# Parkinsonism- Hyperpyrexia Syndrome (PHS) Crisis following Deep Brain Stimulator Battery Depletion

Dear Sir,

Subthalamic nucleus (STN) deep brain stimulation (DBS) is a well-established treatment for advanced Parkinson's disease (PD). The exact mechanism of STN DBS remains an enigma.[1] Parkinsonism-hyperpyrexia syndrome (PHS) is a life-threatening condition, commonly seen with withdrawal of anti-Parkinson medications before DBS surgery or with the malfunctioning of the DBS system.[2] In this report, we are describing two cases of PHS due to DBS battery depletion presented with worsening of parkinsonian features, fever, and abnormal blood investigations.

A 32-year-old male, known case of young onset PD with post STN DBS (done elsewhere), came to emergency department after 4 years of DBS with a primary cell (nonrechargeable) implantable pulse generator (IPG) following bilateral STN DBS surgery. He was drowsy but arousable (E3M6V2), presented with complaints of whole-body stiffness, difficulty in moving limbs, difficulty in swallowing for 4 days, and difficulty in breathing with pooling of saliva in mouth for 1 day. On examination, he was in off phase with extreme whole-body rigidity, bradykinesia, and inability to move any of his limbs. He had stridor with pooling of secretions in his mouth. His saturation on admission was 75%, pulse rate was 90 per minute, and blood pressure was 140/90 mmHg. He was shifted to intensive care unit, subsequently intubated. He had low grade fever (100.1), with increased total white blood cell count (15,400/cmm) and creatinine kinase (CK, 1679 IU/L) counts. He was diagnosed with Klebsiella Pneumoniae infection. His IPG status showed "end of service" and was diagnosed to be in an acute Parkinsonian crisis. In view of active infection, we had to delay his IPG replacement. His PD medications were significantly increased. He responded to the drugs slowly with his rigidity and fever improving along with the procalcitonin (1.29) and CK counts (203 IU/L). He was taken up for change of IPG after 5 days and stimulation was started immediately after surgery. He responded dramatically to the stimulation and was in a full ON phase after surgery, enabling him to weaned off the ventilator and extubated on the first postoperative day. He was able to move around independently at the time of discharge.

In another case, a 55-year-old male, known case of advanced PD post bilateral STN DBS with primary cell (nonrechargable) IPG came to us after 3 years of surgery with the history of sudden increase in his rigidity, bradykinesia, and tremors involving whole body for 2 days. He also had a history of fever, sweating, and palpitations on the day of onset of above Parkinson's symptoms. On checking his IPG, it showed end of service. He was evaluated in ward. On examination, his vitals showed tachycardia with heart rate (HR) of 110/min, blood pressure - 150/90, and respiratory rate (RR) - 26/min. His blood investigations showed increase in total leucocyte count (14,020/cmm), blood urea (32.9 mg%), creatinine (1.6 mg%), LDH (363.5 IU/L), and CK levels (7046 IU/L) with decrease in bicarbonate levels and presence of ketone and albumin in urine (proteinuria). From his clinical and blood investigation, a provisional diagnosis of PHS was made. He was stabilized with IV fluids, antipyretics, and antibiotics for 2 days post admission in the hospital. He was planned for the change of IPG. Following the IPG change, stimulation was started immediately, and he showed improvement in his Parkinson's symptoms. His blood investigations on postoperative day 1 also showed a decrease in total leucocyte count (8,660/cmm) and CK levels (245 IU/L). He was discharged on third postoperative day in good condition.

PHS presents with symptoms indicative of medical emergency which was initially described in the patients of PD in 1981.[3] PHS commonly occurs after sudden discontinuation of anti-Parkinson drugs,[2] including drug-holiday treatment protocols.[4] The clinical presentation is classically with fever, excessive rigidity, autonomic instability, tremors, cognitive decline, diaphoresis, rhabdomyolysis with elevated CK, and LDH count.[3,5] Total leucocyte count may or may not increase and depends upon the infection.[2,5] PHS can lead to complications like aspiration pneumonia, disseminated intravascular coagulation (DIC), venous thromboembolism, and renal failure due to rhabdomyolysis.[2] Mortality due to PHS can be as high as 50%.[6] According to the reports of pre-DBS era, the common trigger factor for PHS was abrupt withdrawal of anti-Parkinson's drugs, mainly Levodopa.[5] As its half-life is very short, sudden withdrawal leads to PHS in perioperative period. Other factors like infection, neuroleptic medications, excessive hot climate, and dehydration can act as triggers for PHS.[7]

The precise theory behind the PHS is unclear; however, some suggest that acute reduction in neurotransmission in hypothalamus, mesocortical dopaminergic system, and nigrostriatal system even without any administration of neuroleptic drugs can lead to PHS.[2,8] Low dopamine metabolite homovanillic acid (HVA) levels in CSF increase the risk for PHS by three fold for each 10 ng/mL decrease in HVA concentration in patients with PD.

