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REVIEW ARTICLE

EMERGENCY CONDITIONS IN PARKINSON'S DISEASE

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Parkinson's disease (PD) is a chronic, neurodegenerative disorder that in certain stages can present a series of acute symptoms and signs, the development of which lasts several hours or days.
Emergencies in PD can be a direct consequence of the pathophysiology of the disease or a secondary consequence of the administration of antiparkinsonian drugs. Urgent conditions in PD can also occur due to falls, infectious diseases, after deep brain stimulation or surgical treatment of other accompanying diseases. This article describes the following emergency conditions: parkinsonism-hyperpyrexia syndrome, dyskinesia-hyperpyrexia syndrome, occurrence of acute psychosis and delirium during PD.
Morbidity and mortality in these disorders are a consequence of the inability to make a timely diagnosis and provide appropriate therapeutic treatment. Timely diagnosis and treatment are very important for reducing the mortality and morbidity rates.

Keywords: Parkinson's disease, emergency conditions, delirium, acute psychosis, parkinsonism-hyperpyrexia syndrome, dyskinesia-hyperpyrexia syndrome

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INTRODUCTION

Movement disorders that require urgent therapeutic treatment are presented with a clinical course that takes several hours or days to develop. Morbidity and mortality in these disorders are a consequence of the impossibility of establishing a timely diagnosis and providing the appropriate therapeutic treatment (1).

Parkinson's disease (PD) is a common neurodegenerative disease characterized by the classic motor features of parkinsonism and progressive loss of dopaminergic neurons in the substantia nigra pars compacta. Clinical challenges are the difficulties to accurately diagnose the symptoms at the earliest stage and manage them at later stages (2).

Although PD is a chronic, neurodegenerative, progressive disorder, the affected individuals may have a series of acute symptoms and signs at certain stages of the clinical picture development (3).

Timely diagnosis and treatment are very important to reduce the mortality and morbidity rate. Emergency conditions in PD can be a direct consequence of the pathophysiology of the disease or a secondary consequence of the use of anti-parkinsonian drugs. Urgent conditions in PD can also occur due to falls caused by postural instability or bronchopneumonia and urinary infections. Emergencies in parkinsonian patients may also occur after deep brain stimulation (DBS) or surgical treatment of diseases not directly related to PD (4).

PARKINSONISM-HYPERPYREXIA SYNDROME

Parkinsonism-hyperpyrexia syndrome (PHS) is a rare complication of PD (5) characterized by hyperthermia, autonomic dysfunction, altered consciousness, severe rigidity, and elevated serum creatine kinase levels. PHS can be caused by infections, a decrease in the dose of a dopaminergic drug, or dehydration.

Potentially life-threatening complications include deep vein thrombosis and pulmonary embolism, aspiration pneumonia, and renal failure (6).

PHS is presented by an acute “akinetic attack”, a severe complication, with an incidence of 0.3% and a mortality of 4% (7). The practice of hospitalizing parkinsonian patients to stop levodopa therapy ("levodopa holidays") was abandoned after reports of severe and potentially fatal PHS mimicking neuroleptic malignant syndrome (8). It may follow a sudden change in dopaminergic medication, although there are various other possible precipitating factors. This syndrome was first observed in patients with advanced PD who underwent “levodopa holidays” to try to limit levodopa-induced motor and neuropsychiatric complications (9). After sudden discontinuation of antiparkinsonian therapy, a syndrome of fever, rigidity, autonomic instability, with elevation of creatine kinase in the serum may occur, which is very similar to neuroleptic malignant syndrome. PHS represents a central hypodopaminergic state (10). This syndrome has been described in PD patients who stopped or reduced antiparkinsonian therapy, as well as in patients treated with DBS where the stimulators were inadvertently turned off (11), and even in patients who did not adequately adjust the doses of antiparkinsonian drugs (12).

PHS usually develops over several days, and can follow the changes in dopaminergic treatment or be caused by trauma, surgery and infections of the lungs, gastrointestinal and urinary tracts, although sometimes there is no obvious cause. In severe cases, patients do not respond to the reintroduction of dopaminergic drugs, parkinsonism rapidly worsens, and they become progressively more immobile and rigid (3).

