A Fatal Case of Prochlorperazine-Induced Neuroleptic Malignant Syndrome: A Case Report and Literature Review

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Abstract Neuroleptic malignant syndrome (NMS) is a medical emergency associated with the use of neuroleptics and antiemetics. NMS is characterized by a distinctive clinical syndrome of altered mental status, rigidity, hyperthermia, and autonomic dysfunction. NMS occurs as a result of changes in presynaptic or postsynaptic dopamine signaling. Central D2 receptor blockade in the hypothalamus, nigrostriatal pathways, and spinal cord leads to increased muscular rigidity and tremor via extrapyramidal pathways. Hypothalamic D2 receptor blockade results in an elevated temperature set point and impairment of heat-dissipating mechanisms. The reported mortality rates for NMS vary between 5 to 20 percent and the occurrence of medical complications and disease severity are the strongest predictors of mortality. This is a case of a 51 year old Caucasian female who presented with altered mental status, temperature of 109°F, diffuse muscular rigidity and autonomic dysfunction manifested as labile blood pressure, tachypnea, hypoxemia and tachycardia after consuming 18 tablets of Prochlorperazine over three days for gastrointestinal upset. Her clinical presentation and laboratory work up were consistent with NMS and she developed fatal complications and multi-organ dysfunction secondary to Prochlorperazine-induced neuroleptic malignant syndrome.

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1. Introduction

Neuroleptic malignant syndrome (NMS) is a medical emergency associated with the use of antipsychotics (Neuroleptics) and anti-emetics. NMS is characterized by a distinctive clinical syndrome of mental status alteration, muscular rigidity, hyperthermia and autonomic dysfunction. The syndrome was first described by Delay and colleagues in 1960, in patients treated with high-potency antipsychotics and it was named (Akinetic hypertonic syndrome) [1]. Incidence rates for neuroleptic malignant syndrome range from 0.07 to 2.2 percent among patients taking antipsychotic agents [2]. Mortality has declined from the earliest reports in the 1960s of 76 percent to 10 – 20 percent [3,4].

NMS occurs as a result of changes in dopamine signaling. The most accepted mechanism by which NMS occurs is dopamine D2 receptor antagonism. In this mechanism, central D2 receptor blockade in the hypothalamus, nigrostriatal pathways, and spinal cord leads to increased muscular rigidity and tremor via extrapyramidal pathways. Hypothalamic D2 receptor blockade results in an elevated temperature set point and impairment of heat-dissipating mechanisms. Peripherally, antipsychotics lead to increased calcium release from the sarcoplasmic reticulum, resulting in increased contractility, which can worsen the hyperthermia, rigidity, and muscle cell breakdown.

Symptoms usually develop during the first two weeks of neuroleptic therapy, however the association of the syndrome with drug use is idiosyncratic, which means that NMS can occur after a single dose, or after treatment with the same agent at the same dose for many years.

Physicians are advised to have a high index of suspicion for NMS and consider other related conditions like serotonin syndrome, malignant hyperthermia, acute lethal catatonia, and central nervous system infection (meningitis/encephalitis) in the differential diagnosis and clinical workup.

2. Case Presentation

The patient is a 51 year old Caucasian female who was transferred to our medical intensive care unit from other hospital emergency room due to status epilepticus. She initially presented to the emergency room with altered mental status, hyperthermia with a temperature of 109 °F, tachycardia, tachypnea and hypotension that was shortly followed by persistent seizures. Her medical history included osteoarthritis, depression, and history of substance abuse. Her surgical history included appendectomy, lumbar fusion and cholecystectomy. Her medications included Pepcid 40 mg orally twice daily, Ibuprofen 400 mg orally three times daily as needed, Trazodone 50 mg orally once daily, and Prochlorperazine (Compazine) 5 mg orally three times daily as needed. Her family reported that she took around 18 tablets of Prochlorperazine in the last 3 days for nausea and gastrointestinal upset, and this was confirmed by calling her pharmacy to confirm the last date of refill and doing a manual pill count.

