Neuroleptic Malignant Syndrome Induced by Clozapine: A Case Report and Discussion

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ABSTRACT:
Neuroleptic malignant syndrome induced by clozapine: a case report and discussion

Objective: Neuroleptic malignant syndrome (NMS) is a rare, but life-threatening condition associated with the use of antipsychotics. Although NMS is mainly associated with typical antipsychotics, it can also be induced by atypical antipsychotics. In this paper, we report a case of NMS associated with clozapine use and describe the classic and atypical manifestations of NMS. The case and discussion highlight the importance of considering NMS as part of the differential diagnosis for any patient using neuroleptics.

Case: This case was about a 52-year-old female suffering from pneumonia, who was diagnosed as having NMS after a dosage increase of clozapine. NMS is a rare but serious adverse reaction to an antipsychotic drug. It is essentially characterized by hyperthermia, muscle rigidity, which may be accompanied by other extra pyramidal effects (EPS), autonomic instability and mental status changes. Laboratory examinations showed significantly higher creatine kinase. A typical treatment usually involves supportive medication and an immediate withdrawal of the antipsychotic drug.

Conclusion: Incomplete or extraordinary NMS cases have been reported due to clozapine. However, this case was remarkably associated with the complete and typical presentation of NMS. Given the routine and regular writing of prescriptions of neuroleptics by physicians in a variety of medical disciplines, physicians need to recognize and appropriately manage NMS.

Keywords: neuroleptic malignant syndrome, clozapine, diagnosis

INTRODUCTION

NMS is a rare, but severe clinical syndrome usually caused by antipsychotic drugs. According to the DSM-IV3, an essential feature of NMS is the “development of severe muscle rigidity and elevated temperature associated with the use of antipsychotic medication”. These features must be accompanied by two or more of the following symptoms: diaphoresis, dysphagia, tremor and incontinence, changes in the level of consciousness, mutism, tachycardia, elevated or labile blood pressure, leukocytosis or laboratory evidence of muscle injury (e.g., elevated CK). A common theory for the development of NMS is that it results from the hypodopaminergic state caused by antipsychotic blockade5. Other neurotransmitters, such as serotonin, γ-aminobutyric acid, acetylcholine and norepinephrine may be involved in the occurrence of the syndrome6.

NMS has been mainly related to the inappropriate use of dopamine antagonists (especially typical antipsychotics, such as haloperidol) and with the withdrawal of anti-parkinsonian medications. NMS is thought to occur in fewer instances with atypical neuroleptics than with typical antipsychotic drugs. Although clozapine-associated NMS cases have been observed with different clinical manifestations compared with other atypical antipsychotic-induced NMS cases, physicians need to recognize
and accurately diagnose NMS\textsuperscript{4}.

The following case of clozapine-associated NMS describes a patient who exhibited all classical forms and persistent intestinal flatulence.

**CASE REPORT**

A 52-year-old female, with a history of severe depression, was taken to the emergency room with the main complaint of disorientation and high fever for two days. Two days before being admitted to the hospital, she developed hypermyotonia, tremor and lapsed into unconsciousness. She had a body temperature of 41°C accompanied by diaphoresis.

**Physical examination:** Blood pressure was 125/85 mmHg, heart rate was at 120-130 beats/min. Other signs included: disorientation, normal pupil size, normal reflection of light; normal lung and heart, bulging abdomen, drum percussion sounds, weak bowel sounds. The muscle tension was high with tremor and the dual Babinski sign was negative. Laboratory investigation revealed leukocytosis (leukocyte count 15.29×10\textsuperscript{9}/L), with a shift to the left (neutrophil count 12.60×10\textsuperscript{9}/L). Her PCT was normal (0.03ng/ml). Arterial blood acidity and gas analyses results included: pH, 7.373; PO\textsubscript{2}, 78torr; PCO\textsubscript{2}, 45torr; FiO\textsubscript{2}, 25%; and HCO\textsubscript{3}, 33mmol/L. Electrolyte level test along with liver and renal function tests all yielded normal results. A head CT scan did not show any acute abnormalities, but a chest X-ray showed pneumonia and an abdominal X-ray showed extensive intestinal dilatation (Figure 1).

The patient was given the antibiotic cefuroxime for symptomatic treatment for two days but the symptoms did not display any significant improvement. On day 3 of hospitalization, she continued to suffer from hyperthermia, muscle rigidity and persistent changes in the level of consciousness. We asked about the patient history again in detail. Her anti-psychotic medications included clozapine 200 mg daily, estazolam 2 mg daily and trihexyphenidyl 8 mg daily. About 10 days prior to this event, due to worsening depression, she had taken clozapine (25 mg/tablet) from 100 mg every 12-hours to 800 mg every 8-hours. Furthermore, a toxicology screen was conducted, which showed the patient’s clozapine serum concentration to be 0.45 mg% (toxic dose >0.2 mg%). Further laboratory analysis showed a markedly elevated creatine kinase (CK) level (927 U/L) and her urine myoglobin test was positive. According to positive symptoms, signs and laboratory examinations, a firm diagnosis of NMS was made. Clozapine was withheld and therapy with supportive medication was started. To deal with flatulence, decompression and cathartic treatment were carried out. After a few days, the patient’s NMS symptoms improved and her biochemical parameters returned to normal but the intestinal flatulence remained abnormal. However, due to aggravated complications of pneumonia, the patient was put into ICU with continued treatment. She was discharged one month later and six months after discharge she remained stable and was able to engage in regular activities. Table 1 shows the changes in the patient’s vital signs and clinical indicators.
DISCUSSION

NMS was originally described in 1968 by the French psychiatrist Delay. Almost all antipsychotic drugs have some level of risk of NMS. The frequency of the syndrome ranges from 0.07 to 2.2% and the mortality is 10-30%.

