Single Dose Does Matter! An Interesting Case of Parkinsons Hyperpyrexia Syndrome

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Keywords: Parkinsons-hyperpyrexia syndrome; Neuroleptic malignant syndrome; Dysautonomia; Rigidity; Encephalopathy

Introduction

The Parkinsonism-hyperpyrexia syndrome (PHS) is a rare yet potentially fatal condition occurring in patients with parkinsons disease (PD), following reduction or cessation of anti-parkinson medications mimicking neuroleptic malignant syndrome (NMS) with rigidity, pyrexia, autonomic instability and encephalopathy with elevated creatine phosphokinase (CPK) [1-5]. One should not reduce anti PD drugs suddenly as PHS can lead to complications like acute renal failure (ARF) due to rhabdomyolysis, disseminated intravascular coagulation (DIC) and aspiration pneumonia [6]. PHS should be considered in any PD patient who has acute deterioration in symptoms [1]. Replacement of dopaminergic drugs with supportive care is the mainstay of treatment. As it is a fatal condition, it has to be recognized early and prompt treatment should be initiated [1,4].

Case Report

A 70 year old male, known case of diabetes mellitus (on insulin), hypertension and PD presented to us with history sudden onset of fever, altered sensorium and increased parkinsonian features since a day. He was diagnosed to have PD 5 years back for which he was on twice daily syndopa 250 mg and selegiline 5 mg, with which his symptoms of bradykinesia and rigidity were well under control. On examination patient was confused, febrile with profuse sweating and had rigidity in all the four limbs. He had tachycardia and fluctuation in blood pressure to suggest autonomic dysfunction. His speech was slurred, low volume and incomprehensible. There was no history of cough, expectoration, vomiting, diarrhea or burning micturition. Since the patient was taking anti-PD medications by his own self, his wife had reduced even when patients are under continuous STN stimulation might prevent PHS, fatal PHS can occur when the PD medications are reduced even when patients are under continuous STN stimulation. Though STN-DBS might prevent PHS, fatal PHS can occur when the PD medications are reduced even when patients are under continuous STN stimulation [2].

Discussion

PHS was first described in 1981 and was called as dopa-withdrawal malignant syndrome and acute dopamine depletion syndrome. The pathophysiology of PHS is similar to that of NMS [4,7]. PHS apart from dopamine withdrawal can get precipitated by intercurrent infections and dehydration similar to NMS [8]. Commonly, sudden cessation or abrupt reduction of dopaminergic medication causes PHS, rarely cases of PHS have been reported after STN-DBS (subthalamic nucleus- Deep brain stimulation). Without any further delay, his anti-PD medications were re-initiated at the dose of Syndopa Plus (125 mg) q.i.d, same as total dose previously but in increased frequency and in divided doses along with selegline 5 mg b.i.d.

Within 24 hours patient showed dramatic improvement, he became afebrile, his rigidity reduced and sensorium improved. He was well oriented by the 4th day narrated his own history that he had missed one night dose of syndopa 250 mg. His CPK normalized on day 5.
The clinical presentation of PHS includes hyperpyrexia, rigidity, altered consciousness, dysautonomia, leukocytosis, and elevated CPK [1,4]. Although PHS and NMS are phenotypically nearly identical, PHS is distinct in that it is triggered by removal or effective loss of dopaminergic therapy in a PD patient [1,2,4]. The mainstay of PHS treatment is rapid replacement of effective anti-PD therapy [4]. The pathophysiology underlying PHS is generally accepted to be a hypodopaminergic state, and its clinical features can be explained as sequelae of central dopamine depletion. Mortality is approximately 4% if treated and 16% if untreated [9,10]. Among survivors, 30% have worsening of symptoms of parkinsonism and never return to their baseline [11].

Mild cases may be mislabelled as sepsis or worsening of parkinsonism.

A close differential diagnosis of PHS is NMS [3,4] which is recognized as a hypodopaminergic state characterized by rigidity, hyperthermia, encephalopathy, autonomic dysfunction and elevated CPK levels occurring usually due to exposure to antipsychotic medications particularly butyrophenones and phenothiazines [12-14]. Though dopamine receptor blockade has been postulated as the mechanism for NMS [15], a neuroimmunologic hypothesis has also been proposed [16,17].

Although withdrawal of levodopa is still the most common cause of PHS, withdrawal of other anti-PD agents including amantadine, dopamine agonists, and catechol-O-methyltransferase inhibitors (COMT) has also been associated with PHS [18,19]. Patients with PD are susceptible to PHS due to a dopamine-depleted state, but PHS has also been reported in patients with atypical parkinsonism and Parkinson’s plus syndromes like multiple system atrophy and progressive supranuclear palsy [20]. Even metabolic factors like hypernatraemia can precipitate PHS [21]. Our patient had idiopathic Parkinson’s disease without any atypical features and was not on other medications like amantadine or COMT inhibitors but was on MAO inhibitor seligiline.

Though sudden cessation of levodopa has been attributed to the relative dopamine deficiency state leading to PHS, a NMS mimic, it is not definite that how abrupt the stoppage should be or how many doses need to be missed to cause such symptoms. Our case is an eye opener to show that missing even a single dose of levodopa can induce PHS, a potentially preventable and treatable condition which if untreated can mimic sepsis and is fatal.

To conclude we like to mention that PD patient should not miss even a single dose or delay their usual scheduled dose of levodopa. Family members should be made aware of this possible condition and should be actively involved in maintaining the patient’s compliance as proper compliance alone can prevent this fatal condition. Clinicians should be aware of this condition and keep a high index of suspicion and take proper history of any missed dose. But as PHS and NMS can get precipitated by sepsis and dehydration, evaluation for sepsis should always be completed.

References