Her initial vital signs upon arrival to the first treating facility were a temperature of 109 °F, heart rate of 137 beat/minute, respiratory rate of 25 breaths/minute, oxygen saturation of 71% on room air and blood pressure of 72/32 mmHg. She was actively seizing and hemodynamically unstable, so she was intubated in the emergency department of the first arrival facility, and central venous access was secured to start intravenous fluids and broad spectrum antibiotic coverage with vancomycin, cefepime and levofloxacin per sepsis protocol, this is in addition to ice packs to decrease her temperature. Due to severe acidosis she was also started on bicarbonate drip and got a total of 3 doses of diazepam to abort her seizure.

Initial laboratory work up in the emergency department included complete blood count: (White cell count: 4.9 x10^9/L, Hemoglobin: 11.6 g/dL, Platelets: 279 x10^9/L), complete metabolic profile: (Potassium: 5.7 mmol/L, Sodium: 138 mmol/L, Bicarb: 10 mmol/L, Creatinine: 1.7 mg/dL, AST: 73 U/L, ALT: 35 U/L, Total Protein: 6.6 g/dL), lactic acid: 18.5 mg/dL, arterial blood gas (PH: 7.05, PCO2: 29 mm Hg, HCO3: 8 meq/L, PO2: 55 mm Hg), serum alcohol level: none, acetaminophen level: negative, salicylate level: negative, urine drug screen: negative, urine analysis : trace bacteria, troponin-I: 2.5 ng/mL.

Initial EKG showed sinus tachycardia (Figure 1). Computed tomography (CT) of the head did not show any acute process. CT chest showed bilateral basal atelectasis. CT abdomen and pelvis showed no acute process. Lumbar puncture results were (RBCs: 158 cells/µL, WBC: 2 cells/µL, Glucose: 61 mg/dL, Protein: 28 mg/dL).

The patient did not show any clinical improvement so she was transferred to a higher level of care. Upon arrival to our intensive care unit (ICU) she was already intubated and off sedation, her vital signs were (T: 99 °F, HR: 124 beat/minute, BP: 115/72 mmHg). No signs of bodily trauma. Head atraumatic and normocephalic. Pupils dilated and non-reactive. Cardiovascular examination revealed tachycardic S1 and S2. Respiratory examination revealed bilateral wheezes. Abdominal examination revealed abdominal wall rigidity. She already had an indwelling Foley catheter with cola colored urine in the bag. Her skin was diffusely warm with no visible rash, bruising, hematoma or IV track marks. Central nervous system examination showed an intubated patient with no response to noxious stimulation, however she had significant rigidity in the upper and lower limbs in addition to increased muscle tone. Her deep tendon reflexes were diffusely absent.

At our intensive care unit we continued intravenous fluid resuscitation, bicarbonate drip and broad spectrum antibiotics. Laboratory investigations were repeated to follow the patient clinical response to the initial resuscitation measures. Her ABG showed (PH: 7.3, PO2: 286 mm Hg, PCO2: 30 mm Hg, HCO3: 15 meq/L). Complete blood count (White cell count: 9.5 x 10^9/L, Hemoglobin: 12.1 g/dL, Platelets: 130 x10^9/L). Urine analysis (Bilirubin: Large, Blood: large, Ketone: Positive, Protein >300 mg/dL, Nitrite: Positive, Leukocyte esterase: Positive). Microscopic urine analysis showed (WCC: 5-10 WBCs/hpf, RBC: 5-10 cells/hpf, Casts: Hyaline and Fine granular). Complete metabolic profile (K: 3 mmol/L, Na: 142 mmol/L, Cl: 117 mmol/L, HCO3: 10 mmol/L, BUN: 15 mg/dL, Cr: 1.84 mg/dL, Ca: 5.6 mg/dL, Albumin: 2.9 g/dL, Protein: 5.3 g/dL, Alkaline phosphatase: 53 U/L, AST: 502 U/L, ALT: 117 U/L). Serum Myoglobin > 1000 mg/dL. Creatine kinase (CK) 28234 U/L. Troponin-I > 50 ng/mL. CRP < .4 mg/L. ESR: 8 mm/hour. Repeat urine drug screen was positive for benzodiazepines only.
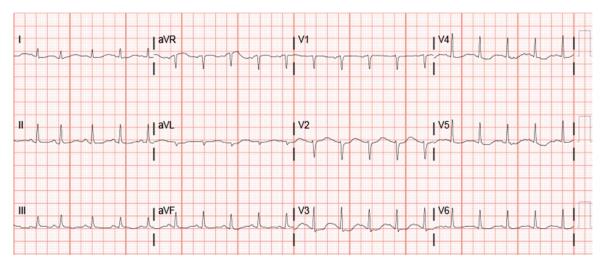

