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Case Report

When Parkinson's disease encounters high fever: two case reports and literature review

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Abstract: Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder. Acute hyperthermia syndrome (AHS) associated with PD is a critical neurological condition requiring immediate intervention. This article presents two cases of patients with PD with hyperthermia and provides a comprehensive comparative analysis across multiple dimensions, including etiology, pathogenesis, clinical features, diagnostic approaches, therapeutic strategies, and outcomes. The first patient exhibited motor dysfunction followed by hyperthermia, which was alleviated by adjusting the dosage of dopaminergic medication. In contrast, the second patient was initially misdiagnosed with sepsis, and his condition significantly improved with dopaminergic therapy. This report aimed to enhance clinicians' understanding of this syndrome, improve diagnostic precision, and facilitate the development of more effective treatment protocols for optimizing patient outcomes.

Keywords: Parkinson's disease, acute hyperthermic syndrome, parkinsonism-hyperpyrexia syndrome, dyskinesia-hyperpyrexia syndrome, serotonin syndrome

Introduction

In the middle to advanced stages of Parkinson's disease (PD), patients may experience worsening motor symptoms and severe non-motor complications. Acute hyperthermia syndromes associated with PD are a group of clinical syndromes characterized by high fever, altered consciousness, muscle rigidity, elevated white blood cell (WBC) counts, increased levels of creatine kinase (CK), transaminase abnormalities, and metabolic acidosis. These syndromes include parkinsonism-hyperpyrexia syndrome (PHS), dyskinesia-hyperpyrexia syndrome (DHS), and serotonin syndrome (SS) [1, 2]. With an aging population, the prevalence of PD is increasing annually, and its associated complications have become a focal point of research. Owing to the similarities in triggers, clinical manifestations, and laboratory findings as well as the potential overlaps between these syndromes, accurately differentiating and diagnosing them poses a significant challenge. However, the etiologies and corresponding treatments for these syndromes differ markedly, and failure to achieve a timely and precise diagnosis may lead to treatment delays that result in serious patient outcomes.

In this article, we present two representative cases - one case of DHS characterized by dyskinesia followed by hyperthermia and another of PHS that was initially misdiagnosed as sepsis. We analyzed and summarized these clinical cases, compared the similarities and differences between the syndromes, and aimed to provide a theoretical basis and practical guidance for diagnosing and treating acute hyperthermia syndromes associated with PD.

Case reports

Case 1: DHS with initial motor disturbances followed by high fever

A 56-year-old woman presented with an 8-year history of involuntary limb tremors accompanied by stiffness and bradykinesia, particularly

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during periods of rest or emotional stress. She was subsequently diagnosed with PD, and treatment with levodopa and benserazide was initiated. The patient also had a history of hypertension. Six months prior to presentation, the patient was diagnosed with lacunar cerebral infarction, which had worsened more than 2 months prior to presentation, manifesting as persistent generalized involuntary shaking. The patient's treatment regimen was adjusted to include levodopa and benserazide 0.25 g qid and piribedil (50 mg twice daily). Despite these adjustments, the patient's symptoms did not significantly improve. During this period, the patient attempted suicide by cutting her wrists and neck. Four days prior, she developed fever with a maximum temperature of 38.9°C. Despite the administration of ibuprofen granules and paracetamol plus amantadine hydrochloride capsules, fever persisted and could not be effectively controlled.

The patient had a temperature of 38.9°C, heart rate of 103 beats/min, and respiratory rate of 21 breaths/min. Neurological examination revealed grade III muscle strength in the left limb and grade IV muscle strength in the right limb with increased muscle tone in all limbs, showing cogwheel-like rigidity accompanied by paroxysmal involuntary movements and hyperreflexia. Sensory deficits were noted in the distal portions of both upper limbs. Chest CT revealed multiple proliferative foci in the upper lobes of both lungs, along with calcification of the left coronary artery. Electrocardiography revealed sinus tachycardia, whereas head CT revealed no significant abnormalities. Thyroid ultrasonography identified mixed echogenic nodules in both lobes, classified as TI-RADS grade 3. Routine blood tests showed a red blood cell count of 3.06×10^{12}/L and a hemoglobin concentration of 99 g/dL. Coagulation tests revealed a fibrinogen level of 1.93 g/L. Electrolyte analysis revealed sodium levels of 124 mmol/L, chloride levels of 97 mmol/L, and calcium levels of 1.95 mmol/L. Liver function tests indicated aspartate aminotransferase level of 84 U/L and albumin level of 34.1 g/L. Specific results for the CK are shown in **Figure 1A**.

The patient experienced recurrent hyperthermia, with a peak temperature of 40.3°C during hospitalization; however, no definitive evidence of infection was identified. Considering the patient's long history of PD, lack of clarity regarding her previous treatment regimen, and the development of dyskinesia 2 months prior to admission, along with an intake of up to 1 g of levodopa and benserazide per day, a possible comorbidity with DHS was suspected. Based on this assessment, we adjusted the treatment regimen as follows: piribedil 50 mg bid, levodopa and benserazide 0.125 g qid, and amantadine hydrochloride 0.1 g qd. Following these adjustments, the patient's involuntary limb movements significantly improved, the high fever gradually subsided, and her body temperature normalized completely after 5 days (for details, see **Figure 1B**). After discharge, the patient adhered to the prescribed medication regimen and underwent regular follow-up examinations without symptom recurrence during the 6-month follow-up period. The timeline of these events is shown in **Figure 2**.

Case 2: PHS initially misdiagnosed as sepsis

A 78-year-old man was diagnosed with PD 11 years prior to presentation and was taking long-term medication including amantadine hydrochloride, taken twice daily at two tablets per dose, and trihexyphenidyl hydrochloride, also taken twice daily at two tablets per dose. Three days prior to presentation, due to a cold, the patient developed a fever, with a peak temperature of 40.6°C, accompanied by chills, shivering, and convulsions. He was administered an ibuprofen suspension, which temporarily normalized his temperature; however, recurrent fever persisted. Four hours prior to admission, he experienced chills and high fever again, with his temperature rising to 40°C. In addition, he had difficulty defecating.

