

Atypical Neuroleptic Malignant Syndrome on Clozapine?: A case report

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INTRODUCTION

- Neuroleptic Malignant Syndrome (NMS) is a life threatening medical emergency associated with the use of dopamine blocking agents. There are extensive reports in the literature of this syndrome's association with the use of typical antipsychotics
- There is a lower incidence of NMS in patients commenced on atypical antipsychotics with fewer cases describing this idiosyncratic reaction in patients on Clozapine. The evidence further suggests that the symptoms of NMS for patients on this medication may be different to the classic presentation
- To fulfill a diagnosis of NMS, the DSM V criteria must satisfy all 3 major symptoms which include; exposure to a dopamine blocking agent, severe muscle rigidity and fever. At least 2 'other criteria' are needed from diaphoresis, dysphagia, tremor, incontinence, altered level of consciousness, mutism, tachycardia, elevated/labile blood pressure, leukocytosis or elevated creatinine kinase (CK)

UNIQUENESS OF CASE

- There are extremely few reported cases of Clozapine associated NMS without fever
- In a case review by Murri et al in 2015, tachycardia, tachypnoea, blood pressure lability, and other autonomic symptoms were very frequent and severe, possibly related to the high affinity of clozapine for adrenergic and muscarinic receptors. Extrapyramidal symptoms (EPS) and fever were less reported symptoms
- If the DSM V criteria were applied to this case, the patient would not have met the threshold for diagnosis of NMS due to the absence of fever on repeated measurements

CASE REPORT

- The patient is a 44 year old male well known to mental health services with an established diagnosis of Paranoid Schizophrenia. This admission was warranted secondary to poor compliance with oral antipsychotic medication in the community leading to a deterioration in his mental health
- Due to his psychotic symptoms not controlled on various antipsychotics such as Olanzapine, Risperidone and Paliperidone, the multidisciplinary team decided to commence him on Clozapine
- The patient developed autonomic side effects such as dizziness, hypotension and tachycardia as early as day 2
- These symptoms eventually subsided however, over the next 5 days, the patient appeared increasingly withdrawn, spending more time in his bed space, increasingly thought disordered and drooling. He remained intermittently tachycardic with other vital signs in the normal range and all blood tests were normal
- His symptoms worsened by day 10 as he developed dyskinesia, diaphoresis, truncal rigidity and altered mental state. He was tachycardic with the highest recorded heart rate as 135 beats per minute. His temperature remained <38°C at all times
- The patient, whilst in a state of confusion charged into a closed door and was referred to A&E for a thorough physical examination as he suffered bruises to his face and to rule out a head injury
- Clozapine was discontinued and a CK level was 651 (40-320). Due to the mild rise in CK, Clozapine was restarted at a lower dose (25mg once daily dose) with a view to frequently monitor CK levels. The CK level rose to 1757 on the same evening. Clozapine was permanently stopped and the patient admitted to the medical ward for further management
- The patient's kidney function tests continued to remain within normal range for the entire duration. His CK normalised 11 days after permanently stopping Clozapine with a significant improvement in his physical and mental state

TIMELINE

- Day 2 • Autonomic side effects such as dizziness, hypotension and tachycardia (HR 110). Night time Clozapine dose omitted
- Day 3-7 • Clozapine continued at standard titration as per trust protocol. Patient appeared withdrawn spending more time in his bed space and increasingly thought disordered
- Day 7 • Reviewed by responsible clinician (RC) in ward round. Patient reporting excessive drooling, incoherent, thought disordered and expressively dysphasic. Intermittently tachycardic, however other vital signs, blood tests and ECG normal
- Day 9 • Patient reported medication giving him 'electric shocks'. Unwilling to elaborate on this
- Day 10 • Developed dyskinesia, truncal rigidity, unsteadiness and confusion. Patient charged into a closed door and was referred to A&E. CK- 651 (40-320). Clozapine restarted at low dose 25mg once daily.
- Day 11 • CK level 1757. Discussed with medical registrar and patient was transferred to hospital for IV fluids. Clozapine permanently stopped
- Day 12 onwards • Significant improvement in the patient's physical and mental state over the next 11 days

DISCUSSION

- The pathophysiology of NMS at a receptor level involves a decrease in central dopaminergic activity at the Dopaminergic D2 receptor. This leads to the patient's characteristic physical symptoms which include autonomic dysfunction, muscle rigidity, hyperthermia and mental state changes
- A case review by Murri et al. in 2015 demonstrated a pattern of lower and delayed increase in CK levels with reduced incidences of EPS.
- The lack of significant EPS correlates with Clozapine's weak affinity for D2 receptors. This case review assessed 44 patients who developed Risperidone associated NMS of whom 94.3% developed a temperature >38°C. This was in contrast to patients on Clozapine where out of 36 patients, 79.2% developed hyperpyrexia
- Paliperidone 150mg LAI (long acting antipsychotic) injection was administered 23 days prior to commencing Clozapine. Given the median half life of Paliperidone to be 25-50 days, this might have played a role in development of his symptoms
- If the Levenson criteria were used, the patient would have met the threshold for diagnosis of NMS having 2 core symptoms (rigidity and a rise in CK) and 4 minor symptoms (diaphoresis, tachycardia, abnormal blood pressure and altered consciousness)

CONCLUSION

- Tachycardia should raise suspicion of NMS. Diaphoresis is also very common, and not often thought of as a hallmark sign of NMS.
- Elevation of CK is frequent, but is not always extreme and may actually be absent in some cases
- It may be clinically safe if patients taking clozapine are monitored with Levenson's criteria as this would lower the threshold for investigating NMS
- Waiting for rigidity or the development of a fever may delay the diagnosis of NMS in patients taking Clozapine
- In the absence of fever with the presence of other core symptoms of NMS, an atypical presentation should be considered

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