# Chapter 3
# Parkinsonism-Hyperpyrexia Syndrome in Parkinson's Disease

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This chapter contains video segments that can be found on the accompanying DVD.

**Abstract** Parkinsonism-hyperpyrexia syndrome (PHS) is a rare but potentially life-threatening complication of Parkinson's disease (PD). PHS was first described in 1981 and has been reported in dozens of cases since then. The clinical presentation of PHS includes hyperpyrexia, rigidity, altered consciousness, dysautonomia, leukocytosis, and elevated creatine kinase. Although PHS and NMS are phenotypically nearly identical, PHS is a distinct entity in that it is triggered by removal or effective loss of dopaminergic therapy in a parkinsonian patient. The mainstay of PHS treatment is rapid replacement of effective anti-parkinsonian therapy. While abrupt levodopa withdrawal is the classic trigger of PHS, a variety of other inciting scenarios have been described. The pathophysiology underlying PHS is generally accepted to be a hypo-dopaminergic state, and its clinical features can be explained as sequelae of central dopamine depletion. PHS is a neurological emergency, with significant morbidity and mortality. Early recognition and rapid reintroduction of anti-parkinsonian medications are keys to the successful management of this syndrome.

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## Patient Vignette [1]

A 44-year-old right-handed man with a 14-year history of Parkinson's disease (PD) presented to the emergency department with an acute onset of fever, confusion, rapidly progressive difficulty with ambulation, and dysphagia. He originally presented in 1987 with left upper limb tremor and slowness. Workup for secondary parkinsonism was unrevealing, and treatment was initiated first with anticholinergic agents and then levodopa. By 1991, he had developed bilateral symptoms and signs. Motor fluctuations and complications emerged within 5 years of the onset, with related anxiety and behavioral problems as well. He required high doses of dopaminergic agents for the last 8 years.

He had been fully able to communicate, perform activities of daily living, and ambulate 48 hours prior to presentation. He had recently been incarcerated, and during his confinement his medication doses were abruptly and substantially diminished for unclear reasons. His usual dosing schedule included carbidopa/levodopa (C/L) 25/100 one tablet every 2 hours starting at 6:00 a.m. to 8:00 p.m., with two tablets at 10:00 p.m., midnight, and 2:00 a.m. In addition, he was also prescribed pergolide 1 mg three times/day, and quetiapine 25 mg five 1/2 tablets each day in divided doses. In July 2000, he underwent deep brain stimulation (DBS) surgery, with bilateral leads placed in the subthalamic nuclei. They were operational as of the last office visit. DBS surgery led to improved off times and less dyskinesias, but allowed only minimal change in levodopa dose.

In the emergency department, the patient appeared acutely ill. He was febrile, with a temperature of 101 °F, heart rate of 100 bpm, blood pressure of 140/90, and respiratory rate of 24. He was awake but confused and unable to follow commands or intelligibly communicate. His mucus membranes were dry. He appeared diffusely stiff, with severe rigidity of the neck and limbs. A coarse tremor was present in both upper extremities, but no other involuntary movements were seen. No signs of trauma were found. Pupils were symmetrical and reactive to light, and fundoscopic exam was normal. Reflexes were present and symmetric, with no pathologic reflexes.

Laboratory studies revealed a white blood cell count (WBC) of 16,000 cells/$mm^3$, blood urea nitrogen of 39 mg/dl, and normal red blood cell indices. No iron indices were measured. Creatine kinase (CK) was >4,000. A cranial CT revealed bilateral DBS leads without acute pathology. A lumbar puncture with CSF analysis was normal. The diagnosis of parkinsonism-hyperpyrexia syndrome (PHS) was made: a nasogastric tube was placed and levodopa and pergolide were reinstituted, with intravenous fluids. Despite treatment, his condition worsened, with medically refractory hypertension, respiratory distress, seizures, and ultimately renal failure. He expired 3 days after presentation. Postmortem exam revealed bilateral pulmonary emboli with infarction. Examination of the brain revealed marked depigmentation of the substantia nigra and the locus ceruleus, with Lewy bodies confirming the diagnosis of PD.