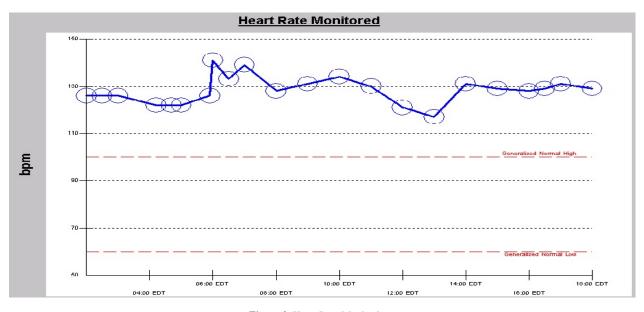**Figure 1.** Sinus Tachycardia in NMS
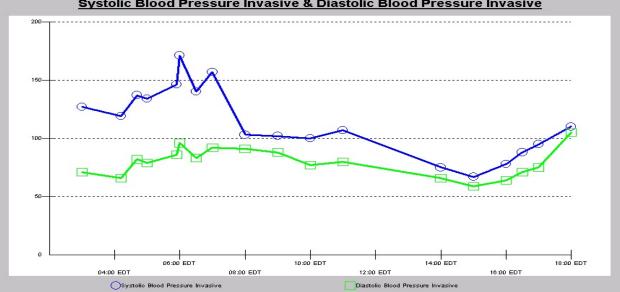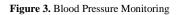
Heart Rate Monitored

Figure 2. Heart Rate Monitoring

Systolic Blood Pressure Invasive & Diastolic Blood Pressure Invasive

Figure 3. Blood Pressure Monitoring
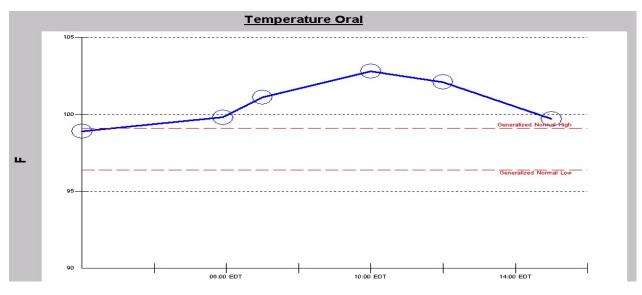
Temperature Oral

Figure 4. Temperature Monitoring

Her heart rate was persistently ranging between 120-140 beat/minute (sinus tachycardia) (Figure 2), blood pressure was labile with multiple hypotensive episodes (Figure 3). Temperature ranged from 100 – 104 °F (Figure 4). She seized again so Levetiracetam (Keppra) was initiated and she was placed on continuous electroencephalogram (EEG) which showed a low amplitude flat line without reactivity throughout. She became hypotensive later so a vasopressor (norepinephrine) was started. Electrolytes abnormalities were continuously corrected and monitored per our electrolytes replacement protocol. Dantrolene was given per neurologist recommendation.

Few hours later the patient developed pulseless ventricular tachycardia, so cardiopulmonary resuscitation (CPR) was initiated with no success in return of spontaneous circulation (ROSC). After multiple cycles of failed CPR the family requested stopping resuscitation measures; and patient ceased. Follow up on the initial blood cultures and urine cultures finalized as no growth in both.

