A CASE REPORT ON HALOPERIDOL-INDUCED NEUROLEPTIC MALIGNANT SYNDROME (NMS)

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ABSTRACT
Neuroleptic malignant syndrome (NMS) is one of the life-threatening adverse drug reactions caused by dopamine receptor-antagonists, such as high-potency typical antipsychotics. A case of a 16-year-old male patient who developed NMS after administration of haloperidol is reported. He demonstrated classic features of NMS, including generalized muscle rigidity, rhabdomyolysis, fever, altered mental status, autonomic instability, and increasing creatine phosphokinase (CPK) level and leukocyte count. His NMS resolved after proper management, including cessation of haloperidol and the initiation of supportive care therapy and pharmacological agent, was given. The pathogenesis, clinical presentation, and proper management of NMS are discussed in this case report.

Keywords: Neuroleptic malignant syndrome (NMS), dopamine receptor-antagonists, antipsychotics, haloperidol

1. INTRODUCTION
Neuroleptic malignant syndrome (NMS) is a life-threatening complication caused by an adverse reaction to medications with dopamine receptor-antagonist properties or the rapid withdrawal of dopaminergic medications [1-2]. The primary trigger of NMS is dopamine receptor blockade and the standard causative agent is an antipsychotic. Potent typical antipsychotics such as haloperidol, fluphenazine, chlorpromazine, trifluoperazine, and prochlorperazine have been most frequently associated with NMS and thought to confer the greatest risk [1]. The diagnosis of NMS is based on history and the presence of certain physical examination and laboratory findings. The onset of symptoms varies from early in treatment to months later. NMS develops rapidly over the course of 24 to 72 hours [3]. Cardinal signs and symptoms of NMS are characterized by fever, severe muscle rigidity, dysautonomia, and mental status changes [2-4]. However, its presentation can be quite heterogeneous, as reflected in the current Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition [DSM-IV] criteria [1]. Laboratory evaluation, although considered nonspecific, frequently shows leukocytosis with or without a left shift, increases in creatine phosphokinase (CPK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and myoglobinuria [3].

Treatment of NMS is individualized and based on the clinical presentation. Treatment should always begin with cessation of the suspected offending pharmacologic agent and supportive care [1,3]. In many cases that alone is effective. The role of adjunctive agents is unclear, yet they are often used in clinical settings. Dopamine agonists such as bromocriptine and amantadine reduce rigidity, fever, or CPK. Dantrolene has been used as a skeletal muscle relaxant, with effects on temperature, heart rate, respiratory rate, and CPK [3]. Several clinical reports suggest that benzodiazepines, administered orally or parenterally, may ameliorate symptoms and hasten recovery in NMS, particularly in milder cases, given that NMS has been considered an extreme form of catatonia [2]. This case demonstrates a patient admitted to the ward for aggressive behavior, insomnia, and hallucination, requiring the administration of haloperidol. However, he developed NMS which resolved after proper treatment was given.

2. CASE REPORT
A 16-year-old male patient was admitted to the ward due to aggressive behavior, insomnia, hallucination, and loss of appetite for approximately one week. Prior to hospital admission, he had one suicidal attempt. He had no known medical illness prior to the hospital admission. Upon admission, a diagnosis of major depressive disorder with psychotic features was made. Due to aggressiveness, he was given one dose of intramuscular (IM) haloperidol 10 mg and two doses of IM diazepam 5 mg. The patient was physically restrained and oral (PO) sertraline 25 mg twice daily (BD) was started.

On day 2, the patient had one spike of fever at 38.2°C. Treatment plan was continued. Sertraline dose was increased to 50 mg BD and intravenous (IV) diazepam 5 mg as needed (PRN) was initiated. On day 3, the diagnosis was changed to acute psychosis to rule out schizophrenia. The treatment plan was to discontinue sertraline and to start antipsychotic. The patient showed one spike of fever at 37.9°C on day 3.
On day 4, the patient showed aggressive behavior in the morning and one dose of IM diazepam 5 mg was given. Since the diagnosis of acute psychosis to rule out schizophrenia was made on day 3, sertraline was discontinued and the patient was initiated on PO haloperidol 5 mg BD and PO benzhexol 2 mg at night (ON). The patient showed two spikes of fever at 38.0°C and 39.0°C on day 4. A diagnosis of to rule out meningocencephalitis was also made on day 4 in view of spiking fever and elevated total white blood cell (TWBC) on day 1 and day 3 (15.4 x 10^9 cells/L and 17.7 x 10^9 cells/L, respectively) [normal range 4 – 11 x 10^9 cells/L]. However, neurological examination was not able to be performed because the patient did not obey command and was not fully alert. The patient’s family members also refused for lumbar puncture to be performed on the patient.

