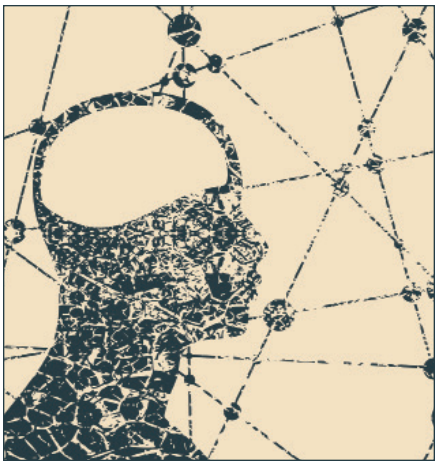

CASE REPORT

Atypical Neuroleptic Malignant Syndrome Precipitated by Clozapine and Quetiapine Overdose: A Diagnostic Challenge

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ABSTRACT

Neuroleptic malignant syndrome (NMS) is a rare, idiosyncratic, but life-threatening adverse reaction associated with the use of antipsychotic drugs. It is characterized by a tetrad of fever, rigidity, autonomic instability, and altered mental status. Failure to diagnose NMS early and institute appropriate treatment can result in serious medical complications and death. While diagnostic criteria for NMS exist, atypical presentations that lack one or more characteristic features pose a diagnostic dilemma to clinicians. The concept of atypical NMS has been proposed for such cases but remains controversial. We report a case of atypical NMS associated with overdose on clozapine and quetiapine and discuss the diagnostic challenges of an atypical presentation. In this case, the diagnosis was delayed due to the absence of rigidity, but later made after serum creatine kinase was found to be markedly elevated. Clinicians should have a high index of suspicion for NMS. Routine checking and trending of serum CK in patients on antipsychotic drugs who present with features of NMS is recommended to facilitate diagnosis. Future research is needed to define and validate threshold scores for existing diagnostic criteria for NMS.

Keywords: Neuroleptic malignant syndrome, diagnosis, antipsychotics, clozapine, quetiapine, creatine kinase, drug overdose

Neuroleptic malignant syndrome (NMS) is a rare, idiosyncratic, but life-threatening adverse reaction associated with the use of antipsychotic drugs. It is characterized by a tetrad of altered mental status, rigidity, fever, and autonomic instability.[1] Early recognition and intervention are crucial because NMS can lead to severe complications, such as rhabdomyolysis, respiratory failure, acute kidney injury, seizures, and death. It has a reported mortality rate of between 10 and 20 percent.[2,3]

Different diagnostic criteria have been proposed for NMS. Most include the classical tetrad, as well as elevated serum creatine kinase (CK) and leukocytosis.[4–8] However, variations exist between these criteria. Furthermore, NMS is a diagnosis of exclusion, as a variety of medical conditions can present with similar symptoms.[9] Consequently, the diagnosis of NMS remains controversial and presents a significant challenge to clinicians.

The advent of atypical or second generation antipsychotics (SGAs) has further complicated the diagnosis of NMS. It has been hypothesized that SGAs might determine atypical forms of NMS due to their different pharmacological properties.[10] Case reports and reviews suggest that the clinical features of NMS associated with SGAs differ from that precipitated by typical or first generation antipsychotics (FGAs).[11–13] Atypical presentations have been classified in the literature as atypical NMS. Atypical NMS has been reported with the use of SGAs such as clozapine, risperidone, aripiprazole, and olanzapine.[14–17]

Failure to recognize NMS early can result in delayed diagnosis, disease progression, and death.[2,3] Diagnosis and appropriate treatment can be delayed when a patient does not present with classical signs of NMS.

Here, we report a case of atypical NMS in which diagnosis was delayed because of the absence of rigidity. It was precipitated by an overdose on clozapine and quetiapine in a patient with treatment-resistant schizophrenia.

CASE REPORT

A 43-year-old man with a history of treatment-resistant schizophrenia, diabetes mellitus, and hypertension was brought by his mother to the emergency room after he overdosed on a mixture of medications, including clozapine, quetiapine and venlafaxine. On the day of admission, his mother witnessed him overdosing on medications from his pill box. He reported hearing voices of god telling him to overdose on his medications to protect himself from others who were out to harm him.

In the emergency room, the patient was alert and non-toxic. He was febrile with a

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temperature of 38.8°C. His pulse rate was 112 beats per minute, blood pressure 128/84mmHg, and SpO_2 was 98 percent on room air. Physical examination was unremarkable. He was admitted to the general ward with a presumptive diagnosis of aspiration pneumonia after drug overdose and started on intravenous (IV) antibiotics. All psychotropic medications were suspended on admission because of the reported overdose.

On the second day, the patient developed respiratory distress. His SpO_2 dropped to 80 percent and only increased to 90 percent on a non-rebreather mask. He was transferred to the medical intensive care unit where he was later able to maintain saturations on supplemental oxygen via nasal prongs. He remained febrile and became intermittently confused and agitated. His speech was incomprehensible at times. His blood pressure was labile with systolic and diastolic fluctuations of up to 50mmHg. He was tachycardic (heart rate up to 145 beats per minute) and tachypnoeic (respiratory rate of 30 per minute). Bibasal crepitations were heard on auscultation. His white blood cell count (WBC) was $14.6x10^3$/uL. Serum creatine kinase (CK) was 17,248U/L. Chest X-ray showed patchy airspace opacities in the right upper-to-mid zones and left cardiac region. Computed tomography (CT) scan of his brain showed no acute infarct or haemorrhage. In view of his markedly elevated serum CK, urgent psychiatric consultation was sought for possible NMS.