On examination, patients may present with a delirious state with pronounced global slowness and generalized muscle rigidity. They may develop hyperthermia and elevated serum muscle enzymes, following muscle damage due to severe rigidity. In some patients, dysautonomic features develop, such as tachycardia and unstable blood pressure (13).

The main clinical manifestations are hyperthermia, worsening parkinsonism and elevated creatinine kinase. At least two of the following clinical manifestations are necessary for the diagnosis: altered mental status, autonomic dysfunction, hyperhidrosis, myoclonus, rhabdomyolysis, dystonia, and dehydration. Differential diagnosis should exclude the following conditions: neuroleptic malignant syndrome, serotonin syndrome, dyskinesia-hyperpyrexia syndrome, heatstroke, intracranial infection, autoimmune encephalitis, septic shock, drug intoxication, and thyroid crisis. An alternative syndrome should be considered if an expert physician, based on complete clinical manifestations and ancillary assessments, believes that an alternative condition is more likely than PHS (14).Systemic complications can develop as the akinesia progresses rapidly, including aspiration pneumonia due to

decreased level of consciousness and rigidity and acute renal failure due to rhabdomyolysis and dehydration. Deep vein thrombosis, pulmonary thromboembolism or disseminated intravascular coagulation may also occur (3).

Treatment of PHS depends above all on quick recognition. Early diagnosis is essential. In addition to searching for and correcting the underlying cause, levodopa administration is the basis of treatment (15). Patients must be hospitalized in an intensive care unit for careful monitoring of vital signs, control of metabolic disorders, and supportive measures such as antipyretic therapy, intravenous fluid infusion, electrolyte replacement, and prophylactic anticoagulant administration. The treatment is based on the use of levodopa and dopamine agonists. If antiparkinsonian medications are reduced or discontinued, they should be immediately readministered. The dopaminergic agonists ropinirole or pramipexole can be used. We routinely use levodopa by nasogastric tube administration if necessary (16).

Pulse corticosteroid therapy (1 g daily methyl-prednisolone until symptom improvement) may help, but there is limited evidence of its effectiveness (17).

A double-blind, placebo-controlled study of this disorder suggests that 1g of methylprednisolone per day shortens the time to recovery (18).

If PHS is caused by a reduced dose of dopaminergic drugs, the previous dosing regimen should be immediately reestablished and the oral dose of levodopa gradually increased. In patients with swallowing problems, a nasogastric tube can facilitate the administration of dopaminergic medications. If increasing the levodopa dose fails, apomorphine (intermittent injections or continuous infusion), transdermal rotigotine, or intravenous amantadine sulfate should be tried (13). The most refractory cases may be considered for titrated nasogastric levodopa-carbidopa gel infusion. Other treatments such as oral dantrolene sodium are recommended, but there is no strong evidence of efficacy (9). Patients should have routine checks of serum muscle enzymes, kidney function, and coagulation status. The prognosis can be favourable if adequate treatment is started early, although the majority of patients do not return to their previous functional level (9).

Suggested treatment protocol:

1. Treat the underlying triggers immediately.
2. Provide adequate supportive treatments including vital function support, administration of intravenous fluids, and antipyretic medications.
3. Antibiotic treatment is not necessary, but it should be applied if there is an infectious syndrome.
4. When the diagnosis of PHS is confirmed, dopaminergic drugs should be administered immediately, orally or by nasogastric tube.
5. If a delirious state occurs, it should be treated with intravenous benzodiazepine infusion (taken as needed).
6. If the patient develops multiple organ insufficiency, treatment in the intensive care unit and multidisciplinary treatment should be started immediately (14).

DYSKINESIA-HYPERPYREXIA SYNDROME

Acute hyperpyrexia is a common cause of emergency admission of patients with PD (16). When a patient with PD is referred for examination because of acute hyperpyrexia, an infectious condition is considered first (19, 20).

Dyskinesia-hyperpyrexia syndrome (DHS), an acute complication of PD, was first defined as an emergency in 2010 (21), and is often caused by abuse of antiparkinsonian drugs. In addition, there are a number of other factors that provoke DHS (14), a rare but life-threatening condition with the appearance of severe dyskinesias (dyskinetic status), leading to muscle wasting, rhabdomyolysis, hyperthermia, and confusion (22).

