

Review

Parkinsonism-Hyperpyrexia Syndrome and Dyskinesia-Hyperpyrexia Syndrome in Parkinson's Disease: Two Cases and Literature Review

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Abstract. Parkinsonism-hyperpyrexia syndrome (PHS) and dyskinesia-hyperpyrexia syndrome (DHS) are rare but life-threatening complications in Parkinson's disease (PD). We herein presented two cases of PD patients and performed a comprehensive and comparative literature review for these two syndromes. The first case was diagnosed as PHS with cerebral salt wasting syndrome caused by abrupt withdrawal of antiparkinsonian medication. Her symptoms were gradually remitted with reinstatement of the medication. The second one was an early-stage PD patient diagnosed as DHS in association with abuse of antiparkinsonian drugs. Her symptoms were gradually remitted with reduced dosage of dopaminergic drugs. Results of literature reviews revealed a total of 56 and 13 cases of PHS and DHS, respectively, and they were more likely to occur in elderly and long-term PD patients. These two syndromes showed different female-to-male ratio, similar mortality, and different recovery time. There were stark differences between PHS and DHS, including triggers (abrupt drug stoppage versus drug abuse), symptoms (worsened tremor and rigidity versus continuous dyskinesia), and treatment (drug reinstatement versus drug reduction). In summary, our reports and the review provide new insights into PHS and DHS in association with PD and may facilitate rapid discrimination of the syndromes for timely and proper treatment to reduce mortality.

Keywords: Parkinsonism-hyperpyrexia syndrome, dyskinesia-hyperpyrexia syndrome, Parkinson's disease, emergency, complication

BACKGROUND

Parkinson's disease (PD) is a common neurodegenerative disease characterized by classical motor features of parkinsonism and a progressive loss of dopaminergic neurons in the substantia nigra pars compacta. The clinical challenges of PD include difficulties to accurately diagnose at the earliest stage

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and to manage symptoms at later stages [1]. Acute critical syndromes may occur in PD patients [2]. For instance, parkinsonism-hyperpyrexia syndrome (PHS), also known as malignant syndrome or akinetic crisis [3], is often caused by abrupt withdrawal of dopaminergic drugs. Dyskinesia-hyperpyrexia syndrome (DHS), another acute complication of PD, was first defined as an emergency in 2010 [4] and often caused by antiparkinsonian drug abuse. Besides, there are a number of other factors that provoke PHS and DHS.

Both PHS and DHS are rare but life-threatening complications of PD. Compared with PHS, DHS is even rarer. Hyperthermia occurs in both PHS and DHS. Although hyperthermia is believed to be resulted from massive dyskinetic movements [4], it is also considered to be attributed to dysfunction of central thermoregulation [5]. Many pathological processes in PD may result in abnormal thermoregulation. Autonomic dysfunction, a common non-motor symptom, may lead to abnormal sweating and skin cooling in high temperature [6, 7]. Hypothalamic dopamine release, which is disturbed in PD patients, may increase when temperature rises [8]. Indeed, autonomic dysfunction and altered metal status are often observed in patients with PHS and DHS. However, pathological mechanisms by which PHS and DHS occur in PD remain unclear.

Herein, we reported two cases of PD patients who were diagnosed with PHS and DHS, as well as performed a comprehensive literature review and a comparative analysis of these two syndromes.

CASE DESCRIPTION

Case 1: PD with PHS

The patient was a 57-year-old woman with a 6-year history of PD. She had regular follow-up visits to the Second Affiliated Hospital of Wenzhou Medical University. The patient has been treated with pramipexole (0.75 mg/day) and madopar (625 mg/day) since the age of 56. Her medical history was unremarkable. The patient was transported to the emergency department because she developed a confusional state, fever, diaphoresis, and severe tremor. Six days before, she discontinued the antiparkinsonian prescription drugs herself because of slight dyskinesia.

In the emergency department with a confusional state, her body temperature was 38.6°C and heart

rate was 102 beats per minute. Neurological examinations showed that she developed severe tremor and rigidity on her four limbs, dysphagia, and diaphoresis. Meningeal and other neurological signs were unremarkable. Blood tests showed high creatinine kinase level (465 IU/L), low serum sodium level (119.7 mmol/L), and low serum uric acid level (61 μ mol/L). Leukocyte number (5.08×10^9 /L) was within the normal range. Urinalysis showed normal urine specific gravity (1.024), high urine sodium level (415.2 mmol per 24 h), and high urine chloride level (415.7 mmol per 24 h). Bacteriological culture of blood was negative.

