CASE REPORT

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Neuroleptic Malignant Syndrome Masquerading as Sepsis

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Abstract

Neuroleptic malignant syndrome (NMS) is a rare complication secondary to exposure to a dopamine antagonist or withdrawal of a dopamine agonist. Differential diagnoses of NMS include other conditions associated with increased body temperature such as sepsis, drug withdrawal, thyrotoxicosis, malignant hyperthermia, and serotonin syndrome. Sepsis, as a cause in this setting, has to be ruled out since NMS is a diagnosis of exclusion, which may cause considerable delay. We present a patient who was admitted to the Cardiothoracic Intensive Care Unit after a redo-coronary artery bypass grafting. He was administered two doses of metoclopramide, a dopamine antagonist, for postoperative gastroparesis and as a second-line antiemetic agent. He developed increased body temperature the following day, which did not return to baseline until administration of bromocriptine. The patient was on vasoactive support and invasive ventilation, which impeded the clinical diagnosis of NMS. The only positive features were raised creatine phosphokinase levels and increased body temperature. The patient eventually succumbed to multi-organ failure post-surgery even though NMS was treated. Administration of agents known to potentially cause NMS should always be viewed with suspicion, especially in acute settings where signs and symptoms could be masked. Response to bromocriptine, rise in creatine kinase levels, and persistent increased body temperature may aid in the diagnosis of NMS in a susceptible patient.

Keywords: Bromocriptine; Creatine phosphokinase; Neuroleptic malignant syndrome; Sepsis.

Introduction

Neuroleptic malignant syndrome (NMS) is a diagnosis of exclusion. The syndrome, by definition, constitutes hyperthermia, rigidity, autonomic dysfunction, altered mental status, elevated creatine kinase (more than four times the normal limit), and exposure to a dopamine antagonist or withdrawal of a dopamine agonist within the previous 72 hours of symptom onset.[1] Neuroleptic malignant syndrome is a clinical diagnosis and can be masked by other causes of raised body temperature, including fever. In patients with sepsis requiring sedation and invasive mechanical ventilation, diagnosing NMS might be challenging. NMS is an idiosyncratic reaction to drugs such as typical and atypical antipsychotics.[2] Among these drugs, metoclopramide and haloperidol are commonly used

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medications in intensive care unit (ICU) patients. Metoclopramide is a dopamine antagonist that is used as an antiemetic and a prokinetic agent for improving gastric motility. We report a patient who developed metoclopramide-induced NMS in the ICU after a redo-coronary artery bypass grafting (CABG), who required invasive mechanical ventilation and vasoactive drug infusions with intra-aortic balloon pump (IABP) support postoperatively for shock.

Case Report

A 60-year-old male patient was admitted to the Cardiothoracic Intensive Care Unit after redo-CABG. Postoperatively, he was sedated and ventilated with IABP support and vasoactive drug infusions for cardiogenic shock. On postoperative day (POD) 2, bedside clinical examination revealed abdominal distension. He was on nasogastric (NG) feeding and had not passed stools for more than 48 hours. He had large NG aspirates and vomiting. Serum electrolytes were normal, and a bedside chest X-ray showed a distended stomach. Feeds were withheld and the NG tube was aspirated to decompress the stomach. Two intravenous doses of 10 mg metoclopramide were administered 12 hours apart to improve gastric motility and as a second-line antiemetic agent.

On POD 3, he developed increased body temperature (Fig. 1, Table 1) with elevated white blood cell (WBC) counts and purulent endotracheal secretions, suggestive of chest infection and sepsis. Antibiotics were escalated after sending blood and deep tracheal aspirate for cultures. With no improvement in the clinical status, indwelling catheters were replaced and drains were removed. All the cultures, tropical fever work-up, computed tomography (CT) imaging of the thorax and abdomen were negative for the source of suspected sepsis.