Typical antipsychotic drugs have greater antagonistic effects on dopamine receptors as compared to atypical ones. Consequently, NMS is thought to occur in fewer instances with atypical neuroleptics than with typical antipsychotic drugs due to their mechanism of action (Table 2). Therefore, NMS cases induced by clozapine are not prevalent as reported in the literature. Atypical NMS associated with atypical antipsychotics has been defined as rare small increases in CK, minor muscle rigidity and mild fever. In the presented case, the complete NMS presentation with severe muscle rigidity and unusually elevated CK differentiated this condition from most other clozapine-induced cases, which have been rarely reported in the literature. Furthermore, abnormalities in dopaminergic activity and dopamine receptor functions have been associated with genetic factors. Therefore, we concluded that the potential mechanism might be that the patient was extraordinarily sensitive to the blockade of dopamine, which led us to think that she might have had an individual predisposition for NMS.

Clozapine is an atypical antipsychotic drug with a broad range of receptor affinity (dopamine, 5HT, muscarinic and adrenergic receptor) and multiple receptor antagonistic activity. Therefore, the pathophysiology of NMS is complex, involving a cascade of dysregulations in multiple neurochemical and neuroendocrine systems. However, unlike other reports of clozapine-associated NMS, our patient had some signs of significant abdominal distension and her abdominal X-ray showed extensive intestinal dilatation, which might have been related to a greater antagonistic effect on muscarinic receptors.

Clozapine is a tricyclic dibenzodiazepine derivative mainly used in various subtypes of both acute and chronic schizophrenia to treat the associated emotional symptoms. It is also used to treat mania or other psychotic disorders, such as agitation, hallucinations, and delusions. According to the patient’s medical history, depression was diagnosed at another hospital, and the psychiatrist did prescribe clozapine. This situation is common in some rural areas, where health care infrastructure is very underdeveloped. The main feature of poisoning with this class of drugs is consciousness disturbance and cardiovascular dysfunction. Clozapine poisoning usually manifests as impaired consciousness, ranging from somnolence to coma or agitation, and delirium, tachycardia, abnormal blood pressure, and seizures. The symptoms of clozapine toxicity are due to its complex receptor-binding characteristics. The usual dose of clozapine is 300 to 450 mg daily, and the maximum dose is 900

### Table 1: Clinical indicators of changes over time

<table>
<thead>
<tr>
<th>Clinical indicators</th>
<th>1 day</th>
<th>3 days</th>
<th>5 days</th>
<th>7 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest temperature(°C)</td>
<td>41.0</td>
<td>39.1</td>
<td>37.5</td>
<td>37.2</td>
</tr>
<tr>
<td>Muscle rigidity</td>
<td>++++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>GCS score</td>
<td>10</td>
<td>12</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Blood pressure (mm hg)</td>
<td>125/85</td>
<td>120/75</td>
<td>115/70</td>
<td>120/80</td>
</tr>
<tr>
<td>Heart beat (beats /min)</td>
<td>120-130</td>
<td>110-120</td>
<td>90-100</td>
<td>85-95</td>
</tr>
<tr>
<td>CK level (U/L)</td>
<td>Not checked</td>
<td>927.4</td>
<td>425.0</td>
<td>163.5</td>
</tr>
</tbody>
</table>

Note: +light extent of muscle rigidity, ++++more severe extent of muscle rigidity

### Table 2: Antipsychotic drugs associated with neuroleptic malignant syndrome

<table>
<thead>
<tr>
<th>Typical antipsychotic drugs</th>
<th>Atypical antipsychotic drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol (+++)</td>
<td>Clozapine (+)</td>
</tr>
<tr>
<td>Chlorpromazine (+)</td>
<td>Olanzapine (+)</td>
</tr>
<tr>
<td>Fluphenazine (+)</td>
<td>Quetiapine (+)</td>
</tr>
</tbody>
</table>

Note: +rarely associated with NMS, +++more commonly associated with NMS. Data from Adnet.
mg. After ingestion of 2400 mg clozapine daily for about 10 days, intoxication was observed that was ultimately secondary to NMS.

Hyperthermia and unconsciousness are the most important manifestations of NMS. Therefore, infections, lethal catatonia, malignant hyperthermia and serotonin syndrome were considered to be the main differential diagnoses\textsuperscript{11}. In this case, we initially gave the patient an anti-infective treatment but it did not work. We conducted a thorough analysis and our case was in an active phase of a chronic mental illness in the presence of a relatively rapid increase in the dose of clozapine. Furthermore, the accompanying pneumonia might have contributed to the development of NMS.

**CONCLUSION**

NMS is a known but potentially lethal idiosyncratic disorder. NMS is easy to misdiagnose and the performance of patients may initially appear to be atypical or with complications. As such, early identification is the key to patient wellness and recovery.

**References:**


6. Harrison PA, Mc Erlane KS. Neuroleptic malignant syndrome. AJN 2008;108(7):35-8. [CrossRef]