We diagnosed the patient as PHS. The diagnosis of cerebral salt wasting syndrome (CSWS) was based on low serum levels of sodium and uric acid, normal urine specific gravity, and high urine levels of sodium and chloride. For PHS, she was treated with madopar (250 mg; thrice daily) via a nasogastric feeding tube and sedated with benzodiazepines. For CSWS, she was given intravenous fluids and sodium supplementation. During the hospitalization, the patient developed pulmonary infection and urinary tract infection such that antibiotics were also administered. Her clinical conditions were worsened in the first few days but were then gradually improved. Her body temperature returned to 37.0°C on day 22 after the hospitalization. The leukocyte number rose in the first three days and returned to normal on day 4. The rise and recovery might be caused by the infection and the use of antibiotics, respectively. Creatinine kinase and serum sodium levels became normal on day 7 and day 18, respectively. As a note, serum sodium level was declined from day 2 to day 4 even with sodium supplementation. Because her tremor was remitted on day 4, we prescribed the patient with madopar (625 mg/day) and pramipexole (0.75 mg/day). Since then, her rigidity and mental state were improved steadily. On day 23, she was able to follow instructions and perform rehabilitation training. She has been taking antiparkinsonian medication as prescribed and returning for follow-up visits regularly since being discharged from the hospital.

Case 2: PD with DHS

The patient aged 74 when she visited the Second Affiliated Hospital of Wenzhou Medical University and was diagnosed as PD. We treated the patient with piribedil (150 mg/day) and selegiline (10 mg/day) and she did not show symptoms of motor fluctuation.

She had displayed bradykinesia and resting tremor in her left limbs in the past 4 years. Her medical history included hypertension, diabetes, and osteoporosis. In a September afternoon, the patient was transported to the emergency department due to severe choreiform dyskinesia, hyperthermia, and hallucination in the past 9 hours. Prior to the emergency visit, the patient disregarded doctor's prescription and took madopar (1500 mg/day; prescribed from another hospital) and selegiline (30 mg/day) by her own decision for 3 consecutive days.

In the emergency department, she was in a confusional state with hallucination. Her body temperature was 39.7°C and heart rate was 123 beats per minute. Neurological examinations revealed continuous dyskinesia over her head, trunk, and four limbs, with her skin being sweaty. Meningeal and other neurological signs were unremarkable. Blood tests showed high levels of creatinine kinase (821 IU/L), myohemoglobin (1937 ng/mL), and leukocytes ($13.36 \times 10^9/L$). Aspartate aminotransferase and creatinine levels were slightly elevated (49 U/L and 101 $\mu\text{mol/L}$, respectively). Chest computerized tomography and cranial magnetic resonance imaging were negative. Bacteriological culture of blood was negative.

We diagnosed the patient as DHS. She was sedated with intravenous midazolam infusion and hydrated with normal saline. Oral antiparkinsonian drugs were suspended on day 0. In an attempt to prevent from being rebounded to PHS, we monitored the patient's condition and gave her a small dose of madopar (62.5 mg) when mild parkinsonism symptoms appeared. Physical antipyretic measures were administered to lower her body temperature. Since then, her clinical condition had gradually improved. The hallucination disappeared on day 2. On day 4, her body temperature (37.2°C) and leukocyte number ($7.79 \times 10^9/L$) were back to normal. Her dyskinesia was remitted completely on day 5. Creatinine kinase and myohemoglobin levels became normal on day 14 (207 IU/L and 165 ng/mL, respectively). Before she was discharged from the hospital, we prescribed her with a low dose of madopar (250 mg/day). Since then, the patient has been taking antiparkinsonian medication as prescribed and showing stable conditions in the telephone follow-ups.

The study was approved by the Ethics Committee of the Second Affiliated Hospital and Yuying Children's Hospital, Wenzhou Medical University. Written informed consents for publication were obtained from the patients.

LITERATURE REVIEW AND DISCUSSION

PD patients may experience life-threatening complications such as PHS and DHS. These two syndromes share significant similarities but also show major differences in several aspects including causes, clinical manifestations, and treatments. As summarized in Fig. 1, we herein present two cases of patients who developed PHS or DHS. We then review all known up-to-date cases of PHS and DHS in PD and provide a comparative analysis of these two syndromes.