At admission, the patient's temperature was 39.1°C. Auscultation of both lungs revealed coarse breath sounds with occasional wet rales. The patient exhibited poor mental status, mask-like facial rigidity, and limited speech function. The pupils were equal in size and regular in shape but demonstrated sluggish light reflexes. Neck stiffness was also observed. Muscle tone was increased in the limbs, and resting tremors were observed. The results of ancillary examinations were as follows. Chest CT revealed interstitial fibrosis with bilateral inflammatory changes, calcified foci in the left coronary artery, and bilateral pleural thickening. Electrocardiography revealed sinus tachy-

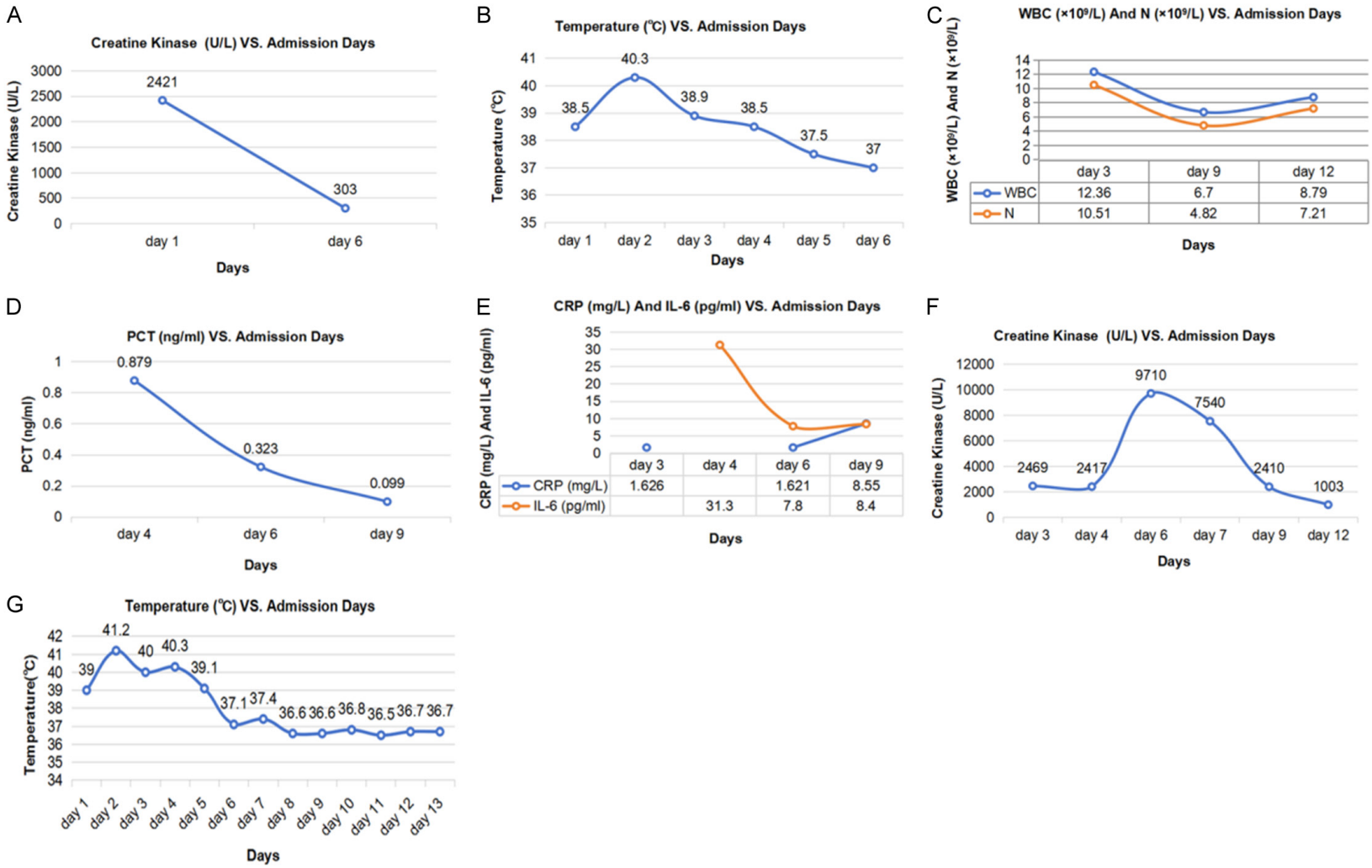

Figure 1. Graphs of changes in multiple indicators during hospitalization for two patients. A. The CK test results of the first patient at different times. B. The daily body temperature change chart for the first patient. C. It shows the WBC and neutrophil test results of the second patient at different times. D. The results of multiple PCT tests for the second patient. E. The test results of CRP and IL-6 for the second patient at different time points. F. The CK test results of the second patient at different times. G. The daily body temperature change chart for the second patient. Note: White blood cell (WBC) count ranges from 3.5 to 9.5 × 10^9/L; absolute value of neutrophils (N) is within the range of 1.8 to 6.3 × 10^9/L. C-reactive protein (CRP) ranges from 0.068 to 8.2 mg/L; interleukin-6 (IL-6) is less than 7.0 pg/mL; procalcitonin (PCT) is less than 0.046 ng/mL. Creatine kinase (CK) ranges from 38 to 174 U/L.

