Case Reports

Neuroleptic malignant syndrome

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ABSTRACT

We report 37-year-old man admitted to the psychiatric ward with acute depression. Antidepressive medications were initiated including: promethazine hydrochloride, hydroxyzine hydrochloride, lorazepam and haloperidol. In an attempt to control his depression, doctors increased the dose of haloperidol. Five days later he developed fever, cough, confusion and he was unable to eat. Accordingly, he was transferred to the medical ward for further assessment. On examination he was febrile, confused, there was neck stiffness and generalized rigidity with flexor planters. Both serum myoglobin and creatine kinase level were elevated. The urine myoglobin test result was positive. He was diagnosed with neuroleptic malignant syndrome. Dantrolene was started for 3 days, followed by bromocriptine. The clinical syndrome resolved over the next couple of days.

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Neuroleptic malignant syndrome (NMS) refers to the combination of hyperthermia, rigidity, and autonomic dysregulation that can occur as a serious complication of the use of antipsychotic drugs. The syndrome is usually associated with the use of depot and oral neuroleptic drugs such as phenothiazines and butyrophenones. Among the injected neuroleptics, fluphenazine enanthate, fluphenazine decanoate, haloperidol, thioxanthenes, and pipotiazine (pipotiazine) palmitate have been implicated. Even the newer atypical antipsychotics, which are not classified accurately as neuroleptics, can cause this syndrome. Haloperidol is a butyrophenone derivative with antipsychotic properties that has been considered particularly effective in the management of hyperactivity, agitation, and mania. Haloperidol is an effective neuroleptic and possesses antiemetic properties; it has a marked tendency to provoke extrapyramidal effects and has relatively weak alpha-adrenergic properties. It may also exhibit hypothermic and anorexiant effects and potentiates the action of barbiturates, general anesthetics, and other central nervous system (CNS) depressant drugs. The case presented in this report highlights the importance of considering NMS in the differential diagnosis of fever, muscle rigidity, and autonomic instability in any patient under haloperidol.

Case Report. A 37-year-old man was admitted to the psychiatric ward with a diagnosis of acute depression. Antidepressive medications were initiated including: promethazine hydrochloride 25 mg once daily orally (PO), hydroxyzine hydrochloride 50 mg 3 times daily PO, lorazepam 1 mg once daily PO at night and haloperidol 2 mg intravenously (IV) 3 times daily. During his stay in the psychiatric ward, his dose of haloperidol was increased to 5 mg IV 3 time daily, in an attempt to control his depression. Five days later he developed fever, cough and he was unable to eat. His condition deteriorated over the next 24 hours, and he became increasingly confused. Accordingly, he was transferred to the medical ward for further assessment. On examination, he was conscious, confused, with a temperature of 39.1°C; pulse 120/
minute, BP 140/90 mm Hg. There was neck stiffness and generalized rigidity with flexor planters. Chest examination showed scattered crepitations at the right lung, but chest x-ray was normal (Figure 1). Brain CT showed normal study (Figure 2). Initial investigations showed hemoglobin level of 13 g/dL, total leucocyte count 12000/mm$^3$ with a normal differential, platelet count of 112000/mm$^3$, erythrocyte sedimentation rate (ESR) 10 mm/hour. Blood chemistry, liver profile, and coagulation studies were within normal limits. Both serum myoglobin and creatine kinase (CK) level were elevated, with normal CK isoenzyme fraction and cardiac troponin levels. The urine myoglobin test result was positive while septic workup yielded normal results. The rhabdomyolysis was managed with vigorous hydration and urine alkalinization, as well as cautious monitoring of serum potassium and other electrolyte levels. Tazocin (piperacillin-tazobactam) IV was started to cover suspected hospital acquired infection. However, his hyperthermia persisted despite acetaminophen, nonsteroidal anti-inflammatory drugs, and ice bag use. On the 7th day, lumber puncture was carried out, but cerebrospinal fluid study was normal. The psychiatrist was consulted again, and he added amitriptyline 75 mg orally once daily, and Prozac 25 mg orally once daily; however, his condition continued to deteriorate. Ten days after admission, all medications were stopped except lorazepam, and he was diagnosed with NMS. Dantrolene was started at a dose of 60 mg IV 3 times daily, followed by bromocriptine at a dose of 2.5 mg orally 3 times daily. Over the next few days, his temperature dropped and he became more relaxed, he was able to eat, drink, and walk easily and his CK level returned to normal. Dantrolene was stopped after 3 days and he was kept on bromocriptine and lorazepam. In order to control his depressive disorder, he was kept on Prozac and lorazepam. His condition improved, and he was discharged in stable condition. After 6 months, he was seen in the clinic, and was well.

