Clinical Case of the Month

A 48-Year-Old Man With Fever and Abdominal Pain of One Day Duration

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A 48-year-old man residing in a mental health department inpatient program with a history of schizoaffective disorder presented to the emergency department with a chief complaint of fever and intense abdominal pain for one day. The patient stated he initially fell in the shower and afterwards experienced back pain. He was transferred to an acute care unit within the facility for further evaluation. The facility physician noted that the patient had a mild temperature elevation and abdominal rigidity on exam. At that time, he was given two doses of benztropine intramuscularly, and transferred to our hospital for further evaluation. The patient exhibited fever, diffuse abdominal pain and a nonproductive cough, but denied chills, dysuria, urinary frequency, hematuria, weakness, diarrhea, melena or hematochezia. He did have a one-week history of constipation for which he was given sodium phosphate enemas, magnesium citrate and docusate sodium, eventually resulting in a bowel movement. He also complained of new onset dysphagia. There were no recent changes to his medications, which included clonazepam, divalproex sodium extended release, olanzapine and risperidone. He denied use of tobacco, alcohol or illicit drugs.

Upon presentation, his vital signs included a rectal temperature of 103.1° F, heart rate of 108 beats/min, blood pressure of 134/99 mmHg, respiratory rate of 43 breaths per minute and oxygen saturation of 100% on ambient air. He weighed 84.5 kg and his body mass index was 27.5. He appeared distressed and tremulous. He was alert and oriented to person, place and time, but required frequent re-direction and whispered to answer questions. His pupils were equal, round and reactive to light. There was no thyromegaly. He was tachycardic. Lung exam revealed decreased breath sounds at the bases, but no crackles or wheezes. His abdominal muscles were visibly contracting. Decreased bowel sounds were noted, but no abdominal rebound or tenderness to palpation was appreciated. He had increased muscle tone and was hyperreflexic throughout.

Laboratory studies revealed a white blood cell count of 10,800/µL (4,500-11,000/µL) with a bandemia of 19% and thrombocytopenia of 112,000/µL (130,000-400,000/µL). His serum creatine kinase level was 103,275 U/L (<230 U/L). He also had transaminitis with serum AST level of 1,660 U/L (<45 U/L) and ALT of 356 U/L (<46 U/L). Of note, his urine and blood toxicology screens, blood and urine cultures, HIV test and acute hepatitis panel were all negative. A CT of the head did not reveal any abnormalities and a CT of the abdomen and pelvis showed a mildly dilated transverse colon.

He was admitted to the intensive care unit for management of presumed neuroleptic malignant syndrome. All of his medications were stopped. Cooling blankets, fans, and ice packs were used to manage his hyperthermia. He was placed on telemetry and his vital signs were monitored closely. He received aggressive intravenous fluid supplementation. He received bromocriptine and valium as needed for agitation and received one dose of dantrolene. Due to his history of schizoaffective disorder, he was restarted on divalproex sodium. His bandemia, renal failure, transaminitis, rhabdomyolysis and hyperthermia eventually resolved. His muscle rigidity improved immensely. He was eventually discharged to a rehabilitation facility where he received tapering doses of bromocriptine.

DISCUSSION

Epidemiology and Risk Factors

Neuroleptic malignant syndrome (NMS) in association with haloperidol was first described by Delay et al. in 1960 in a patient who presented with symptoms of pallor and hyperthermia as well as respiratory and psychomotor abnormalities.[1,2] This syndrome is classically associated with the use of high potency first generation antipsychotics such as fluphenazine and haloperidol. However cases have also been described with newer atypical agents[3], as well as other classes of anti-dopaminergic drugs such as metoclopramide and promethazine. A similar syndrome has also been reported in the setting of dopamine agonist withdrawal in patients with Parkinson's disease[4] and GABA agonist withdrawal from intrathecal baclofen cessation[5]. The incidence in patients receiving neuroleptics is 0.02-2.44%[3], a range of frequencies that may be due to population differences, diagnostic criteria and clinical settings.