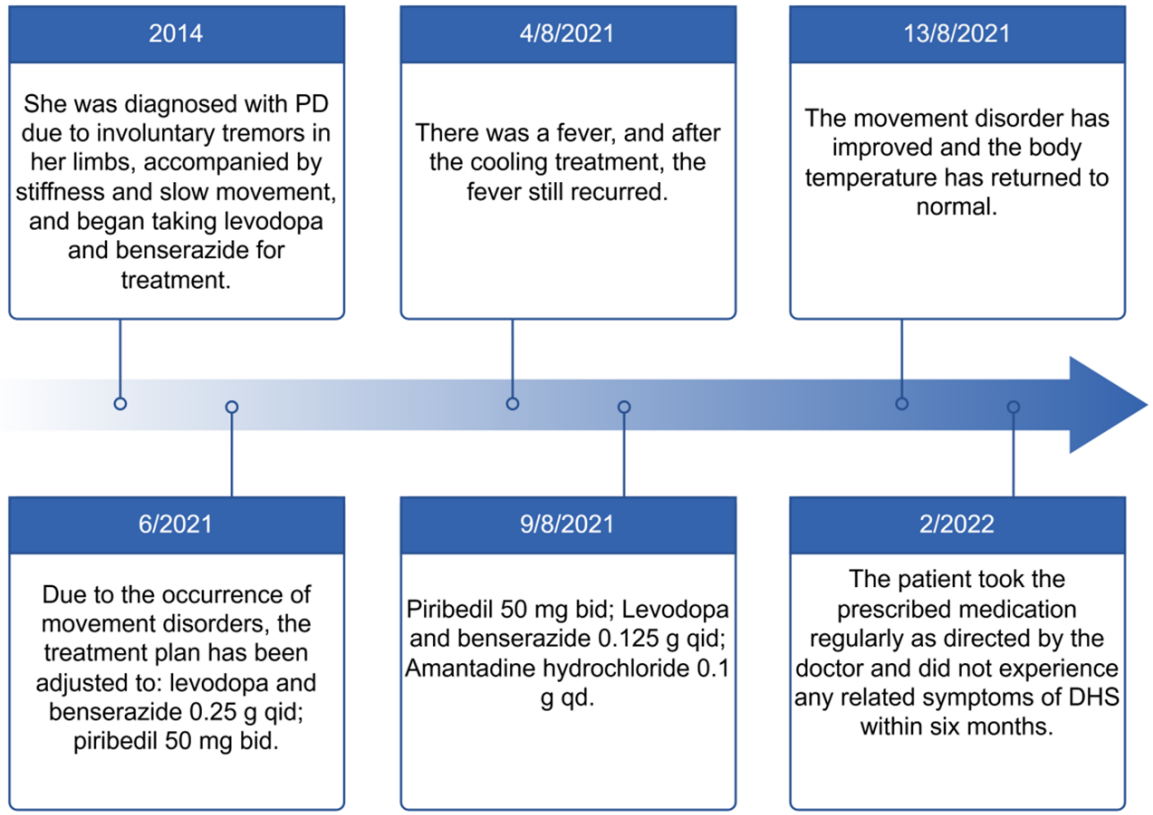

Figure 2. A timeline with relevant data from the episode of care for the first patient. Note: PD: Parkinson's disease, DHS: dyskinesia-hyperpyrexia syndrome.

cardia. Cranial CT showed mild demyelinating lesions in the bilateral white matter of the brain, along with cerebral atrophy. Cardiac ultrasonography revealed an impaired resting left ventricular diastolic function. Ultrasonography of the extremities revealed thrombus formation in the intermuscular veins of both lower legs. Hematological tests revealed a significantly elevated D-dimer level of 3.87 μg/mL. Liver function tests revealed an elevated alanine aminotransferase level of 94 U/L and a decreased albumin concentration of 35.2 g/dL. Renal function tests revealed elevated urea level (11.8 mmol/L). Myocardial infarction markers showed significantly elevated levels of myoglobin (1,297 ng/mL), high-sensitivity troponin T (394.50 ng/mL), and B-type brain natriuretic peptide precursors (2,453 pg/mL). Immune function tests revealed abnormal T-cell subpopulations, including total T lymphocytes (29%, absolute value of 830 cells/μL), T helper cells (14%, absolute value of 411 cells/μL), and T suppressor cells (13%). WBC counts are shown in **Figure 1C**, procalcitonin levels in **Figure 1D**, CRP and IL-6 levels in **Figure 1E**, and CK levels in **Figure 1F**.

On admission, the patient was administered meropenem to control infection and intravenous methylprednisolone to mitigate the inflammatory response. Symptomatic treatment was administered to alleviate coughing and promote expectoration. Despite these interventions, his fever continued to recur, with a peak temperature of 40°C. Given that the patient was male with aggravated symptoms of PD, elevated CK levels, tachycardia, leukocytosis, and abnormal liver and kidney functions, the patient was ultimately diagnosed with PHS. The treatment regimen was subsequently adjusted as follows: oral administration of piribedil 25 mg tid, levodopa and benserazide 0.0625 g tid, amantadine hydrochloride 0.2 g tid. Trihexyphenidyl hydrochloride was discontinued. Following these adjustments, the patient's persistent fever gradually subsided and his body temperature normalized by day 8 (see **Figure 1G** for the detailed temperature trend). After

