A Delayed Form of Neuroleptic Malignant Syndrome after Discontinuation of Chlorpromazine Monotherapy

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Abstract—Neuroleptic malignant syndrome (NMS) is a potentially fatal syndrome that is characterized by the combination of hyperthermia, limb spasticity, and autonomic dysfunction. This serious complication usually occurs during the course of a neurological or antipsychotic drug's use. However, it is less frequently seen in patients after having stopped the offending drug. Chlorpromazine is one of the classic neuroleptic medications; however, there is a paucity of data incriminating chlorpromazine as a cause of NMS, especially the delayed form. We had the experience of diagnosing and treating a fatal case of NMS occurring four days after discontinuation of chlorpromazine that had been prescribed for the treatment of intractable hiccups.

Keywords — chlorpromazine, dantrolene, neuroleptics, neuroleptic malignant syndrome, NMS.

I. INTRODUCTION

Neuroleptic malignant syndrome (NMS) is an uncommon but potentially fatal syndrome, which occurs in susceptible individuals exposed to neuroleptic medication. The first case of NMS, precipitated by haloperidol use, was reported by Dr. Delay, a French psychiatrist in 1960 (1). The typical case of NMS is characterized by muscle rigidity, hyperpyrexia, altered mental status, and a disturbance in the autonomic system. NMS has been reported in all age groups, from one to 78 years of age, but most of the sufferers are young adults (2-5). Men are twice more likely than women to develop NMS (3,6). Incidence of NMS varies from 0.02 to 3 percent among patients taking neuroleptic agents (2,7). Mortality reached as high as 76% in the 1960s, but then reduced to 10-20% in 1980s (8). It further reduced to less than 10% in recent reports due to earlier recognition and improved management (9). In addition to the classic neuroleptic agents, anecdotal reports also incriminated atypical antipsychotics (e.g., clozapine, risperidone, carbamazepine, lithium, and L-dopa) causing NMS (2,10-15). Surprisingly, there is a paucity of medical literature incriminating chlorpromazine monotherapy as a cause of NMS. In an attempt to expand the understanding of the NMS clinical continuum, we are reporting a case of chlorpromazine-induced NMS of the delayed form.

II. CASE PRESENTATION

A 66-year-old man who was previously healthy on no medications became suddenly ill three weeks after attending a child's birthday party. He developed acute nonspecific gastrointestinal symptoms described as nausea, vomiting, diarrhea and hiccups. After seeking medical attention, his primary care physician prescribed oral chlorpromazine 25 mg every six hours as needed for his hiccups. He took the chlorpromazine for three consecutive days but still his hiccups persisted. The dosage of chlorpromazine was then increased to 50 mg every six hours. His hiccups had improved over the next four days and the chlorpromazine was weaned off over a three-day period. Unfortunately, his hiccups soon relapsed. Without the advice from a medical professional, he began to self-administer chlorpromazine. Over the course of the next four days, he consumed 450 mg of the medication. He then had an episode described as “suddenly passed out for about a minute”, but without postictal somnolence or confusion. His primary care physician recommended he stop taking the chlorpromazine. Four days after his abstinence from chlorpromazine, he developed intermittent limb stiffness and two witnessed convulsions described as “unresponsiveness and shaking of all four limbs that lasted for a minute with clenching teeth and urinary incontinence”, obviously concerning for seizure episodes. The family also reported that he had a personality change described as “mean, short temper, and nasty” since starting chlorpromazine. He suffered a 12-pound weight loss since starting taking chlorpromazine and had alternating periods of feeling hot and cold. He was then admitted to the hospital for evaluation and management.