3. Discussion

Neuroleptic malignant syndrome (NMS) is a medical emergency associated with the use of antipsychotics (neuroleptics) and anti-emetics. The syndrome is characterized by a tetrad of mental status change, muscular rigidity, hyperthermia and autonomic dysfunction. The syndrome was first described by Delay and colleagues in 1960, in patients treated with high-potency antipsychotics and it was named (Akinetic hypertonic syndrome) [1]. Incidence rates for neuroleptic malignant syndrome range from 0.07 to 2.2 percent among patients taking antipsychotics [2]. Mortality has declined from the earliest reports in the 1960s of 76 percent to 10 – 20 percent [3,4,5].

NMS occurs as a result of changes in presynaptic or postsynaptic dopamine signaling. The first mechanism by which antipsychotics cause neuroleptic malignant syndrome is that of dopamine D2 receptor antagonism. In this mechanism, central D2 receptor blockade in the hypothalamus, nigrostriatal pathways, and spinal cord leads to increased muscle rigidity and tremor via extrapyramidal pathways. Hypothalamic D2 receptor blockade results in an elevated temperature set point and impairment of heat-dissipating mechanisms [6,7,8,9]. The second mechanism is reduced dopamine signaling resulting from sudden withdrawal of dopaminergic agents or when the drug dosage is abruptly reduced in people taking dopaminergic drugs such as levodopa for Parkinson's disease [10].

Peripherally, antipsychotics lead to increased calcium release from the sarcoplasmic reticulum, resulting in increased muscular contractility which in turn worsens hyperthermia, rigidity, and rhabdomyolysis [11]. Genetic factors play a role in NMS. Case reports of neuroleptic malignant syndrome occurring in identical twins as well as in a mother and two of her daughters have been reported [12]. Genetic studies have shown that the presence of a specific allele of the dopamine D2 receptor gene is over-represented in NMS patients [13].

While symptoms usually develop during the first two weeks of neuroleptic therapy, the association of the syndrome with drug use is idiosyncratic which means that NMS can occur after a single dose or after treatment with the same agent at the same dose for many years [14]. The most common causative medications are antipsychotics and anti-emetics (Table 1 and Table 2). NMS is most often seen with high-potency first-generation antipsychotic agents (e.g Haloperidol, Fluphenazine). However, every class of antipsychotic drugs has been implicated, including the low-potency (eg, Chlorpromazine) and second-generation antipsychotic drugs (eg, Clozapine, Olanzapine) as well as anti-emetic drugs (eg, Metoclopramide, Promethazine). NMS is also seen in patients treated for parkinsonism in the setting of withdrawal of L-Dopa or dopamine agonist therapy, as well as with dose reductions and a switch from one agent to another [10,15].

The main risk factors for NMS are high-potency neuroleptic use, high-dose neuroleptic use, rapid increase in neuroleptic dose, depot injectable neuroleptic use and prior episodes of neuroleptic malignant syndrome. Other potential risk factors include dehydration, malnutrition, organic brain syndromes and Lithium use.

Table 1. Antipsychotic Agents

Haloperidol
Fluphenazine
Clozapine
Chlorpromazine
Aripiprazole
Olanzapine
Zotepine
Amisulpride
Ziprasidone
Thioridazine
Risperidone
Quetiapine
Perphenazine
Paliperidone

Table 2. Antiemetic Agents

Prochlorperazine
Promethazine
Metoclopramide
Domperidone
Droperidol

The tetrad of NMS symptoms typically evolves over one to three days and includes hyperthermia, muscular rigidity, mental status alterations and autonomic instability. Mental status change is the initial symptom in the majority of patients [16]. This often manifests as agitated delirium, confusion, encephalopathy and eventual coma. Autonomic instability typically takes the form of tachycardia, labile blood pressure, tachypnea, diaphoresis, dysrhythmias and hypoxemia [17]. (Figure 5)

