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Fever and Irritability in a 15-year-old Boy With Autism

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CASE PRESENTATION

A 15-year-old boy with a history of autism presents with fever and irritability. He is hospitalized and ultimately diagnosed with a right-sided pneumonia due to *Mycoplasma pneumoniae*. He is intubated in the pediatric intensive care unit for respiratory failure. Throughout his stay, he requires multiple sedating medications, including fentanyl, midazolam, dexmedetomidine, lorazepam, and haloperidol. On day 14 of admission, he is extubated to bilevel positive airway pressure but continues to require sedating medications to improve compliance and maintain his safety.

On day 15 of admission, following medication for escalating agitation, he suddenly becomes unresponsive. Physical examination reveals diaphoresis. His vital signs include a temperature of 38.9°C (102°F), heart rate of 180 beats/min, respiration rate of 30 breaths/min, blood pressure of 176/112 mm Hg, and oxygen saturation of 50%. He displays tonic-clonic seizure activity and subsequently becomes very rigid throughout his body. An emergent venous blood gas reveals: pH 7.18, carbon dioxide 51 mEq/L (51 mmol/L), oxygen 37 mEq/L (37 mmol/L), bicarbonate 16 mEq/L (16 mmol/L), and lactate 16.7 mg/dL (1.9 mmol/L). His airway is secured with jaw thrust and repositioning. He is placed on a non-rebreather and his oxygen saturations improve to normal. He is given 2 mg of lorazepam for the seizure activity followed by a bolus of fentanyl for possible narcotic withdrawal. He remains hemodynamically stable, although still exhibiting tachycardia, hypertension, and hyperthermia.

After consideration of the differential diagnosis for his signs and symptoms, he eventually is given a medication that gradually resolves his rigidity and mental status abnormalities and improves his vital signs.

CASE DISCUSSION

The medication that resolved this patient's symptoms was bromocriptine, which was administered for suspected neuroleptic malignant syndrome (NMS) triggered by haloperidol. Clinicians surmised that the combination of antipsychotic and sedating medications that the patient was receiving led to the development of NMS. The exact cause of this life-threatening neurologic disorder is unknown, but the primary theory asserts that symptoms are related to dopamine receptor blockade, which leads to Parkinsonian-type rigidity and

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tremor. Central dopaminergic blockade in the hypothalamus causes symptoms of hyperthermia and autonomic instability. Familial clusters of NMS have been documented, which suggests a genetic predisposition. The possible link may lie in overexpression of a specific allele of the dopamine D2 receptor gene.

The Condition

NMS is associated with the use of antipsychotic or antiemetic medications. Although the incidence is low, mortality can be high if the condition is not recognized. Patients commonly present with a tetrad of fever, rigidity, altered mental status, and autonomic instability. Without immediate recognition of the syndrome and prompt discontinuation of the offending drug, mental status changes can rapidly progress from drowsiness and confusion to coma and eventually death. Among the most common causative agents are high-potency antipsychotics such as haloperidol and fluphenazine. Low-potency antipsychotics, including chlorpromazine, and several atypical antipsychotics, such as clozapine, risperidone, and olanzapine, have been implicated as well. Clinicians should also be aware of the potential risk with antiemetic medications such as metoclopramide and promethazine.

Associated laboratory findings may include elevated creatinine phosphokinase (CK), lactate dehydrogenase, alkaline phosphatase, and liver enzymes as well as leukocytosis (with or without a left shift). Acute renal failure may result when rhabdomyolysis is present. Low serum iron is a relatively sensitive but nonspecific finding in patients with NMS.

Differential Diagnosis

The differential diagnosis for NMS is broad and centers primarily on the possible adverse effects associated with many inciting medications. One possibility is serotonin syndrome (SS), which is commonly linked to selective serotonin reuptake inhibitor medications. Some unique presenting symptoms of SS that are not usually seen in NMS are hyperreflexia, myoclonus, and ataxia. Another possible diagnosis is malignant hyperthermia, which is most commonly caused by succinylcholine and halogenated inhalational anesthetic agents. The presenting symptoms can closely mimic those of NMS. Also on the differential diagnosis list is central anticholinergic syndrome, which commonly presents with encephalopathy and hyperthermia. It may differ from NMS with the absence of rigidity, diaphoresis, or elevated CK.

Another differential diagnosis consideration is the effects of acute intoxication with recreational drugs in a patient presenting to the emergency department. A particular substance of abuse that can mimic NMS is 3,4-methylenedioxy-methamphetamine (MDMA, aka Ecstasy), which is a potent stimulant that can cause delirium, hyperthermia, and rhabdomyolysis. Other potential mimicking conditions include central nervous system infection, status epilepticus, thyrotoxicosis, pheochromocytoma, and withdrawal states (eg, alcohol or benzodiazepine withdrawal).

Diagnosis

The diagnosis of NMS is typically one of exclusion in the appropriate clinical setting. Brain magnetic resonance imaging or computed tomography scan may be considered to rule out

infectious or structural causes of the symptoms. These tests typically yield normal results in NMS. Lumbar puncture may also be considered when infection is suspected or electroencephalography may be obtained to rule out status epilepticus. Results of both studies are typically within normal limits in patients with NMS.

Management

Initial management of NMS includes stabilization of the patient by addressing the ABCs of emergency medical care. The causative agent should be simultaneously discontinued during these first steps of care. Once the patient is stable, treatment should focus on supportive measures, including high-volume hydration, electrolyte replacement, and correction of metabolic disturbances. Antihypertensive medications may be needed to lower the patient's blood pressure and cooling blankets are sometimes employed to correct the hyperthermia.

Two specific medications that have a role in the treatment of severe NMS are dantrolene and bromocriptine. Dantrolene acts as a skeletal muscle relaxant, which reduces rigidity and heat production. It is usually avoided in the setting of elevated liver function tests. Bromocriptine is a dopamine agonist that can be initiated upon symptom onset and is usually continued for approximately 10 days after NMS is controlled. A slow taper of both dantrolene and bromocriptine is usually required to prevent relapse.

Clinicians must be familiar with the signs and symptoms of NMS so that it is included in the differential diagnosis of acute mental status change in a patient receiving neuroleptic or antiemetic medications. Timely recognition of NMS is important in initiating appropriate interventions and withdrawing the triggering medication to ensure the most favorable outcome. When diagnosed and treated aggressively, patients usually recover completely within days to weeks. Possible adverse outcomes that can occur in the setting of delayed or inadequate management include disseminated intravascular coagulation, cardiac arrhythmia, cardiopulmonary arrest, or renal failure.

The patient in this case made a full recovery without any long-lasting disability from the syndrome. In the future, antipsychotic and antiemetic medications should be avoided in this patient because NMS can recur.

Lessons for the Clinician

- Although NMS is a rare condition, clinicians may encounter the syndrome in children treated with antipsychotic or antiemetic medications.
- Due to its potentially life-threatening course, clinicians must recognize the NMS tetrad of fever, rigidity, altered mental status, and autonomic instability so as to initiate appropriate treatment.
- The key steps in the management of NMS are initial stabilization of the patient, institution of supportive measures, and administration of dantrolene or bromocriptine for severe cases.

Suggested Readings

1. Berman BD. Neuroleptic malignant syndrome: a review for neurohospitalists. *Neurohospitalist*. 2011; 1(1):41–47. [PubMed: 23983836]
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