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Bengal Journal of Psychiatry

Case Report

Neuroleptic Malignant Syndrome (NMS) Induced by Clozapine at a Very Low Dose

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Received: 05 September 2024
Accepted: 14 October 2024
Epub Ahead of Print: 04 December 2024
Published: 10 December 2024

DOI
10.25259/BJPSY_6_2024

Quick Response Code:

ABSTRACT

This report describes a case of the clozapine-induced neuroleptic malignant syndrome (NMS) in a 25-year-old woman with schizophrenia. The patient developed NMS symptoms after restarting clozapine following a period of discontinuation. Atypical presentations of NMS, challenges in diagnosis, and the possibility of a dose-dependent relationship are discussed. Key points of the reports are as followed. Clozapine-induced NMS can present atypically, lacking the classic triad of fever, rigidity, and altered mental status. Clinicians should consider a broader range of symptoms when diagnosing NMS, especially with clozapine. The exact threshold for clozapine-induced NMS is unknown, but it may occur even at low doses as 25mg per day. Early diagnosis and intervention are crucial for successful management. The report concludes by highlighting the need for further research to better understand clozapine-induced NMS, including risk factors, dose thresholds, and biomarkers for early diagnosis.

Keywords: Clozapine, Neuroleptic malignant syndrome (NMS), Drug reactions

INTRODUCTION

Clozapine, a dibenzodiazepine atypical antipsychotic, is a mainstay treatment for treatment-resistant schizophrenia. Despite its efficacy, clozapine carries a rare but potentially life-threatening side effect: neuroleptic malignant syndrome (NMS). NMS is a clinical emergency characterized by a constellation of symptoms, including fever, muscle rigidity, autonomic dysfunction, and altered mental status. While the exact mechanisms remain unclear, NMS is thought to be associated with dopamine receptor blockade, a key pharmacological action of clozapine.

CASE REPORT

The patient was a 25-year-old Muslim married female, primary pass, suffering from treatment-resistant schizophrenia for the last 10 years, with no family history of psychiatric illness. She had been under regular treatment and follow-up for the last 5 years, and she was on tab clozapine 200 mg in two divided doses over the last 2–3 months but discontinued medications because of her psychopathology for the last 10 days. Following the stoppage of medication, the patient developed catatonic symptoms characterized by rigidity, mutism, and refusal of food and fluid for the next 7 days. Because of her symptoms, she was admitted to our hospital, and after stabilizing her vitals, relevant investigations were sent. A psychiatric referral was taken. After suspecting catatonia, she was given inj Lorazepam 2 mg IV BD, and clozapine was restarted after a detailed history of taking and review of past medications. She was started on

Tab Clozapine 12.5 mg on D1, and after 2 days, the dose was increased to 25 mg per day. On D4, she suddenly developed high-grade fever, low oxygen saturation, and disorientation. There was an elevated heart rate (130 bpm) and low BP (90/60 mmHg). She was quickly shifted to the ICU, and relevant investigations were sent (as mentioned below in Table 1). A high total leukocyte count and raised serum creatine phosphokinase (CPK) level were noted. She was provisionally diagnosed with NMS. Clozapine was stopped. She was monitored closely. Her vitals were stabilized. She was managed with an infusion of paracetamol 1 g for her fever, an injection of cefuroxime for sepsis coverage, and Moist O_2 for breathing difficulties. Her fever subsided, and she was oriented within 2 days. She was started on Tab Olanzapine 5 mg at night, and the dose of Tab Lorazepam was increased to 2 mg in two divided doses. No autonomic instability or fever was noted after that details of his vitals and investigations reports are summarized in Table 1. However, mutism and poor oral intake persisted.

DISCUSSION

Atypical Presentations and Challenges in Diagnosis

Unlike classical NMS associated with typical antipsychotics, clozapine-induced NMS often presents atypically. Several case reports highlight this challenge.[1–3] Patients might exhibit some core symptoms like fever and rigidity but lack others, leading to delayed diagnosis and potentially worse outcomes. For instance, a 2017 case report describes a patient with fluctuating consciousness, disorientation, muscle rigidity, and elevated creatine kinase levels but with a normal body temperature.[1] This case emphasizes the importance of considering a broader spectrum of symptoms beyond the classical triad (fever, rigidity, and altered mental status) when evaluating for clozapine-induced NMS.