Due to the low incidence of NMS, there is no randomized-controlled trial assessing management of this syndrome. Most articles are case reports or case-controlled studies, and the numbers of patients included are small. In the past, NMS was generally associated with middle-aged men; however its occurrence spans all ages[6] and it is unclear whether there truly is a gender bias.[2] In 2012, Nielsen et al. published a longitudinal case-control study that included a total of 83 patients.[7] The mean age of onset for men with NMS was found to be 47.3 years and for women it was 55.8 years; however the standard deviations were 15.1 and 17, respectively. Fifty-two percent of the patients were men and forty-eight percent were women with an increased mortality reported in women. The study

found an increased risk of NMS in patients receiving high- and mid-potency first generation antipsychotics, atypical antipsychotics and depot administration of antipsychotics, as well as lithium and benzodiazepine use in the previous three months prior to admission. In addition, there was an increased incidence of NMS in patients who were prescribed antipsychotic polypharmacy, which was defined as picking up two or more prescriptions for different antipsychotics within three months of diagnosis.[7] There are also possible associations between TaqI polymorphisms for dopamine D2 receptors and the tendency to develop NMS. A retrospective study of 15 NMS patients and 138 schizophrenic patients without NMS reported a higher frequency of the A1 allele in the TaqI gene in patients who developed NMS than in the control group. This allele is associated with a lower density of D2 receptors and dopaminergic activity in the striatum and caudate nucleus.[8]

Pathophysiology

Various mechanisms have been proposed to explain the pathogenesis of NMS. Since extrapyramidal symptoms are present in NMS and all antipsychotics are associated with some degree of D2 receptor inhibition, it is speculated that NMS is secondary to dopamine receptor antagonism. NMS has even been reported with clozapine use, which is a low affinity D_2 receptor antagonist.[9] Sympathoadrenal hyperactivity has also been proposed to contribute to the autonomic dysfunction seen in NMS.[10] In one study, urinary catecholamines and metabolites were found to be frequently, but not consistently, elevated in patients with NMS.[11] Another hypothesis involves immunologic processes causing an acute phase response resulting in leukocytosis, thrombocytosis, elevated CRP and decreased serum iron levels.[12] None of these theories alone is sufficient to explain all aspects of the syndrome. Further studies are needed in order to better understand the pathophysiology of NMS.

DIAGNOSIS

The diagnosis of NMS is largely a clinical one based on presentation and laboratory findings. It is also a diagnosis of exclusion, so it is imperative to rule out other diagnoses that may present similarly. One of the earliest documented criteria formulated were known as Levenson's Criteria.[13] This diagnostic approach requires three major or two major and four minor criteria to be met in order to establish the diagnosis. The three major criteria are fever, rigidity and elevated creatinine phosphokinase (CPK) levels. The minor criteria are: tachycardia, abnormal blood pressure, altered consciousness, diaphoresis, leukocytosis and tachypnea (Table 1).

In 1994, the Diagnostic and Statistical Manual of Mental Disorders (DSM) published by the American Psychiatric Association included its own criteria for the diagnosis of NMS. The DSM-IV-text revision requires both severe muscle rigidity and elevated temperature to be present after recent administration of antipsychotics as well as two associated signs, symptoms or lab findings not better accounted for by a substance-induced, neurological or general medical condition. Signs and symp-

Table 1. Levenson's Criteria for NMS: Must meet 3 major or 2 major and 4 minor

Major	Fever Rigidity Elevated CPK
Minor	Tachycardia Abnormal blood pressure Altered consciousness Diaphoresis Leukocytosis Tachypnea

Levenson's Criteria for NMS. Adapted from Levenson J. Neuroleptic malignant syndrome. Am J Psychiatry 1985;142:1137.