On day 5, in view of high grade spiking fever and elevated TWBC (17.9 x 10^9 cells/L on day 4), IV acyclovir 500 mg thrice daily (TDS) and IV ceftriaxone 2 g BD were initiated for meningocencephalitis. Haloperidol and benzhexol were continued. Laboratory results for day 3 and day 4 were obtained. The CPK and LDH were elevated for both of the days. The CPK and LDH levels on day 3 were 10901 U/L [normal range 24 – 195 U/L] and 1262 U/L [normal range 0 – 248 U/L], respectively. On day 4, the CPK and LDH levels were 5497 U/L and 1514 U/L, respectively. The patient was still feverish on day 5, with the highest temperature of 38.5°C.

On day 6, the patient was stupor, did not respond to pain stimuli and was presented with high grade fever. In view of high grade fever, elevated TWBC, CPK and LDH, the patient was diagnosed to have NMS. Haloperidol and benzhexol were withheld. Supportive management was initiated. The patient was given IV fluids 2.5 L (1.5 L dextrose 5% and 1 L normal saline solution) over 24 hours. PO paracetamol 1000 mg four times daily (QID) was also initiated. Routine monitoring of laboratory parameters such as CPK, LDH and renal profile was ordered. Signs and symptoms of acute renal failure were also watched out. Further plan was to initiate atypical antipsychotics if indicated. The patient was feverish throughout day 6, with the highest temperature of 39.0°C.

On day 7, the patient was transferred to high dependency unit (HDU) for close monitoring. The CPK and LDH levels for day 6 were obtained and the results were 1794 U/L and 983 U/L, respectively. The patient was still feverish throughout day 7, with the highest temperature of 38.5°C. Besides, there was one reading of elevated blood pressure at 153/95 mmHg [normal range: 140/90]. The care plan on day 6 was continued and the plan to keep patient normothermia was ordered. The patient was also initiated on one dose of IV dantrolene 175 mg (2.5 mg/kg; patient’s estimated body weight was 70 kg) to be run over 10 – 15 minutes.

On day 8, the patient was still feverish in the morning presented with rigidity. The CPK and LDH levels for day 7 were obtained and the results were 1898 U/L and 701 U/L, respectively. The TWBC for day 7 was 11.9 x 10^9 cells/L. There was one reading of tachycardia at 118 pulses/minute [normal range: 60 – 100 pulses/minute] on day 8. The care plan for day 8 was to send urine sample for myoglobinuria and to initiate PO bromocriptine 5 mg TDS. In the evening, fever started to subside with the highest temperature of 36.2°C after 6:00 p.m. Therefore, PO paracetamol 1 g QID was changed to PRN dosing.

On day 9, the patient’s condition improved. He became alert and conscious. There was one spike of fever at 37.8°C. The CPK and LDH levels for day 8 were obtained and the results were 1080 U/L and 447 U/L, respectively. The TWBC for day 8 was 14.3 x 10^9 cells/L. He was transferred out from HDU. IV fluid was discontinued and the patient was initiated on nasogastric tube feeding of 2 L per day.

On day 10, the patient’s condition was stable. He was alert and conscious. However, there was one spike of fever at 38.5°C. The CPK and LDH levels for day 9 were obtained and the results were 664 U/L and 564 U/L, respectively. The care plan on day 9 was continued.

On day 11, the patient was alert and conscious. However, there was still one spike of fever at 38.0°C. Nasogastric tube feeding was discontinued and the patient was allowed to take food orally. Besides, IV acyclovir and ceftriaxone were discontinued because the patient’s presentation was not suggestive of meningocencephalitis.