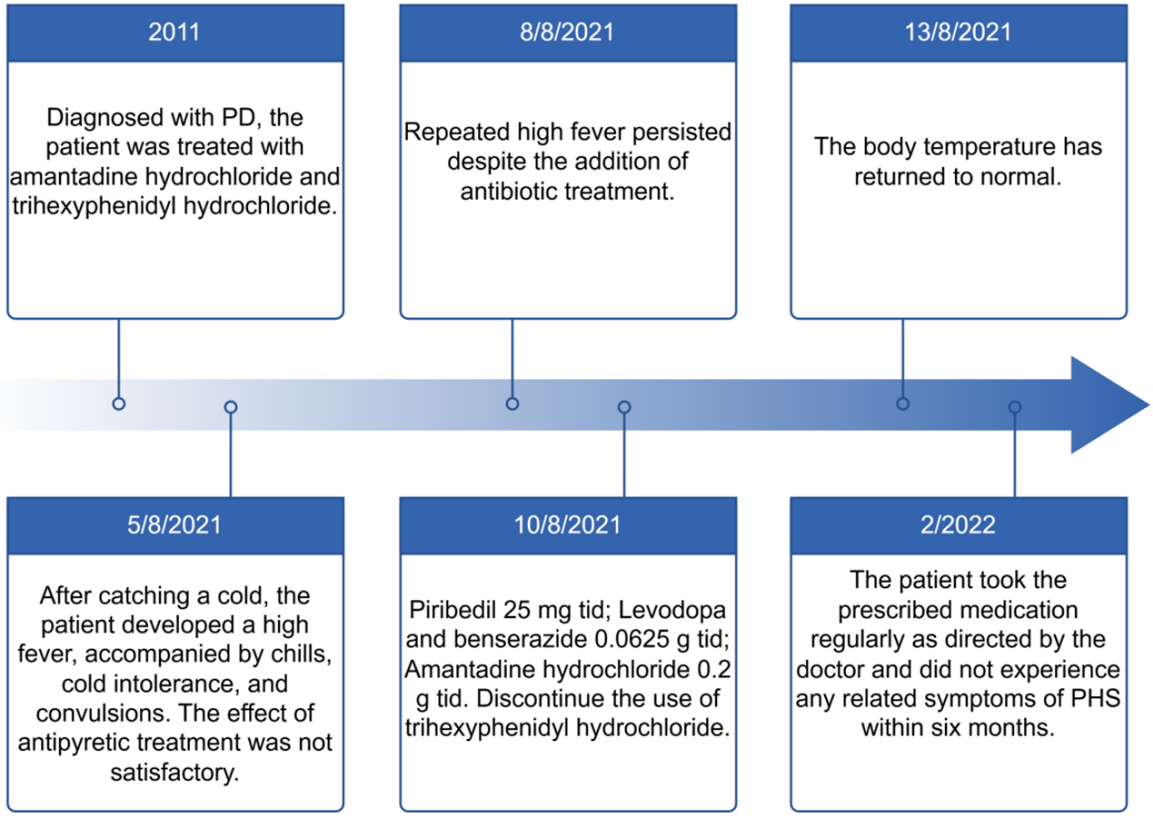

Figure 3. A timeline with relevant data from the episode of care for the second patient. Note: PD: Parkinson's disease, PHS: parkinsonism-hyperpyrexia syndrome.

discharge, the patient strictly adhered to his medication regimen and was followed up for 6 months without recurrence. The chronological progression of these events is shown in **Figure 3**.

Discussion

DHS is a rare yet severe neurological emergency typically associated with PD. This phenomenon was first reported in 2010 [3]. To date, 18 cases of DHS have been documented in 15 studies [4-6]. The hallmark features of DHS include the acute onset of persistent generalized dyskinesia accompanied by elevated CK levels, hyperthermia, and altered mental status [2]. This condition tends to occur more frequently in patients with a longer disease duration, marked motor fluctuations, and long-term exposure to high doses of dopaminergic medications. Similar to PHS, DHS may be triggered by various factors, including changes in dopaminergic medication regimens, infections, hot environments, dehydration, trauma, gastrointestinal dysfunction, and changes in deep brain stimulation (DBS) [2].

The pathogenesis of DHS has not been fully elucidated. In patients with advanced PD, degeneration of nigrostriatal dopaminergic neurons affects the compensatory synthesis, release, storage, and reuptake of dopamine. This process is further complicated by postsynaptic dopamine receptor dysfunction, which collectively leads to a reduced dopamine buffering capacity. When the dose of a dopaminergic drug is increased or switched to a sustained-release formulation, presynaptic dopamine is released in a pulsatile manner, resulting in a significant elevation in dopamine levels in the brain, potentially inducing hyperthermia [2]. Furthermore, under high-dose dopaminergic stimulation, the nigrostriatal dopaminergic system activity is excessively enhanced, thereby triggering severe dyskinesia [7]. Concurrently, synaptic plasticity in the striatum is altered and characterized by a diminished depolarization response and enhanced long-

term potentiation, which further exacerbates the hyperexcitability of the central dopaminergic system. Once exposed to triggering factors, DHS may recur repeatedly, thereby establishing a self-perpetuating cycle. Dopamine dysregulation syndrome (DDS) is a relatively rare complication of PD pharmacotherapy and is characterized by addictive behavior and the excessive use of dopaminergic medications. Levodopa is more frequently associated with DDS than other dopaminergic agents, and its administration is linked to higher rates of dyskinesia and motor fluctuations. According to Warren, at-risk individuals may exhibit reduced function in the inhibitory dopaminergic pathways. Therefore, we hypothesized that DDS might be a potential trigger for DHS [8].

Autonomic dysfunction is prevalent in patients with advanced PD, and abnormal thermoregulation is a significant clinical manifestation. Nigrostriatal and hypothalamic dopaminergic systems play crucial roles in thermoregulation. Stimulation of these dopaminergic systems in mice resulted in a decrease in body temperature when the ambient temperature was below 22°C, potentially mediated by reduced metabolic rate and cutaneous vasodilation. In contrast, when the ambient temperature exceeded 30°C, stimulation of the same dopaminergic pathways led to an elevation in body temperature, accompanied by increased dopamine release in the striatum [9, 10]. Further evidence indicates that the administration of dopaminergic receptor antagonists at high ambient temperatures can delay the increase in body temperature in mice [11]. Moreover, rats exposed to high environmental temperatures exhibited significantly elevated levels of dopamine and glutamate in the systemic circulation, along with inflammatory responses in the hypothalamic region, which may further impair normal thermoregulatory function [12]. Studies have also suggested that high summer temperatures can affect the transmission efficiency of the dopaminergic system and the sensitivity of its receptors [13]. Collectively, at high ambient temperatures, an overactive dopaminergic system may contribute to elevated body temperatures, thereby increasing the risk of DHS.

Currently, there is no clear evidence of a direct association between summer or high ambient temperatures and dyskinesia in patients with PD. However, clinical observations suggest that symptom severity in patients with PD may fluctuate seasonally. Studies using mouse models have demonstrated that the substantia nigra pars compacta is thermosensitive [14]. Cooling reduces its activity, whereas heating enhances it, indicating that high ambient temperatures may increase the activity of the presynaptic dopaminergic system. Furthermore, the daylight duration positively correlates with D2/D3 receptor activity in the human striatum, and the daylight duration in summer is significantly longer than that in other seasons [15]. Therefore, prolonged summer daylight may enhance postsynaptic dopaminergic system activity. Collectively, these factors suggest that, in patients with advanced PD, high-dose dopaminergic therapy is more likely to induce dyskinesia during summer when elevated ambient temperatures enhance presynaptic dopaminergic activity and extended daylight enhances postsynaptic dopaminergic activity.

