OMM diagnosis and treatment becomes a time- and cost-effective means of delivering care. It will further assure patients of receiving a higher quality of healthcare.

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JAOA

Case reports

Neuroleptic malignant syndrome: Case report and review

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Neuroleptic malignant syndrome is a rare but potentially fatal disorder that has been associated with the use of antipsychotic medications. Because neuroleptic malignant syndrome is rare, clinicians often have a low index of suspicion for the disorder which may lead to delayed treatment and increased mortality. This article describes a case of neuroleptic malignant syndrome and briefly reviews current diagnostic criteria and treatment options.

(Keywords: Neuroleptic malignant syndrome, hyperthermia, antipsychotics)

Neuroleptic malignant syndrome (NMS) is a drug-induced hyperthermic disorder first described by Delay and associates[1] in 1960. Although discrepancy exists in the reported incidence of the disorder, most of the literature suggest that the disorder occurs in 0.07% to 2.2% of those patients treated with antipsychotic medications.[2] Recently, particular attention has been drawn to a possibly higher incidence of NMS in those patients treated with a combination of haloperidol and lithium carbonate.[3,4]

When NMS occurs, it carries a mortality rate of 10% to 20%.[2,5] Reduction in mortality appears to be directly related to the early recognition of symptoms and risk factors by healthcare workers.[6] This article therefore presents a case of NMS, with a brief review of current diagnostic criteria and treatment options to familiarize clinicians with the disorder.

Report of case

A 49-year-old man was admitted to a community hospital from a local extended care veterans facility in August 1996 with periumbilical pain as his chief complaint. The patient's medical history was remarkable for schizophrenia, bipolar disorder, and Barrett's esophagus with gastroesophageal reflux disease. A known manifestation of his schizophrenia was psychogenic polydipsia, with resulting past bouts of abdominal discomfort and hyponatremia. His medications included the following: Omeprazole (Prilosec), 20 mg/d; lithium carbonate, 600 mg twice a day; clomipramine hydrochloride (Anafranil), 50 mg at bedtime; trifluoperazine hydrochloride (Stelazine), 20 mg at bedtime; and benztropine mesylate (Cogentin), 2 mg at bedtime. He was admitted to the service of an attending general surgeon.

Workup of the patient's abdominal pain revealed evidence of right colonic dilation of 18 cm in the greatest dimension. After a failed attempt at decompressive colonoscopy, the patient was taken to surgery and a successful right hemicolectomy was performed. The patient was allowed to have his medications at the outpatient dosages, with sips of water on the second postoperative day.

On the third postoperative day, the nurses reported that the patient was drinking large amounts of water despite their surveillance. A patient sitter was ordered,

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and the room's water was turned off. That afternoon, the patient was found drinking from the water source attached to the room's toilet, and his abdomen was more distended on examination. A nasogastric (NG) tube was placed, and he was given lorazepam (Ativan), 0.5 mg intravenously (IV) every 8 hours as needed for agitation. In addition, his routine medications were changed as follows: benztropine mesylate, 2 mg intramuscularly (IM) at bedtime; trifluoperazine hydrochloride, 2 mg IM every 4 hours; and lithium carbonate elixer, 10 mL by NG tube at noon and at bedtime. He was kept on clomipramine hydrochloride, 50 mg at bedtime, as previously ordered. The patient continued to be agitated, and later that day, he was restrained. Haloperidol (Haldol), 3 mg IM, and lorezapam, 1 mg IV, were administered by the surgical resident. Approximately 4 hours later, the night intern who was called to see the patient, ordered another dose of haloperidol, 3 mg IM, and lorezapam, 1 mg IV.

On the morning of the fourth postoperative day, the patient's temperature was 99°F; it increased to 101.6°F by noon. His medication regimen was changed back to oral administration at the outpatient dosages, acetaminophen was ordered, and a workup for postoperative infection was initiated.

On the fifth postoperative day, the patient's temperature rose to 103.5°F, whereupon, a general internal medicine consultation was ordered. On examination, the consulting internist noted the patient's increased muscle tone, tremor, and rigidity. Neuroleptic malignant syndrome was considered in the differential diagnosis, and lithium and all antipsychotic drugs were discontinued. The patient was given dantrolene sodium IV, 1 mg/kg every 6 hours; benztropine mesylate, 1 mg IV every 8 hours; and diphenhydramine hydrochloride (Benadryl), 50 mg IV every 8 hours. When laboratory examination results were reported later that day, the patient was found to have a creatinine kinase (CK) level of 24,940 U/L and deteriorating renal function. The following morning (sixth postoperative day), the CK level rose to 29,250 U/L, and the patient's renal function deteriorated even further. His temperature was recorded again in the 103°F range. Consequently, he was transferred to the intensive care unit, and treated appropriately for rhabdomyolysis.

On the seventh postoperative day, the CK level was measured at 15,410 U/L, and the patient's temperature fell into the 100°F range. The medication regimen previously described was continued, and for the next several days, the patient's temperature and CK level returned to normal. None of the cultures or other studies done to rule out an infectious cause of the increased temperature yielded positive results.