Hyperthermia is a defining symptom, temperatures of more than 38°C are typical, but even temperatures greater than 40°C are not uncommon (40 percent) [5]. Muscular rigidity is typically generalized with associated increased tone, and described as "lead-pipe rigidity".
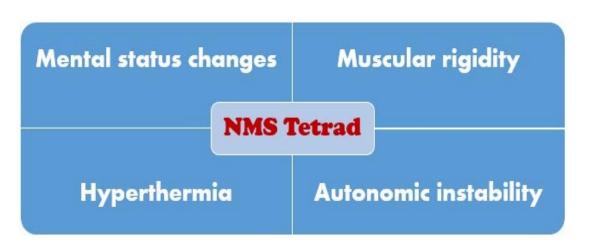
Figure 5. NMS Tetrad

Physical examination will show signs of autonomic dysregulation including hyperthermia, diaphoresis, tachycardia, tachypnea, hypoxemia and labile blood pressure. Signs of decreased dopaminergic activity including muscular rigidity, dystonia and dyskinesia. In addition to signs of psychomotor agitation and altered mental status ranging from agitation to drowsiness, confusion, and coma.

The syndrome occurs within the first two weeks of therapy initiation. However, 90 percent of cases occur within 10 days. In an analysis of 340 cases, 70 percent of patients followed a typical course of mental status changes appearing first, followed by rigidity, then hyperthermia, and autonomic dysfunction [16].

Multiple laboratory abnormalities will be seen in NMS. Complete blood count will show leukocytosis and thrombocytosis. Electrolyte abnormalities like hypocalcemia, hyponatremia, hypernatremia, hyperkalemia, and metabolic acidosis are frequently seen. Elevated creatine kinase (CK) which is typically more than 1000 international units/L [7,16,17,18]. CK elevation correlates with disease severity and prognosis [18]. Elevations of lactate dehydrogenase, alkaline phosphatase, and liver transaminases are common. A low serum iron concentration is sensitive but not specific marker for NMS among acutely ill psychiatric patients [17,19]. Myoglobinuric acute renal failure can result from rhabdomyolysis and correlates with prognosis.

In patients with possible NMS, brain imaging studies and lumbar puncture are required to exclude structural brain disease and infection. Magnetic resonance imaging (MRI) and computed tomography (CT) are typically normal. Cerebrospinal fluid is usually normal, but a nonspecific elevation in protein can be seen.

Electroencephalography (EEG) may be done to rule out non-convulsive status epilepticus. In NMS patients EEG may show a generalized slow wave activity.

Physicians are advised to keep in mind other differential diagnosis that can have similar signs and symptoms including cholinergic crisis, central nervous system infection (meningitis/encephalitis), heat stroke, delirium tremens, pheochromocytoma, thyroid storm and septic shock. Detailed medical history, comprehensive physical examination, in addition to appropriate laboratory testing and imaging can help in narrowing the differential diagnosis. Other clinical syndromes can mimic NMS and should always be included in the differential diagnosis of NMS like serotonin syndrome which is characterized by the triad of altered mental status, autonomic dysfunction, and movement disorder (tremor and abnormal involuntary movement) following exposure to serotonergic agent. The mechanism of serotonin syndrome is excessive 5-hydroxytryptamine (5-HT or serotonin) stimulation. Laboratory findings characteristic of neuroleptic malignant syndrome (eg, elevated creatine kinase level, liver function test abnormalities, and low serum iron level) do not occur in serotonin syndrome. The serotonin syndrome can be distinguished from neuroleptic malignant syndrome by a detailed history of medication use, and the presence of tremor and abnormal movements but the absence of severe rigidity. Treatment includes removal of the offending drug and supportive management [20,21,22,23].

Lethal catatonia occurs in people with schizophrenia or during manic episodes. Neuroleptics might either improve or worsen the symptoms of lethal catatonia. Lethal catatonia tends to have a prodrome of excitement and agitation prior to the onset of rigidity, while neuroleptic malignant syndrome tends to begin with rigidity [24,25,26].