On day 12, the patient requested to be discharged against medical advice (DAMA). The TWBC for day 11 was obtained and it was normalized at 10.4 x 10^9 cells/L. The patient was allowed DAMA with the final diagnoses of acute psychosis and NMS secondary to haloperidol. The discharge medications were PO bromocriptine 5 mg TDS and PO paracetamol 1000 mg PRN. No antipsychotics were prescribed upon DAMA. The patient was given a psychiatric clinic follow up one week thereafter.

One week after DAMA, the patient was seen in the psychiatric clinic. He was presented with neat appearance and reserved mood. He had no aggressive behavior, was not feverish and no seizure attacks throughout the week. The patient was allowed home with no medications.

3. DISCUSSION

Haloperidol is a high-potency typical antipsychotic used widely in the treatment of schizophrenia [5]. It is a dopaminergic antagonist, with pharmacologic activity attributed to the blockade of central dopamine receptors, particularly the Dopamine-2 (D2) receptors [3,5]. Patients typically develop NMS within hours or days after exposure to a causative drug, with most exhibiting symptoms within 2 weeks and nearly all within 30 days [1]. The
use of haloperidol caused NMS to occur in this patient. Based on the clinical presentation, the patient developed NMS approximately 48 hours following one dose of IM haloperidol which was given on day 1. He demonstrated classic features of NMS, including generalized muscle rigidity, rhabdomyolysis, fever, altered mental status, autonomic instability, and increasing CPK level and leucocyte count.

The underlying pathophysiologic mechanisms of NMS are complex, but most agree that a marked and sudden reduction in central dopaminergic activity resulting from D2 dopamine receptor blockade within the nigrostriatal, hypothalamic, and mesolimbic/cortical pathways helps explain the clinical features of NMS including rigidity, hyperthermia, and altered mental status, respectively. This theory is supported by the observation that the primary cause of NMS is the use of antipsychotic drugs that specifically block dopamine receptors, and in particular D2 receptors [1], such as haloperidol in this case.

Another system that also appears to play a role in the signs and symptoms of NMS is the peripheral skeletal muscle system. Direct changes in muscle mitochondrial function and release of calcium has been shown to be increased from the sarcoplasmic reticulum of muscle cells with antipsychotic usage, possibly leading to increased muscle contractility and rigidity, breakdown of muscle, and hyperthermia [1,4].

A primary role has also been proposed for a disrupted modulation of the sympathetic nervous system, manifesting in increased muscle tone and metabolism and unregulated sudomotor and vasomotor activity leading to ineffective heat dissipation, labile blood pressure and heart rate. In this model, dopamine antagonists precipitate symptoms by destabilizing normal dopamine regulation of efferent sympathetic activity [4].

Familial clusters of NMS suggest a genetic predisposition to the disorder. Genetic studies have shown that the presence of a specific allele of the dopamine D2 receptor gene is overrepresented in NMS patients. This allele is associated with reduced density and function of dopamine receptors as well as decreased dopaminergic activity and metabolism [4].

Characteristic laboratory abnormalities are associated with NMS, although they are neither specific for the diagnosis nor present in all cases. For example, patients with NMS may have rhabdomyolysis, resulting in significant increases in serum CPK, LDH, aldolase, and transaminases concentrations. When rhabdomyolysis is present, it can be severe enough to cause subsequent myoglobinuric renal failure, requiring hemodialysis [1-2].

NMS in hospitalized patients is considered a neurologic emergency as a delay in treatment or withholding of therapeutic measures can potentially lead to serious morbidity or death. Therefore, the first step is cessation of the suspected offending pharmacologic agent [1]. The patient’s PO haloperidol was discontinued on day 6 when the diagnosis of NMS was made in view of high grade fever, muscle rigidity, altered mental status, and elevation of TWBC, CPK and LDH. NMS is a self-limited iatrogenic disorder, and in many cases cessation of antipsychotic medication may suffice to reverse the symptoms [2].

