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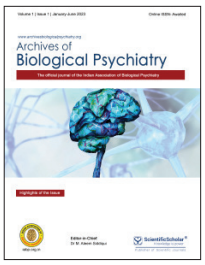

Case Report *Psychiatry*

Neuroleptic malignant syndrome presenting without hyperthermia: A case report of an atypical presentation

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ABSTRACT

Neuroleptic malignant syndrome (NMS) is a life-threatening complication of antipsychotic medications. NMS is characterized by four key symptoms: Changes in mental status, muscular rigidity, hyperthermia, and autonomic dysfunction. Despite its key clinical symptoms, which are easily recognizable in a classic presentation, NMS occasionally does not present with all the described clinical characteristics. Atypical presentations of NMS pose a diagnostic conundrum for clinicians, leading to late recognition and treatment of a potentially treatable life-threatening condition. We present a case of NMS presenting without hyperthermia and autonomic instability but with elevated creatine kinase.

Keywords: Neuroleptic malignant syndrome, Catatonia, Atypical neuroleptic malignant syndrome

INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a life-threatening complication of antipsychotic medications. NMS is characterized by four key symptoms: Changes in mental status, muscular rigidity, hyperthermia, and autonomic dysfunction.[1]

According to the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria, to make a diagnosis of NMS, all three core features (exposure to the dopamine-blocking agent, severe muscle rigidity, and fever) are required, along with two of the minor criteria.[2] Despite its key clinical symptoms, which are easily recognizable in a classic presentation, NMS occasionally does not present with all the described clinical characteristics.[3] Such atypical presentations of NMS have been conceptualized as atypical NMS. A consensus definition of atypical NMS is still lacking in major diagnostic criteria sets. Still, Picard *et al.*, in 2008, have given the concept of the NMS spectrum and have emphasized the need to consider atypical presentations of NMS when any one of these typical presentations is absent.[4] They presented several cases where atypical NMS, mostly caused by second-generation antipsychotics, did not cause hyperthermia or extrapyramidal symptoms. Notably, clozapine, olanzapine, risperidone, and aripiprazole were the most common ones to cause atypical presentation of NMS.[4] Despite clinical caution, cases of NMS are often missed due to the atypical presentations, leading to delays in the appropriate management of this life-threatening condition. With this background, we present a case of NMS preceded by Catatonia and presenting without hyperthermia and autonomic instability but with elevated creatine kinase (CK).

CASE REPORT

A 21-year-old unmarried male, hailing from rural India, with nil contributory past or family history of psychiatric illness and well-adjusted pre-morbid personality was brought to the outpatient department of our institute with an acute onset and gradually worsening illness characterized by decreased sleep, fearfulness, crying spells, reduced social interaction, low mood for 1 month, not talking, maintaining of abnormal posture, and not taking food or water voluntarily for 4 days. According to informants, the symptoms started after he experienced a setback in an examination. Physical examination was unremarkable apart from posturing. On behavioral observation, the patient was alert and awake, mute, prolonged posturing was present, eye blink rate and motor activity were reduced, and he was repeating the interviewer's actions. Bush Francis Catatonia Rating Scale (BFCRS) score was found to be 14. A provisional diagnosis of major depressive disorder, single episode, severe with psychotic symptoms, and Catatonia associated with another mental disorder was made according to DSM-5. He was admitted to the acute ward of our institute.

