

Parkinsonism-hyperpyrexia syndrome following globus pallidus internus deep brain stimulation withdrawal: a report of two cases and literature review

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Case Report

Keywords: parkinsonism-hyperpyrexia syndrome, deep brain stimulation, globus pallidus internus, IPG cessation, device-first, metabolic hysteresis

Posted Date: July 14th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10276529/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background

Parkinsonism–hyperpyrexia syndrome (PHS) is a life-threatening neurologic emergency. Deep brain stimulation (DBS) withdrawal is a recognized precipitant, yet most reported cases involve the subthalamic nucleus (STN). In contrast, detailed descriptions of PHS following globus pallidus internus (GPi) DBS withdrawal remain scarce, particularly regarding the temporal relationship between the resolution of hyperthermia and the normalization of serum biochemical markers (creatine kinase) after device reactivation.

Case presentation:

We describe two cases of GPi-DBS withdrawal PHS triggered by accidental implantable pulse generator shutdown. Case 1 involved a 67-year-old woman with fulminant PHS (peak temperature 39.5°C; creatine kinase 2486 U/L) and case 2 involved a 71-year-old man with prodromal PHS (temperature 38.2°C; creatine kinase 770 U/L). In both cases, device reactivation resulted in rapid resolution of hyperthermia within 2–4 hours and creatine kinase levels normalized only after 5–9 days of intensive intravenous hydration. This temporal dissociation between clinical improvement and biochemical recovery has not been well understood in GPi-DBS withdrawal PHS.

Conclusions

These cases demonstrate that in GPi-DBS withdrawal PHS, body temperature can normalize rapidly despite persistently elevated serum creatine kinase. Resolving hyperthermia in the setting of ongoing rhabdomyolysis creates a deceptive clinical impression that can lead to the premature de-escalation of supportive care. Our findings underscore the importance of the “Device-first” principle, and emphasize that continuous biochemical monitoring remains crucial even after apparent clinical stabilization.

Background

Parkinsonism-hyperpyrexia syndrome (PHS) is a life-threatening emergency with severe rigidity, hyperthermia, autonomic dysfunction and rhabdomyolysis – reported mortality up to 4% [1]. With the widespread use of deep brain stimulation (DBS), the most frequent trigger for PHS has gradually changed from the traditional “dopaminergic medication withdrawal” to “stimulation dependent withdrawal” [2–5]. In one recent multicenter cohort study, severe withdrawal syndromes needing intensive care are rare after implantable pulse generator (IPG) battery – a small but clinically important subset of patients, they are rare but warrant strict vigilance [3]. Once the basal ganglia–thalamocortical circuit homeostasis maintained by DBS is disrupted, even prompt supplementation with levodopa can not stop clinical deterioration and disease progresses rapidly to multiple organ failure [4]. International guidelines now emphasize that checking DBS system function should be a priority and should not be delayed by empirical medication adjustments or other diagnostic workups [6]. Most reported cases of DBS-related PHS involve stimulation of the subthalamic nucleus (STN) but systematic descriptions of PHS following withdrawal of GPi DBS, especially the time pattern after device reactivation is rare.

We report two cases of PHS following withdrawal of GPi-DBS due to accidental implantable pulse generator shutdown—one fulminant and one prodromal. These cases highlight the decisive prognostic role of prompt device interrogation and demonstrate that clinical stabilization does not equate to biochemical recovery – a dissociation that may create a deceptive picture of resolved illness.

Case presentation

Case 1

A 67-year-old woman was diagnosed with Parkinson's disease (PD) in April 2011. Levodopa and pramipexole provided inadequate control, with prominent wearing-off and dyskinesia. Bilateral GPi-DBS was performed in 2013 at Hoehn-Yahr stage 4 (Model: PINS G102RZ – Dual Channel Rechargeable Implantable Pulse Generator for Deep Brain Stimulation). Pre-operative UPDRS-III: off-state 58, on-state 38; post-operative at two months: off-state 32, on-state 14. Maintenance: levodopa 0.25 g three times daily, pramipexole 0.25 mg once daily.