## Introduction

Neuroleptic malignant syndrome (NMS) is a potentially fatal drug-induced movement disorder that was first described by Delay and associates in 1960 [2, 3]. These authors reported it as the "most serious but also rarest and least known of complications of neuroleptic chemotherapy" [3]. Since the 1980s, it has been a considerable concern in relation to the treatment of psychiatric patients because of its potentially high mortality rate of 5–20% [4, 5]. The characteristic clinical features include hyperthermia, muscle rigidity, dysautonomia, and mental status change. Hyperthermia is present in nearly all cases of NMS, and muscle rigidity is reported in more than 90% of patients [4–8]. Alterations in mental status can range from fluctuating alertness, to agitation and delirium, to frank stupor or coma [7, 9]. Muteness is also seen, although less commonly than catatonia. Unstable blood pressure, cardiac arrhythmia, dyspnea, pulmonary edema, and bladder incontinence are common signs of dysautonomia, and diastolic hypertension possibly being a specific feature [4]. Several laboratory abnormalities support the diagnosis, including elevated creatine kinase, elevated WBC count, and diminished serum iron [4].

It was initially believed that NMS only occurred in psychiatric patients, particularly those with schizophrenia and affective disorders who were treated with neuroleptics. Although particular risk factors in these patient populations have been delineated, it has become clear that any patient exposed to these agents is at risk for developing NMS [4]. This constellation of symptoms has since been recognized in patients exposed to other agents such as dopamine depleters (tetrabenazine) [10], a related syndrome (serotonin syndrome) associated with exposure to serotonin-specific reuptake inhibitors [11], and cocaine [12].

In 1981, a similar disorder was described in a patient with PD triggered by sudden withdrawal of dopaminergic medications, specifically levodopa, amantadine, and biperiden. Several dozen other cases have since been reported. The syndrome seen in PD has been reported under a variety of different names, including NMS, neuroleptic malignant-like syndrome (NMLS) [13, 14], levodopa-withdrawal hyperthermia, PHS [15], lethal hyperthermia [16], dopaminergic malignant syndrome [17], and acute dopamine depletion syndrome [18]. PHS is the most specific and clinically descriptive term and the one currently most accepted for this disorder. As we will show, levodopa withdrawal is not the only cause of this entity, and the word dopaminergic pertains to any NMS-like syndrome. It is important to draw a distinction between true NMS and PHS. From this point forward, when discussing this syndrome in parkinsonian patients we will use the term PHS. This chapter reviews the clinical entity of PHS and discusses its management. Interest in this syndrome has been on the rise in recent years, evidenced by the publication of several review articles on the subject [19–22].

## Clinical Features

Although PHS is rare, several situations are common triggers. The scenario most commonly reported is the "levodopa holiday" [14, 23–25]. These cases were all reported in the 1980s when drug holidays were still utilized for therapeutic purposes. They were recommended in patients with intractable "off" periods and psychosis, although their utility was controversial [26, 27]. Drug holidays often involved rapid reduction and complete cessation of dopaminergic medication. Patients would remain off for up to 14 days, despite well-known risks associated with immobility such as aspiration pneumonia and pulmonary embolism. Drug holidays are no longer used; however there are other situations when dopaminergic medications are discontinued posing an equal risk. In several reports, the medications were abruptly stopped by the patients themselves because of side effects, misunderstanding in medication instructions, or a desire to try alternative treatments [13, 17, 18]. In one case the medications were stopped because physicians thought that the patient had psychogenic parkinsonism [18]. PHS has also been seen in PD patients with partial withdrawal of dopaminergic therapy, or when medication regimens were substantially changed. Iwuagwu [28] described a case with the onset linked to discontinuing tolcapone. When the patient became confused, the treating physician thought that this was exacerbated by levodopa; after it was stopped, PHS escalated. Cunningham [29] described a patient who developed hyperthermia, rigidity, and dysautonomia when immediate-release levodopa was switched to controlled release, and bromocriptine was tapered off from 40 mg/day to 0 in a few days. Peak serum levodopa levels are notably lower with controlled-release formulations than immediate release. Keyster [18] reported a similar case where PHS occurred when a patient was switched from levodopa to bromocriptine.

