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LETTER TO THE EDITOR

# A case of differantial diagnosis: Clozapine induced delirium or neuroleptic malignant syndrome?

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Dear Editor,

Clozapine is a gold standard medication and drug of choice in treatment resistant schizophrenia. Among many of its fatal side effects, delirium is less reported and difficultly recognized by clinicians. Clozapine has serotonergic, adrenergic and histaminergic blocking activity and it is also a potent muscarinic acetylcholine receptor antagonist (1). It has been well-established that clozapine is an effective treatment for treatment-resistant patients (2). Although its hematological, metabolic and neurological side effects are well known, delirium is less reported and recognized. There are a few case reports of resulting delirium after abrupt withdrawals of clozapine in schizophrenic patients (3). We could find three cases which reports delirium after restarting clozapine till date (4-6). Here in we present a case of paranoid schizophrenia who developed delirium after clozapine was restarted.

A 52 years old female from Ankara, Turkey who had been followed with a diagnosis of schizophrenia about 20 years and had been used clozapine for four years as a dose of 400 mg. It was learned that she started to use her medication irregularly three weeks before her admission and then stopped. When her psychotic symptoms appeared, clozapine treatment was titrated and recommended to start again by her follow-up doctor. Due to the agitation of the patient, the drugs were given by her husband at a dose of 400 mg/day for three days and at the same time, haloperidol 20 mg was administered intramuscularly in the emergency room one day apart. After using clozapine for three days she presented to our emergency service. She was confused and agitated. Disorientation was overtly observed, along with impaired short-term memory she has inappropriate speech, and a disheveled appearance. Also, there was deviation in her left eye and her gait was ataxic. Rigidity was evident in the upper extremities. Liver function tests and creatine phosphokinase (CPK) levels was 6 and 8 times higher than normal and also her blood pressure was variable, and her body temperature was about 37.2 degrees centigrade. The clozapine stopped and 1500 cc isotonic solution per a day was started. Urine catheter was inserted to the patient. 500 cc urine was present in 30 minutes. We consulted her immediately with intensive care unit, internal medicine and neurology. They did not detect any pathology to explain this situation and advised close vital monitoring and continued hydration for patient. Vital follow up was performed 24 times a day. Her cranial MRG was normal and her EEG was consistent with mild dysfunction of cerebral bioelectric activity in the left temporal region. On the third day of drug interruption, the isotonic solution was given to 1000 cc per a day. The symptoms of the patient began to regress. She was able to walk so we removed the urinary catheter. She was able to talk and eat her meal by her husband's help. On the fourth day of her hospitalization her CPK level was decreased from 7417 to 4829. Her liver function tests also decreased. Her orientation became normal, deviation in left eye regressed in the third day of the treatment. She was

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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 as 25 mg per day. Her control EEG was normal. Her liver function tests became normal in the end of first week of hospitalization. Her vitals were stable. Her intravenous hydration was stopped. The dose of clozapine 25 mg was increased every three days. We discharged her in the 14th day of hospitalization with dose of clozapine 75 mg/day because the patient her family wanted to continue the treatment as an outpatient. After discharge, the patient continued regular follow-up visits at the outpatient clinic and still continues clozapine 400 mg/day.

A few reports have documented emergence of delirium associated with use of clozapine (3). Even if clozapine treatment is interrupted for only a short time it is important that the 'new' course begins with a low dosage and is increased very cautiously until it reaches the former, tolerated level. Clozapine alone or in combination with other agents have been observed as a causative factor for delirium (7). There are several cases that of patients receiving clozapine treatment, delirium developed during slow titration and vitality was stable and also there was no pathology in liver function tests of those patients (6,8). Although a clozapine-version of a neuroleptic malignant syndrome (NMS) could not be ruled out. Neuroleptic malignant syndrome (NMS) is a rare, idiosyncratic, but life-threatening adverse reaction associated with the use of antipsychotic drugs. The motor and behavioral symptoms include muscular rigidity and dystonia, akinesia, mutism, obtundation, and agitation. The autonomic symptoms include hyperthermia, diaphoresis, and increase pulse and blood pressure. Laboratory findings include an increased white blood cell count and increased levels of creatinine phosphokinase, liver enzymes, plasma myoglobine, and myoglobinuria, occasionally associated with renal failure (9). The complication of the diagnosis in our case was that the patient met all NMS criteria except hyperthermia as reflected in Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition [DSM-5] criteria) (10). That's why we ruled out NMS according to DSM-5 criteria. On the other hand, what is confusing in our case was that our patient met the criteria of Levenson for the diagnosis (11). Our patient presented with two Levenson's major criteria except fever and met all the minor criteria.