She was admitted with one month of worsening bradykinesia, tremor, and rigidity. Baseline investigations were normal (CK 40 U/L). DBS parameters were optimised (right: C + 1- 3.30 V/90 us/130 Hz; left: C + 5- 3.20 V/90 us/130 Hz). On the third hospital day, IPG charging was transferred to a nursing assistant; a handover failure caused interrupted charging and inadvertent IPG shutdown. The following morning the patient developed low-grade fever. By 19:15 that evening, her condition deteriorated abruptly: temperature 39.5°C, heart rate 143 bpm, respiratory rate 30/min, blood pressure 149/88 mmHg, with somnolence, diaphoresis, and severe cogwheel rigidity. Emergency levodopa and physical cooling were ineffective. Laboratory tests showed CK 2486 U/L, WBC 13×10^9 /L, myoglobin 814 µg/L, and CRP 42 mg/L. Programmer interrogation confirmed accidental IPG shutdown.

The IPG was immediately restarted, accompanied by adjunctive physical cooling, intravenous fluids, methylprednisolone, and empirical cefoperazone-sulbactam for antimicrobial coverage. A subsequent comprehensive infectious evaluation, including blood, urine, and sputum cultures, was negative, and chest radiography showed no acute infiltrates, thereby ruling out sepsis or severe focal infection as the primary cause of hyperthermia. Approximately four hours after the IPG was restarted, the patient's consciousness returned and rigidity resolved, the core temperature dropped from 39.5°C to 37.8°C. Body temperature normalized by the following day (Fig. 1), while CK remained at 1435 U/L, WBC 11.2×10^9 /L and myoglobin at 88 µg/L. By day 9, CK was 73 U/L, WBC 8×10^9 /L, CRP 11 mg/L, and creatinine 63.12 µmol/L. PD symptoms were stable at 1-year follow-up, with UPDRS-III score of 25 on-state and 32 off-state.

Case 2

A 71-year-old man was diagnosed with PD in June 2019 and underwent bilateral GPi-DBS in August 2022 at Hoehn-Yahr stage 4 (Model: PINS G102RZ — Dual Channel Rechargeable Implantable Pulse Generator for Deep Brain Stimulation). His pre-operative UPDRS-III scores were: off 62, on 38; at two months post-operatively, they improved to: off 24, on 12. His maintenance regimen consisted of levodopa 0.25 g three times daily and pramipexole 0.25 mg nightly. He had a history of hypertension, well controlled with amlodipine 5 mg daily.

On the morning of admission, he underwent 3.0-T MRI at an outside facility for evaluation of chest pain. DBS compatibility was not checked and MRI safety mode was not activated, leading to inadvertent IPG shutdown. That evening, his PD symptoms worsened abruptly. Additional self-administered levodopa provided no relief. He arrived by wheelchair with marked worsening of upper-limb tremor and bradykinesia, new-onset dysphagia (Kubota grade II), fever, and diaphoresis. On admission, his temperature was 38.2°C, HR 112 bpm, RR 22/min, and BP 147/85 mmHg.

Following the Device-first principle, a programmer interrogation confirmed shutdown with normal electrode impedance, and then the IPG was restarted and the original parameters were restored (right: C + 1– 3.2 V/90 µs/135 Hz; left: C + 5– 3.1 V/90 µs/135 Hz). A CT head scan ruled out electrode displacement and new intracranial pathology. Initial laboratory investigations showed WBC $11.2 \times 10^9/L$, CRP 35 mg/L, and CK 770 U/L. Within 30 minutes of IPG reactivation, rigidity and tremor improved markedly. Approximately two hours later, the temperature had fallen to 37.2°C. By the following morning, the temperature was 36.8°C and the patient’s usual medications were resumed. On day 2, WBC was $7.8 \times 10^9/L$, CRP 8 mg/L, and CK 305 U/L; CK was 105 U/L at discharge on day 5. Progression to full PHS was prevented. At the six-month follow-up, the patient remained stable with good quality of life, with UPDRS-III scores of 15 in the on-state and 20 in the off-state.