Another situation where PHS has been reported is in PD patients treated for a coexisting psychiatric disorder with neuroleptics. One such patient with schizophrenia and PD treated with neuroleptics for their primary psychotic disorder became gravely ill after cessation of anti-parkinsonian medications [30]. In another case, a patient admitted to the hospital for drug-induced psychosis had their levodopa stopped and haloperidol started at the same time. It is not unreasonable to refer to these cases as NMS also, since it is unclear if symptoms started because of dopaminergic drug withdrawal or neuroleptic initiation. Severe "off" periods associated with motor fluctuations can also trigger such events. Pfeiffer and Sucha [16] reported a single patient developing repeated PHS features with "off" episodes. Events occurred for years, lasting 1 or 2 h and clearing when he turned "on." He ultimately died during a severe episode associated with a fever of 107 °F.

Three other situations have been reported in single cases that occurred without change in medication regimen. One involved peri-menstrual "off" times with symptoms of PHS [31]. In this case, it is believed that elevated estrogen and progesterone levels may have decreased CNS dopaminergic stimulation in a manner similar to cutting medication doses. Another case involved metabolic alteration, particularly hypernatremia [32]; the mechanism by which this caused PHS is unclear. In a third

case a patient in the intensive care unit developed the symptoms of PHS after his enteric feed was changed from a formulation with lower protein content to one with higher protein content [33]. The PHS cleared after the enteric feed was changed back to the formulation with lower protein content. His home regimen of PD medications was continued unchanged throughout his course. In this case the development of PHS was attributed to decreased absorption of his PD medications caused by increased protein content in his enteric nutrition. Despite these cases and others like them, it should be noted that PHS, for the most part, refers to a disorder that occurs with withdrawal of CNS dopaminergic stimulation. Metabolic changes and infection may increase the risk for PHS. However, while they can, on their own, cause worsening of parkinsonian symptoms, it is unclear if they do so via the same mechanism. Therefore, we propose that the term PHS should have a specific meaning, indicating the presence of the NMS-like constellation of symptoms on the background of dopaminergic drug withdrawal.

Our patient vignette suggests an additional risk for PHS in PD patients. DBS of the subthalamic nucleus (STN) is not infrequently used as a treatment for advanced fluctuating PD. When performed properly it leads to a substantial decrease in "off" time and severity. This improvement can in turn lead to a decrease in levodopa requirements by about 30% [34]. Some authors advocate discontinuing levodopa altogether [35], but others have voiced concern regarding this objective [36]. Our patient had subthalamic DBS implanted and abruptly stopped medications, although not as part of the programming plan. He developed PHS and pulmonary embolism, which was ultimately fatal. Other scenarios leading to PHS surrounding DBS have more recently been described. One case report (see Case 4 in Section "Illustrative Cases from the Literature" below) describes a patient who developed PHS repeatedly after his STN DBS was turned off for repeated stimulation-associated manic episodes [37]. One could assume that stopping DBS would have an equivalent effect of dopaminergic drug withdrawal. In another case report the authors describe the onset of PHS following medication withdrawal preoperatively in preparation for DBS surgery the night before [38].

The frequency of PHS in PD has not been studied formally, but the disorder appears to be rare. We identified more than 80 cases reported in the literature. The details of the cases were varied. One paper was a therapeutic trial that included 40 cases [39]; two papers reported 11 cases each [17, 40]; two reports described 3 cases each [14, 18]; and the rest were single case reports. Serrano-Duenas [17], with one of the larger cohorts, reported that 11 cases accounted for 3.6% of his PD patient population and 0.04% of total patient consultations for PD. In the study by Sato [39] 40 cases were seen over a 3-year period. These findings may suggest that PHS may be more prevalent than previously recognized but this requires further study.