**Discussion.** The NMS is a rare, but life-threatening, idiosyncratic reaction to a neuroleptic medication. It was first described in 1960 as akinetic hypertonic syndrome. The frequency of the syndrome ranges from 0.07-2.2% among patients receiving neuroleptic medications while the mortality ranges from 10-30%. Most neuroleptic medications have some risk of NMS associated with them. A rapid change in neuroleptic dose is a major risk factor for the syndrome, especially if it occurs within 5 days before the onset of symptoms, and the risk can persist for 20 days or more after discontinuing the neuroleptic therapy. Other risk factors for NMS include stress, humidity and concomitant use of lithium, anticholinergic agents or some antidepressants. The NMS usually occurs with the use of therapeutic doses of neuroleptic drugs and commonly develops during the initial phases of treatment, when the drug dose is being stepped up, or when a second drug is introduced. In our patient, a change in haloperidol dose was the main risk factor for NMS. He developed NMS 5 days after changing the dose of haloperidol, which is high on the list of causative medications. The symptoms usually develop over 24-72 hours and can last from 1-44 days (approximately 10 days on average). There is no typical sequence of symptoms, but extrapyramidal symptoms usually occur before autonomic ones.

Patients with NMS (as in our case) often have a psychiatric history and present with high fever, altered mental status, muscle rigidity, autonomic dysfunction, and elevated level of CK. Generalized rigidity, described as “lead-pipe,” is a core feature of NMS, and is usually associated with myonecrosis.
Cogwheeling, myoclonus, and coarse tremors are often described. Mental status changes include clouding of consciousness ranging from delirium to stupor and coma. Autonomic activation and instability are common, manifested by tachycardia, oscillations in BP, and tachypnea. No laboratory abnormalities are specific or pathognomonic for the diagnosis, but neutrophil leucocytosis and raised CK concentrations lend weight to the diagnosis. Our patient had leukocytosis and high CK.

One of the key interventions for decreasing the lethality in NMS is early detection. To make an early diagnosis, a high index of suspicion is required. Many diagnostic criteria have been proposed for NMS, but because of its variable presentation, no single set of criteria is used universally. In our patient, the diagnosis of NMS was made because of the clinical triad of hyperthermia, muscle rigidity, and autonomic imbalance associated with altered consciousness which occurred after increasing the dose of haloperidol. This patient developed rhabdomyolysis, which is the most serious complication of NMS. Rhabdomyolysis produces extremely high levels of serum CK, hyperkalemia, myoglobinuria, and acute renal failure. Other complications of NMS include: aspiration pneumonia, renal failure, seizures, sepsis, respiratory failure, and cardiac arrest. Other conditions that might cause a similar syndrome include: thyroid storm, heat stroke, anticholinergic syndrome, serotonin syndrome, and cocaine overdose. The most important intervention is to discontinue all antipsychotics. In most cases, symptoms will resolve in 1-2 weeks. The NMS precipitated by long-acting depot injections of antipsychotics can last as long as a month. During the course of NMS, the use of physical means of cooling, as in other types of the pyrexial syndrome, should be instituted early. There are a variety of other effective medications that can be used; the 2 most frequent ones include dantrolene sodium and bromocriptine (individually or combined). These drugs reduce the mortality and shorten the course of the syndrome.

Our patient improved dramatically after the usage of both drugs. Electroconvulsive therapy is an option if unresponsive to pharmacotherapy.

If neuroleptics are to be re instituted, they should be administered at relatively low doses, if possible, 2 weeks after an episode. Use of a different antipsychotic may minimize the risk of recurrence of NMS. Our patient was discharged on a different antipsychotic (Prozac). If the patient is discharged, close follow-up care should be given to monitor residual symptoms. This patient was seen after 6 months in the clinic, and found well.

In summary, when using haloperidol in a patient with psychosis or critical care, the development of NMS should be suspected if the patient develops fever, muscle rigidity, and autonomic instability, since early recognition and treatment of NMS will minimize the mortality and morbidity associated with this syndrome.

References