Discussion

Among published reports of PHS after DBS withdrawal, cases involving the subthalamic nucleus (STN) predominate [4, 7–17] (Table 1). This predominance most likely reflects the broader worldwide use of STN-DBS and the typically greater reductions in dopaminergic medication that follow, rather than a higher intrinsic risk associated with the STN target itself. In contrast, systematic descriptions of PHS after withdrawal of globus pallidus internus (GPi) DBS are exceedingly rare. The two cases presented here both involved GPi targets and illustrate the clinical spectrum of this complication: Case 1 represents the fulminant, fully developed syndrome, whereas Case 2 captures an early prodromal phase identified and treated before full decompensation.

Table 1. Systematic summary of previously published cases of deep brain stimulation (DBS) withdrawal-induced parkinsonism-hyperpyrexia syndrome (PHS).

Relevant cases were identified through a PubMed search (from database inception to January 2026) using the combined terms (“parkinsonism-hyperpyrexia syndrome” OR “akinetic crisis” OR “withdrawal syndrome”) AND (“deep brain stimulation” OR “DBS”). Additional cases were identified by manually cross-referencing the bibliographies of all retrieved articles.

Report	Gender/ Age	PD/DBS dur. (yrs)	Target	Cause	Duration interruption	Peak temp (°C)	Lab results	Treatment	DBS restoration	Outco
[7] Artusi et al. (2015)	M/63	13/5	STN	Battery depletion	NR	38.5°C	CK 2820 U/L CRP 50.1 mg/L WBC 10.0x10 ⁹ /L	Levodopa, Conservative	IPG reimplanted	Recov
[8] Kadowaki et al. (2011)	M/60	17/8	STN	DBS switched off	NR	38.7°C	CK 1878 U/L CRP 10.3 mg/L WBC 12,600/ μ L	Conservative	DBS switched on	Recov
[4] Grimaldi et al. (2023) – Case 1	M/71	24/12	STN	Battery depletion	11 days	NR	NR	IV dopamine	Battery replaced	Recov
[4] Grimaldi et al. (2023) – Case 2	F/68	20/3	STN	Battery depletion	20 days	NR	CK 989 U/L	Levodopa	Battery replaced	Recov
[4] Grimaldi et al. (2023) – Case 3	F/64	26/15	STN	Battery depletion	4 days	NR	CK 115 U/L	Levodopa, conservative	Battery replaced	Recov
[4] Grimaldi et al. (2023) – Case 4	M/71	25/20	STN	Battery depletion	80 days	NR	CK 346 U/L	Levodopa, conservative	Battery replaced	Recov
[4] Grimaldi et al. (2023) – Case 5	M/54	24/16	STN	Battery depletion	NR	NR	NR	Levodopa	Battery replaced	Recov
[9] Neuneier et al. (2013)	M/77	18/5	STN	Battery depletion	NR	41°C	CK 1642 U/L	Levodopa, IV amantadine, conservative	IPG reimplanted	Death
[10] Azar et al. (2022) – Case 1	F/76	14/9	STN	Battery depletion	NR	40°C	CK 1250 U/L CRP 6.6 mg/L WBC 21.500/ μ L	Levodopa, conservative	Battery replaced	Recov
[11] Díaz-Castela et al. (2024)	M/67	NR/NR	STN	Device malfunction	NR	39°C	CK 10476U/L	Levodopa, conservative	NR	Death
[12] Rajan et al. (2016) – Case 1	M/51	11/7	STN	Battery depletion	NR	104°F	CK 4380 U/L	Levodopa/carbidopa, pramipexole, amantadine, conservative	IPG reimplanted	Recov
[12] Rajan et al. (2016) – Case 2	F/54	NR/11	STN	Battery depletion	NR	NR	CK 606 U/L	Levodopa, pramipexole, amantadine , conservative	IPG reimplanted	Recov
[13] Reuter et al. (2015) – Case 1	M/52	20/8	STN	IPG removal (infection)	NR	NR	NR	Levodopa, IV amantadine, conservative	IPG reimplanted	Recov
[13] Reuter et al. (2015) – Case 2	M/74	24/10	STN	IPG removal (infection)	NR	NR	NR	Levodopa, IV amantadine, conservative	IPG not reimplanted	Death
[13] Reuter et al. (2015) – Case 3	M/75	19/9	STN	IPG removal (infection)	NR	NR	NR	Levodopa, IV amantadine, conservative	IPG not reimplanted	Death