On admission, he was febrile (T-max 38.8 Celsius; the next day after admission T-max raised to 40.0 Celsius), hypotensive (blood pressure 71/50 mmHg), and had tachycardia. He was alert, but mildly agitated, and was able to respond to simple questions without dysarthria or aphasia. He demonstrated hyperreflexia with hypertonia,
diffuse tremulous involuntary movements and an intermittent asymmetric myoclonic jerking seen in all four limbs. Laboratory studies showed pancytopenia (hemoglobin 10.8 gm/dL, white blood cell 2,000/mcL, platelets 32,000/mcL), acute hepatic injury and dysfunction (alanine aminotransferase- ALT 3,014 unit/L, aspartate aminotransferase- AST 3,656 unit/L, bilirubin 1.5 mg/dL), acute kidney injury (blood urea nitrogen- BUN 23 mg/dL, creatinine 2.99 mg/dL, estimated creatinine clearance rate- CrCl 21.7 mL/min), a coagulopathy (international normalized ratio- INR 2.3, partial thromboplastin time- aPTT 40.8 seconds, prothrombin time- PT 26.0 seconds), hyponatremia (serum sodium 127 mEq/L ), and elevated creatine kinase (CK 1,485 IU/L). The other laboratory studies were normal, including serum electrolytes and alkaline phosphatase, urinary analysis, and serum/urine drug screen. Brain magnetic resonance imaging (MRI) without gadolinium revealed no evidence of acute intracranial processes and only mild nonspecific white matter changes. Electroencephalography demonstrated diffuse slowing but no epileptiform discharges. Blood cultures and an X-ray of the chest were unyielding.

Based on all the clinical information, particularly his recent use of chlorpromazine, followed by an increased body temperature with muscle rigidity and an increased level of CK, the provisional diagnosis of NMS was made (2). His hypertonia progressed to “lead pipe” rigidity within hours of hospital admission. The administration of intravenous dantrolene was immediately added together with the other supportive medical cares. The patient’s respiratory status rapidly declined and he was subsequently incubated with mechanical ventilation. An intravenous infusion of bromocriptine was added to the dantrolene regimen. Unfortunately, his medical condition continued to deteriorate. He went on to develop disseminated intravascular coagulation (DIC) and multi system organ failure. He subsequently died on the fourth hospital day.

III. DISCUSSION

In this article, we presented a case of NMS caused by chlorpromazine, which according to the literature is extremely rare. By adding our observations to the literature, we hope to alert others to the potential of this harmful entity when administering chlorpromazine in clinical practice.

The diagnostic criteria for NMS as outlined by Levenson (2) are based on the symptoms of hyperthermia, encephalopathy, autonomic instability, skeletal muscle rigidity, rhabdomyolysis, hyponatremia, elevated hepatic enzymes, and recent administration of neuroleptic or antipsychotic agents. The severity and other comorbidities of NMS are the most reliable predictors of mortality in NMS (10). Deaths from NMS usually occur as a result of multi system organ failure and in the first several days of the course. The prominent classic features of NMS are hyperthermia, encephalopathy, skeletal muscle rigidity, and autonomic instability which were evident in our case. NMS typically develops over 24-72 hours after administration of the offending agents but can occur at any time during the course of taking the medication, which is classically described as a neuroleptic or other psychiatric drug. Morris and colleagues reported a case of severe NMS developing 24 hours after acute olanzapine and chlorpromazine self-poisoning (15). Notably, although less frequently, NMS can occur several days after discontinuing the offending neuroleptic drug, as seen in our patient who developed NMS four days after discontinuing chlorpromazine.

Haloperidol is the most frequently cited drug causing NMS in clinical practice. The atypical antipsychotic agents have a lower affinity to dopaminergic receptors than classic neuroleptics and thus have a much lower incidence of NMS. However, NMS caused by atypical antipsychotics has also been reported in case reports (16,17).

Chlorpromazine is approved by the U.S. Food and Drug Administration and has been used clinically for more than a half century for treating psychotic disorders, such as schizophrenia, schizoaffective disorder, acute mania, and psychotic depression (18,19). Additionally, chlorpromazine can also be effective in treating intractable hiccups (19,20) via its mechanism of central dopamine antagonism in the hypothalamus (20). Common adverse effects of chlorpromazine include anticholinergic effects, sedation, weight gain, blurred vision, erectile dysfunction, and oligomenorrhea. Chlorpromazine at high doses may cause extrapyramidal symptoms and anticholinergic reactions due to its antidopaminergic and anticholinergic properties. These potential side effects that are associated with its underlying mechanisms of action include antagonizing brain dopamine D2 receptors, inhibiting hypothalamic and hypophyseal hormone release, as well as depressing the reticular activating system (21-23).

The pathophysiology underlying NMS involves a cascade of reactions caused by multiple neurochemical and neuroendocrine dysfunctions resulting in the constellation of clinical findings seen in NMS. Neuroleptics, including chlorpromazine, produce dopamine receptor blockade which is the key event in the development of NMS. In addition, the severity of NMS is proportional to the dopamine- receptor-binding affinity of the drugs (24). However, the exact pathogenesis remains to be well-understood.