Literature related to PHS and DHS in PD were searched in Medline via PubMed up to May 1, 2022. The searching term for PHS was “((((neuroleptic malignant-like syndrome) OR (Neuroleptic-like Malignant Syndrome)) OR (Parkinson hyperpyrexia syndrome)) OR (Parkinsonism hyperpyrexia syndrome)) OR (((Parkinson's Disease[Title/Abstract]) OR (Parkinson Disease[Title/Abstract])) OR (Parkinsonism[Title/Abstract])) AND (((Fever) OR (Hyperpyrexia)) OR (Pyrexia)) OR (Pyrexias)) OR (malignant syndrome))”. The searching term for DHS was “((((fever[Title/Abstract]) OR (hyperpyrexia[Title/Abstract])) OR (pyrexia[Title/Abstract])) OR (pyrexias[Title/Abstract])) AND (((dyskinesia[Title/Abstract]) OR (dyskinesias[Title/Abstract])) OR (hyperkinetic[Title/Abstract]))”. To increase search hits, the “Parkinson”-associated terms were not included for the DHS search. As a result, 688 and 141 literatures on PHS and DHS were obtained, respectively. After additional title and abstract screening, we eventually retrieved 48 articles for PHS and 9 for DHS (Supplementary Tables 1 and 2).

PHS was first described as a neuroleptic malignant syndrome-like syndrome in a PD patient after discontinuation of his antiparkinsonian medication [9]. As summarized in Table 1 and Supplementary Table 1 including our case, 56 such cases have been reported since 1981 and twenty-four of them are women [10–56]. The onset of PHS ranges from 43 to 79 years of age with PD duration between 1 to 25 years. Seven of the reports with 10 patients recorded the onset of PHS in summertime [10, 11, 16, 17, 23, 26, 50]. The most common cause of PHS is determined to be the reduction or withdrawal of antiparkinsonian medication (26 cases), followed by battery depletion of deep brain stimulation (DBS) impulse generator (7 cases). Other triggers include experiencing the “Off” state, premenstrual period, diabetic coma, heatwave, cessation of fava bean intake, hyponatremia, infection,

