutic option for patients with severe dysphagia and/or gastroparesis, were also fruitless [5]. Only the patient who received IPG replacement recovered; the two treated with higher doses of levodopa died 50 and 16 days after the removal of DBS implant.

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Table 1 Clinical features of patients with PHS after STN-DBS discontinuation

Report	Age/sex	PD duration/ DBS duration at PHS onset (years)	Type of DBS	PHS latency	LEDD at PHS onset	Therapy	Laboratory findings	Outcome
Kadowaki et al. [3]	60 M	17/8	Bilateral STN-DBS	3 days	n.a.	"Standard infusion therapy"	↑CK (1878 U/L) ↑CRP (10.3 mg/L)↑WBC (12,600/μL)	Recovery
Neuneier et al. [4]	77 M	18/5	Bilateral STN-DBS	6 days	150	-↑Levodopa -iv fluids -iv amantadine -paracetamol -ice packs	↑CK (1642 U/L)↑CRP (50 mg/L)	Death
Reuter et al. [5]	52 M	20/8	Bilateral STN-DBS	n.a.	250	-↑Levodopa -iv amantadine -apomorphine -antibiotic[a] therapy	n.a.	Recovery
Reuter et al. [5]	74 M	24/10	Bilateral STN-DBS	1 day	800	-↑Levodopa -iv amantadine -antibiotic[a] therapy	n.a.	Death
Reuter et al. [5]	75 M	19/9	Bilateral STN-DBS	n.a.	700	-↑Levodopa -iv amantadine -antibiotic[a] therapy	n.a.	Death
Current case	63 M	13/5	Bilateral STN-DBS	1 day	900	-↑Levodopa -iv fluids-clonazepam -paracetamol	↑CK (2820 U/L) ↑CRP (50.1 mg/L) ↑WBC (10,000/μL)	Recovery

CK creatine kinase, *CRP* C-reactive protein, *DBS* deep brain stimulation, *LEDD* levodopa equivalent daily dose, *n.a.* not available, *PD* Parkinson's disease, *PHS* parkinsonism-hyperpyrexia syndrome, *STN-DBS* subthalamic nucleus—deep brain stimulation, *WBC* white blood cells

[a] DBS implant was removed because of hardware related infection

Taken together, these reports suggest that abrupt withdrawal of DBS, independent of changes in dopaminergic therapy, may induce PHS. Chronic high-frequency stimulation of basal ganglia may lead to adaptive phenomena, similar to those observed with dopaminergic stimulation. Moreover, PHS occurrence for DBS withdrawal, despite the administration of high doses of dopaminergic therapies, might indicate different targets of action in the nigral pathways for STN-DBS and oral therapy.

Our experience and that of Kadowaki et al. [3] suggest that prognosis is optimal with prompt DBS restoration; fatal outcomes, reported in 50 % of the cases, were associated with delayed or no restoration of DBS and with older age at PHS onset [4, 5].

In conclusion, abrupt discontinuation of DBS increases the risk for life-threatening PHS. Rapid restoration of DBS represents the most important therapeutic measure, while sole reliance on compensatory increases in dopaminergic supplementation appears inadequate.

Compliance with ethical standards

Informed consent The patient described in the article gave his written informed consent.

Conflicts of interest Dr. Espay is supported by the NIH (K23MH092735) and has received grant support from Great Lakes Neurotechnologies and the Michael J Fox Foundation; personal compensation as a consultant/scientific advisory board member for Abbvie, Chelsea Therapeutics, TEVA, Impax, Merz, Pfizer, Acadia, Cynapsus, Solstice Neurosciences, Lundbeck, and USWorldMeds; royalties from Lippincott Williams & Wilkins and Cambridge University Press; and honoraria from Abbvie, UCB, USWorldMeds, Lundbeck, Acadia, the American Academy of Neurology, and the Movement Disorders Society. Dr. Artusi, Dr. Merola, Dr. Zibetti, Dr. Romagnolo, Dr. Lanotte and Dr. Lopiano report no disclosures.

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