[14] Rai et al. (2023) – Case 1	M/32	NR/4	STN	Battery depletion	NR	100.1°F	CK 1679 IU/L WBC 15.4x10 ⁹ /L	NR	IPG reimplanted	Recov
[14] Rai et al. (2023) – Case 2	M/55	NR/3	STN	Battery depletion	NR	NR	CK 7046 IU/L WBC 14,02x10 ⁹ /L	conservative	IPG reimplanted	Recov
[15] Azar et al. (2019)	F/67	23/7	STN	Battery depletion	NR	39°C	CK 1615 U/L CRP 10.6 mg/L WBC 16.5x10 ⁹ /L	Levodopa, pramipexole, conservative	Battery replaced	Recov
[16] Liu et al. (2017)	M/69	16/9	STN	Battery depletion	NR	39.4°C	CK 1250 U/L WBC 12.1x10 ⁹ /L	Levodopa, bromocriptine, conservative	Battery replaced	Recov
[17] Hocker et al. (2013)	F/74	–/4	STN	DBS switched off	NR	40°C	CK 2845 U/L	Levodopa, conservative	IPG restarted, IPG replaced	Recov
Our case 1	F/67	13/11	GPI	Accidental IPG shutdown (charging handover failure)	~24 h	39.5°C	CK 2486 U/L Myoglobin 814 µg/L WBC 13x10 ⁹ /L CRP 42 mg/L	Levodopa, methylprednisolone, conservative	IPG restarted	Recov (day 1)
Our Case 2	M/71	5/2	GPI	Accidental IPG shutdown (3.0T MRI, no safety protocol activated)	~12 h	38.2°C	CK 770 U/L WBC 11.2x10 ⁹ /L CRP 35 mg/L	IPG restarted only	IPG restarted	Recov (day 1)

Abbreviations: DBS, deep brain stimulation; GPI, globus pallidus internus; STN, subthalamic nucleus; CK, creatine kinase; CRP, C-reactive protein; WBC, white blood cell count; NR, not reported; IV, intravenous; IPG, internal pulse generator; PD, Parkinson's disease; PHS, parkinsonism-hyperpyrexia syndrome. "Conservative" treatment refers to supportive measures including intravenous fluids, antibiotic, antipyretics, cooling measures, and/or sedatives.

STN-DBS-related PHS is generally attributed to severe nigrostriatal degeneration in advanced Parkinson's disease, together with the sudden disruption of long-standing dopaminergic and electrical modulation when high-frequency stimulation is discontinued [13]. A review of historical cases (Table 1) indicates that almost all reported DBS-withdrawal PHS episodes occurred after STN battery depletion and were characterized by generalized hyperthermia and elevated CK. GPI and STN play different roles in basal ganglia circuitry (GPI is the main output nucleus and STN as an intermediate relay) and whether these anatomical and functional differences result in PHS that differs in severity and rate of onset remains to be determined by future prospective studies [18, 19].

During management of these two cases, core body temperature normalised substantially faster than serum creatine kinase declined following IPG reactivation, yielding a marked temporal dissociation between the two recovery trajectories (Figure 1). We refer to this pattern descriptively as "clinical-biochemical decoupling," – a lag between the rapid resolution of systemic autonomic and motor abnormalities and the considerably slower clearance of tissue-level metabolic injury.

This temporal dissociation reflects the marked difference in time scales between central neurological recovery and peripheral tissue repair. Sudden discontinuation of GPI-DBS causes a rapid rebound in GABAergic output from the internal globus pallidus, which in turn triggers severe rigidity and tremor [20, 21]. These motor phenomena generate a substantial amount of endogenous heat through sustained muscle contractions while decreasing effective heat dissipation by autonomic dysregulation. Following IPG reactivation, the near-instantaneous restoration of high-frequency stimulation rapidly suppresses pathological pallidal output [22], resulting in prompt resolution of rigidity and tremor. The consequent abrupt decline in endogenous heat production, together with the restoration of normal autonomic thermoregulatory responses, can support rapid defervescence even while muscle injury persists. By contrast, release of creatine kinase and myoglobin from damaged myocytes, and subsequent inflammatory and renal clearance, occur much longer time scales. 5- to 9-day CK clearance interval is broadly similar to expected resolution time for muscle fibre necrosis of this severity [23]. The unusual feature is therefore not a delayed CK clearance per se, but a body temperature recovery that is disproportionately rapid relative to ongoing muscle injury. Thermoregulation is tightly orchestrated by central neural circuits, primarily centered in the preoptic area of the hypothalamus [24, 25]. Whether GPI-DBS reactivation directly modulates the hypothalamic thermoregulatory set-point remains speculative; the observed rapid cooling kinetics are more plausibly explained by the swift cessation of massive myogenic heat production (secondary to resolving severe rigidity) together with the rapid restoration of autonomic thermoregulatory capacity.