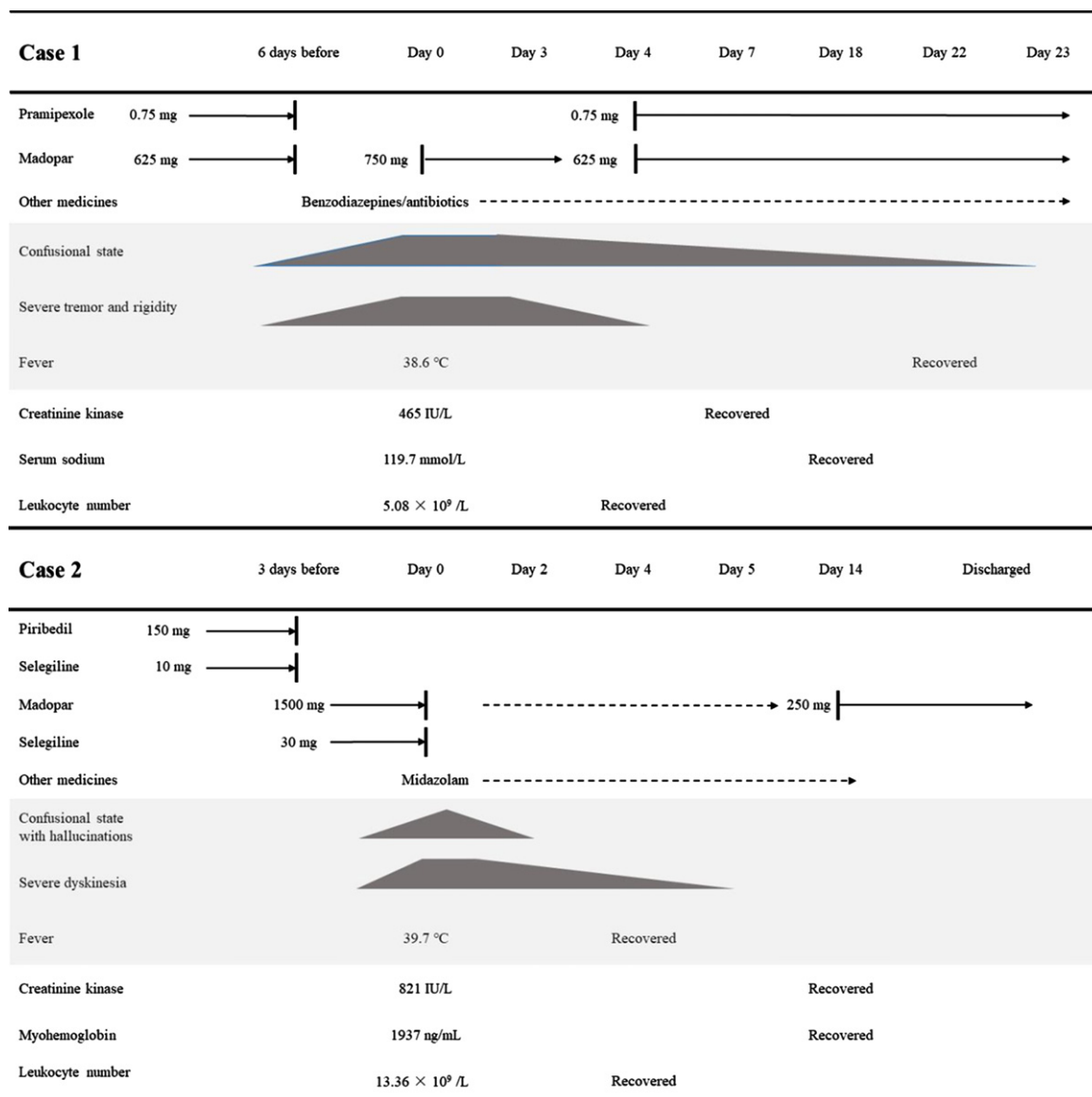


Fig. 1. Summary of the symptoms and treatments for these two cases. Day 0, the day of hospitalization; dashed arrow line, taken when needed; solid arrow line, taken daily; dark patterns, reduced severity with lower height.

constipation, diarrhea, and drinking too little fluids. In recent years, the DBS surgery number for PD patients has been increasing dramatically. Thus, it should be brought into attention as to the likelihood of PHS due to perioperative antiparkinsonian drug discontinuation and DBS stimulator battery depletion. Given the relatively long operation time of DBS, anesthesia, surgery, and stress may become potential triggers for PHS. It may be important to maintain a certain dose of antiparkinsonian medication during the perioperative period. Compared with traditional drug therapy,

the efficacy of DBS is more effective and stable to control parkinsonism. As a result, follow-up visits of such patients may become irregular. Therefore, clinicians should remind patients to have follow-up visits regularly as well as to warn them of potentially severe outcomes if the battery power is depleted.

The main clinical manifestations of PHS are hyperthermia, worsened tremor and rigidity, altered mental status, autonomic dysfunction, and diaphoresis (Table 1 and Supplementary Table 1). Other less common symptoms include dysphagia, myoclonus,

Table 1
Comparative analysis of PHS and DHS in PD patients

	PHS	DHS
Subject, n	56	13
Gender, F/M	24/32	10/3
Age, y (mean \pm SD)	63.2 \pm 9.2	71.3 \pm 6.0
PD duration, y (mean \pm SD)	12.0 \pm 5.8	17.1 \pm 8.2
Mortality, n (%)	12 (21.4)	2 (15.4)
Recovery ratio, n (%)	44 (78.6)	11 (84.6)
Recovery time, days (IR) ^a	13 (5–22)	4 (3.5–6)
Triggers (%) ^b	Reduction/withdrawal of antiparkinsonian medication (46.4)	Antiparkinsonian drug change/abuse (38.5)
	Battery depletion of DBS impulse generator (12.5)	Heatwave (38.5)
	Heatwave (5.4)	Infection (23.1)
	Constipation/diarrhea (5.4)	Trauma (15.4)
	Infection (3.6)	Gastrointestinal dysmotility (7.7)
	Premenstrual period (1.8)	
	Diabetic coma (1.8)	
	Experience of the “Off” state (1.8)	
	Hyponatremia (1.8)	
	Without common trigger (16.1)	
Manifestations (%) ^b	Hyperthermia (98.2)	Hyperthermia (100)
	Worsened tremor and rigidity (94.6)	Continuous dyskinesia (100)
	Altered mental status (73.2)	Altered mental status (76.9)
	Autonomic dysfunction (76.8)	Autonomic dysfunction (46.2)
	Diaphoresis (48.2)	Diaphoresis (23.1)
	Myoclonus (7.1)	Dehydration (15.4)
	Rhabdomyolysis (5.4)	Rhabdomyolysis (15.4)
	Dystonia (3.6)	
	Dehydration (3.6)	
Treatments	Reinstitution of antiparkinsonian medication, vital function support, intravenous fluids, antipyretic drugs, and physical antipyretic measures	Reduction of dopaminergic drugs, vital function support, intravenous fluids, antipyretic drugs, and physical antipyretic measures