PHS treatment comprises of simultaneous initiation of supportive and restorative care. As this condition is rare, early diagnosis is crucial for initiating these two modalities of treatment. Patients should be admitted in intensive care unit for monitoring of oxygen saturation, arterial blood pressure, central venous pressure, and body temperature. Supportive treatment includes intravenous fluid therapy, cooling of

body temperature with antipyretics, and monitoring of vitals. Close monitoring of CK, renal function, coagulation factors, and urine myoglobin should be done. Restorative therapy includes initiation of all the previous Parkinson's drugs and early replacement of IPG. Apomorphine subcutaneously has also been used as a successful alternative in couple of cases reported in the literature.[9] Most of the patients reported with fatal outcome due to delay in replacement of Parkinson drugs and IPG.[2,7] Along with PHS, there are other syndromes which mimic the same symptomatology and it is important for them to be differentiated [Table 1].[10]

PHS following STN DBS surgery due to anti-Parkinson's drugs reduction/discontinuation has been reported in literature which were successfully treated with the administration of dopamine agonists, fluid replacement, and activation of DBS [Table 2].[11]

**Table 1: Clinical features of Parkinson-hyperpyrexia syndrome (PHS), Dyskinesia-hyperpyrexia syndrome (DHS), Serotonin syndrome (SS), and Neuroleptic malignant syndrome (NMS)**

| | Parkinson Hyperpyrexia Syndrome (PHS) | Dyskinesia Hyperpyrexia Syndrome (DHS) | Serotonin Syndrome (SS) | Neuroleptic Malignant Syndrome (NMS) |
|---|---|---|---|---|
| 1. Triggers | -Dopamine reduction/ discontinuation<br>-DBS implant malfunctioning<br>-Trauma<br>-Infection<br>-High ambient temperature | -Dopamine excess/increase in drug dosage<br>-Trauma<br>-Infection | -Serotonin drug excess/ elevation | -Dopamine antagonists/abrupt cessation of dopaminergic drugs |
| 2. Duration | Up to 2 weeks | Up to 2 weeks | Within 24 hours | Gradual (days-weeks) |
| 3. Neuromuscular signs | -Tremors<br>-Dystonia<br>-Rigidity<br>-Akinesia<br>-Opisthotonous | -Dyskinesia | -Clonus<br>-Myoclonus<br>-Tremors<br>-Rigidity<br>-Hyperreflexia<br>-Akinesia | -Lead pipe rigidity<br>-Hyporeflexia |
| 4. Autonomic dysfunction | -Tachycardia<br>-Tachypnoea<br>-Hypertension<br>-Hypotension<br>-Sweating | Rarely seen | -Tachycardia<br>-Tachypnoea<br>-Hypertension<br>-Hypotension<br>-Sweating<br>-Diarrhoea<br>-Mydriasis | -Hypertension<br>-Tachycardia<br>-Tachypnoea<br>-Hyperthermia<br>-Hyper salivation |
| 5. Conciousness | -Confusion<br>-Drowsiness<br>-Lethargy/stupor<br>-Coma | -Confusion<br>-Hallucinations<br>-Lethargy/stupor<br>-Coma | -Anxiety<br>-Agitation<br>-Confusion<br>-Coma | -Variable mental status<br>-Lethargy/stupor<br>-Coma |
| 6. Treatment | -Supportive therapy<br>-Levodopa replacement<br>-Change of malfunctioning DBS system | -Reduction in dopamine medication<br>-Rehydration and electrolyte replacement<br>-DBS for long-term control | -Central serotonin receptor antagonist like, Cyproheptadine, Chlorpromazine alone or in combination with Benzodiazepam | -100% $FiO_2$, increase ventilation<br>-Discontinue the triggering factors<br>-Bromocriptine<br>-Administer dantrolene |

**Table 2: Case reports of PHS post STN DBS**

| Case Reports | Age/ Sex | Drug withdrawl time (Post-op) | Onset of PHS | Symptoms | Treatment | Outcome |
|---|---|---|---|---|---|---|
| Linazasoro *et al*. 2004[12] | 58/F | 12 h | Day 2, post STN DBS | Hyperthermia, Tachycardia, Hypertension | Restoration of drugs with activation of DBS system | Recovered |
| Kim JH *et al*. 2010. | 66/F | 12 h | Day 1, post STN DBS | Fever, hypertension, tachycardia | Restoration of Parkinson drugs along with conservative management for the symptoms. | Recovered |
| Themistocleous MS *et al*. 2011 | 54/M | 12 h | Day 1, Post STN DBS | Fever, rigidity, Tremors | IV dentrolene, subcutaneous apomorphine, Parkinson drugs through RT. | Recovered |
| Urasaki E *et al*. 2013 | 75/M | Reduced when DBS system switched ON | Day 24 post STN DBS | Severe tremor, diaphoresis, and elevated body temperature | intravenous fluid and oral levodopa/ bens- erazide (150 mg/37.5 mg) | Day 33, expired (Cardiac arrest) |
| Govindappa ST *et al*. 2015[11] | 49/M | 12 h | Day 1, Post STN DBS | Severe rigidity, tremors, high grade fever , tachycardia, drowsiness. | IV fluids, paracetamol, cold sponging, empirical antibiotics, and levodopa doses were increased. | Expired (sepsis) |