Infection and trauma are potential risk factors for dopamine-induced DHS [16]. After infection or trauma, the body releases substantial amounts of inflammatory mediators. Inflammatory cytokines can reportedly induce the overexpression of GTP cyclohydrolase I, thereby promoting tetrahydrobiopterin synthesis. Since dopamine synthesis is dependent on BH4, this pathway ultimately results in elevated DA levels. Petrulli et al. [17] also reported that striatal dopamine levels significantly increased in response to acute or short-term systemic inflammatory stimuli. Furthermore, peripheral inflammatory cytokines may trigger behavioral alterations by acting on the dopaminergic system within the basal ganglia. Clinical observations suggest that women with middle- and advanced-stage PD are more prone to developing dyskinetic hyperthermia syndrome than men, which may be attributed to female-specific hormonal profiles that enhance their susceptibility to levodopa-induced dyskinesia [18].

DHS shares many clinical similarities with PHS, as both can present with high fever, elevated CK levels, autonomic dysfunction, and altered consciousness. However, symptoms associated with PD differ significantly from those associated with PHS. The neuromuscular manifestations of DHS are typically characterized by generalized, persistent dyskinesia that may precede hyperthermia, which can sometimes

be absent in the early stages of DHS [4]. Fever in DHS may result from increased thermogenesis due to dyskinesia but can also be influenced by environmental temperature changes and alterations in dopamine receptor activity. Notably, not all patients with DHS exhibit elevated CK levels; therefore, elevated CK should not be considered a diagnostic marker of DHS. In addition, when hyperthermia was excluded, the incidence of autonomic dysfunction in patients with DHS was low, with only a minority of patients presenting with tachycardia. The impairment of consciousness in patients with DHS is usually mild. In addition, one study has highlighted the critical role of early MRI of the head in the diagnosis of DHS. In patients with DHS, brain MRI may reveal bilateral asymmetric vascular-origin cortical and subcortical edema, particularly in the temporal and occipital lobes [19]. This finding indicates the potential presence of reversible encephalopathy, which typically resolves as the symptoms improve. However, no specific laboratory or imaging markers directly associated with dopaminergic DHS have been identified. Given the limited number of clinical reports on DHS, further accumulation of clinical data is necessary to identify potential biomarkers for the diagnosis of DHS. Notably, when patients present with a coma, respiratory failure, renal failure, heart failure, disseminated intravascular coagulation, or infectious shock, their prognoses are often poor. Furthermore, older age and a history of prolonged illness may strongly associate with multi-organ dysfunction and adverse outcomes.

Currently, there are no standardized diagnostic criteria for DHS; however, the following criteria may be used for diagnosis: essential symptoms, including severe generalized dyskinesia, a core symptom of high fever, and supportive symptoms, including elevated CK levels or rhabdomyolysis, altered mental status, and autonomic dysfunction. In patients with acute exacerbations, DHS can be diagnosed when both essential and core symptoms are present. Probable DHS can be diagnosed if essential symptoms are accompanied by at least two supportive symptoms. Nevertheless, the sensitivity and specificity of these diagnostic criteria require validation using extensive clinical data.

Adjustment of the dopaminergic medication dosage remains the most critical intervention in managing DHS, and appropriate adjustment of device parameters should be considered in patients undergoing DBS surgery. For patients with refractory dyskinesia, sedation should be cautiously administered for symptom relief, provided that relevant contraindications are excluded. Furthermore, supportive therapy, including intravenous rehydration, physical cooling, anti-infective measures, and maintenance of electrolyte and acid-base balance, is essential to prevent complications such as pulmonary infections, pulmonary embolism, and acute renal failure. Most patients with DHS improve within a few days of aggressive treatment, and their overall prognosis is relatively good. Among the 18 reported DHS cases, 15 experienced symptom relief through dose reduction of anti-parkinsonian medications, and one patient demonstrated marked symptom improvement within days after DBS surgery. Unfortunately, two patients died due to complications such as pneumonia, renal failure, or acute pulmonary edema [20].

The patient in the first case described herein had PD for >8 years and was on regular long-term medication with satisfactory symptom control. However, symptoms of dyskinesia began 2 months prior to admission, during which time the patient's dyskinesia was not relieved by a total daily dose of up to 1 g of dopaminergic medication. Four days before admission, the patient developed a high-grade fever that recurred despite physical cooling measures. Upon admission, comprehensive evaluations including blood tests, chest CT, and other relevant investigations revealed no evidence of infection. Considering the patient's female sex, high fever, persistent involuntary movements, tachycardia, elevated CK levels, increased respiratory rate, and a prolonged history of high-dose dopaminergic medication use, the patient was diagnosed with DHS. The treatment regimen was subsequently adjusted as follows: piribedil, 50 mg bid; levodopa and benserazide, 0.125 g qid; and amantadine hydrochloride 0.1 g qd. After several days of treatment, the patient's body temperature gradually returned to normal and the symptoms of abnormal movement gradually improved.

Unlike previous reports, this patient developed hyperthermia after 2 months of persistent dyskinesia, which may be attributed to the patient's long disease duration. This duration is

characterized by an impaired dopamine buffering capacity due to the degeneration of nigrostriatal dopaminergic neurons and dysfunction of postsynaptic dopaminergic receptors. Following prolonged use of medications for PD, the patient developed symptoms of dyskinesia. These symptoms persisted for 2 months owing to a lack of timely, standardized diagnosis and adjustment of the treatment regimen; however, the disease did not progress significantly during this period. It is hypothesized that this stability in symptoms may result from relatively constant brain dopamine levels maintained through certain compensatory mechanisms, potentially involving enhanced peripheral dopamine metabolism. However, the exact underlying mechanism requires further investigation. Additionally, the patient's symptoms began in August, when the average local ambient temperature was 31°C. The high-temperature environment may have increased the activity of presynaptic dopaminergic receptors, which could be a critical factor in the development of DHS.