^aThe recovery time with an exact number is included for calculation. ^bThe percentage numbers are calculated in relation to the total subjects. DBS, deep brain stimulation; DHS, dyskinesia-hyperpyrexia syndrome; F, female; IR, interquartile range; M, male; PHS, parkinsonism-hyperpyrexia syndrome; SD, standard deviation.

rhabdomyolysis, dystonia, and dehydration. Our patient is additionally diagnosed with CSWS. Hyponatremia has been reported in another case and considered as a cause of PHS [28]. We believe that hyponatremia is an outcome of CSWS resulting from PHS because serum sodium level continues to decline within the first four days even with sodium supplementation to the patient. The treatment of PHS includes vital function support, reinstatement of antiparkinsonian medication, intravenous fluids, empiric antibiotics, benzodiazepines, antipyretic drugs, and physical antipyretic measures. Among the 56 cases, 12 patients died shortly or in a few days and 44 patients were recovered from the symptoms within 2–32 days.

A total of 13 PD patients with DHS has been reported including our case [4, 5, 57–63] (Table 1 and Supplementary Table 2). The onset of DHS ranges from 62 to 80 years of age, and 10 of them are women. According to 4 reports, 6 patients developed the syndrome in summer [5, 59–61]. Two cases including

ours occurred in early autumn when the ambient temperature might still be relatively high [57]. Indeed, heatwave is one of the common triggers of DHS. It has been conceived that DHS usually occurs in advanced PD patients [64], with disease duration ranging from 10 to 34 years. Nonetheless, our case suggests that DHS may also occur in early-stage PD patients.

Two most common provocation factors for DHS are antiparkinsonian drug change or abuse and heatwave (5 cases each; Table 1 and Supplementary Table 2). Excessive dopaminergic stimulation is destructive given that PD patients are defective in the maintenance of dopamine status. Other DHS triggers include infection, trauma, and gastrointestinal dysmotility. Clinical manifestations of DHS include hyperthermia, continuous dyskinesia, altered mental status, and to a less extent, autonomic dysfunction, diaphoresis, dehydration, and rhabdomyolysis. The treatment of DHS includes vital function support, reduction of dopaminergic drugs, intravenous infusions, antipyretic drugs, and physical antipyretic

Box 1. Suggested diagnostic criteria and management schemes for PHS

Diagnosis

1. Clear triggers before the onset. These include reduction/withdrawal of antiparkinsonian medication, battery depletion of DBS impulse generator, and heatwave. Of note, a small percentage of patients may lack any of such triggers.
2. Core clinical manifestations are required. These include hyperthermia, worsened parkinsonism, and elevated creatinine kinase.
3. At least two of the following clinical manifestations are required. These include altered mental status, autonomic dysfunction, diaphoresis, myoclonus, rhabdomyolysis, dystonia, and dehydration.
4. The following conditions should be excluded: neuroleptic malignant syndrome, serotonin syndrome, dyskinesia-hyperpyrexia syndrome, heat stroke, intracranial infection, autoimmune encephalitis, septicemic shock, drug intoxication, and thyroid crisis.
5. An alternative syndrome should be considered if the expert physician, based on full clinical manifestations and auxiliary assessments, feels that an alternative condition is more likely than PHS.

Management

1. Treat the underlying triggers immediately.
2. Provide adequate supportive treatments including vital function support, intravenous fluids, antipyretic drugs, and antipyretic measures.
3. Antibiotics treatment is not necessary, but spectrum antibiotics should be applied immediately if the patient is infected.
4. Oral or nasogastric dopaminergic drugs should be used immediately when the diagnosis of PHS is confirmed.
5. Delirium in patients should be treated with intravenous benzodiazepines infusion (Taken when needed).
6. If the patient develops multiple organ failure, intensive care unit treatment and multidisciplinary care should be initiated immediately.

measures. Among the 13 cases, 2 patients died in a few days due to pneumonia and renal failure or acute pulmonary edema [60]. The remaining 11 patients were recovered within 2–10 days.

