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Case Report

# NEUROLEPTIC MALIGNANT SYNDROME: THE NEED FOR A HIGH INDEX OF CLINICAL SUSPICION EVEN WHEN ON ATYPICAL ANTIPSYCHOTICS IN ASIAN POPULATION – A CASE REPORT

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**ABSTRACT**

Neuroleptic malignant syndrome (NMS) is a rare life-threatening neurological disorder associated with the use of antipsychotic medications. Second-generation antipsychotics were assumed to have a lower risk of developing NMS; however, cases are being reported nowadays. Here, we are discussing of a 64-year-old male patient with underlying coronary artery disease, chronic obstructive pulmonary disease, and recurrent depressive disorder for which he was on an atypical antipsychotic, olanzepine from an outside center admitted in our hospital with the syndrome of NMS. He was brought to the emergency department with complaints of delirium, confusion, and urinary incontinence. On examination, he had fever, disorientation, and cogwheel rigidity with raised creatine phosphokinase values in blood tests. He was diagnosed with NMS after ruling out other causes for delirium and similar manifestations such as serotonin syndrome and malignant hyperthermia. This case illustrates the fact that the incidence of NMS due to atypical antipsychotics is not negligible and the need for monitoring elderly patients who take this class of drug, especially while escalating doses as the condition is fatal. Our case report also looks into other probable predisposing as well as precipitating factors which need to be considered with caution.

**Keywords:** Neuroleptic malignant syndrome, Creatinine phosphokinase, Electroencephalogram.

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## INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a rare, unpredictable adverse reaction associated with antipsychotic drug use. It is generally characterized by rigidity, tremors, fever, dysregulated sympathetic nervous system hyperactivity, alterations of mental status, leukocytosis, and creatine kinase elevation. If not promptly recognized and treated, NMS can lead to patient death or permanent damages, such as neurological sequelae [1]. Known risk factors include dehydration, malnutrition, agitation, young age, first-generation antipsychotics (formerly called "typical antipsychotics"), parenteral antipsychotics, as well as co-medication with lithium, preexisting organic brain damage, alcohol and drug addiction, and a history of NMS. NMS complications are electrolyte imbalance, thrombosis, pulmonary artery embolism, pneumonia, seizures, rhabdomyolysis, acute renal failure, sepsis, and multi-organ failure. Other fatalities have resulted from sudden cardiorespiratory arrest, aspiration pneumonia, pulmonary emboli, and disseminated intravascular coagulation [2]. The incidence of NMS was found to be within the range of 0.2–3.23% in patients treated with neuroleptics. According to a study performed in a hospital in the Indian setting, the incidence of NMS was 1.41/1,000 cases treated with neuroleptics (95% confidence interval, 0.71–2.14/1,000) and the mortality from NMS was 38% [3].

It has been suggested that the cause of NMS may be multifactorial. The pathophysiology of NMS is not entirely understood, although it has been established that acute reduction of dopamine activity in the brain is the basic underlying mechanism. Currently, NMS is thought to be caused by central or peripheral dopaminergic blockade, resulting in muscle rigidity and core temperature elevation. Dopamine blockade in the nigrostriatal pathway is the source of the muscular rigidity or lead-pipe rigidity (i.e., a type of increased muscle tone, in which pathologic resistance to passive extension of a joint is constant throughout the range of motion), whereas blockade in the hypothalamus can result in hyperthermia. It is unlikely the dopaminergic blockade theory is the sole explanation given serotonergic, noradrenergic, and cholinergic pathways are also implicated. It is thought that glutamate also plays a role, which explains why the drug amantadine (an N-methyl-D-aspartate S-type glutamate receptor antagonist) is used to treat NMS [2].

NMS is usually seen in treatment with high potency typical neuroleptics, depot and intramuscular preparations, and very infrequently with atypical antipsychotics. Olanzapine is a thienobenzodiazepine atypical antipsychotic related to clozapine that acts on dopaminergic, serotoninergic, histaminergic, and muscarinic receptors. Olanzapine was supposed to be less frequently associated with the occurrence of NMS [4]. Johnson and Bruxner published the first case of NMS associated with olanzapine use in 1998.

## CASE REPORT

A 64-year-old male patient with underlying recurrent depressive disorder, coronary artery disease, and chronic obstructive pulmonary disease presented to our hospital with complaints of delirium, disorientation, and restlessness. The patient had a history of restlessness for the past 2 days with 2 episodes of urinary incontinence, fever, confusion, and decreased food intake.

The patient was disoriented to time, person and place, agitated, and was febrile with a temperature of 100.8 F and labile blood pressure ranging from 170/100 mmHg to 130/100 mmHg. The patient also had tachypnea (RR-32 breaths/min), tachycardia (HR-115 beats/min), and diaphoresis. On examination, it was found that the patient had tremors and rigidity of both upper and lower limbs. Lab investigations showed an elevated creatine phosphokinase (CPK) value 1521 units/L on the day of admission, increased to 20,269 U/L on 2$^{nd}$ day, and leukocytosis

13,000 cells/mm$^3$. Magnetic resonance imaging brain was done in view of worsening neurological function and was within normal limits. Patient's electroencephalogram report shows a mild degree of generalized nonspecific electrophysiological dysfunction. Recording with the patient in an awake state showed the background activity in the theta range (slowing in theta region) which is found in NMS.