The patient was not rechallenged with antipsychotic drugs during his hospital stay. However, when his NMS symptoms had resolved, a regimen of divalproex sodium (Depakote) was started at increasing dosages titrated to his valproic acid level, in consultation with his psychiatrist. Interestingly, later in his hospitalization, the patient again became febrile, but without signs of muscular rigidity or tremor. Workup for an infectious etiology was positive, and he was managed successfully by the surgical team. The patient was discharged from the hospital with divalproex as his sole psychiatric drug, and with instructions to follow up with his psychiatrist at the veterans facility.

Checklist

- ☐ Treatment with neuroleptic drugs within 7 days of onset (within 2 to 4 weeks for depot neuroleptic drugs)
- ☐ Hyperthermia (temperature ≥100.4°F [38°C])
- ☐ Muscle rigidity
- ☐ Five of the following occurring concurrently:
  - — Change in mental status
  - — Tachycardia
  - — Hypertension or hypotension
  - — Tachypnea or sialorrhea
  - — Tremor
  - — Incontinence
  - — Elevation of creatinine kinase level or myoglobinuria
  - — Leukocytosis
  - — Metabolic acidosis
- ☐ Exclusion of other drug-induced, systemic, or neuropsychiatric cause

Figure. *Diagnostic criteria for neuroleptic malignant syndrome. (Source: Caroff SN, Mann SC: Neuroleptic malignant syndrome.* Med Clin North Am *1993;77: 185-202.)*

Discussion

Several risk factors for NMS have been suggested in the literature.[3] The few prospective studies suggesting risk factors are not completely consistent. However, there is fairly broad-based support for including the following: a greater degree of premorbid psychomotor agitation, higher dosages of neuroleptic drugs, and greater rates of dosage increase.[2] In addition, there is some evidence that concurrent treatment with lithium may lead to higher rates of NMS, although this evidence is controversial.[4] The single most agreed on risk factor in all the literature reviewed for this study is an increased rate of neuroleptization.

Diagnostic criteria for NMS are also controversial, and have led to inconsistent reporting in clinical investigations of NMS.[7] The most comprehensive, recent, and commonly used criteria have been proposed by Caroff and coworkers,[3] and are listed in the *Figure*. Among these criteria, so-called lead-pipe muscle rigidity, hyperthermia, elevated CK level, and mental status change are the most consistently listed diagnostic criteria in the literature overall.[3]

Treatment of NMS consists of a three-step approach. First, as soon as the diagnosis of the disorder is suspected, all psychotropic medications should be discontinued, and appropriate sup-

Table
Drug Regimens Commonly Used To Treat Neuroleptic Malignant Syndrome

Drug Generic (Trade)	Dosage	Route*	Frequency
☐ Dantrolene sodium (Dantrium)	0.8 mg/kg to 1.5 mg/kg	IV	Every 6 hours
☐ Bromocriptine mesylate (Parlodel)	2.5 mg to 10.0 mg	PO	Three times a day
☐ Amantadine hydrochloride (Symmetrel)	100.0 mg	PO	Three times a day
☐ Benztropine mesylate (Cogentin)	1.0 mg to 4.0 mg	PO, IV or IM	Once or twice a day

*IV = Intravenous; PO = oral; IM = intramuscular.

portive treatment instituted. Particular attention should be directed to fluid replacement; reduction of temperature; and support of cardiac, respiratory, and renal functions.[3]

Second, specific pharmacotherapy may be instituted. Dantrolene has been shown to significantly reduce the time to clinical improvement, and also to decrease mortality.[8] The effects of dantrolene stem from its muscle relaxant properties. Because the hyperthermia associated with NMS results from the heat generated by muscular rigidity, and dantrolene blocks this rigidity, the drug's impact on NMS is easily understood. In addition to dantrolene, treatment with drugs designed to control extrapyramidal disorders (such as benztropine and amantadine), and dopamine agonists (such as bromocriptine) may be helpful.[8] The recommended dosages for common drugs used to treat NMS are listed in the *Table*.

The third step in the treatment is to consider rechallenge with neuroleptic medications when there is clinical resolution of NMS, and when the patient's function is significantly impaired by the underlying disorder that originally necessitated antipsychotic therapy. Most investigators suggest that it is safe to restart the neuroleptic medication regimen 2 weeks after an episode of NMS has resolved.[6, 2] Furthermore, choosing a neuroleptic drug of lower potency on rechallenge is recommended as prudent, even though no evidence exists that the potency significantly affects recurrence of NMS.[9]

In addition to the three-step treatment approach, trials have also been conducted on the effects of electroconvulsive therapy (ECT) on NMS. Recommendations concerning the efficacy of ECT versus conventional therapy cannot be made at present. The clinical picture of NMS has been shown to improve with ECT in some trials.[2,10]

Comment

Neuroleptic malignant syndrome is a rare but potentially fatal disorder. If the clinician maintains a high index of suspicion in patients with appropriate risk factors and institutes treatment early, morbidity and mortality can be prevented.

Although NMS is rare, the potential for physicians in almost any specialty to encounter patients with the disorder exists. Those physicians who practice in facilities where neuroleptic drugs are often used, such as hospitals, psychiatric facilities, and nursing homes, have a greater chance of seeing NMS. This case report illustrates many of the risk factors, diagnostic criteria, and treatment options in NMS. Although case reports are not as educational as managing an actual case of NMS, familiarization with the disorder through reports such as this may help physicians in making the correct diagnostic and management decisions in this potentially lethal syndrome.

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