



LETTER TO THE EDITOR

A differential diagnosis: clozapine-induced delirium or neuroleptic malignant syndrome?

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Dear Editor,

Clozapine is a gold-standard medication and drug of choice for treatment-resistant schizophrenia. Nonetheless, there are several potentially fatal side effects. Delirium can be difficult for clinicians to recognize as a side effect of the drug and thus far, there is only limited reporting on this development. Clozapine has serotonergic, adrenergic, and histaminergic-blocking properties, and it is also a potent muscarinic acetylcholine receptor antagonist (1). It has been well-established that clozapine can be effective for refractory schizophrenia (2). Although hematological, metabolic, and neurological side effects are well known, delirium is less recognized. There are a few case reports of delirium resulting after abrupt withdrawal of clozapine in schizophrenic patients (3). A literature review yielded 3 cases reporting delirium after restarting clozapine (4-6). Neuroleptic malignant syndrome (NMS) is a rare but potentially deadly disorder associated with antipsychotic medications. Herein, we present the case of a paranoid schizophrenic who developed delirium after the reinitiation of clozapine treatment.

A 52-year-old female from Ankara, Turkey had been in follow-up with a diagnosis of schizophrenia for about 20 years and had used clozapine 400 mg per day for four years. Some 3 weeks prior to the present admission she had begun to use her medication irregularly and then stopped altogether. When psychotic symptoms appeared, clozapine treatment was titrated, as recommended by her follow-up doctor. Due to the agitation of the patient, the

drug was administered by her husband at a dose of 400 mg/day for 3 days and haloperidol 20 mg was administered intramuscularly in the emergency room one day apart. After 3 days of clozapine treatment, she was brought to the emergency department, confused and agitated. Disorientation was overtly observed, along with impaired short-term memory, inappropriate speech, and a disheveled appearance. There was a deviation in her left eye and her gait was ataxic. Rigidity was evident in the upper extremities. Liver function tests and creatine phosphokinase (CPK) level values were both 6 to 8 times higher than normal. Her blood pressure was variable, and her body temperature was 37.2°C. She was admitted and clozapine treatment was terminated. Treatment of 1500 cc isotonic solution per day was initiated. A urine catheter was inserted and 500 cc of urine was recorded in 30 minutes. The intensive care unit, internal medicine, and neurology departments were consulted immediately. No pathology to explain the conditions was found, and it was advised that close vital monitoring and hydration be continued. The patient's vital signs (pulse, respiratory, temperature, blood pressure) were checked 24 times a day. Magnetic Resonance Imaging (MRG) was normal and an electrocardiogram (EEG) was consistent with mild dysfunction of cerebral bioelectric activity in the left temporal region. On the third day of drug cessation, the isotonic solution therapy was reduced to 1000 cc per day. The symptoms began to regress. She was able to walk and the urinary catheter was removed. She was able to talk and eat with her husband's help. On the fourth day of hospitalization, her CPK level had decreased from 7417

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U/L to 4829 U/L. Her liver function test values also decreased. Her orientation normalized, and the deviation in the left eye regressed on the third day of treatment. She was able to talk to her husband and did not describe auditory or visual hallucinations. On the seventh day of drug interruption, her clozapine dose was restarted at 25 mg per day. A control EEG was normal. Her liver function test results were normal at the end of the first week of hospitalization. Her vitals were stable. Intravenous hydration was terminated. The 25 mg dose of clozapine was increased every 3 days and she was discharged on the 14th day of hospitalization with a daily dose of clozapine of 75 mg/day because the patient and her family wanted to continue treatment as an outpatient. After discharge, the patient continued regular follow-up visits at the outpatient clinic and now continues to take clozapine at a dose of 400 mg/day.

A few reports have previously documented the emergence of delirium associated with use of clozapine (3). Even if clozapine treatment is interrupted for only a short time, it is important that a subsequent course begin with a low dosage and be increased very cautiously until it reaches the formerly tolerated level. Clozapine alone or in combination with other agents has been observed as a causative factor for delirium (7). There are several cases of patients who were receiving clozapine treatment and developed delirium during slow titration while vital signs remained stable and there was no pathology observed in liver function tests (6,8). In the present case, a clozapine-version of NMS, a rare, idiosyncratic, but life-threatening adverse reaction associated with the use of antipsychotic drugs, could not be ruled out. The motor and behavioral symptoms of NMS include muscular rigidity and dystonia, akinesia, mutism, obtundation, and agitation. The autonomic symptoms include hyperthermia, diaphoresis, and increased pulse and blood pressure. Laboratory findings include an increased white blood cell count and increased levels of creatinine phosphokinase, liver enzymes, plasma myoglobin, and myoglobinuria, occasionally associated with renal failure (9). The patient in this case met all of the NMS criteria as defined in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) except hyperthermia (10). However, while NMS could be eliminated according to the DSM-5 criteria, the patient met 2 major and 4 minor of Levenson's criteria (11). Our patient presented with 2 of Levenson's major criteria (no fever) and met all of the minor criteria.

Our patient may have developed an atypical presentation of NMS, given the autonomic instability other than fever, liver enzyme findings, and CPK

elevation. Analysis of the literature reveals that atypical NMS cases without fever have been reported related to atypical antipsychotics, including aripiprazole and olanzapine (12,13). The EEG results were not consistent with those usually reported in patients with NMS: A non-generalized slowing on an EEG has been reported in patients with NMS (14). An atypical NMS case has previously been reported associated with clozapine use and delirium in an afebrile patient (15).

In conclusion, the delirium our patient experienced may have developed due to NMS. Since delirium associated with clozapine has rarely been reported, clinicians should be able to recognize this condition and investigate the causes thoroughly in order to create optimal structured treatment options.

Informed consent: Written consent was obtained from the patient.

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