1st week: After a failed trial of oral lorazepam up to 8 mg thrice daily for 6 days, modified electroconvulsive therapy (ECT) was started. 2nd week: After 3 sessions of ECT, the patient's symptoms improved. The BFCRS score was reduced to 1. 3rd–5th week: He was started on oral olanzapine (titrated up to 20 mg/day at the rate of 5 mg every 5 days) and fluoxetine (titrated up to 40 mg). Oral lorazepam was slowly titrated down (at the rate of 2 mg every 3 days), and ECT continued for up to 8 sessions. 6th week: Within 3 days after ECT was stopped, symptoms of Catatonia reappeared (BFCRS-7). Computed tomography of the brain showed no significant abnormality. ECT was restarted. 7th–9th week: Olanzapine was cross-titrated with oral aripiprazole (started at 10 mg and titrated up to 15 mg after 5 days). After 2nd session of ECT, he was found to be disoriented to time, place, and person with dystonic posturing of the neck, having cogwheel rigidity of limbs, talking irrelevantly, and suspicious about his surroundings. Picking behavior was observed. These features had an acute onset. The rest of the physical examination was unremarkable, including the absence of hyperthermia. Delirium was suspected, and all medications were stopped; only intramuscular lorazepam 2 mg in the evening and on as per requirement (SOS) was given. Leucocyte count, serum electrolytes, and liver function tests were normal, but urine sugar and protein were 2+, and CK-N-acetyl-cysteine (NAC) activated was 3055 IU/L. In view of this clinical picture, a diagnosis of NMS was considered. MRI report revealed prominent cortical sulci and gyri with prominent cerebellar folia, suggestive of diffuse brain volume loss. As he was unable to take food and medications, he was started on IV fluids and was catheterized under the cover of broad-spectrum antibiotics. Intake-output charting was started. Before the onset of this clinical picture, no injectable psychotropic apart from lorazepam was used. Tab Amantadine 200 mg was started due to availability issues at our place with the more preferable agents such as dantrolene and bromocriptine. ECT was restarted for managing NMS as he was not improving with medication. ECT was continued for eight sessions. After 2 weeks, he started showing improvement. 10th week: Oral quetiapine 50 mg/day (titrated up to 150 mg/day) and sertraline 50 mg/day (titrated up to 200 mg/day) were started. Memantine 10 mg/day was added to the regimen, considering its role as an adjunctive agent in the management of NMS.[5] His orientation improved and he started talking relevantly. Repeat investigations after 3 weeks, including CK-NAC, came to be within physiological range. His effect became cheerful, and mental state examination did not reveal any active psychopathology. He was discharged on quetiapine 200 mg/day, sertraline 150 mg/day, memantine 10 mg/day, and amantadine 200 mg/day. On his follow-up visits after 2 weeks and 1 month of discharge, he was maintaining well without any new complaints. On follow-up visits, memantine and amantadine were gradually stopped.

DISCUSSION

The clinical picture in our case suggested the following possibilities: post-ECT delirium, malignant Catatonia, or NMS. Evidence suggested that modern-day usage of anesthesia and muscle relaxants in modified ECT does not lead to a significant alteration in both brain type and muscle type CK.[6,7] One study even reported a reduction in total CPK levels after modified ECT.[8] Moreover, clinically too, muscular rigidity and dystonic posturing are relatively less commonly seen in delirium. Therefore, we considered this clinical picture as NMS rather than post-ECT delirium. Continuing ECT further improved his condition, rather than worsening the neurocognitive symptoms, further supporting a diagnosis of NMS over post-ECT sequelae.

Our case was preceded by Catatonia, which threw the initial dilemma of diagnosing NMS. Research suggests that NMS and malignant catatonia share a common spectrum and, thereby, share clinical features and pathophysiology.[9] Several reports have suggested a diagnostic dilemma between these two syndromes, while few have proposed one being a risk factor for the other.[10-15] When compared with NMS, catatonia shares muscle rigidity, and malignant catatonia shares all the clinical features except for antipsychotic exposure. Hyperthermia was absent in this case. Although easily recognized in its classic presentation, NMS is often heterogeneous in its clinical picture. Often, in its "atypical" presentation, either hyperthermia or rigidity is absent, or it develops slowly over many days.[4] Several sets of diagnostic criteria have tried to describe NMS. Picard *et al*.[4]

have critically appraised five sets of diagnostic criteria for NMS. All except one considers concurrent hyperthermia and muscle rigidity as essential to diagnose NMS.[4,16] Levenson[16] suggested that NMS should be considered in patients who either meet the three major manifestations: Fever, rigidity, elevated CK level, or two of these precedent major manifestations accompanied by at least four of the minor manifestations: tachycardia, abnormal blood pressure, tachypnea, altered consciousness, diaphoresis, and leukocytosis. None of the three major symptoms (fever, rigidity, and elevated CK level) is an essential requirement to diagnose NMS here. In atypical presentations, elevated CK levels have helped clinicians to detect and monitor NMS. Several mechanisms, including agitation, hyperactivity, hyperthermia, physical muscle injury, agitation, rhabdomyolysis, and medication, have been thought to increase CK levels in these cases.[17-19] Contrary to this, NMS has been diagnosed without elevated CK[20,21], and elevated CK is not necessarily always associated with NMS.[22] In our case, preceding Catatonia could have been the reason for precipitating NMS.

CONCLUSION

Our case highlighted that the absence of hyperthermia and the presence of elevated CK should cause suspicion of NMS in a case with treatment with psychotropics, more notably with second-generation antipsychotics. Early identification of atypical cases of NMS can help clinicians effectively manage a lethal but potentially treatable condition.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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