This complication shares some of the clinical characteristics of PHS, but differs in dyskinesias that dominate the clinical picture instead of rigidity. DHS, unlike PHS, should be treated by reducing the dose of dopaminergic drugs, especially dopamine agonists (6). If the correct diagnosis is not established, timely and optimal treatment cannot be given. This can lead to severe consequences for patients with these syndromes (22).

The results of a retrospective literature review revealed a total of 56 PHS and 13 DHS cases, and were more likely to occur in older patients with longer duration of PD. These two syndromes showed a different ratio of women to men, similar mortality and different recovery time. There are significant differences between PHS and DHS, including triggers (abrupt discontinuation of antiparkinsonian drugs vs. antiparkinsonian abuse), symptoms (worsened tremor and rigidity vs. persistent dyskinesia), and treatment (reintroduction vs. drug reduction) (14).

Although hyperthermia in DHS is thought to be the result of massive dyskinetic movements (21), it has also been attributed to dysfunction of central thermoregulation (23).

Many pathological processes in PD can lead to abnormal thermoregulation. Autonomic dysfunction, a common non-motor symptom of PD, can lead to abnormal sweating and cooling of the skin at high temperature (24, 25). The release of dopamine in the hypothalamus, which is impaired in patients with PD, can be increased when the temperature rises (26). Autonomic dysfunction and altered metal status are frequently observed in PHS and DHS patients. However, the pathological mechanisms by which PHS and DHS occur in PD remain unclear.

The two most common provoking factors for DHS are a change or misuse of antiparkinson medication. Excessive dopaminergic stimulation is destructive given that PD patients have a dopamine deficiency in the central nervous system. Other DHS triggers include infection, trauma, and gastroin-testinal disturbance. Clinical manifestations of DHS include hyperthermia, persistent dyskinesia, altered mental status, and, to a lesser extent, autonomic dysfunction, hyperhidrosis, dehydration, and rhabdomyolysis. Treatment of DHS includes supporting vital functions, tapering dopaminergic medications, intravenous fluid infusions, and antipyretics. Thirteen cases of DHS have been described, of which two patients died within days due to pneumonia and renal failure or acute pulmonary edema (27). The remaining eleven patients recovered in 2-10 days (14).

Both PHS and DHS tend to occur in older parkinsonian patients with longer disease duration. DHS mainly occurs in women, PHS is predominantly found in men. The recovery rate for both syndromes is around 80% despite faster recovery in DHS than in PHS patients. Apart from PHS and DHS, an elevated level of creatinine kinase can occur in rhabdomyolysis, myositis, myocardial infarction, muscular dystrophy, etc. The diagnosis of rhabdo-myolysis requires not only a high creatinine kinase level but also elevated myohemoglobin in the blood and urine. Therefore, elevated creatinine kinase alone does not mean rhabdomyolysis, which is present only in a small percentage of PHS and DHS cases. However, a major difference between the two syndromes is that worsening tremors and rigidity predominate in PHS, but persistent dyskinesia is found exclusively in DHS patients. PHS may be caused by abrupt discontinuation of antiparkin-sonian therapy, such as drug withdrawal or loss of DBS stimulator power, whereas DHS is likely caused by the abuse of antiparkinsonian drugs. Accordingly, the primary treatment for PHS is a reintroduction of antiparkinsonian drugs, and for DHS, anti-parkinsonian drug reduction. Other adjunctive treatments are basically similar. Therefore, a careful examination of the drug history and appropriate neurological examinations are essential for the rapid recognition and treatment of the syndrome (14).

Reported case fatality rates are 21.4% for PHS and 15.4% for DHS. Among the 14 cases of deceased patients, there is a total of 12 patients older than 50 years and 12 with more than nine years of PD duration. The causes of death and the number are: hyperthermic coma—three patients, respiratory failure—ten patients, renal failure—seven patients, heart failure—three patients, disseminated intravascular coagulation—two patients and septic shock—one patient. These data suggest that patients of an older age and longer duration of the disease may be more susceptible to the development of multisystem organ failure and a fatal outcome. People with multiple organ failure should start treatment in the intensive care unit and multidisciplinary treatment immediately to reduce the potential mortality (14).

