

Case Report

Atypical neuroleptic malignant syndrome. “Doing more harm than gain”

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ABSTRACT

Neuroleptic malignant syndrome (NMS) a rare, idiosyncratic, and potentially fatal adverse reaction can be deceptive especially when the hallmark features are lacking. Most diagnostic criteria include fever and muscle rigidity, although NMS may present without either. Delirium, agitation and catatonia can be the earliest features of NMS and in acute care settings, concomitant use of sedatives and anti-psychotics by the attending clinicians may even obscure the sentinel signs of NMS and further aggravate the underlying insult. A strong clinical suspicion based on clinical history is crucial for early diagnosis and treatment and the strict adherence to the classical criteria of NMS may lead to a diagnostic delay and dire consequences for these patients and sometimes this delay can procure death.

Keywords: Neuroleptic malignant syndrome, Idiosyncratic, Muscle rigidity

INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a rare life-threatening idiosyncratic reaction to antipsychotic drugs. There is a marked risk with rapid dose adjustment and with parenteral administration even when the drug levels are in the therapeutic range. Every class of neuroleptic drugs has been implicated, including the newer ‘atypical’ antipsychotics.¹ A number of diagnostic criteria are currently in use, however there is no consensus of opinion and fever, muscle rigidity and altered level of consciousness are the most common and classical features of this syndrome.² When the above typical features are lacking, the patients may be treated for an exacerbation of a their primary psychiatric disorder, suspected neurological infections or adverse drug effects hence delaying the diagnosis of a rare but life threatening condition. A case is described that illustrates an atypical presentation of NMS in a patient with schizophrenia which includes an unusual course of the syndrome and absence of muscular rigidity and highlights some of the

challenges met in making the diagnosis and the final outcome of this delay.

CASE REPORT

A fifty year old female having schizophrenia on atypical antipsychotics (Olanzapine 10 mg and quetiapine 200 mg qd) for last few years sought a psychiatry consultation at a community hospital for evaluation of altered behaviour in the form of incoherent talking and agitation which was noticed by her family for past four days. She had a history of being non compliant to the treatment in the recent past. She was afebrile and in view of her psychiatric illness, a provisional diagnosis of exacerbation of psychosis was made and she received intramuscular 5 mg of haloperidol and 0.5 mg of clonazepam twice daily. However her agitation remained unchanged. She continued to be on the above prescribed drugs and two days after she was referred to this hospital for further evaluation. She was sweating, anxious and had gross confusion upon arrival in the emergency department. On examination her pulse was 116 beats/min,

blood pressure 130/90 mmHg, respiratory rate 18 breaths/min and oral temperature of 100°F. Cardiovascular, respiratory and abdominal examinations were unremarkable. She was non co-operative and a 5 mg intramuscular dose of haloperidol was given for sedation and oral haloperidol 2.5 mg twice daily was prescribed. Neurologic examination showed normal deep tendon reflexes, absent neck rigidity and normal muscle tone. Magnetic Resonance Imaging (MRI) scan of the brain showed no intracranial insult. Laboratory investigation revealed leukocyte count of $13 \times 10^3/\mu\text{L}$ with normal differential count, serum bilirubin -1.2 mg/dl, aspartate transaminase (AST) - 85 IU/L, alanine transaminase (ALT) -40 IU/L, alkaline phosphatase -150 U/l, serum urea -156 mg/dl, serum uric acid 6.5 mg/dl and serum creatinine - 1.3 mg/dl. Serum electrolytes showed potassium - 4.9 meq/l, sodium - 143 meq/l and calcium - 0.89 mmol/l. TSH (thyroid stimulating hormone) was normal and serum creatine phosphokinase (CPK) was 290 IU/L. Electrocardiogram revealed sinus tachycardia and cerebrospinal fluid (CSF) study was normal. She had no history of any drug abuse or alcohol intake. The working diagnosis of sepsis with encephalopathy was made and antibiotics (ceftriaxone plus acyclovir) were started, together with other supportive treatment. However eight hours after her admission to the hospital she was still febrile (102.9 F) and tachypneic (28 breaths/min). Although her agitation abated, re-examination added no new signs except for worsening sensorium. In addition, other laboratory abnormalities revealed serum urea -110 mg/dl, serum uric acid - 12mg/dl and serum creatinine - 4.1 mg/dl. AST was 345 IU/L, ALT -100 IU/L, CPK -10,900 IU/L, Lactate dehydrogenase (LDH) 2590 IU/L and her condition deteriorated. She tested negative to HbsAg, Anti - HCV antibody, ANA and her coagulation profile was normal. The arterial blood gas analysis showed pH 7.25, pO₂ - 94 mmHg, pCO₂ - 49 mmHg, lactic acid - 3.3 mmol/L and bicarbonate- 22 mmol/L suggesting worsening acidosis and she was intubated for ventilatory support. The diagnosis at this stage remained uncertain, but rhabdomyolysis with hyperthermia and neuroleptic malignant syndrome (NMS) were considered although there was no muscle rigidity. All psychotropic medications were discontinued and supportive therapy with hydration for acute kidney injury was started and a prompt decision for bromocriptine administration was taken. However the patient developed malignant cardiac arrhythmia and ultimately succumbed to cardiac arrest before any specific therapy was administered. The patient's family refused any hospital autopsy.

