Parkinsonism-hyperpyrexia syndrome

Broadening our differential diagnosis in the ICU

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A 74-year-old woman with Parkinson disease was admitted to the hospital for evaluation of dizziness and falls. She had undergone bilateral subthalamic nucleus (STN) implantation of a deep brain stimulator (DBS) 4 years prior to presentation (Activa PC Neurostimulator, model 37601, Medtronic, Minneapolis, MN). Symptoms resulting from Parkinson disease including rigidity and tremor were reasonably controlled with the bilateral STN DBS in addition to carbidopa-levodopa 25–100 mg every 2 hours while awake and 25–100 mg extended release at bedtime. On admission, her vital signs were normal. She was alert and oriented and in no distress, with diffuse moderate rigidity. The next day, on routine nursing assessment, she was found to have tachypnea, tachycardia, and confusion. These assessments were performed every 6 hours; hence onset of her clinical decompensation occurred somewhere between 28 and 34 hours after admission.

The patient was transferred to the medical intensive care unit where initial evaluation was notable for pyrexia (40°C), tachypnea, tachycardia, hypertension, diaphoresis, disorientation, and rigidity with tremors and dystonia (see the video).

Serum creatine kinase level was 2,845 U/L. Aggressive hydration and cooling were initiated. The patient was treated with 1 mg/kg of IV dantrolene, a skeletal muscle relaxant that decouples excitation from contraction. Within 20 minutes of dantrolene administration, her vital signs began to normalize (figure). Meanwhile, a medication review determined that during hospitalization, she had been receiving the incorrect formulation of carbidopa-levodopa, resulting in the administration of 1,250 mg of levodopa instead of the 500 mg she would have received had she been prescribed her home regimen.

Although this error resulted in the administration of excessive carbidopa-levodopa, the symptoms were more consistent with parkinsonism-hyperpyrexia syndrome (PHS) rather than of dopamine excess. The patient had not received any dopamine antagonists. Her DBS was therefore emergently interrogated and was found to be off. No other device abnormalities were noted during the interrogation. It was quickly reactivated to the previous settings. This resulted in the immediate onset of dyskinesias which resolved over a period of hours. Her home dose of carbidopa-levodopa was reinstituted and over 24 hours, all symptoms resolved.

Video

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Figure Heart rate, blood pressure, and temperature plotted over time

Time zero is the time of transfer to the intensive care unit. The timing of dantrolene administration and commencement of deep brain stimulation (DBS) are shown. BP = blood pressure.

No precipitants of the device's inactivation could be identified. Because of the unexplained device malfunction, the implantable pulse generator of the DBS unit was replaced. She was discharged to her nursing home the following day.

DISCUSSION

PHS is one of a group of acute dysautonomias that share common features: autonomic instability, pyrexia, and rigidity. Others include the neuroleptic malignant syndrome (NMS), serotonin syndrome, malignant hyperthermia, and malignant catatonia. These disorders are only distinguishable by the implicated drugs or setting in which they occur.^{1,2} Whereas NMS is triggered by neuroleptic use, PHS occurs most commonly in the setting of withdrawal or rapid titration of L-dopa or a dopamine agonist. Cases have been reported in parkinsonian patients with co-administration of a neuroleptic agent, dehydration, exposure to excessively hot weather, or discontinuation of DBS.³⁻⁵ A mortality of up to 4% has been reported, with an additional one-third of patients experiencing permanent sequelae.⁶ Symptoms typically commence between 18 hours and 7 days following the trigger.⁷ The classical symptoms of rigidity, tremor, and progression to an immobile state followed by the development of pyrexia, confusion, and autonomic dysfunction were manifested in this patient's presentation. Acute kidney injury due to rhabdomyolysis, a common complication of PHS, was likely avoided by the prompt administration of dantrolene, aggressive hydration, and restoration of dopamine balance. This allowed time to identify and reverse the trigger (DBS malfunction). Resuming DBS produced dyskinesias because the patient had been receiving 2.5 times her normal dose of levodopa, producing a dopamine excess syndrome.

When a patient manifests even 2 features of the triad of pyrexia, dysautonomia, and rigidity, NMS and serotonin syndrome are at the top of the differential diagnosis. Consideration should be given to PHS in patients with known parkinsonism of any cause. As the emerging

Table Steps to treating parkinsonism-hyperpyrexia syndrome

Step 1: Identify the syndrome
Severe generalized “lead-pipe” rigidity; tremor or dyskinesias like dystonia or opisthotonus may also be present
Presence of hyperpyrexia
Elevations in serum creatine kinase, sometimes with a mild leukocytosis
Autonomic dysfunction (tachypnea, tachycardia, elevated or labile blood pressure, diaphoresis)
Altered level of consciousness
Presence of predisposing factor (use of dopamine antagonists, recent changes in L-dopa administration, possible inactivation of deep brain stimulation [DBS], intercurrent infection, anorexia) in a patient with known Parkinson disease ⁶
Step 2: Identify and remove the precipitant
Identify and discontinue offending drugs (ie, dopamine antagonists)
If treatment with L-dopa has been interrupted, resume treatment
If DBS is present, interrogate device to ensure it is functioning
Step 3: Implement treatment
Rehydration: titrate IV fluids to maintain a urine output of 50–100 mL/hour ¹
Control hyperthermia with cooling blankets or ice packs at groin and axilla
Monitor and stabilize vital signs with endotracheal intubation and nasogastric tube placement to avoid aspiration
Consider use of IV dantrolene at 1–2.5 mg/kg; this can be repeated to a maximum of 10 mg/kg/day
Other medications such as bromocriptine or amantadine may be considered ^{1,6}

applications of DBS continue to expand, awareness of potential complications become increasingly important. While the incidence of hardware malfunction is probably low, clinicians should consider DBS device malfunction in the differential of a patient with underlying Parkinson disease presenting with pyrexia, dysautonomia, or rigidity. The risk of PHS in the hospital is likely higher than in the outpatient setting given that antiparkinson medications are often omitted, purposefully discontinued, or prescribed incorrectly.⁸

In suspected PHS or NMS, immediate treatment with dantrolene, antipyretics, and cooling should be considered to avoid significant morbidity and mortality, while attempting to identify the triggering event (table). In such situations, interrogation of the DBS and careful medication review is of paramount importance.

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