ACUTE PSYCHOSIS IN PARKINSON'S DISEASE

Psychosis is relatively common among patients in the advanced stages of PD and is associated with a certain degree of cognitive dysfunction. Acute onset of psychosis is often provoked by the same agents used to treat motor symptoms of PD (levodopa, dopamine agonists, anticholinergics, amantadine, COMT and MAO-B inhibitors). In addition, other comorbidities, such as respiratory and urinary infections, metabolic or other neurological disorders, can be provocative factors for the development of acute psychosis in PD (28, 29).

Psychotic manifestations usually include visual hallucinations, persecutory delusions, confusion, and psychomotor agitation. Psychosis is perhaps the most common reason for PD patients to be hospitalized. The clinical picture of psychosis begins with visual illusions, misidentifications of real visual timuli. Over time, patients may develop hallucinations that are typically visual, often seeing unfamiliar people or animals. Later on, patients may lose the insight that their hallucinations are not real. Fixed illusions are one of the most severe forms of psychosis. Illusions or visual hallucinations with retained insight are rarely problematic, but progression to loss of insight or fixed delusions can quickly put patients at risk. Patients may react

to their visual hallucinations, feel threatened by them, and react in ways that threaten their own safety or the safety of others, leading to emergency room visits and subsequent hospitalization. It is important to recognize that not all patients follow this stereotypical pattern. Some patients may immediately develop psychosis or delusions without progressing through the other stages (15).

After treatment of potential comorbidities, a gradual withdrawal of potentially related medications should be initiated, starting with anticholinergics, then MAO-B inhibitors, dopamine agonists, amantadine, and COMT inhibitors. It is often necessary to introduce second-generation antipsychotics, such as clozapine or quetiapine. Other options include risperidone or olanzapine, with a significant risk of worsening the motor symptoms (6).

Vaughan and Goldman proposed a useful practical algorithm for treating psychosis in PD (30). Precipitating factors such as systemic disease, metabolic disorders, infection (especially urinary tract infection) or subdural hematoma due to falls should be ruled out first. Anticholinergics, amantadine, monoamine oxidase-B inhibitors, catechol-O-methyl-transferase inhibitors and dopamine agonists should be gradually withdrawn from therapy. Most patients with noninsightful hallucinations cannot tolerate such medications and will do better when treated with levodopa as the sole dopaminergic stimulant. Hallucinations without insight or fixed illusions usually require addition of quetiapine or clozapine. Typical neuroleptics and other atypical neuroleptics (risperidone, aripiprazole, ziprasidone) should be avoided, as these drugs may worsen parkinsonian symptoms (15).

DELIRIUM IN PARKINSON'S DISEASE

Delirium is an acute condition characterized by a fluctuating level of consciousness and orientation. Among hospitalized patients, the prevalence ranges between 10% and 20%. Risk factors for deirium include predisposing factors such as older age, male sex, dementia, visual and hearing impairment, alcoholism, hip fractures and metabolic disorders, while immediate precipitating factors include the use of certain drugs, occult infections, surgery, pain, physical limitations, and admission to intensive care (31). The general treatment of delirium is to identify and address the precipitating factors, while antipsychotics can be used to control the agitated patient (32). Parkinson's disease is an independent risk factor for delirium (33). Treatment of delirium in PD is a unique challenge. Antipsychotics are contraindicated for the treatment of delirium in PD because, in addition to exacerbating parkinsonism, they also present a risk of precipitation of neuroleptic malignant syndrome. Short-acting benzodiazepines may be used if control of an agitated patient is required. Among antipsychotics, quetiapine and clozapine are considered relatively safer for use in PD because of their effects on non-D2 receptors (34, 35).

An accurate and timely diagnosis of delirium is especially crucial because it often stems from a comorbidity that may require specific treatment (36). However, its symptoms (including inattention, disorganized thinking, fluctuating symptoms, visual hallucinations) often overlap with other cognitive disorders associated with PD, which may lead to misdiagnosis (37). The absence of a specific definition of delirium in PD or a reliable complementary test further complicates the establishment of the diagnosis. During the progression of PD, concomitant cognitive impairment becomes increasingly pronounced, which is a risk factor for the development of delirium (38, 39).

Despite several changes in criteria over the past few decades, the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines delirium as an acute disturbance of attention, awareness, and cognitive performance with fluctuating features over time (40). Two subtypes of delirium are recognized: hyperactive delirium with agitation represents 25% of cases, while hypoactive delirium with reduced level of consciousness represents 75% of cases (41).

