

# Neuroleptic malignant syndrome and subsequent clozapine-withdrawal effects in a patient with refractory schizophrenia

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**Abstract:** Here, we report a female patient developing neuroleptic malignant syndrome following the use of a combination of clozapine and haloperidol. Subsequently, the patient presented withdrawal effects after an abrupt discontinuation of clozapine. Psychiatrists not aware of possible clozapine-withdrawal effects may misdiagnose as a part of the primary mental illness or as the initial symptoms worsening, if unrecognized.

**Keywords:** clozapine, neuroleptic malignant syndrome, withdrawal effect, schizophrenia

## Introduction

Neuroleptic malignant syndrome (NMS) is a rare but the most severe side effect associated mostly with the use of antipsychotics.<sup>1</sup> The most frequent signs and symptoms of NMS include fever, muscle rigidity, autonomic dysfunction (eg, tachycardia, labile blood pressure, tachypnea), confused mental state, and changes in laboratory findings, and untreated NMS can lead to a life-threatening coma.<sup>2</sup>

Clozapine-withdrawal effects are characterized by psychotic and somatic symptoms. Delusions, hallucinations, altered consciousness, insomnia, motor restlessness, and autonomic dysfunction have been reported.<sup>3,4</sup> Rapid withdrawal effects of clozapine present usually in the first 2 weeks.

We report a case of a patient who developed NMS following the use of a combination of clozapine and haloperidol. Subsequently, the patient presented with clozapine-withdrawal effects after abrupt clozapine discontinuation. Recognition of sudden clozapine-withdrawal effects is important during prolonged clozapine therapy in the psychiatric clinic.

## Case report

Ethical written informed consent was obtained from the patient in accordance with protocols approved by the Clinical Research Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University. The patient, who met the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM)-IV criteria for schizophrenia, was a 37-year-old female. Treatment with antipsychotics was initiated at 18 years of age, and the patient had been treated in our department since that time. The patient had been treated with clozapine (350 mg/day) for more than 5 years. With the exception of slight hypotension, the patient showed no tremor or other side effects.

Seven days before admission to hospital, she was reported to present with anxiety and insomnia, because her only daughter would leave her to go elsewhere.

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She presented exacerbation of the psychotic symptomatology with delusions and hallucinations, which required her to be readmitted to our department. She had no family history of psychiatric illness, and no alcohol or substance abuse was reported. Physical and neurological examinations were normal (pulse rate 90 per minute, body temperature 36.4°C, and blood pressure 110/70 mmHg). Initial laboratory tests, which included erythrocyte-sedimentation rate, glucose levels, cholesterol levels, thyroid-function tests, rheumatoid factor, complete blood count, kidney and liver assessments, and urinalysis, were within normal ranges.

Clozapine was subsequently increased to 425 mg/day upon her admission and increased to 475 mg/day after 5 days of hospitalization. At the time, she had suicidal ideas and impulsive behavior. Haloperidol 10 mg/day intramuscularly was added. After 6 days of hospitalization, the patient presented with agitation, diaphoresis, finger tremor, and mild muscle rigidity. These symptoms were thought to be due to extrapyramidal symptoms. At that time, trihexyphenidyl (4 mg/day) was added to control her extrapyramidal symptoms. After 7 days of hospitalization, she presented with lethargy and delirium. Her vital signs at the time included a heart rate of 170 bpm, blood pressure of 160/70 mmHg, respiratory rate of 38, and temperature of 39.5°C. Laboratory investigations revealed a serum creatine kinase (CK) level of 1,166 U/L (normal range: 24–184 U/L) with a normal myocardial component (CK-MB) and a white blood-cell count of  $12.41 \times 10^9$  cells/mm<sup>3</sup>. The electrocardiogram, thorax and abdomen radiography, and other laboratory results were normal. Apart from treatment with the previous drugs, there were no other risk factors for conscious disturbance identified in the patient. She was diagnosed with NMS.