Despite appropriate empiric therapy, there was persistent fever and clinical deterioration. On POD 6, NMS was suspected and creatine phosphokinase (CPK) level was 94,037 U/L. Tablet bromocriptine 5 mg was administered every eight hours, and body temperature normalized within 24 hours, thereby confirming the diagnosis of NMS. However, with worsening shock and acute kidney injury, continuous renal replacement therapy (CRRT) was initiated (on POD 9). The patient developed multi-organ failure and succumbed to his illness on POD 12.

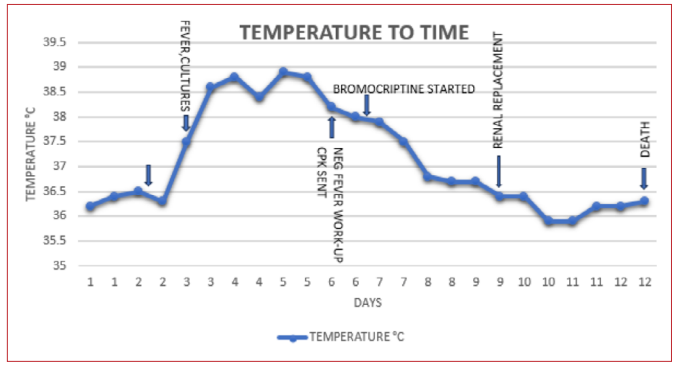

Figure 1. Temperature to time graph.

Table 1. Timeline of key clinical data and interventions

Postoperative Day (POD)	Temperature Trend (see Figure 1)	Key Laboratory Findings	Clinical Events/Interventions
POD 2	Afebrile	Normal laboratory results	Abdominal distension, large NG aspirates; 2 IV doses of metoclopramide (10 mg 12 hours apart) given for gastroparesis.
POD 3	Fever spike	↑ WBC counts	Purulent endotracheal secretions → Antibiotics escalated after sending cultures.
POD 4–5	Persistent fever	Cultures negative; tropical fever work up negative	Catheters and drains replaced; continued suspicion of sepsis despite lack of improvement.
POD 6	Persistent hyperthermia	CPK 94,037 U/L	NMS suspected → Bromocriptine 5 mg started.
POD 7	Temperature normalized within 24 hours	CPK trending down	Response to bromocriptine confirmed NMS diagnosis.
POD 9	Afebrile	Worsening renal parameters	CRRT initiated for acute kidney injury.
POD 10–12	Afebrile	Progressive multi organ dysfunction	Despite interventions, patient succumbed on POD 12.

Discussion

Though uncommon, NMS is a potentially fatal complication secondary to exposure to neuroleptic medications, with mortality rates reported between 10-30%.[3] Among the patients who develop NMS, two-thirds manifest within 48 hours of exposure to the offending agent.[4] Other than the offending drug, major risk factors for NMS reported are increased age, comorbidities, dehydration, use of physical restraint, and previous history of NMS.[5]

Patients admitted to ICU are susceptible to infections and sepsis, depending on their clinical profile. Our patient underwent a redo CABG surgery and postoperatively required multi-organ support. He also had multiple catheters and drains, putting him at high risk for developing sepsis. Intravenous metoclopramide is recommended by the U.S. Food and Drug Administration (FDA) for gastroparesis.[6] Our patient was administered two doses of intravenous (IV) metoclopramide for postoperative gastroparesis to improve gut motility and as a second-line antiemetic agent.

The classical presentation of NMS includes altered mental status and rigidity, but both can be obscured in ICU settings due to sedation and paralysis. Hence, in such patients, an increase in body temperature could be the only clinical sign. However, our patient was also hemodynamically unstable with increased total counts and multi-organ failure, so we considered septic shock as a possible diagnosis. He also had many risk factors associated with sepsis in post-cardiac surgical patients.[7]

He required continuous sedation and paralysis due to severe hypoxia and high ventilator support. Negative blood cultures, lack of clinical improvement despite 72 hours of antibiotic therapy, persistent hyperthermia, and markedly elevated CPK levels prompted us to consider the diagnosis of NMS. A potential diagnosis of NMS in our patient was considered after a meticulous drug chart review, given that all the cultures were negative and potentially offending catheters and invasive lines were either removed or replaced. Other causes like tropical fever were also ruled out (malaria, typhoid, and dengue). As a diagnosis of exclusion, hyperthermia with elevated creatine kinase levels and subsequent worsening renal parameters also pointed toward NMS.