Malignant hyperthermia is distinguished from NMS by its clinical setting. It is caused by an autosomal dominant mutation in the ryanodine receptor, which leads to excessive calcium release from the sarcoplasmic reticulum in skeletal muscles when potent halogenated inhalational anesthetic agents or succinylcholine are administered. Treatment is supportive care, use of Dantrolene to decrease calcium release, and subsequent avoidance of precipitating medication [27,28,29,30].

Treatment of NMS consists of general measures and specific medications. The most important intervention is to discontinue all antipsychotics and removal of other potential contributing psychotropic agents if possible. Maintaining euvolemic state and cardiorespiratory stability. Alkalization of urine to help preventing acute renal failure and enhance excretion of muscle breakdown products. Controlling fever using cooling blankets, ice water, gastric lavage and ice packs, in addition to using benzodiazepines to control agitation and rigidity.

Specific treatments include: Dantrolene, Bromocriptine, Amantadine and Benzodiazepine-Antispasmodic agents.

1. **Dantrolene** is a direct-acting skeletal muscle relaxant and is effective in treating malignant hyperthermia (MH). Doses of 1 to 2.5 mg/kg IV are typically used in adults and can be repeated 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. There is associated risk of hepatotoxicity, and Dantrolene should probably be avoided in the setting of abnormal liver function tests. Common side effects include headache, nausea, vomiting, confusion and hallucinations.

2. **Bromocriptine** is a dopamine agonist prescribed to restore lost dopaminergic tone. It is recommended to be continued for 10 days after NMS is controlled and then tapered slowly. Common side effects include nausea, headache, rhinitis and dizziness.

3. **Amantadine** has dopaminergic effects and is used as an alternative to bromocriptine. An initial dose is 100 mg orally or via gastric tube and is titrated upward as needed to a maximum dose of 200 mg every 12 hours. Common side effects include hallucinations, dizziness, orthostatic hypotension, pre-syncope and syncope.

A reasonable approach is to start with benzodiazepines (Lorazepam or Diazepam) along with Dantrolene in moderate or severe cases, followed by the addition of Bromocriptine or Amantadine [31].

The role of electroconvulsive therapy in NMS:

In patients with neuroleptic malignant syndrome, electroconvulsive therapy (ECT) helps with the alteration of temperature and level of consciousness. ECT should be considered in patients not responding to medical therapy in the first week, those in whom residual catatonia persists after other symptoms have resolved, and those in whom lethal catatonia is suspected as an alternative or concomitant disorder [32,33,36,37,38]. In a case series study of 15 patients who had neurocognitive or schizophrenia spectrum disorders and developed NMS after exposure to multiple antipsychotic drugs. All patients received bi-temporal ECT after failed pharmacotherapy for NMS. Electroconvulsive therapy resulted in a remission rate of 73.3%. Patients showed early initial response to ECT (mean of 4.2 treatments), but an average of 17.7 treatments was necessary to minimize recurrence of catatonic signs [36].

ECT is generally safe, however, serious treatment-related complications including cardiac arrest and ventricular fibrillation have been reported [32-38].

Prognosis:

The reported mortality rates for NMS vary between 5 to 20 percent. Disease severity and the occurrence of medical complications are the strongest predictors of mortality [39,40].

4. Conclusion

Neuroleptic malignant syndrome is a medical emergency associated with the use of neuroleptic agents and characterized by a distinctive clinical syndrome of mental status change, rigidity, hyperthermia and dysautonomia. The most common causative medications are antipsychotics and anti-emetics. NMS can occur after a single dose or after treatment with the same agent at the same dose for many years. It is not a dose-dependent phenomenon, but higher doses are a risk factor.

Physicians are advised to have a high index of suspicion and consider other related differential diagnosis in the clinical workup, as early recognition and treatment is of pivotal importance to reduce morbidity and mortality of this fatal entity.

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