PHS was one of the earliest recognized acute hyperthermia syndromes associated with PD and was first reported by Toru in 1981 [21]. This syndrome is a rare but potentially life-threatening complication of PD, with key clinical features including hyperthermia, autonomic dysfunction, altered consciousness, acute exacerbation of preexisting PD symptoms, and elevated serum CK levels [22, 23]. Clinically, PHS presents with features similar to those of neuroleptic malignant syndrome (NMS), a condition often associated with antipsychotic medication use (i.e., neuroleptics).

PHS usually occurs after the discontinuation or abrupt reduction of anti-parkinsonian medications and involves medications such as levodopa, amantadine, dopamine receptor agonists, anticholinergic drugs, and catechol-O-methyltransferase inhibitors (COMTIs) [23-26]. In addition, insufficient dopamine levels in the brain under certain conditions can serve as a common trigger for PHS. These conditions include malfunctioning of DBS devices (e.g., battery depletion or inadequate maintenance), perioperative discontinuation of anti-PD medications, postoperative attempts to reduce medication doses, prolonged surgical time, anesthesia, and surgical stress [23, 27]. Several additional factors may also increase the risk of developing PHS. Conditions such as infection, anorexia, diarrhea, constipation, dysphagia, premenstrual syndrome, diabetic ketoacidosis, fava bean consumption, trauma, inadequate medication adherence, and suboptimal nursing care can impair medication intake or absorption, indirectly contributing to the onset of PHS [28, 29]. Moreover, hypovolemic hypernatremia resulting from exposure to high temperatures, concurrent use of antipsychotic drugs, dehydration, or reduced water intake may disrupt the normal metabolism of dopaminergic neurotransmitters in the hypothalamus, representing a rare yet plausible trigger for PHS [30]. Importantly, fluctuations in PD symptoms potentially linked to diminished dopamine receptor stimulation or receptor desensitization during the 'off' phase may also precipitate PHS. However, its precise pathogenesis remains unclear [31].

Increasing evidence indicates that an acute reduction in neurotransmission within the hypothalamus, nigrostriatal system, and midbrain cortical dopaminergic system may be critical factors in its development [21, 23]. In patients with advanced PD who are highly reliant on pharmacologic dopamine receptor stimulation, a sudden decrease in dopaminergic medications may disrupt receptor function, thereby impairing dopamine release and eliciting a "withdrawal"-like response [32]. Furthermore, dopamine depletion may affect limbic and cortical pathways in the midbrain, potentially leading to alterations in mental status. In patients implanted with DBS devices, abrupt cessation of DBS may independently induce PHS, even in the absence of changes in dopaminergic medication. This may arise because chronic high-frequency DBS induces adaptive changes and possibly a rebound effect, rendering patients less responsive to high-dose dopaminergic drug therapy [33]. This suggests that DBS-associated PHS acts on distinct targets within the nigrostriatal circuit via a mechanism different from that of dopaminergic drugs. Additionally, other studies have suggested that infectious agents may contribute to the onset and progression of PD and its syndromes by affecting relevant neural pathways, either directly or through the synergistic effect of inducing neuroinflammation [34].

The clinical features of PHS include hyperthermia (body temperature exceeding 38°C), myotonia (which may or may not be accompanied

by tremor), altered consciousness (ranging from confusion to coma), and autonomic dysfunction (e.g., fluctuating blood pressure, tachycardia, hyperhidrosis, and urinary incontinence). Dysarthria and dysphagia may also occur [35]. Hyperthermia is one of the most common manifestations of PHS and typically occurs in the early stages of the disease. Myotonia tends to present with severe systemic involvement, while other motor abnormalities such as tremor, dystonia, or rigidity may also develop during the course of the disease. Elevated serum CK levels represent a key laboratory feature of PHS, often ranging from several hundred to more than 10,000 IU/L. Patients with PHS frequently exhibit elevated WBC counts, abnormal liver function, and metabolic acidosis. The common complications associated with this syndrome include acute renal failure, acute myocardial infarction, rhabdomyolysis, aspiration pneumonia, deep vein thrombosis/pulmonary embolism, disseminated intravascular coagulation, respiratory failure, seizures, and sepsis [35, 36].

Currently, no unified diagnostic criteria have been established for PHS; however, the modified Levenson neuroleptic malignant syndrome diagnostic criteria can serve as a reference [37]. The primary manifestations of this condition include fever, exacerbation of PD symptoms, and elevated serum CK levels. Secondary manifestations include tachycardia, blood pressure fluctuations, an increased respiratory rate, altered consciousness, abnormal sweating, and leukocytosis. PHS is diagnosed when the patient exhibits three or two primary manifestations in conjunction with four secondary manifestations.

Early recognition is crucial for the effective management of PHS, and the prompt reinstatement of dopaminergic medications along with the elimination of potential triggers is a core principle of treatment. Most patients gradually recover within a few days to 2 weeks following the initiation of treatment. For patients who are unable to take medications orally, early administration via a nasogastric tube or intravenous infusion is recommended. Dopamine agonists (e.g., bromocriptine, pramipexole, ropinirole, rotigotine transdermal patch, and apomorphine) may be used in combination, as required. Additionally, symptomatic supportive treatments, such as rehydration and cooling measures, play a key role in the recovery process of PHS. Patients who develop severe complications require intensive care, including antibiotic therapy for coinfections, mechanical ventilation for respiratory failure, and timely initiation of hemodialysis for acute renal failure. Dantrolene may be used to alleviate the symptoms of myotonia, whereas benzodiazepines may help relieve limb tremors. If PHS is caused by malfunctioning DBS devices, restoration of normal DBS function should be prioritized. Advanced age, severe myotonia, significant motor retardation, profound impairment of consciousness, and serious complications such as severe pneumonia, disseminated intravascular coagulation, and acute renal failure are strongly associated with poor prognosis.