During the consultation, he was alert but disoriented to time. His speech was dysarthric. He reported ongoing auditory hallucinations and overdosing on clozapine, quetiapine and venlafaxine. There was no rigidity or tremors on physical examination. Nonetheless, a diagnosis of atypical NMS was made based on the presence of fever, autonomic instability, altered mental status, and markedly raised serum CK on the background of an overdose on antipsychotic medications. Other possible causes of elevated serum CK, such as recent falls, were excluded. Serotonin syndrome was also considered in view of his reported overdose on venlafaxine. However, hyperreflexia or myoclonus were not elicited. Furthermore, the markedly elevated serum CK was more suggestive of NMS. Antipsychotic medications were held off despite his active psychotic symptoms. Oral lorazepam was started with a view to start IV dantrolene if rigidity developed. Supportive care was instituted with aggressive intravenous hydration.

TABLE 1. Trend of serum creatine kinase, white blood cell count, alanine transaminase, and aspartate transaminase

LAB TESTS	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7	DAY 14
Creatine kinase, serum (U/L)	np	17,248	30,764	27,548	15,383	6,091	2,582	280
WBC count x 10^3/uL	14.6	np	9.4	12.6	9.9	np	np	8.5
Alanine transaminase (U/L)	50	52	60	55	98	np	np	np
Aspartate transaminase (U/L)	61	145	194	185	306	np	np	np

ALT: alanine transaminase; AST: aspartate transaminase; CK: creatine kinase; WBC: white blood cell count; np: lab test not performed on this day

His serum CK levels rose to a peak of 30,764U/L on the third day of admission. He also developed transaminitis (Table 1 shows the trend of his serum CK, WBC count, and transaminases). He remained febrile, tachycardic, and had labile blood pressure. By the fourth day, he was less confused and his vital signs stabilized. He was subsequently transferred to a tertiary psychiatric institution for further management with a note to closely observe him for the re-emergence of NMS upon re-initiating his antipsychotic medications. Clozapine was eventually restarted 10 days after his initial presentation without any recurrence of NMS.

DISCUSSION

NMS is a rare but potentially fatal condition associated with antipsychotic drug use. It is a diagnosis of exclusion since none of the diagnostic criteria are specific to NMS.[9] Because of its severity, it warrants a high index of clinical suspicion. Early diagnosis and intervention of NMS can be life-saving. However, the diagnosis of NMS is often complicated by variability in clinical presentations.

While there has been growing acceptance of the existence of atypical NMS, it remains a controversial entity.[18] Atypical presentations that lack the full criteria could represent early stages of the condition.[19] This phenomenon could be the result of greater vigilance by clinicians who make the diagnosis and intervene early before progression and the full range of signs and symptoms is allowed to manifest.

An international multispecialty panel reached a consensus regarding the following diagnostic criteria for NMS: recent dopamine antagonist exposure, or dopamine agonist withdrawal; hyperthermia; rigidity; mental status alteration; creatine kinase elevation; sympathetic nervous system lability; tachycardia plus tachypnoea; and a negative work-up for other causes. It also reached a consensus on the relative importance of these criteria and suggested priority scores for each. However, to date, no threshold score has been defined and validated for making a diagnosis of NMS.[1]

In our case, the patient fulfilled all of the above-mentioned criteria except for rigidity. Unfortunately, the diagnosis was delayed because NMS was not initially considered. Aspiration pneumonia following drug overdose was the initial working diagnosis as it adequately explained his fever, tachypnoea, and desaturation. The development of fluctuating mental state and autonomic instability prompted the checking of serum CK, which turned out to be markedly elevated. This prompted the diagnosis of atypical NMS.

Though not specific for NMS, serum CK levels are important to detect and monitor the progress of the condition.[20] Hence, it is recommended that serum CK levels should be routinely checked and trended in patients on antipsychotic medications who present with features of NMS.

Abrupt and profound dopamine D_2 receptor blockade by antipsychotic drugs has been proposed to be the cause of the signs and symptoms of NMS.[9,12,21] In this case, the patient was reported to have overdosed on the SGAs clozapine and quetiapine. The resulting abrupt increase in dopamine D_2 receptor blockade is likely to have precipitated the symptoms of NMS. Clozapine and quetiapine are antipsychotic drugs with low propensity to cause extrapyramidal side effects.[22] This could explain the absence of rigidity in this case.

SGAs are now the most commonly prescribed antipsychotic drugs because of their relative lack of extrapyramidal side effects.[23] NMS induced by SGAs has been found to have lower incidence, less severe, and less frequent lethal outcomes than NMS induced by FGAs.[13] The differences in pharmacological properties of SGAs likely account for the varied presentations of patients who develop NMS while on SGAs.

Discontinuation of the offending agent followed by supportive treatment is the mainstay of management of NMS.[19,24] A delay in diagnosis and failure to stop the offending agent can prolong the course of NMS, leading to greater morbidity and mortality. Conversely, an incorrect diagnosis of NMS can result in abrupt discontinuation of antipsychotics and worsen the patient's psychiatric condition.

Atypical presentations support a spectrum-based concept of NMS.[9,19] Consequently, research to define and validate threshold scores for a diagnosis of NMS based on the criteria proposed by Gurrera and colleagues will be instrumental in guiding clinicians through this diagnostic dilemma.[1]

CONCLUSION

In conclusion, NMS is a potentially life-threatening condition with variable clinical presentation. Clinicians should have a high index of suspicion for NMS in patients on antipsychotic medications. NMS can have atypical presentations especially when precipitated by SGAs, such as clozapine and quetiapine. A diagnosis of atypical NMS should be considered even in the absence of rigidity or other classical symptoms. Serum CK should routinely be checked and trended to facilitate diagnosis in these cases. Future research is needed to define and validate threshold scores for existing diagnostic criteria for NMS.

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