Patients developing PHS were male (47 of 83 (56%) reported) or female, with duration of PD ranging from 2 to 16 years and baseline levodopa dose at the time of onset ranged from 200 to 2,100 mg/day. Not all patients had motor complications. In the report by Ueda [40] only 4 of 11 cases experienced this problem at the onset of PHS.

The clinical features of PHS are nearly identical to NMS, and the clinical presentation seems fairly stereotyped. The time of onset of symptoms after change in dopaminergic therapy ranged from 18 hours to 7 days. The initial feature in most patients was severe rigidity along with tremor, with progression to an immobile state [17, 18, 40]. Within 72–96 hours, most patients were hyperpyrexic with altered mental status ranging from agitation and confusion to stupor and coma. Autonomic signs such as tachycardia, tachypnea, labile blood pressure, urinary incontinence, pallor, and diaphoresis often accompany this. In some cases hyperthermia, mental status changes, and autonomic dysfunction may occur from the outset, along with worsening of parkinsonism [40]. Temperatures as high as 107 °F have been reported [14, 16]. Laboratory findings usually reveal leukocytosis (as high as 26,000) and elevated CK (ranging from 260 to 50,000 in reported cases). There have been no reports where iron levels were examined. Respiratory distress is not uncommon, and mechanical ventilation may be necessary [23, 30]. Mutism, as part of the mental status derangement, was reported by several authors [13, 29, 32]. Other neurological features include seizures [24] and myoclonus [15].

Although this description seems very similar to NMS, there appear to be some differences. Serrano-Duenos [17] performed a comparison looking at 11 PHS patients and 21 NMS patients. They found that the latency to the onset of symptoms after the inciting event was twice as long (93 h vs. 49 h) for PHS than NMS. In addition, in PHS the elevation of CK and WBC was significantly less robust. The duration of hospitalization was also shorter (8.4 days vs. 12.2 days). As expected, PHS patients were older than the NMS group. These findings suggest that NMS is a more aggressive disorder than PHS, and caries a poorer prognosis.

As with NMS, PHS may be associated with serious long-term effects. Some patients only partially recover from the event, and are left with significantly worse parkinsonism [17, 18]. In one case a patient at Hoehn and Yahr stage 2 prior to the incident became wheelchair-bound (stage 5) afterwards [17]. Medical complications are also a concern. Deep venous thrombosis is a serious complication, and may ultimately result in pulmonary emboli (as occurred in our illustrative case). Several patients have developed aspiration pneumonia during a bout of PHS and two cases developed renal failure [14, 18], complications well described in NMS. Finally, four of the reported cases (including ours) were fatal [14, 16, 23]. Two died in hyperthermic coma with no other explanation, one died with aspiration pneumonia and renal failure, and one from pulmonary embolism [1].

## Illustrative Cases from the Literature

The following four cases from the literature illustrate this disorder, three from drug withdrawal and one related to DBS. In addition, Table 3.1 summarizes the time frame involved in development of PHS after dopaminergic drug withdrawal, and recovery after therapy in six representative cases [17, 18].

**Table 3.1** Summary of selected clinical cases from two publications [17, 18] illustrating the time frames involved in the onset and recovery of PHS

| Patient demographics | Medication discontinued | Clinical features within 24 h | Clinical features within 96 h | Improvement within 24 h | Improvement within 96 h |
|---|---|---|---|---|---|
| 75-Year-old man with PD for 1 year | C/L 300 mg/day | None reported | Weak, rigid, tremulous, diaphoretic | None reported | Full resolution within 5 days |
| 67-Year-old woman with PD and schizophrenia | C/L 250 mg/q.i.d | Febrile (41.2°C) Mute, tremulous, rigid | Same | Afebrile, improved sensorium | Full resolution within 48 h |
| 64-Year-old man with PD for 7 years | C/L 250 mg/q.i.d. Benz. 2 mg/day Trihex. 4 mg/day | Tremulous, rigid | Febrile (39.4°C) Mute, confused, severe tremor, and rigidity | Less rigid and tremulousness, improved sensorium | Progressive improvement without return to baseline after 10 days |
| 74-Year-old woman with PD (H&Y III) | C/L 750 mg/day Seleg. 10 mg/day | Rigid, unable to ambulate or feed self | Febrile (37.9°C) Stupor, severe rigidity | Afebrile, alert, much less rigid | Progressive improvement without return to baseline after 10 days |
| 69-Year-old man with PD (H&Y II) | C/L 750 mg/day Bromo. 7.5 mg/day | Severe rigidity, unable to ambulate | Febrile (38.7°C) Somnolent, severe rigidity | Afebrile, alert, much less rigid | Progressive improvement without return to baseline after 10 days |
| 69-Year-old woman with PD (H&Y IV) | C/L 1,125 mg/day Seleg. 10 mg/day | Febrile, severe rigidity, unable to ambulate | Febrile (39.2°C) Stupor, severe rigi dity | Afebrile, alert, much less rigidity | Progressive improvement without return to baseline after 10 days |