The patient had a medical history of recurrent depressive disorder for almost 8 years for which the patient was on tablet olanzepine 5 mg 1–0–1 (10 mg daily), tablet fluoxetine, and tablet quitepine from another Centre. Furthermore, patient had a recent history of hospital admission due to aggressive behavior and agitation, after which medications were changed – tablet quitiepine and tablet Fluoxetine were stopped, a dose of olanzapine was doubled from 10 mg/day to 20 mg/day, tablet sertaline 1–1/2–0, and tablet nitrazepam 10 mg 0–0–1/2 were added. He took the medications for 2 weeks before he was presented with the abovementioned symptoms.

Psychiatry consultation was sought from the emergency department as the patient was on antipsychotics and in the casualty as NMS was considered a differential diagnosis all antipsychotic medications were stopped and an initial CPK value was sent. The patient was admitted to general medicine department and other causes of delirium infectious, autoimmune, and metabolic were ruled out. In view of elevated CPK, lead pipe rigidity of both upper and lower limb, hyperthermia, tachycardia, tachypnea, and diaphoresis. NMS was considered as a differential diagnosis after ruling out chances of serotonin syndrome as the patient did not show any symptoms such as myoclonus, mydriasis, or hyperreflexia. Bromocriptine was initiated at 2.5 mg twice daily and injection lorazepam was given. Intravenous fluids administered for hydration and prevention of renal failure. Gradually, CPK values declined from 20,269 units/L to 18,052 units/L on day 2 then to 8314.5, 3679.3, and 551,437 units/L and other symptoms such as tachycardia, tachypnea, and rigidity also resolved. Although the symptoms of NMS gradually improved, the patient developed restlessness, and disorientation for which the patient was treated with lorazepam. However, as the symptoms were not controlled, atypical antipsychotics were reintroduced and tablet clozapine 12.5 mg twice daily was started and the patient tolerated. Patient's sensorium improved gradually and slowly became oriented to time, place, and person and the patient was hemodynamically stable and was discharged after a few days of hospital stay.

The Fig. 1 represents improvement in CPK values when olanzepine was withhold from the day of admission.

## DISCUSSION

NMS is an uncommon, yet potentially fatal neurologic emergency linked with, as the name implies, the use of neuroleptic drugs. Although its reported occurrence varies between only 0.02% and 2.4% of patients taking neuroleptic drugs, NMS carries a significant mortality rate, which mandates early recognition and intervention [5].

There are several sets of criteria by which NMS is diagnosed: the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV), the Adityanjee criteria, the Levenson criteria, and the Pope criteria. Muscle rigidity and fever are essential diagnostic features of these four sets of criteria. Rigidity is usually generalized throughout the body and is described as lead-pipe or unbreakable in quality [2]. The DSM-5 classifies NMS as a subform of drug-induced movement disorders. Diagnostic criteria of NMS based on DSM-5 include rigidity, hyperthermia, diaphoresis, exposure to dopamine antagonist within hours (major symptoms) tachycardia, hypertonia, sialorrhea, urinary incontinence pallor, tachypnea, dyspnea, delirium, tremor akinesia, dystonia, myoclonia laboratory findings- leukocytosis, elevated CPK, myoglobin, creatinine metabolic acidosis, hypoxia, increased serum creatinine, and catecholamines. Exclusion criteria – the abovementioned symptoms are not due to another substance or a neurological or general medicine condition.

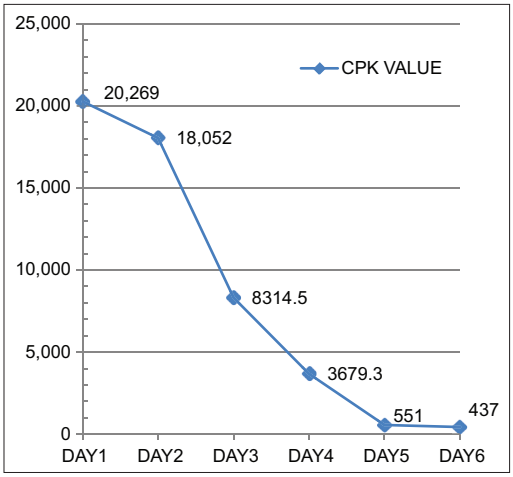


**Fig. 1: Patient's creatine phosphokinase values**

**Table 1: Naranjo's causality assessment scale**

| Question | Yes | No | Don't know | Score |
|---|---|---|---|---|
| 1. Are there previous conclusive reports on this reaction? | +1 | 0 | 0 | +1 |
| 2. Did the adverse event appear after the suspected drug was administered? | +2 | −1 | 0 | +2 |
| 3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered? | +1 | 0 | 0 | +1 |
| 4. Did the adverse event reappear when the drug was readministered? | +2 | −1 | 0 | 0 |
| 5. Are there alternative causes that could on their own have caused the reaction? | −1 | +2 | 0 | +2 |
| 6. Did the reaction reappear when a placebo was given? | −1 | +1 | 0 | 0 |
| 7. Was the drug detected in blood or other fluids in concentrations known to be toxic? | +1 | 0 | 0 | 0 |
| 8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased? | +1 | 0 | 0 | +1 |
| 9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? | +1 | 0 | 0 | 0 |
| 10. Was the adverse event confirmed by any objective evidence? | +1 | 0 | 0 | +1 |