Table 2. DSM-IV Criteria for NMS

Recent administration of antipsychotics, elevated temperature, severe muscle rigidity and 2 of the following:

- Diaphoresis
- Dysphagia
- Tremor
- Incontinence
- Changes in level of consciousness (confusion, coma, or mutism)
- Tachycardia
- Increased or labile blood pressure
- Leukocytosis
- Laboratory evidence of muscle injury

Levenson's Criteria for NMS. Adapted from Levenson J. Neuroleptic malignant syndrome. Am J Psychiatry 1985;142:1137.

Table 3. Delphi method for the diagnosis of NMS

- Exposure to dopamine antagonist or dopamine agonist withdrawal within the past 72 hours
- Hyperthermia (≥100.4°F or ≥38°C orally on at least 2 occasions)
- Rigidity
- Altered Mental Status (reduced or fluctuating level of consciousness)
- CPK elevation (≥ 4x the upper limit of normal)
- Sympathetic nervous system liability, two or more of the following:
  - BP elevation (systolic or diastolic ≥25 percent above baseline)
  - Blood pressure fluctuation (≥25mm Hg systolic change within 24 hours)
  - Diaphoresis
  - Urinary Incontinence
- Hypermetabolism
  - Heart rate ≥25 percent above baseline AND respiratory rate ≥50 percent above baseline
- Negative workup for infectious, toxic, metabolic, or neurologic causes

Delphi method for the diagnosis of NMS. Adapted from Gurrera RJ, Caroff SN, Cohen A, Caroll BT, DeRoos F, Francis A. An international consensus study of neuroleptic malignant syndrome diagnostic criteria using the Delphi method. Journal of Clinical Psychiatry. 2011;72(9): 1222-1228.

toms include: diaphoresis, dysphagia, tremor, incontinence, changes in level of consciousness, tachycardia, increased or labile blood pressure, leukocytosis and lab evidence of muscle injury such as increased CPK levels (Table 2).[14] The 2013 DSM-5 no longer lists specific criteria but discusses diagnostic features in a broader fashion.

The latest proposed diagnostic criteria were developed in 2011. A seventeen member international expert panel including psychiatrists, neurologists, anesthesiologists and emergency medicine physicians developed the first consensus based criteria for the diagnosis of NMS using the Delphi method.[15] The criteria include: exposure to a dopamine antagonist or dopamine agonist withdrawal within the past 72 hours; hyperthermia (defined as ≥100.4° F or ≥38° C orally on at least 2 occasions); rigidity; mental status alternation (reduced or fluctuating level of consciousness); increased CPK (four times the upper limits of normal); hypermetabolism (heart rate ≥25 percent above baseline); increased respiratory rate (≥50 percent from baseline); and sympathetic nervous system lability. Sympathetic lability is defined as the presence of ≥3 of the following features: increased blood pressure ≥25 percent above baseline, blood pressure fluctuation ≥25 mm Hg systolic change within 24 hours, diaphoresis, and urinary incontinence. As there are several diagnoses that mimic NMS, a negative workup for infectious, toxic, metabolic and neurologic causes is required to make the diagnosis (Table 3).

TREATMENT

Supportive measures focus on preventing further complications and maintaining organ function with particular attention to the respiratory and cardiovascular systems. Fluid resuscitation and regulation of electrolyte abnormalities are basic treatment objectives. Moreover, treatment options to reduce the degree and duration of hyperthermia are essential.

Benzodiazepines

Benzodiazepines, administered orally or parenterally, may lessen symptoms and aid in recovery. Diazepam has been suggested to be efficacious at higher doses with periodic IV infusions or a continuous infusion based on a review of two case reports.[16, 17] In these two case reports, the patient had no response or equivocal responses to oral diazepam. However, a patient with NMS was successfully treated as an outpatient with high doses of daily oral diazepam.[18] Yaccub, et al. examined three cases of NMS that were treated with only supportive care and lorazepam; both fever and muscular rigidity improved and resolved in 24–72 hours.[19] A trial of only lorazepam or diazepam may be attempted if benefits outweigh the risks.