The next key step in the management of NMS is the initiation of supportive medical therapy. Aggressive hydration is often required, especially if highly elevated CPK levels threaten to damage the kidneys [1-2]. The patient was given hydration with IV fluids 2.5 L (1.5 L dextrose 5% and 1 L normal saline solution) over 24 hours from day 6 to day 9. Serial monitoring and correction of electrolyte abnormalities is critical. Intensive medical care should include careful monitoring for complications, including cardiopulmonary failure, renal failure, aspiration pneumonia, and coagulopathies, and may involve support of cardiac, respiratory, and renal function [1-2]. For this patient, he was transferred from general medical ward to HDU for intensive care monitoring.

There is no general consensus on specific pharmacological treatments for NMS. Due to its rarity, systematic clinical trials in NMS are difficult to perform and so no evidence-based treatment approach exists [1]. Therefore, recommendations for specific medical treatments in NMS are based upon case reports and clinical experience and their efficacy is unclear and disputed. Commonly used agents include dantrolene, dopaminergic agents and benzodiazepines [4].

Dantrolene is a direct-acting skeletal muscle relaxant that works by inhibiting calcium release from the sarcoplasmic reticulum. It is also effective in treating malignant hyperthermia [1,4]. Dantrolene can be administered intravenously starting with an initial bolus dose of 1 – 2.5 mg/kg followed by 1 mg/kg every 6 hours up to a maximum dose of 10 mg/kg/day. Efficacy includes reduction of heat production as well as rigidity, and effects are reported within minutes of administration. Oral dantrolene is used in less severe cases or to taper down from the intravenous form after a few days with doses that range from 50 to 200 mg/day. Due to a risk of hepatotoxicity, dantrolene is typically discontinued once symptoms begin to resolve [2,4]. One dose of IV dantrolene 175 mg (2.5 mg/kg; patient’s estimated body weight was 70 kg) was given to this patient on day 7.

Bromocriptine, a dopamine agonist, is prescribed to restore the lost dopaminergic tone. It can be initiated with 2.5 mg 2 or 3 times daily and increasing doses by 2.5 mg every 24 hours until a total daily dose of 45 mg if necessary. It is recommended that bromocriptine is continued for at least 10 days after NMS is controlled and then tapered slowly [1,2,4]. This patient was initiated with PO bromocriptine 5 mg TDS on day 8 and continued as discharge medication.
An interesting model has been proposed in which benzodiazepines increase dopamine activity by indirect actions on the basal ganglia and substantia nigra. An alternative basis for the efficacy of benzodiazepines in NMS derives from the clinical similarity of NMS and catatonia, a condition for which benzodiazepines have been shown to be effective [6]. Several clinical reports suggest that benzodiazepines, administered orally or parenterally, may ameliorate symptoms and hasten recovery in NMS, particularly in milder cases. This observation is not surprising given that NMS has been considered an extreme form of catatonia [2]. The recommended first-line benzodiazepines to be used in NMS are lorazepam and clonazepam. However, this patient was prescribed with diazepam. Recurrences of NMS do occur, especially when a patient is restarted on a typical antipsychotic with high potency or too quickly after their initial episode. Most patients who require continued antipsychotic treatment, though, are able to have an antipsychotic safely reintroduced with proper precautions including very slow titration and careful monitoring after a waiting period of about 2 weeks for an oral antipsychotic or at least 6 weeks for a depot form. Although NMS is considered an idiosyncratic reaction, it is generally felt to be prudent to use a different antipsychotic than the one that was originally associated with the development of the syndrome, preferably low-potency typical antipsychotics or atypical antipsychotics [1-2]. As mentioned in the case report, the patient was normal upon follow up in the psychiatric clinic one week after discharge and hence no antipsychotic was prescribed.

4. CONCLUSION
NMS is a life-threatening complication caused by an adverse reaction to medications with dopamine receptor-antagonist properties, such as haloperidol, a high-potency typical antipsychotic in this case. Clinicians must be aware of the clinical features of NMS and vigilant in detecting early signs. Primary management of NMS lies in prevention through conservative use of antipsychotics, reduction of risk factors, early diagnosis, prompt discontinuation of offending medications, and supportive medical management.

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6. REFERENCES