Subsequently, her medications, including clozapine, haloperidol, and trihexyphenidyl, were stopped. She received supportive therapy and additional treatments, including a urapidil hydrochloride injection to control pulse rate and blood pressure, an ice blanket to reduce her temperature, intravenous administration of diazepam (50 mg/day) for muscular rigidity and agitation, and mannitol to reduce brain edema. After 14 days of hospitalization, a marked improvement in NMS symptoms was noted, and her vital signs included normal heart rate, blood pressure, respiratory rate, and temperature.

However, the patient presented in a confused state with insomnia and auditory hallucinations. This condition remained unimproved over the course of 2 months, despite her being treated with olanzapine (daily dose of 20 mg) and risperidone (daily dose of 6 mg) for 4 weeks. Afterward, she

was given only a rechallenge with clozapine at a starting dosage of 25 mg/day. The psychotic symptoms gradually remitted. The dose was slowly increased to 250 mg/day over 20 days. She was discharged in good condition after 3 weeks.

## Discussion

At the beginning, the patient's condition was recognized as NMS caused by the combination of clozapine and haloperidol. The following NMS symptoms were observed in the case: impaired consciousness, rigidity, autonomic dysfunction (eg, tachycardia, labile blood pressure, tachypnea, diaphoresis), tremor, and delirium. The abnormal laboratory findings were elevated serum CK and white blood-cell count. The patient described fully met the criteria for NMS as proposed in the *DSM-IV*.

Although the precise pathophysiological mechanism underlying NMS remains unknown, it is believed to be related to striatal dopaminergic hypofunction caused by a blockade of striatal dopamine receptors. The antidopaminergic properties of antipsychotics could cause NMS, which is supported by the disorder's response to dopamine agonists, such as bromocriptine.<sup>5</sup> A genetic association study has sought to identify polymorphisms influencing susceptibility to NMS, especially with respect to the dopamine D<sub>2</sub> receptor, serotonin receptor, and cytochrome p450 2D6.<sup>6</sup> It has been suggested that serotonergic and noradrenergic receptors might have a role in the pathophysiology of NMS.<sup>7</sup> Sympathoadrenal hyperactivity has been reported as one of the types of pathophysiology of NMS.<sup>8</sup> NMS symptoms are remitted only by drug discontinuation and supportive care.<sup>9</sup> Diazepam is useful for treating muscular rigidity and agitation.<sup>10</sup>

After an episode of NMS, the patient presented with altered mental status, and two principal hypotheses were considered: 1) the condition was due to reexacerbation of chronic schizophrenia and 2) the condition was due to clozapine withdrawal. There was, especially after an episode of NMS, a therapeutic dilemma about the treatment of this case. At least 2 weeks should elapse before a rechallenge with antipsychotic medications, and the second medication should be different from the medication implicated in the initial NMS episode.<sup>11</sup>

NMS is the one extreme of neuroleptic-related toxicity.<sup>12</sup> It was questionable whether it was proper to give a patient who presented with symptoms of NMS a medication that could cause such a condition or even worsen it, especially because of its unclear clinical picture and lack of drug concentrations in the serum.

We propose that abrupt clozapine withdrawal induced mental status changes after NMS-symptom resolution in the patient. The fact that it persisted despite her receiving other medications, and the rapid improvement observed after clozapine readministration, further supports this contention.

Clozapine-withdrawal effects have not received much attention. Clinicians need to be aware of the withdrawal effects of neuroleptics when they are suddenly discontinued. Cholinergic overdrive  $\gamma$ -aminobutyric acid supersensitivity may contribute to many of the symptoms of acute clozapine withdrawal.<sup>3</sup> Clinically, whenever possible, clozapine should be slowly tapered. If side effects necessitate rapid withdrawal, the use of anticholinergics would help to improve at least some of the symptoms.<sup>13</sup>

## Conclusion

In conclusion, psychiatrists not aware of possible clozapine-withdrawal effects may misdiagnose as a part of the primary mental illness or initial symptoms worsening if unrecognized.

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## Disclosure

The authors report no conflicts of interest in this work.

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