Delirium is conceptualized as a cerebral dysfunction caused by various underlying predisposing factors (aging, cognitive impairment, sensory impairment) and acute triggering factors (drugs, electrolyte and glucose metabolism disorders, uremia, surgery) (42). The presence of multiple predisposing factors reduces the number of triggering factors required to cause delirium. The exact molecular pathways that cause different triggers to converge into a similar syndrome are not yet fully understood. Three main mechanisms are believed to be involved in its pathophysiology: 1. Normal brain functioning relies on significant amounts of energy, and brain metabolic insufficiency—either due to lack of oxygen or glucose—can lead to delirium in various scenarios. 2. Inflammation is a known trigger of delirium and several circulating cytokines

found in patients with delirium, which can have significant effects on the nervous system. 3. Several neurotransmitter deficits have been identified including acetylcholine, dopamine, glutamate, GABA, histamine, and noradrenaline, but none (not even acetylcholine, which is believed to have the strongest implication) has been consistently associated with every case (43). This suggests that a wide range of underlying features and triggers can cause a similar syndrome, although certain mechanisms such as acetylcholine deficiency may be more commonly involved. Ultimately, these mechanisms lead to brain network dysfunction in which several structures are implicated in delirium symptoms, including the hippocampus, thalamus, basal forebrain, and cerebellum as their interconnections (44).

The diagnosis of delirium is clinical, and the Confusion Assessment Method (CAM) is the most widely used and reliable screening tool in clinical practice (45). Once the diagnosis is confirmed, additional diagnostic tests such as laboratory testing, brain imaging, and electroencephalography (EEG) can be helpful in uncovering potential treatable triggers. Traditionally, delirium has been considered a transient condition that resolves once the factors causing it are resolved. However, a growing body of evidence indicates that symptoms can last for months in one-third of patients (46, 47).

PD is associated with an increased risk of developing delirium; however, studies in this area vary considerably in the definition of delirium, in the methods used to diagnose delirium and PD, and in the characteristics of the included patients (48). A recent prospective study, using a standardized diagnostic algorithm based on the DSM-5, estimated the prevalence of delirium of 31% among hospitalized PD patients (49). The susceptibility of parkinsonian patients to develop delirium is thought to stem from the convergence of several overlapping mechanisms between these two conditions: a systemic inflammatory response, neurotransmitter imbalance (including disturbances in the cholinergic system), and alpha-synuclein pathology, which is independently associated with postoperative delirium in cases of gastrectomy (50). Delirium is correlated with cognitive impairment in PD, which increases the likelihood of delirium, emphasizing its importance as a key interacting factor (51).

Clinical features of cognitive impairment in PD and delirium show similarities, including attentional dysfunction, cognitive fluctuations, hallucinations, sleep disturbances, and excessive daytime sleepiness, commonly found in both syndromes (48). Of note, assessment tools to detect delirium, such as the CAM, have not been validated for use in PD, which may lead to misdiagnosis of delirium with long-standing PD symptoms (39).

Delirium is a common and serious complication after DBS, which improves motor complications in patients with advanced PD. Advanced age, cognitive decline, and severity of PD may be risk factors for delirium. The presence of delirium may also affect cognitive function and prognosis. Neurotransmitters such as acetylcholine and dopamine may be involved in the occurrence of delirium. Furthermore, inflammation, effects of microlesion of local nuclei, and brain atrophy may also play a role in the development of delirium after DBS (52).

During the evolution of the clinical picture in PB, the acute appearance of urgent conditions is possible, among which the syndrome of parkinsonism—hyperpyrexia, dyskinesia—hyperpyrexia syndrome, acute psychotic state and delirium have been described. The etiopathogenesis of these acute conditions differs, so the diagnostic and therapeutic approaches are different. Early and adequate recognition of these syndromes is very important for patients' survival and recovery. Lifesustaining measures are mandatory in patients affected by these emergencies and hospitalization in intensive care units is necessary. Survival and recovery of patients depend on appropriate therapeutic procedures that differ in these emergency conditions with the necessary team cooperation of medical professionals.

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Competing Interest

The authors declare no relevant conflicts of interest.

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