DISCUSSION

This case illustrates one of the many clinical presentations possible with NMS with the depot use of potent anti psychotic drug in a patient who was earlier on stable atypical anti psychotic therapy. She had several sentinel findings suggestive of NMS including, leukocytosis, diaphoresis, change in mentation and

tachycardia but together they did not qualify for the most commonly used criteria set for NMS.² Our patient was treated for exacerbation of her psychiatric illness initially with the same class of drugs in emergency department. Later the patient was empirically treated for infective encephalopathy instead. The diagnosis of NMS was established based on the typical history of depot drug administration and other characteristic features including high fever, worsening mentation, greater elevations of serum CPK levels, and rhabdomyolysis although there was no muscle rigidity present throughout the course. In over 80% of cases altered mental status presenting as delirium, catatonia or agitation is the first sign of NMS before any systemic signs appear.³ Cases without fever and/or absence of rigidity or only mild rigidity have also been described especially with atypical antipsychotic drugs.⁴

Patients with delirium in acute care settings are generally treated with antipsychotics which continue to be the initial choice in the working guidelines.³ In the critical care setting where concomitant use of sedatives may obscure the early signs of NMS, it becomes a tricky situation for the clinician to deal with. NMS if undiagnosed may lead to serious complications like renal failure, thromboembolism, respiratory failure, aspiration pneumonia, and arrhythmia.⁵ Hepatic dysfunction occurs in approximately 25% of patients with rhabdomyolysis.⁶ Our patient landed in to acute kidney injury due to rhabdomyolysis and developed acute metabolic acidosis and ultimately succumbed to cardiac arrest, a documented outcome of NMS before any specific therapy was given. The agreement between various parallel diagnostic criterion of NMS is poor and adherence to a stricter set of criteria like DSM-IV (The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) mandates the presence of fever or muscle rigidity as a major domain for diagnosing NMS.² However employing criteria such as those proposed by Levenson or Nierenberg and colleagues can help the clinicians to grow more suspicion for NMS.⁷ Our patient fulfilled the latter proposed less known criteria for diagnosing NMS. Diagnosing NMS poses a challenge when a patient presents with agitation, mental state changes without marked abnormalities of temperature or muscle tone. The fact that no muscle rigidity was present although severe elevation of CPK levels were noticed suggests that there is a direct drug toxic effect on the skeletal muscle while muscle rigidity seems to be central in origin involving nigrostriatal pathways.¹ A more specific therapy might have changed the course of the ongoing insult in our patient.

Nevertheless even with more sensitive criteria, a high index of suspicion is still necessary for clinicians to make a prompt diagnosis based on clinical history and vigilant detection of early signs because adherence to strict diagnostic criteria may lead to an alternate and/or delayed diagnosis and hence "do more harm than gain" to the patient.

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