*C/L* carbidopa/levodopa, *Ama* amantadine, *Seleg* selegiline, *Bromo* bromocriptine, *H&Y* Hoehn and Yahr

*Case 1*: [18] A 75-year-old man with a diagnosis of PD was treated with immediate release carbidopa/levodopa 25/100 one tablet three times per day for 1 year. When amantadine 100 mg was added for symptomatic benefit, the patient mistakenly discontinued his C/L. Within 5 days he became tremulous, weak, pale, diaphoretic, and dyspneic. Amantadine was increased without clinical benefit. It was discovered that C/L had been discontinued and it was restarted but only at twice-daily dosing. Over the ensuing week, the patient became progressively confused, resulting in the cessation of C/L. Within 48 hours, he worsened considerably and because of continued confusion 9 mg of haloperidol was given. Soon after, the patient became mute, agitated, and severely rigid with a diffuse coarse tremor. Laboratory review revealed leukocytosis, hypernatremia, and an elevated CK (452 U/L). Within 5 hours of this evaluation, the patient's temperature rose to 38.5°C. Bromocriptine (2.5 mg every 6 hours) was started, and within 72 hours, the patient's condition markedly improved. C/L was subsequently restarted, and the patient fully recovered.

*Case 2*: [17] A 74-year-old woman abruptly stopped taking her anti-parkinsonian medication. She had advanced disease (Hoehn and Yahr stage 3), and had been taking C/L 750 mg/day, selegiline 10 mg/day, and propranolol 80 mg/day. She decided to begin an alternative, natural treatment for PD and did not discuss this first with her treating physician. Within a short time, she became markedly rigid, and was unable to walk or feed herself. Within 96 hours, she was diaphoretic, somnolent, febrile (37.9°C), rigid, and stuporous and had a serum CK of 759 U/L on presentation to a local hospital. A diagnosis of PHS due to abrupt medication withdrawal was made, a nasogastric tube was placed, and dopaminergic medication was restarted. Within 9 hours she became alert, and rigidity lessened within 15 hours. On discharge 9 days later, rigidity was worse than prior to the incident.

*Case 3*: [23] A 51-year-old man with a 9-year history of PD was admitted to the hospital because of severe levodopa-induced dyskinesias. His medications on admission included C/L 25/250 three times per day and diphenhydramine 50 mg four times per day. C/L was reduced by one-half for 3 days, and then stopped altogether (drug holiday) and diphenhydramine was cut to BID. Two days later the dyskinesias stopped and were replaced by rigidity, bradykinesia, and tremor. On the third day his temperature rose to 38.2°C, heart rate was 120/min, respiratory rate was 28/min, and he was diaphoretic. The temperature increased further to 40.4°C by day 10 and he remained confused and disoriented. Anti-PD medications were restarted, and intravenous fluids and low-dose heparin were begun. By day 10 CK was 260 U/L and on day 14 WBC was 13,200/mm [3]. Workup for infection was negative, and antibiotics were initiated empirically. Despite therapy, he remained febrile and stuporous. He was intubated and placed on a ventilator, but died in hyperthermic coma on day 15 after discontinuing medications.