Dopamine Agonists

One proposed mechanism of NMS is a low dopaminergic state. Therefore, bromocriptine, a dopamine agonist, has been proposed as a treatment option. Bromocriptine is typically started at 2.5 mg every six to eight hours and titrated up to 40 mg per day. Amantadine, another type of dopamine agonist with anticholinergic effects, is initially dosed at 100 mg with titration to maximum dose of 200 mg every 12 hours. Sakkas et al. performed a case controlled statistical analysis when dopamine agonists (bromocriptine, DOPA, amantadine) were used alone. There was 9 percent reduction in death when dopamine agonists were used alone versus 9.2 percent reduction in death when dopamine agonists were used with dantrolene [20]. Side effects of dopamine agonists may include exacerbation of underlying psychosis, hypotension, vomiting, and aspiration especially in patients with reduced level of consciousness. Bromocriptine and amantadine each decreased mortality rates in patients with NMS relative to the patients who only received supportive care.[20]

Dantrolene

Due to its efficacy in anesthetic-induced malignant hyperthermia, the muscle relaxant dantrolene has been used in the treatment of NMS. Dosing of intravenous dantrolene in the treatment of NMS is 1–2.5 mg/kg body weight and can be repeated to a maximum dose of 10 mg/kg/day. Side effects may include impairment of respiratory or hepatic function. Dantrolene can be combined with benzodiazepines or dopamine agonists, but it should not be co-administered with calcium channel blockers, as cardiovascular collapse can occur.[21]

The majority of reports suggest dantrolene hastens recovery of NMS. [20, 22, 23] However, other reports refute the use of dantrolene in the treatment of NMS. One analysis showed the time to remission was prolonged when dantrolene was combined with bromocriptine, amantadine, or electroconvulsive therapy; the mortality of dantrolene monotherapy was higher[24]. Moreover, this analysis showed the time to remission was not significantly shorter in the dantrolene monotherapy group compared to the group receiving supportive therapy. The authors stated that there were limitations to this study including that patients who received dantrolene monotherapy were more severely ill than patients treated with other medications.

A prospective study of twenty patients with NMS by Rosebush et al. concluded that patients treated with dantrolene and/or bromocriptine had evidence of NMS for a mean of 9.9 days compared to 6.8 days in patients receiving supportive care only.[25]

Electroconvulsive Therapy

Hermesh et al. were the first to describe the successful treatment of NMS with electroconvulsive therapy in 1987.[26] A literature review by Scheftner and Shulman proposed that ECT be considered as an effective treatment modality when there is no response to drug treatment after 48 hours partly because bromocriptine and dantrolene have a mean response time of less than 2 days.[27]

In general, clinicians reported that ECT had a beneficial effect on both NMS and the underlying psychiatric condition. There

is concern that anesthetic agents used in ECT may worsen NMS or produce malignant hyperthermia. The recommendations for ECT are six to ten once daily sessions, maintaining the minimum of six sessions even if there is a response beforehand. This approach minimizes the risk of relapse. Response to ECT is generally seen after six sessions.[28, 29]

RESUMPTION OF ANTIPSYCHOTICS

A two-week waiting period after resolution of NMS is generally suggested before restarting antipsychotics.[19] Olmsted has suggested the following guidelines for administration of neuroleptics after NMS resolution.[23] Neuroleptics should be only considered for psychotic symptoms. Depot neuroleptics and parenteral neuroleptics are contraindicated and relatively contraindicated respectively. Psychotic symptoms should be controlled by oral neuroleptics using the lowest dosage necessary. Neuroleptics should be discontinued if fever, muscular rigidity and/or labile blood pressure are noted. While the patient is undergoing treatment, labs should be checked frequently, particularly CPK levels and complete blood cell counts. Neuroleptics in a class different from the one that caused the initial insult should be chosen and neuroleptics of low potency should be selected.

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