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The Parkinsonism-Hyperpyrexia Syndrome

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Abstract The parkinsonism-hyperpyrexia syndrome (PHS) is a rare but potentially fatal complication seen in Parkinson's disease (PD) patients, most commonly following reduction or cessation of antiparkinson medications. Clinically it resembles neuroleptic malignant syndrome with rigidity, pyrexia, and reduced conscious level. There may be features of autonomic instability, and serum creatine kinase (CK) may be elevated. Complications of PHS include acute renal failure, aspiration pneumonia, deep venous thrombosis/pulmonary embolism, and disseminated intravascular coagulation (DIC). Management consists of dopaminergic drug replacement, supportive measures, and treatment of complications. The prognosis is improved with early recognition and management. Mortality of up to 4% has been reported, but an additional one-third of patients have permanent sequelae. Patients and physicians should be warned against sudden reduction in antiparkinson medications. PHS should always be considered in a patient with parkinsonism who presents with an acute deterioration in symptoms.

Keywords Parkinsonism · Hyperpyrexia · Syndrome

Clinical Vignette

A 53-year-old man without significant past medical history presented with a 12 month history of worsening tremor of the right hand and scuffing of his right foot when walking. Clinical examination demonstrated a mild rest and postural tremor of the right arm, increased tone in the neck and right arm and leg, and generalized bradykinesia. FP-CIT SPECT brain scanning demonstrated reduced striatal uptake of the radioligand, supporting the clinical diagnosis of degenerative parkinsonism. There was little clinical improvement with Madopar (increased to 125 mg four times daily). Subsequent development of impaired speech and vertical eye movements raised the likelihood of progressive supranuclear palsy (PSP), a Parkinson plus disorder. He was admitted to the medical unit with acute confusion, visual hallucinations, and agitation. Dehydration and chest infection were treated intravenously with fluids and Amoxicillin 1 g three times daily and Clarithromycin 500 mg twice daily. On admission, antiparkinson medication was stopped in view of his cognitive state; after 3 days the conscious level dropped, speech became incomprehensible, and he was unable to follow commands. There was a leucocytosis and a chest X-ray showed lobar pneumonia. Despite high-flow oxygen and an adjusted antibiotic regimen (Ceftriaxone 2 g once daily and Metronidazole 500 mg three times daily), his conscious level dropped further over 48 h, he became pyrexial (41°C), and tone was increased axially and in all four limbs. Creatine kinase (CK) was markedly elevated ($>14{,}000$) and parkinsonism-hyperpyrexia syndrome (PHS) was diagnosed. Despite 400 mg/day Madopar (via nasogastric tube) and intravenous fluids, he died 48 h later with respiratory and renal failure.

Recognizing PHS

Neuroleptic malignant syndrome (NMS) was first described in early trials of haloperidol [1]. NMS results from an acute reduction in central dopamine transmission and

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studies of neurotransmitter metabolites in cerebrospinal fluid of patients with NMS are in keeping with central dopamine hypoactivity [2, 3]. It is a rare but potentially fatal side effect of drugs that block D2 dopamine receptors. Clinically it presents with fever, autonomic instability, muscular rigidity, reduced conscious level, diaphoresis, and raised serum CK. It is commoner in young and middle-aged male patients and symptoms typically develop within the first week after introducing a neuroleptic agent. The incidence of NMS is less with atypical antipsychotics, but affects 0.2% of patients started on all antipsychotic medications [4]. NMS is more likely when antipsychotic doses are relatively high, or titrated rapidly, or given parenterally [5, 6].

A very similar syndrome, first described in 1981 in a PD patient who had not been exposed to neuroleptics, occurred after large doses of antiparkinson drugs were discontinued [7]. Many further reports have followed, giving a variety of names including NMS, neuroleptic malignant-like syndrome, levodopa-withdrawal hyperthermia, PHS, dopaminergic malignant syndrome, and acute dopamine depletion syndrome. The term PHS is preferred for the syndrome in the PD patient (by the current authors), since neither neuroleptic drugs nor levodopa withdrawal is essential for its development. Also, PHS occurs in other forms of degenerative parkinsonism (e.g., progressive supranuclear palsy and multiple system atrophy [8, 9]).

There is also similarity with the serotonin syndrome which can present with cognitive (confusion/agitation), autonomic (hyperpyrexia/diaphoresis/tachycardia), and neuromuscular features (myoclonus/hyperreflexia/rigidity/tremor). Diagnosis of this syndrome must be co-incident with the addition or increase of a known serotonergic medication, such as selective serotonin reuptake inhibitors (SSRIs) [10]. There is reason, because of the interplay between dopamine and serotonin systems, to be cautious in using SSRI drugs in the population at risk of PHS but further work in this area is required.