*Case 4*: [37] A 60-year-old man with a 17-year history of PD developed severe motor fluctuations and dyskinesias 9 years after disease onset. He was levodopa responsive, and underwent bilateral STN DBS placement. With stimulation, his motor symptoms improved, but he also developed mania. His mania increased 2 years after the DBS placement and he was admitted to the hospital where the stimulators were

turned off in light of the mania, which was attributed to the stimulation. On the third hospital day, the patient's manic symptoms disappeared, but he developed somnolence, immobility, and rigidity. He became febrile with a temperature of 38.7°C. Heart rate was 120, WBC count was 12,600/μL, and serum CK was elevated to 1,878 U/L. PHS was considered and treatment with medical therapy initiated, and by day 6 in the hospital the patient was afebrile with normal mental status. DBS was then turned back on and the patient had improvement in rigidity and akinesia. However, over the next several years he experienced several more episodes of mania, which did not respond adequately to antipsychotic drugs or DBS stimulation site adjustment. During each episode his DBS had to be turned off, and each time this was done he experienced recurrence of PHS, which responded each time to IV fluids followed by the reintroduction of DBS. His most recent manic episode was reversed by lowering the voltage of the stimulation, not completely turning it off, without emergence of PHS.

## Risk Factors and Pathogenesis

In practice, many PD patients have their doses of dopaminergic medications decreased or stopped and yet only a very small fraction experience PHS. On the other hand, some patients are susceptible enough to develop this with minor medication changes or wearing off. There have been attempts to evaluate potential risk factors in PD patients [40–43]. The most ambitious of these was a study by Ueda [40], examining clinical and neurochemical features over a 3-year period in 98 consecutive hospitalized PD patients. Demographics, disease severity, and cerebrospinal fluid monoamine metabolites including HVA, MHPG, and 5-HIAA were evaluated. Eleven of the ninety-eight had a history of PHS (either remote or leading to the study admission). The PHS group had significantly worse parkinsonism and a greater daily levodopa dose. No difference was seen between groups with respect to gender, age, duration of disease, or maximum levodopa dose. HVA spinal fluid levels were significantly lower in the PHS group, the only feature independently related to the occurrence of PHS. A second study by the same group [41] examined CSF HVA levels in 9 patients during and after an episode of PHS, and compared them to 12 PD patients with simple worsening of PD with discontinuing medications. HVA levels were significantly lower in the PHS group. The authors suggested that the lower baseline level left a "narrow safety margin," leading to an increased susceptibility to the occurrence of PHS. Other studies [42, 43] suggest that the presence of motor fluctuations, psychosis, and dehydration prior to the event represent other possible risks. Overall it appears that those with more severe disease and more profound dopaminergic depletion are at greater risk. Support for this comes from the ELLDOPA trial where 361 early PD subjects treated with up to 600 mg of levodopa for 9 months were withdrawn over a few days. No cases of PHS occurred [44].

It is generally accepted that alterations in dopaminergic transmission in the brain are the primary pathogenic mechanism of NMS [4, 45]. Abnormalities in muscle membrane function, changes in peripheral and central sympathetic outflow, and

alterations in central serotonin metabolism have also been implicated [4]. The occurrence of PHS (a clinically identical syndrome to NMS) with dopaminergic drug withdrawal in PD indicates that a hypodopaminergic state alone is sufficient to trigger both disorders.

The clinical features of PHS can be explained by central dopamine depletion. The motor features of PHS are exaggerated PD symptoms related to decreased dopaminergic activity in the nigrostriatal system. The role of dopamine in thermal regulation is also well known. These dopamine pathways within the hypothalamus include the preoptic area, the anterior hypothalamus concerned with thermal detection, and the posterior hypothalamus involved with generation of effector signals. The thermosensitive neurons respond to local changes in blood temperature as well as to afferent information from peripheral thermosensors. Dopamine and dopamine agonists modulate hypothalamic temperature regulation, while dopamine receptor antagonists block this ability [4]. Dopaminergic depletion can also explain mental status changes through modulation of mesolimbic and mesocortical pathways [4].