Risk Factors for Clozapine-Induced NMS

While the exact etiology of clozapine-induced NMS remains elusive, several risk factors have been identified in case reports. Rapid increases in clozapine dosage have been implicated in some cases.[4,5] This suggests a potential dose-dependent risk, although the exact threshold remains unclear. Concurrent use of medications with dopaminergic blocking properties, like other antipsychotics, may increase the risk.[6,7] Preexisting medical conditions like dehydration, electrolyte imbalances, and infections might act as triggers.[8,9] Limited evidence suggests a potential role of genetic susceptibility.[10]

Is There a Dose-Dependent Relationship?

The question of whether a specific clozapine dose triggers NMS is intriguing but difficult to answer due to limited

Table 1: Data showing various blood investigations reports and vitals during the admission period

Investigations/Vitals (after diagnosing NMS)	1st Day	2nd Day	4th Day	6th Day
Haemoglobin (gm%)	10.4	9.7	10.0	11.4
RBC (mil/mcl)	4.07	3.00	3.73	4.11
Leukocyte (/mcl)	10390	6810	6680	10,000
Neutrophil	83	76	78	81
Lymphocyte	14	14	12	13
Platelets (/ mcl)	1.20 × 100,000	1.85 × 100,000	1.51 × 100,000	1.80 × 100,000
ESR (mm/hour)	40	64	58	29
S. Creatinine (mg/dl)		0.56		
S. Na (meq/L)		141.6	140.90	137.40
S. K (meq/L)		3.2	3.19	2.95
S. CPK (mcg/L)		1406	930	439
Body temp (F)	103	101	99	98
BP (mm of Hg)	90/60	100/60	110/74	110/78
Heart rate (beats per minute)	130	110	90	80
RR (beats per min)	24	18	16	16
SpO_2 (%)	96 (with 4–6 L O_2)	99 (with 2–4 L O_2)	99 (room air)	99 (room air)

NMS: Neuroleptic malignant syndrome, RBC: Red blood corpuscles, ESR: Erythrocyte sedimentation rate, BP: Blood pressure, RR: Respiratory rate, SpO_2: Saturation of peripheral oxygen

literature in this area. In an index case report, symptoms suggestive of NMS were noted at a dose as low as 25 mg. We could lay our hands on only one another similar case reports.[11] It is crucial to consider the following:

- Individual variability: Patients may have differing susceptibilities to NMS at varying dose levels.
- Confounding factors: Preexisting conditions or concomitant medications might play a role in lowering the threshold for NMS, even at seemingly low clozapine doses.
- Limited generalizability: Case reports represent unique clinical scenarios and may not reflect broader population trends. Therefore, the available evidence suggests a possible dose-dependent association, but more robust studies are needed to establish a definitive threshold.

Prompt diagnosis and intervention are crucial for successful management of clozapine-induced NMS. Key strategies include:

- Discontinuation of clozapine: Withdrawing clozapine is the first line of treatment.[12]
- Supportive care: Managing fever, electrolyte imbalances, and hydration is essential.
- Dopamine agonists: Bromocriptine and amantadine, dopamine agonists, can address the underlying dopamine blockade.[13,14]
- Dantrolene: This muscle relaxant can manage severe muscle rigidity.[13]

Future Directions

Further research is needed to gain a deeper understanding of clozapine-induced NMS. Future research should address the following areas: Large-scale prospective studies are needed to identify risk factors and potential dose thresholds for the development of NMS. Investigate the role of genetic polymorphisms in susceptibility to NMS and identify biomarkers that can predict or diagnose NMS early in its course.

CONCLUSION

Clozapine-induced NMS, though rare, remains a serious complication requiring prompt recognition and intervention. The atypical presentations associated with clozapine-induced NMS pose a diagnostic challenge. Clinicians should maintain a high index of suspicion, considering a broader spectrum of symptoms beyond the classical triad. While the exact dose-dependent relationship is unclear, the index case report emphasizes the fact that NMS can occur with a Clozapine dose as low as 25 mg/day. Further research is crucial to elucidate the underlying mechanisms, identify reliable risk factors, and establish definitive dose thresholds. The goal is to ensure the safe and effective use of clozapine while minimizing the risk of this life-threatening side effect.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

Financial support and sponsorship

Nil.

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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How to cite this article: Manna CK, Mondal M. Neuroleptic Malignant Syndrome (NMS) Induced by Clozapine at a Very Low Dose. Bengal J Psychiatry. 2024;29:52–5. doi: 10.25259/BJPSY_6_2024