To conclude, early diagnosis of PHS is important in patients with advanced PD who had an abrupt change in PD medications (in regular follow-ups or in perioperative period) or failure of DBS. Replacement of the previous therapy like PD medications or DBS whichever the patient was on is the definitive treatment. Delay in restoration of the previous therapy can lead to fatal outcomes.

## Acknowledgments

We would like to acknowledge and give our warmest thanks to our investigator Dr. Paresh K Doshi who made this work possible. His guidance and advice carried us through all the stages of this project. We would like to thank our institute and all the staff for helping us in this project.

Above all, we would like to thank our patients for letting us involve in their care and management with full cooperation during this project writing.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

**Neha Rai, Manish Baldia, Paresh K. Doshi**

Department of Functional Neurosurgery, Jaslok Hospital and Research Centre, Mumbai, Maharashtra, India

**Address for correspondence:** Dr. Neha Rai, Clinical Associate, Department of Functional Neurosurgery, 11th Floor South Wing, Jaslok Hospital and Research Centre, Dr. G. Deshmukh Marg, Mumbai - 400 026, Maharashtra, India.
E-mail: neharai2012@gmail.com

## References

1. Benabid AL, Koudsié A, Benazzouz A, Vercueil L, Fraix V, Chabardes S, *et al*. Deep brain stimulation of the corpus luysi (subthalamic nucleus) and other targets in Parkinson's disease. Extension to new indications such as dystonia and epilepsy. J Neurol 2001;248:37-47.
2. Newman EJ, Grosset DG, Kennedy PG. The parkinsonism-hyperpyrexia syndrome. Neurocritical Care 2009;10:136-40.
3. Toru M, Matsuda O, Makiguchi K, Sugano K. Neuroleptic malignant syndrome-like state following a withdrawal of antiparkinsonian drugs. J Ner Ment Dis 1981;169:324-7.
4. Friedman JH. 'Drug holidays' in the treatment of Parkinson's disease. A brief review. Arch Intern Med 1985;145:913-5.
5. Hashimoto T, Tokuda T, Hanyu N, Tabata K, Yanagisawa N. Withdrawal of levodopa and other risk factors for malignant syndrome in Parkinson's disease. Parkinsonism Relat Disord 2003;9:25-30.
6. Reuter S, Deuschl G, Falk D, Mehdorn M, Witt K. Uncoupling of dopaminergic and subthalamic stimulation: Life-threatening DBS withdrawal syndrome. Movement Disorders 2015;30:1407-13.
7. Douglas A, Morris J. It was not just a heatwave! Neuroleptic malignant-like syndrome in a patient with Parkinson's disease. Age Ageing 2006;35:640-1.
8. Ueda M, Hamamoto M, Nagayama H, Okubo S, Amemiya S, Katayama Y. Biochemical alterations during medication withdrawal in Parkinson's disease with and without neuroleptic malignant-like syndrome. J Neurol Neurosurg Psychiatry 2001;71:111-3.
9. Lattanzi L, Mungai F, Romano A, Bonuccelli U, Cassano GB, Fagiolini A. Subcutaneous apomorphine for neuroleptic malignant syndrome. Am J Psychiatry 2006;163:1450-1.
10. Wang M, Wang W, Gao Z, Yin X, Chen T, Jiang Z, *et al*. Dyskinesia-hyperpyrexia syndrome in Parkinson's disease: A systematic review. Clin Auton Res 2021;31:529-42.
11. Govindappa ST, Abbas MM, Hosurkar G, Varma RG, Muthane UB. Parkinsonism hyperpyrexia syndrome following deep brain stimulation. Parkinsonism Relat Disord 2015;21:1284-5.
12. Gurutz Linazasoro, Nadege Van Blercom, Alfonso Castro, Maria Dolores Dapena. Subthalamic deep brain stimulation masking possible malignant syndrome in Parkinson disease. Neurology 2004;63:589-90.

**Submitted:** 12-Jun-2023 **Revised:** 04-Jul-2023 **Accepted:** 16-Jul-2023
**Published:** 09-Oct-2023



**DOI:** 10.4103/aian.aian_517_23