The second patient with a long-standing history of PD presented to our hospital with recurrent hyperthermia that did not significantly improve despite intensive anti-infectious treatment. After adjusting the anti-Parkinson's medication regimen for several days, the patient's symptoms gradually improved. Notably, unlike previously reported cases, the patient did not discontinue or reduce the dosage of anti-Parkinson's medications but experienced significant symptom relief through the use of dopamine preparations and dopamine agonists. The development of PHS may be closely linked to advanced age and prolonged history of PD. When combined with infection, there may be a marked reduction or even exhaustion of central dopamine synthesis and release, leading to the dysfunction of both central and peripheral dopaminergic neurons, along with excessive acetylcholine activity. Additionally, the onset of the patient's illness occurred in August, when the average local ambient temperature was as high as 31°C. High temperatures may have been a critical factor that triggered the onset of his condition. Reportedly, malignant hyperthermia is a rare side effect of prolonged use of trihexyphenidyl hydrochloride, which may interfere with the thermoregulatory center and affect peripheral parasympathetic activity, thereby inhibiting sweat gland secretion and heat dissipation [38]. Given the patient's long-term use of trihexyphenidyl hydrochloride, the medication was discontinued upon adjustment of the treatment plan, after which the patient's body temperature gradually normalized. In conclusion, the development of PHS in our patient

Table 1. Preliminary distinction between PHS, DHS and SS

	PHS	DHS	SS
Frequent causes	Discontinue the use or decrease the dosage of anti-Parkinson's drugs, DBS malfunction.	Long-term administration of high-dose anti-PD medications and dysfunction of the DBS device.	Increases in 5-HT functional drugs and combined use of SSRIs and MAO-B inhibitors.
Common precipitating factors	Infection, high temperature, trauma, and gastrointestinal dysfunction.	High temperature, trauma, and Gastrointestinal dysfunction.	
Gender	It is more prevalent among males.	It is more frequently observed in females (estrogen level, low body weight).	
Persistence time	From several days to two weeks.	From several days to two weeks.	Within 24 hours.
Hyperpyrexia	Fluctuating between 38°C and 40°C, and emerging in the early stage.	Fluctuating within the range of 38.2°C to 42°C, mostly above 40°C, and there may be no high fever in the early stage.	The body temperature of severe patients is higher than 38.5°C.
Elevated CK	Ranging from several hundred to more than 10,000 U/L, it is a laboratory characteristic of PHS.	Secondary to dyskinesia, ranging from several hundred to more than 10,000 U/L, is not necessary for diagnosis.	May have.
PD symptoms	Tremor and rigidity worsen.	Persistent generalized dyskinesia.	Akathisia, tremor, rigidity, clonus, hyperreflexia.
Consciousness disorder	From confusion of consciousness to coma.	The degree is relatively mild, with confusion of consciousness or hallucinations.	Patients with impaired consciousness often have myoclonus and hyperreflexia.
Disorder of autonomic nerve function	Blood pressure fluctuations, tachycardia, hyperhidrosis, urinary incontinence.	Relatively rare.	Hyperhidrosis, tachycardia, flushing, salivation, elevated blood pressure, diarrhea, shortness of breath, dilated pupils, increased bowel sounds.
Therapy	Gradually increase the dose of dopaminergic drugs or restart DBS treatment.	Gradually reduce the dose of dopaminergic drugs or decrease DBS.	Discontinue serotonergic drugs.
Complication	Aspiration pneumonia, DIC, acute renal failure.	Pneumonia, electrolyte imbalance, rhabdomyolysis, acute renal failure.	Severe patients may present with epilepsy, acute renal failure, and DIC
Fatality rate	21.4%	11.1%	<1%

was likely the result of a combination of factors.

In addition to PHS and DHS, SS is another acute hyperthermia syndrome associated with PD that warrants attention. As the name implies, this disorder is closely linked to the use of serotonin drugs, representing a severe and potentially life-threatening adverse drug reaction caused by the overactivation of postsynaptic serotonin (5-HT) receptors in the central and peripheral nervous systems, along with elevated synaptic concentrations of 5-HT. Given that PD is frequently accompanied by depressive symptoms, 5-HT analogs, particularly selective serotonin reuptake inhibitors (SSRIs), have been increasingly used in patients with PD, contributing to an increased incidence of SS. Moreover, low-dose monoamine oxidase B (MAO-B) inhibitors effectively alleviate motor symptoms in patients with PD; however, high-dose MAO-B inhibitors may concurrently inhibit MAO-A, leading to increased intrasynaptic 5-HT concentrations and potentially inducing SS [39]. When these two classes of drugs are combined, the risk of SS is exacerbated.

The severity of SS is positively correlated with the level of 5-HT in the body; it typically develops within minutes to hours after drug administration, rarely exceeding 24 hours [40]. The main clinical features include altered mental status (e.g., anxiety, irritability, confusion, agitation), autonomic dysfunction (e.g., hyperthermia, diaphoresis, tachycardia, flushing, hypersalivation, elevated blood pressure, diarrhea, tachypnea), and neuromuscular abnormalities (e.g., akathisia, tremor, rigidity, clonus, tendon hyperreflexia). These symptoms can vary in severity from mild to severe, and not all patients exhibit all the symptoms of the triad mentioned above.

Currently, there are no specific laboratory tests for SS, and abnormalities, such as CK elevation, leukocytosis, liver enzyme disturbances, and metabolic acidosis, are insufficient to differentiate it from other similar disorders. Diagnosis can be guided by the criteria proposed by Hunter in 2003 [41]: SS can be diagnosed with a history of 5-HT drugs and one of the following: spontaneous clonus; tremor combined with tendon hyperreflexia; evoked