The most common trigger for PHS is withdrawal of antiparkinson medications, especially levodopa. The ‘levodopa holiday’ was commonplace until the 1980s, and involved rapid and deliberate reduction and cessation of dopaminergic drugs to ‘reset’ the dopaminergic system, but became controversial [11] and today is no longer recommended, largely for fear of inducing PHS. However, there remain circumstances in which dopaminergic medications are discontinued. The patient or carer may stop one or more drugs due to side-effects, or on an experimental basis [12]. Antiparkinson medication may be changed or stopped on hospital admission, often in the context of an alternative acute illness (which may be medical or surgical).

Additional precipitants reported in the PD patient include co-prescription of neuroleptic medication, dehydration, excessively hot weather, and the wearing-off phenomenon [13, 14]. PHS has also been reported in two patients with probable dementia with Lewy bodies (DLB) when commenced on the cholinesterase inhibitor donepezil [15]. The importance of infection, intestinal absorption changes, and pre-menstrual state [16–18] is less certain. This syndrome has also been reported following bilateral subthalamic stimulation, during which there was a rapid reduction in antiparkinson medication dosage [19].

Pathophysiology of PHS

As in NMS the underlying pathological mechanism for PHS is sudden suppression of central dopaminergic activity [2]. In addition, changes in peripheral and central sympathetic outflow and alteration in central serotonin metabolism have also been implicated [20]. A reduced CSF concentration of the dopamine metabolite homovanillic acid (HVA), which was attributed to abrupt medication withdrawal, has been found in PD patients who discontinue dopaminergic medications [21, 22]. This (expected) biochemical change was more marked in those patients who went on to develop PHS.

The Clinical Profile

Typically, symptoms develop between 18 h and 7 days following the trigger. The patient becomes rigid, sometimes with tremor, and progresses to an immobile state [20] (see Table 1). Within 72–96 h, most patients develop pyrexia and a reduced conscious level, ranging from confusion to coma. Autonomic dysfunction with tachycardia, labile blood pressure, and diaphoresis follow. Laboratory tests may reveal a leucocytosis, elevated CK, and sometimes deranged liver function tests (elevated CK is not a pre-requisite for the diagnosis). Complications of PHS include aspiration pneumonia, deep venous thrombosis and pulmonary embolism, disseminated intravascular coagulation (DIC), rhabdomyolysis, acute renal failure, and seizures. Poor prognostic indicators in PHS include older age and higher pre-morbid Parkinson severity [8].

In the largest reported series of PHS, 99 episodes occurred in 93 patients (72 patients with PD, 8 with PSP, 6 with MSA, 4 with vascular parkinsonism, 2 with dementia with Lewy bodies, and 1 with parkinsonism secondary to vasculitis) in five Japanese centers. The usual trigger (55% of cases) was cessation or withdrawal (by patient or carer) of dopaminergic drugs, most commonly because of confusion or hallucinations. Other triggers included infection, poor oral intake, dehydration, and intestinal ileus; 69% of episodes resulted in recovery to the pre-morbid state and

Table 1 Clinical features of parkinsonism-hyperpyrexia syndrome

Signs and symptoms
Muscle rigidity (with or without tremor)
Pyrexia (>38°C)
Reduced conscious level (confusion to coma)
Autonomic instability (labile blood pressure, tachycardia, diaphoresis, urinary incontinence)
Dysarthria, dysphagia
Laboratory findings
Raised creatine kinase
Leucocytosis
Deranged liver function tests
Metabolic acidosis
Complications
Acute renal failure
Rhabdomyolysis
Aspiration pneumonia
Deep venous thrombosis/pulmonary thromboembolism
Disseminated intravascular coagulation
Respiratory failure

4% of patients died. This compares with reported mortality from NMS of 11.6% [23]. In both PHS and NMS, development of DIC and renal failure was associated with a poorer outcome.

A further series of 11 PD patients developed PHS following withdrawal of levodopa and other antiparkinson medications [24]. Patients had a mean disease duration of 9 years and developed symptoms of PHS on average 93 h following medication withdrawal. All of the cases had increased rigidity as the presenting sign. No patient died in this series. These 11 cases occurred over 9 years and accounted for 3.6% of the total PD patient population regularly treated by the authors.

Hashimoto et al. [25] described 16 episodes of PHS occurring in 14 PD patients between 1992 and 1999. Discontinuation or withdrawal of dopaminergic drugs preceded 8 of 16 episodes, whilst infection with fever preceded eight episodes.