Both PHS and DHS are prone to occur in elderly PD patients with long disease duration (Table 1). Although DHS mainly occurs in females, PHS is predominantly found in males. The recovery rate for both syndromes is about 80% despite a faster recovery in DHS than in PHS patients. Clinical manifestations of PHS and DHS are mostly similar, including raised creatinine kinase. The raised kinase level may occur in rhabdomyolysis, myositis, myocardial infarction, muscular dystrophy, etc. Diagnosis of rhabdomyolysis requires not only high creatinine kinase but also elevated myohemoglobin in blood and urine. Thus, raised creatinine kinase alone does not mean the occurrence of rhabdomyolysis, which is only present in a small percentage of PHS and DHS cases. However, a stark difference between these two syndromes is that worsened tremor and rigidity is dominated in PHS, but continuous dyskinesia is exclusively found in DHS patients. PHS may be induced by abrupt

stoppage in the antiparkinsonian treatment such as drug withdrawal or DBS stimulator power loss whereas DHS is plausibly induced by the abuse of antiparkinsonian drugs. Accordingly, the primary treatment for PHS is drug reinstatement and for DHS is drug reduction. Other auxiliary treatments are basically alike. Therefore, careful inquiry of medication history and appropriate neurological examinations are indispensable for rapid recognition and treatment of the syndromes. No diagnostic criteria are available for these two conditions to the best of our knowledge. We herein suggest diagnosis criteria for PHS (Box 1) and DHS (Box 2) based on the reported cases and our aforementioned rationales. Structured suggestions are also provided toward the management of PHS (Box 1) and DHS (Box 2) for the reference of clinicians.

The mortality rates of the reported cases are 21.4% and 15.4% for PHS and DHS, respectively (Table 1). Among the 14 deceased patient cases (Supplementary Tables 1 and 2), there are a total of 12 aged 50 or older and 12 with more than 9 years of PD duration, respectively. The causes of death and number are

Box 2. Suggested diagnostic criteria and management schemes for DHS**Diagnosis**

1. Clear triggers before the onset. These include antiparkinsonian drug change/abuse, heatwave, infection, trauma, and gastrointestinal dysmotility. Of note, a small percentage of patients may lack any of such triggers.
2. Core clinical manifestations are required. These include hyperthermia, continuous dyskinesia, and elevated creatinine kinase.
3. At least one of the following clinical manifestations are required. These include altered mental status, autonomic dysfunction, diaphoresis, dehydration, and rhabdomyolysis.
4. The following conditions should be excluded: neuroleptic malignant syndrome, serotonin syndrome, parkinsonism-hyperpyrexia syndrome, heat stroke, intracranial infection, autoimmune encephalitis, septicemic shock, drug intoxication, and thyroid crisis.
5. An alternative syndrome should be considered if the expert physician, based on full clinical manifestations and auxiliary assessments, feels that an alternative condition is more likely than DHS.

Management

1. Treat the underlying triggers immediately.
2. Provide adequate supportive treatments including vital function support, intravenous fluids, antipyretic drugs, and antipyretic measures.
3. Antibiotics treatment is not necessary, but spectrum antibiotics should be applied immediately if the patient is infected.
4. Carefully reduce antiparkinsonian drugs while avoiding rebound to PHS.
5. Delirium in patients should be treated with intravenous benzodiazepines infusion (Taken when needed).
6. If the patient develops multiple organ failure, intensive care unit treatment and multidisciplinary care should be initiated immediately.

hyperthermic coma (3), respiratory failure (10), renal failure (7), heart failure (3), disseminated intravascular coagulation (2), and septicemic shock (1). These data suggest that patients of older age and longer disease duration may be more susceptible to develop multisystem organ failure and malignant outcome. Because some cases may have died before being diagnosed as PHS or DHS and some may be reluctant to get the death endpoint to be published, the mortality is likely to be underreported. Patients may be treated on general wards in general. But with the mortality rate as high as it is, we recommend treating the underlying triggers immediately with adequate supportive treatments. Those with multiple organ failure should be immediately initiated for intensive care unit treatment and multidisciplinary care in monitored settings to reduce potential mortality (Boxes 1 and 2).

In summary, we herein present two cases of PD patients with hyperpyrexia. One was PHS coupled with CSWS caused by abrupt withdrawal of the antiparkinsonian medication, and the other was drug abuse-induced DHS occurred in early-stage PD. Our reports and the comparative review provide new and updated insights into PHS and DHS in PD and may

facilitate rapid discrimination of the syndromes for timely and proper treatment to reduce mortality.

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CONFLICT OF INTEREST

The authors declare that there is no potential conflict of interest.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <https://dx.doi.org/10.3233/JPD-223362>.

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