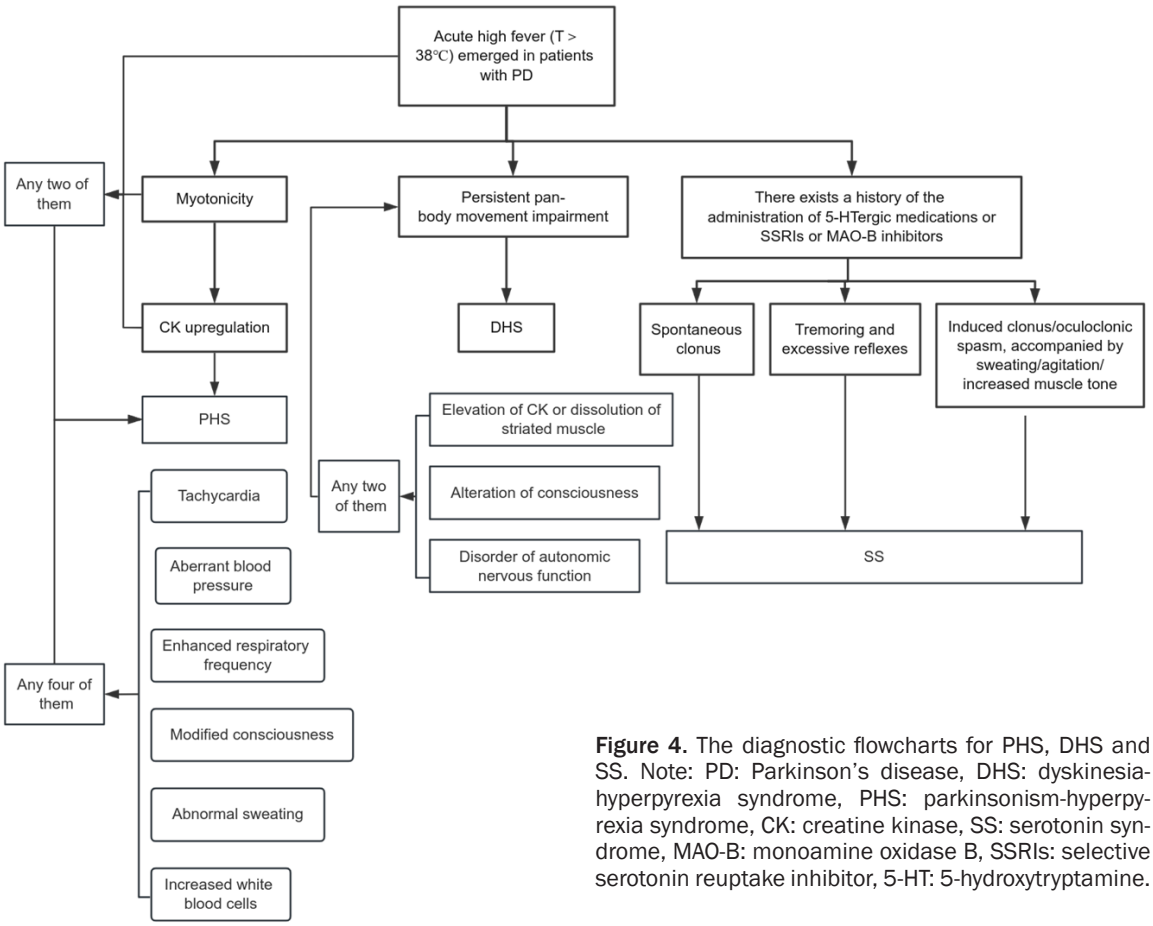

Figure 4. The diagnostic flowcharts for PHS, DHS and SS. Note: PD: Parkinson's disease, DHS: dyskinesia-hyperpyrexia syndrome, PHS: parkinsonism-hyperpyrexia syndrome, CK: creatine kinase, SS: serotonin syndrome, MAO-B: monoamine oxidase B, SSRIs: selective serotonin reuptake inhibitor, 5-HT: 5-hydroxytryptamine.

clonus or ophthalmoclonus accompanied by diaphoresis, agitation, or increased dystonia, along with a temperature exceeding 38°C.

Early recognition of SS is critical because failure to discontinue 5-HT analogs in a timely manner may lead to rapid progression to myotonia, hyperthermia, and altered consciousness. Severe myotonia can obscure manifestations of myoclonus and hyperreflexia. In most patients, symptoms resolve within 24 h of discontinuing 5-HT analogs. Symptomatic supportive therapy, including oxygenation, rehydration, sedation, antihypertensives, and heart rate stabilization, plays an essential role in the management of SS. Overall, the prognosis of SS is relatively favorable, with a case fatality rate of less than 1%. However, complications, such as seizures, acute renal failure, and disseminated intravascular coagulation, often indicate a poor prognosis.

The first patient, who exhibited symptoms of psychosis, had attempted suicide 2 months prior to admission and was evaluated at another hospital. However, details of her antipsychotic medication use remain unclear. Clinically, this case warrants vigilance for the development of SS. Nevertheless, the patient's dyskinesia and hyperthermia persisted for an extended duration, and no interventions specific to the serotonin syndrome were initiated. Following a reduction in the dopaminergic drug dosage, the patient's symptoms improved, and the historical features of the disease did not fulfill the diagnostic criteria for SS. Therefore, accurate differentiation among these three syndromes is critical for early disease management, improvement of patient outcomes, and prevention of complications. In conjunction with previous literature, we systematically summarized the similarities and differences (refer to **Table 1**) among related cases and developed a diagnostic flowchart (see **Figure 4**) for clinical reference. Due to the current lack of multicenter study data, our diagnostic and differential diagnostic recommendations may not be

applicable to all patients with acute hyperthermia syndrome in PD, particularly those with DHS. Further clinical data should be collected to validate the sensitivity and specificity of this diagnostic approach.

Conclusion

When acute hyperthermia occurs in patients with PD, it is crucial to pay close attention to potential comorbidities and obtain a detailed understanding of their medication regimens. Early recognition and timely intervention can reduce the risk of complications and improve patient outcomes. Given the complexity of diagnosing these syndromes, symptomatic supportive treatment should be promptly initiated to alleviate symptoms while determining the underlying cause. In patients with advanced disease, combinations of certain medications should be avoided. If necessary, such combinations should be approached cautiously, with thorough communication of risks to both patients and their families. The prevention of these syndromes is more critical than treatment, and healthcare professionals must enhance their ability to identify and mitigate risk factors in routine clinical practice.

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Disclosure of conflict of interest

None.

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