The different results of the two cases illustrate directly the "Device-first" emergency principle. The key difference in the outcome was not disease stage, DBS programming, or baseline medication; rather, it was speed of IPG status questions. In Case 2, IPG was asked immediately upon admission, and restarted early, preventing progression to full PHS and discharged on Day 5. The rapid defervescence seen in Case 2 occurred without active cooling, suggesting that device reactivation itself (rather than concurrent supportive care) is a key driver of clinical recovery. In Case 1, physical cooling and intravenous methylprednisolone were administered. It is not entirely clear that both these powerful antipyretics contributed to observed temperature normalization. In Case 1, it was not recognized that IPG shutdown during low grade fever occurred early, which led to missed therapeutic window and progression to full-blown PHS. This pattern is consistent with previous reports suggesting early device reactivation or reimplantation can reverse a potentially life-threatening DBS

withdrawal syndrome [26]. These results suggest that if one is suffering from acute neurological loss, early programmer interrogation to confirm IPG function should be prioritized rather than relying on extensive laboratory testing or imaging, especially since it is often difficult to distinguish device withdrawal from sepsis or other infectious diseases in this population [16, 17]. Existing diagnostic frameworks for PHS-like crises such as Levenson criteria for neuroleptic malignant syndrome do not include any component for evaluation of neurostimulation hardware [27]. Based on these two cases, we suggest a triple-verification framework for DBS patients with un-explained hyperthermia and rigidity: (1) clinical recognition – worsening parkinsonism with hyperthermia, rigidity, and high creatine kinase; (2) device verification; (3) medication reconciliation.

The clinical–biochemical decoupling described above can create a misleading impression: rapid improvement in hyperthermia and rigidity may cause clinicians to assume that the crisis has resolved and to reduce or discontinue intravenous hydration and other supportive measures prematurely. This early de-escalation may lead patients to avoidable acute kidney injury as kidneys filter persistently high myoglobin and creatine kinase and increase risk of subsequent multi-organ dysfunction [23,28]. We suggest that a fever and rigidity alone should not be taken as a solution to the rhabdomyolysis.

Out of these specific consequences, we note four lessons. First, in Case 1, device management was delegated to a nursing assistant without a structured handover protocol, and the resulting interruption in charging went unnoticed until the patient had already progressed to fulminant PHS, a scenario consistent with previous reports identifying battery depletion as a common and often under-anticipated trigger of DBS withdrawal syndromes [29]. We therefore suggest that all caregivers involved in DBS device management should receive formal, device-specific training. Second, medication-adherence monitoring remains important even in device-dependent patients: missed doses could be synchronized with hardware malfunction or obscure the initial diagnosis, making medication monitoring as important as hardware surveillance. Third, iatrogenic risk from imaging performed outside specialty DBS centers is under-appreciated: In Case 2, an external radiology facility performed 3.0-T MRI without verifying DBS compatibility or safety mode, a scenario likely to repeat in practice but entirely preventable. Fourth, in this series, pursuing device interrogation alongside, rather than only after, standard infectious work-up appears to be the key factor in averting a crisis. Together, these results suggest that verification of device status may be considered as an element of the initial evaluation of any DBS patient with unreported fever, rigidity or altered consciousness, like vital signs measure. This observation derives from two cases and would require validation in larger, prospective series before any specific protocol could be recommended.