Treating PHS

The main key to treating PHS is early diagnosis, with the underlying cause being identified and corrected. Antiparkinson medications which have been discontinued should be promptly re-started. They can be given orally or via a nasogastric tube (see Table 2). If nasogastric feeding is contraindicated (e.g., because of ileus), levodopa-based treatment can be administered intravenously (50–100 mg of L-dopa infused over 3 h), and this can be repeated four times daily until the patient can take medications orally. Patients should be given the same dose of levodopa as taken prior to onset of PHS. Alternatively, bromocriptine (7.5–15.0 mg) can be given orally. If there has been no alteration in dopaminergic medication, other causes should be sought (e.g., prescription of neuroleptic, infection, dehydration).

Patients often require high dependency or intensive care, with respiratory support and central venous pressure monitoring if necessary [20, 26]. Supportive measures such as intravenous fluid replacement, anti-pyretics, and cooling blankets are recommended. Patients are at high risk of aspiration pneumonia and antibiotics should be commenced early if infection is suspected. Renal function, coagulation factors, and CK should be closely monitored. If CK is elevated, urinary myoglobins should be tested for rhabdomyolysis.

Dantrolene is a skeletal muscle relaxant, inhibiting intracellular release of calcium from the sarcoplasmic

Table 2 Recommended treatment for parkinsonism-hyperpyrexia syndrome

Replace antiparkinson medications
Levodopa (pre-morbid dose) orally, via nasogastric tube or via intravenous infusion (50–100 mg infused over 3 h)
Dopamine agonist therapy, oral or nasogastric: traditionally bromocriptine 7.5–15.0 mg three times daily (ropinirole 1–2 mg three times daily, or pramipexole 0.18–0.36 mg (base) three times daily may be preferred); transdermally: rotigotine 2–4 mg/24 h; subcutaneously: apomorphine 1.0–2.0 mg/h [31]
Supportive measures
Manage patient in high dependency or intensive care setting
Intravenous fluid replacement
Anti-pyretics and cooling measures
Dantrolene (10 mg/kg per day in 3–4 divided doses) (if rigidity is severe and not responding to other measures)
Management of complications
Antibiotics for infection
Mechanical ventilation if respiratory failure
Haemodialysis for acute renal failure

reticulum and has been shown to be efficacious in cases of malignant hyperthermia [27]. Both bromocriptine (5–10 mg three times per day) and dantrolene sodium (10 mg/kg per day in 3–4 divided doses) are traditionally recommended in treatment of PHS, although there are no studies demonstrating efficacy [26, 28]. Other dopamine agonists (oral ropinirole or pramipexole, transdermal rotigotine, or subcutaneous apomorphine) have been used more recently.

In a randomized placebo-controlled trial, 3 days of 1 g intravenous methylprednisolone in 40 cases of PHS shortened the illness duration, but there was significant overlap between the active and placebo groups [29]. All patients in this study also received levodopa, bromocriptine, and dantrolene sodium.

Preventing PHS

The most common trigger for the parkinsonian patient to develop PHS is reduction or cessation of antiparkinson medications. The most common drug implicated is levodopa, but PHS can be caused by acute reduction in any dopaminergic drug. Drug holidays are no longer practiced, but patients and their carers often reduce dopaminergic drugs due to side effects (especially confusion and hallucinations). Patients should be advised not to suddenly stop antiparkinson medication. While dopaminergic drug dose reduction should generally be gradual, the circumstance of acute psychosis in PD patients with an intercurrent illness (typically infective) may necessitate stopping adjunctive dopaminergic therapy (e.g., dopamine agonists, MAO-B inhibitors). Maintaining *some* antiparkinson medication (such as levodopa-based treatment) will help prevent PHS. No specific guidelines inform the correct approach, and clinical judgment should assess the severity of the mental state, pre-existing cognitive problems, and the dose of different drug classes. However, the message should be clear: *complete and abrupt* cessation of established antiparkinson medication in a PD patient should almost always be avoided. The potential risks of neuroleptic drugs mean that they should be used sparingly in PD patients, but they are quite often beneficial in the more advanced PD patient with cognitive problems, hallucinations, and/or agitation. Dehydration should also be avoided in the PD patient, especially if fever is present.

The risk of PHS on admission to hospital is also pertinent. Retrospective audit of all acute hospital admission for PD patients in a District General Hospital in North Kent illustrated poor prescription and knowledge of antiparkinson medications [30]. While 26/35 (74%) of admitted PD patients had antiparkinson medications stopped, omitted, or prescribed inappropriately, further details of this and the 'significant sequelae' in 16/26 (62%) were not reported, although one of their cases did require intensive care support. No case was specifically diagnosed with PHS.

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