It was also thought that the patient may have an atypical NMS in the diagnosis due to autonomic instability other than fever, liver enzymes and CPK elevation. When the literature is analyzed, it was seen that atypical NMS cases without fever were reported related to atypical antipsychotics such as aripiprazole and olanzapine (12,13). Nevertheless, her EEG was not match with the EEG that usually reports in patients with NMS. A non-generalized slowing on an EEG might be reported in patient with NMS (14). It was observed that there was an atypical NMS case reported with clozapine, and this case was also afebrile, and it was reported that the developing delirium was associated with NMS (15).

In conclusion; the delirium may have appeared due to NMS. Since the delirium due to clozapine is rarely reported, clinicians will be able to recognize this condition and investigate its causes, which will help create structured treatment options.

**Informed consent:** Written consent was obtained from the patient.

**Conflict of Interest:** None declared.

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## REFERENCES

1. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988; 45:789-796.
2. Meltzer HY. Treatment-resistant schizophrenia--the role of clozapine. Curr Med Res Opin 1997; 14:1-20.
3. Stanilla JK, de Leon J, Simpson GM. Clozapine withdrawal resulting in delirium with psychosis: a report of three cases. J Clin Psychiatry 1997; 58:252-255.
4. Szymanski S, Jody D, Leipzig R, Masiar S, Lieberman J. Anticholinergic delirium caused by retreatment with clozapine. Am J Psychiatry 1991; 148:1752.
5. Benckhuijsen JA, Keet IP. Delirium on re-starting clozapine after a short break in treatment. Tijdschr Psychiatr 2007; 49:661-665.
6. Khanra S, Sethy RR, Munda SK, Khess CR. An Unusual Case of Delirium after Restarting Clozapine. Clin Psychopharmacol Neurosci 2016; 14:107-108.
7. Crilly J. The history of clozapine and its emergence in the US market: a review and analysis. Hist Psychiatry 2007; 18:39-60.
8. Baweja R, Sedky K, Lippmann S. Clozapine associated delirium. Eastern J Med 2010; 15: 71-72.
9. Sadock BJ, Sadock VA, Ruiz P. Kaplan & Sadock's synopsis of psychiatry: Behavioral sciences/clinical psychiatry. Eleventh ed. Philadelphia: Wolters Kluwer, 2014
10. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders Fifth ed. (DSM-5). Washington DC: American Psychiatric Publishing, 2013.
11. Levenson JL. Neuroleptic malignant syndrome. Am J Psychiatry 1985; 142:1137-1145.

12. Nielsen J, Bruhn AM. Atypical neuroleptic malignant syndrome caused by olanzapine. Acta Psychiatr Scand 2005; 112:238-240.

13. Spalding S, Alessi NE, Radwan K. Aripiprazole and atypical neuroleptic malignant syndrome. J Am Acad Child Adolesc Psychiatry 2004; 43:1457-1458.

14. Caroff SN, Mann SC. Neuroleptic malignant syndrome. Psychopharmacol Bull 1988; 24:25-29.

15. Spivak M, Adams B, Crockford D. Atypical neuroleptic malignant syndrome with clozapine and subsequent haloperidol treatment. Can J Psychiatry 2003; 48:66.