Bromocriptine mesylate, a dopamine agonist, is commonly used to treat NMS. Incremental doses were started at 2.5 mg three times daily. Hyperthermia resolved after 24 hours of starting bromocriptine with an increased dose of 5 mg/dose. Dantrolene was not considered as hyperthermia had settled. Hence, administration of bromocriptine leading to normalization of body temperatures confirmed the diagnosis of NMS.

Metoclopramide-induced neuroleptic malignant syndrome, though rare (incidence 0.02–1.2%, mortality ~20%),[8,9] has been reported in various settings. Early cases include two diabetic patients who recovered with timely management,[10] a two-year-old given high-dose intramuscular metoclopramide with classical NMS signs,[9] and a postoperative adult who developed symptoms after 80 mg of metoclopramide and responded to dantrolene and bromocriptine.[11] Another case involved a 50-year-old with oral metoclopramide use who presented with hyperthermia, rigidity, myoglobinuria, and elevated CPK, managed with carbidopa, baclofen, and supportive care.[12] Most cases occurred in non-critical patients with high-dose exposure and low suspicion for sepsis. In contrast, our critically ill patient presented diagnostic challenges due to sedation, mechanical ventilation, and intermittent neuromuscular blockade, which limited neurological assessment. Nevertheless, the patient showed elevated creatine kinase and responded to bromocriptine, consistent with features reported in previous cases.

The pathophysiology of NMS is complex, with one cause being sudden dopamine receptor blockade or dopaminergic agent withdrawal in nigrostriatal, hypothalamic, and mesothelial/cortical pathways.[13] Other causes may include sympathoadrenal hyperactivity, defects in calcium regulatory proteins similar to malignant hyperthermia, and antipsychotic-induced calcium release from skeletal muscle sarcoplasmic reticulum.[2]

Rhabdomyolysis may occur due to one of the above mechanisms, and its occurrence is not uncommon in NMS.[14] This may lead to renal failure requiring renal replacement therapy. Disseminated intravascular coagulation can also be seen as a fatal sequela.[2]

Despite normalization of body temperature and renal replacement therapy, our patient had worsening multi-organ failure and succumbed on the 12th postoperative day. Poor left ventricular function, post-surgical state, and renal replacement in this patient contributed to his fatality.

Differential diagnosis of NMS includes infection leading to sepsis, drug withdrawals, thyrotoxicosis, malignant hyperthermia, and serotonin syndrome, to name a few. Sepsis in a critical care setting is much more common; hence it needs to be ruled out prior to diagnosing other causes of hyperthermia, causing considerable delay. Other causes of hyperthermia, such as serotonin syndrome, may also present with hyperthermia and autonomic dysfunction, but it is typically associated with clonus, hyperreflexia, and serotonergic drug exposure rather than dopamine antagonism. Malignant hyperthermia shares features of hyperthermia and rigidity, yet it is generally triggered by anesthetic agents such as succinylcholine or volatile anesthetics and occurs intra or perioperatively. Heat stroke and anticholinergic toxicity were excluded on the basis of history, drug exposure profile, and absence of typical features such as dry mucosa or prominent delirium. Thyrotoxicosis was unlikely with no history and clinical features of thyroid excess.

The use of medications known to precipitate neuroleptic malignant syndrome warrants careful consideration, particularly in critically ill patients where clinical signs may be obscured by sedation, mechanical ventilation, or neuromuscular blockade. In such settings, a high index of suspicion is essential. It is also important to recognize that NMS can both mimic and complicate underlying sepsis, further obscuring the clinical picture. Moreover, NMS may present with a delayed onset, emerging days after exposure to the causative agent. Key diagnostic clues include persistent hyperthermia, elevated creatine kinase levels, and clinical improvement following bromocriptine therapy.

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