This paper has several limitations: First, only two retrospective cases of the GPi target were studied, thus we could not perform statistical analysis and compare it directly to STN-DBS withdrawal. Second, although core parameters such as temperature and creatine kinase were continuously monitored, a comprehensive panel of other relevant biomarkers was not systematically obtained due to the emergency nature of the presentations. This limits a broader characterization of the observed clinical–biochemical dissociation. Finally, our mechanistic interpretation of the metabolic hysteresis remains inferential, and the potential confounding effects of concurrent supportive therapies cannot be fully excluded.

Conclusion

Parkinsonism–hyperpyrexia syndrome (PHS) is a life-threatening neurological emergency. This case series demonstrates that the rapid verification of device status is directly associated with patient outcomes, highlighting the critical importance of a “device-first” approach for any DBS patient who presents with acute deterioration. In addition, the consistent clinical–biochemical decoupling observed after IPG reactivation provides a key bedside warning: rapid defervescence does not indicate resolution of the underlying rhabdomyolysis; therefore, extended biochemical monitoring should continue well beyond apparent clinical stabilization.

Abbreviations

BP
blood pressure
CK
creatinine kinase
CRP
C-reactive protein
CT
computed tomography
DBS
deep brain stimulation
GPi
globus pallidus internus
HR
heart rate
IPG
implantable pulse generator
MRI
magnetic resonance imaging
NR
not reported
PD

Parkinson's disease
PHS
parkinsonism-hyperpyrexia syndrome
RR
respiratory rate
STN
subthalamic nucleus
UPDRS-III
Unified Parkinson's Disease Rating Scale,Part III
WBC
white blood cell count.

Declarations

Ethics approval and consent to participate: The studies involving humans were approved by the Ethics Committee of the First Affiliated Hospital of Kunming Medical University (No.2024-L-251). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Consent for publication: Written informed consent was obtained from the patient's legal guardian for publication of this case report.

Availability of data and materials: All data generated or analyzed during this study are included in this published article.

Competing interests: The authors declare that they have no competing interests.

Funding: The author(s) declare that financial support was received for the research and/or publication of this article. This study was supported by the National Natural Science Foundation of China (No. 82460236); Geng Xin, a Project for the Training of Technological Innovation Talents in Yunnan Province [202205AD160006]; Yunnan Health Training Project of High Level Talents Fund Supports the Yunnan Provincial Health Commission's Medical Discipline Leader Training Program (D-2024043); NHC Key Lab of Drug Addiction Medicine[Kunming Medical University]Open Projects Fund[KN202409]; NHC Key Lab of Drug Addiction Medicine[Kunming Medical University]Open Projects Fund[KN202418]; 535 Talent Project of First Affiliated Hospital of Kunming Medical University[2025535Q19]; Yunnan Provincial Education Department Scientific Research Fund Project[2026Y0421].

Authors' contributions: KL, HC, and JC contributed equally as co-first authors. They collected clinical data, performed the literature review, prepared the figures and tables, and drafted the manuscript. YY, XL, XZ, and KS contributed to data collection, follow-up, and manuscript revision. YZ and XG contributed equally as corresponding authors. They secured funding, supervised the study, critically revised the manuscript, and approved the final version. All authors read and approved the final manuscript.

Acknowledgements: Not applicable.

Authors' information: Not applicable.

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Figures

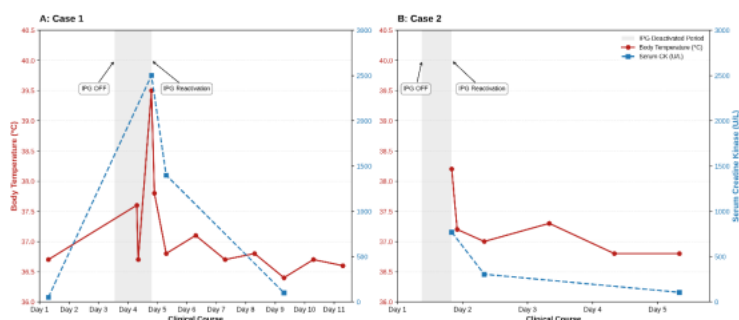


Figure 1

Time-course of body temperature and serum creatine kinase (CK) during and after the parkinsonism-hyperpyrexia syndrome (PHS)