An animal model for NMS which corresponds to the human syndrome (25) of mental status change, muscle rigidity, hyperthermia, and autonomic instability has been developed as a useful tool for studying NMS, but has yet to become fully characterized. Its laboratory studies (25) show rhabdomyolysis, acute renal failure, elevated hepatic transaminases, leukocytosis, and metabolic acidosis. Electroencephalography may reveal generalized slowing consistent with metabolic encephalopathy (26).

The management of NMS has proven to be quite challenging. The patient with NMS may die despite prompt appropriate medical interventions (8). There is no test to predict whether an individual is susceptible to developing NMS when exposed to an antipsychotic agent. As a general rule, it is imperative to recognize the clinical signs
of NMS early. Immediate discontinuation of all possible offending agents is vitally important. Admission of the patient to the intensive unit should be strongly considered in order for critical care management with a multidisciplinary approach (24,27).

There is no general consensus on the specific treatment for NMS. Also, there are no randomized controlled studies to confirm pharmacological efficacy. The general concepts from empiric and off-label treatment approaches (27) are to provide good supportive care, adequate fluid management with electrolyte optimization, maintenance of normothermia, sedation, and respiratory support in the critical care setting. One potential mechanism of NMS might be related to Ca\(^{2+}\)-induced Ca\(^{2+}\) release, resulting in increased free ionized intracellular Ca\(^{2+}\) levels, i.e., Ca\(^{2+}\) overload, causing limb rigidity, central fevers, and autonomic dysfunction (28). Dantrolene sodium acts primarily by affecting Ca\(^{2+}\) flux across the sarcoplasmic reticulum (29), and has been successfully used in the treatment of several rare hypercatabolic syndromes including NMS (30). Amantadine and bromocriptine, both dopamine agonists, may have beneficial effects in patients with NMS, presumably based on their ability to relieve the central dopaminergic blockade (31,32). Our patient received intravenous infusions of both dantrolene and bromocriptine; however, he ultimately died of DIC and multiple organ failure.

In summary, we reported a case of delayed onset NMS after discontinuation of chlorpromazine monotherapy used for intractable hiccups which resulted in death despite prompt medical management. Although it usually occurs during the course of using neuroleptics or atypical antipsychotic drugs, we have documented that NMS can develop days after discontinuing the offending agents.

References

Questions (please choose one single answer):

1. A 42-year-old male brought to ER for intractable hiccups is given 10mg intramuscular haloperidol and discharged home. Later in the evening, the office is called by the family, as the patient was noticed to be having muscle rigidity and fever. It is suspected neuroleptic malignant syndrome (NMS). All of the following are features of NMS except:

   A. Clear consciousness.
   B. Muscle rigidity.
   C. Elevated temperature.
   D. Leukocytosis.
   E. Elevated creatine kinase levels.

   Answer: A.
   Clear consciousness is not a feature of NMS. Patients with NMS have altered mental state. NMS is a medical emergency and needs aggressive treatment including immediate discontinuation of neuroleptic agents. The mortality rate is high, if untreated.

2. A 48-year-old female with a history of schizophrenia presents in a coma, with a fever and limb rigidity. She is diagnosed with neuroleptic malignant syndrome. Which one of the following agents could have caused this syndrome?

   A. Pemoline.
   B. Theophylline.
   C. Theobromine.
   D. Chlorpromazine.
   E. None of the above.

   Answer: D.
   Neuroleptic malignant syndrome is seen with antidopaminergic agents, and chlorpromazine is the only antidopaminergic agent listed. The other medications listed are psychomotor stimulants.

3. A 66-year-old male with a history of multiple psychiatric hospitalizations was recently admitted to the psychiatric unit with acute psychosis. He was given doses of haloperidol. On the fourth day of admission, he developed a fever, increased muscle rigidity in all limbs, and then went into a coma. Which of the following would be the next best step?

   A. Stat dantrolene.
   B. Place cooling blankets.
   C. Stop the neuroleptic agent.
   D. Check creatine phosphokinase level.
   E. None of the above.

   Answer: C.
   All of the above are good options and are part of the management of neuroleptic malignant syndrome. However, stopping the neuroleptic agent should be the first and foremost step in the management.