Total Score: 8, Probable

In this case the patient developed most of the typical features as described by DSM-5 criteria needed to arrive at a differential diagnosis of NMS including lead pipe rigidity, hyperthermia, diaphoresis, tremor, incontinence, altered levels of consciousness with increased confusion, tachycardia, elevated or labile blood pressure, hypersalivation, leukocytosis, and laboratory evidence of muscle injury (elevated CPK levels) except elevated myoglobin value, renal dysfunction as the case was diagnosed at the earliest as NMS and appropriate treatment started.

Case reports of NMS among older adults highlight elders as a vulnerable population due to predisposing factors such as dehydration, malnutrition, agitation, exhaustion, and underlying electrolyte abnormalities [2]. In this case the presence of extreme agitation and disorientation, loss of interest could have led to dehydration which could be a contribution for development along with olanzapine.

Usually, NMS peaks at age 20–25 years and declines steadily thereafter pointing to the fact that NMS is most likely to occur in young adulthood

with very few cases reported in the elderly [6]. This is one of the rare case in which a 64-year-old male patient developed NMS on the use of an atypical psychotic drug, olanzepine. Furthermore, ethnic groups, such as Asian and African Americans, seem to be at a higher risk [7] as in this case.

In this case, it was found that the patient was on 3 medications inducing NMS-olanzepine, quietipine (atypical antipsychotics), and fluoxetine (SSRI) for 8 years. The patient had a history of hospital admission with increased episodes of agitation and depressive disorders after which the dose of olanzepine was increased from 10 mg/day to 20 mg/day, which is the maximum daily dose of olanzepine which the patient has taken for 2 weeks and both quitiepine and fluoxetine was stopped. This leads to the fact that olanzapine may be the reason behind development of NMS that too because of sudden dose escalation, doubling but dosing done within the normal range, and also the other NMS-inducing medications were stopped too. Also by withholding olanzapine, there was a sudden improvement in CPK value and the patient became clinically better with a reversal of tachycardia, tachypnea, hypertension, and leukocytosis. Considering the typical clinical picture and lab investigation reports, a rechallenge of the drug was not required, and it was challenging too as the patient was clinically worsening on admission to intensive care unit (ICU).

We assessed the causality of this adverse reaction by the the Table 1 represents Naranjo Causality Assessment score [8] and the, probability score was found to be 8 indicating the adverse drug reaction as probable.

## CONCLUSION

NMS being an idiosyncratic reaction in response to antipsychotics cannot be fully prevented. However, there is a need to maintain a high index of suspicion for the condition even while using atypical antipsychotics. The predisposing factors in this patient could have been comorbid mood disorder, poor hydration, and also recent history of increase in the dose of olanzepine. In most cases, patients diagnosed with NMS require critical care admission and ICU management of patients which should be avoided by providing utmost care, while increasing doses of NMS-inducing atypical antipsychotics like olanzapine. Existing reports also highlight the fact that NMS is more prevalent in patients belonging to the Asian and African ethnicity [7]. Moreover, this further highlights the importance of understanding probable associations in patients with this ethnicity. Hence, we also urge that we need more reports and studies focusing on the same, especially in people belonging to Asian and African ethnicity in whom the prevalence of NMS is much higher as compared to other populations. Furthermore, atypical antipsychotics must be used in caution in elderly patients and adequate monitoring is necessary along with gradual dosage adjustment. This report also highlights the fact that despite the patient developed NMS on olanzapine dose escalation, the patient tolerated clozapine well, with no adverse reactions. These data suggest that patient who develops NMS on one atypical antipsychotic can still tolerate other atypical antipsychotics as well, but caution must be taken while drug dose elevation. In the management of NMS, the most crucial thing is to have an index of suspicion for NMS from the beginning, start symptomatic management, avoid parenterals and higher antipsychotics and other causes of delirium is ruled out. Furthermore, early diagnosis of drug-induced reaction can prevent serious complications like renal failure. Hence, it is very important to have a formulation on each patient presenting with NMS so that we can be on the lookout for associations and can initiate monitoring for early pickup of these patients with fatal outcomes. It is clearly understood that early diagnosis and management of NMS go a long way in reducing the mortality rate in this condition. For this high index of clinical suspicion and better understanding about probable associations is important. Hence we need more studies focusing on the same.

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## AUTHOR'S CONTRIBUTION

All the authors have equally contributed to the work and also revised the same. All authors have also approved the final form.

## CONFLICTS OF INTEREST

No potential conflicts of interest.

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