## Treatment

PHS is a neurological emergency. The key to treatment is early recognition of the syndrome and rapid reintroduction of withdrawn anti-parkinsonian medication (see Table 3.2). If there is no history of medication schedule alteration, then other causes must be sought including the use of neuroleptics or inadvertent shutting off of their DBS device (drained battery for example). When discontinuation of medication is the cause, the drug most commonly responsible is levodopa, and it should be reinstituted first, via nasogastric tube if necessary. Since PHS has occurred in two patients because of poor absorption of levodopa relating to diet this is an important consideration. Beyond that, the treatment is similar to NMS, including rehydration with intravenous fluids, treatment of hyperthermia with anti-pyretics and cooling blankets, as well as supportive measures such as mechanical ventilation, cardiovascular monitoring, intravenous access, nasogastric suctioning/feeding, and prevention of thrombophlebitis. Metabolic evaluation and workup to exclude infection are necessary. Since these patients are at risk for infection such as aspiration pneumonia, it is reasonable to initiate antibiotic therapy while the workup is under way. Additional medical therapy with bromocriptine or other dopamine agonists and dantrolene should be considered, although there have been no controlled trials. Bromocriptine is orally administered, with an initial dose of 2.5 mg t.i.d., and titrated for effect in increments of 2.5 mg t.i.d. every 24 hours. Dantrolene, a muscle relaxant initially used to treat malignant hyperthermia, is a parental compound typically dosed as 10 mg/kg/day in 3–4 divided doses. With proper therapy, symptoms will reverse in 10 hours to 7 days. Most of the patients described ultimately required a fairly lengthy hospital stay (5–22 days).

One study examined the use of methylprednisolone pulse therapy as an added regimen for PHS in PD [39]. In a randomized trial, all patients received levodopa,

**Table 3.2** Steps in the management of PMS in PD

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|---|
| Recognition of the disorder |
| Verification of patients' medication regimen/compliance |
| Reintroduction of anti-parkinsonian medications |
| Supportive measures: Anti-pyretics/cooling blankets |
| Rehydration |
| ICU monitoring/management (see text) |
| Clinical evaluation for possible comorbid conditions |
| Bromocriptine 2.5 mg po t.i.d., titrated by 2.5 mg t.i.d./daily as necessary |
| Dantrolene sodium 10 mg/kg/day IV in divided doses (t.i.d./q.i.d.) as necessary |

bromocriptine, and dantrolene sodium and patients were randomized to receive placebo or 1,000 mg of methylprednisolone for 3 days. Results suggested that steroid pulse therapy might shorten the course of the illness, perhaps by as much as 10 days, although notable overlap between groups was seen. This is the only double-blind, placebo-controlled trial in PHS or NMS, and further investigation is warranted.

## Conclusion

PHS is a neurological emergency caused by the abrupt withdrawal of dopaminergic therapy that has the potential to end in fatality. In all likelihood, it is under-recognized and more common than the literature might suggest. The use of several terms to describe the diagnosis in the literature has contributed to the confusion. A unifying term could improve awareness, especially if the term relates specifically to those patients with underlying parkinsonism. That is why we believe that PHS, recommended by Gordon and Frucht [15], fulfills that role.

There are several ways to prevent PHS. First, drug holidays are no longer considered an appropriate treatment approach in PD. If reduction in dopaminergic therapy is needed, gradual reduction is mandated and patients should be made aware of the possible occurrence of PHS. This applies to patients with multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration [46]. When lowering doses patients need to remain adequately hydrated. In addition patients should be advised not to stop taking their medications on their own, and the dangers of this should be spelled out. It is important to avoid the use of standard neuroleptics in these patients since they are already at risk for NMS or PHS. Even atypical antipsychotics have the potential to lead to NMS in PD. The agents best tolerated by PD patients are quetiapine and clozapine [47], but they should also be prescribed with caution. Although patients with more severe disease and those taking larger daily levodopa doses are at greater risk [40–43], even patients with early PD taking low doses of levodopa can develop PHS. Once the syndrome does occur, recognition is paramount and rapid reintroduction of dopaminergic medications imperative.

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