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Case Report

Clozapine associated delirium

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Abstract. Delirium is an encephalopathy characterized by disorientation, confusion, and short-term memory impairment. It can be caused by a variety of pharmaceuticals that includes clozapine. The etiology in clozapine cases includes anticholinergic effects and a neuroleptic malignant syndrome-like picture. The risk for a clozapine induced delirium is greater at high dosages, during dose increases, and with polypharmacy. Resolution follows clozapine dose reductions and/or medicine discontinuations.

Key words: Clozapine; clozapine-induced delirium; neuroleptic malignant syndrome; anticholinergic side effects; schizoaffective disorder

1. Introduction

Clozapine is an antipsychotic drug that blocks dopamine-4 receptors (1). Due to serious hematological and metabolic risks, it is most commonly reserved for prescribing to patients with schizophrenia who are treatment-resistant (2). Although not consistently recognized by clinicians, clozapine-induced delirium can occur in upto 10% of treated cases (2). Described is a clinical vignette about a patient with a delirium that occurred following an increase in clozapine dosage.

2. Case report

A 60 year-old Caucasian male had a 30-year history of schizoaffective disorder, bipolar type. His symptomatology included persecutory delusions, auditory hallucinations, and depression or mania. He resided in assisted housing and attended a daily rehabilitation program. He had been stable for years while prescribed clozapine 600 mg at night, sertraline 100 mg in the morning, and aripiprazole 15 mg daily.

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Hypertension, hypercholesterolemia, type-2 diabetes mellitus, and gastroesophageal reflux necessitated daily therapy with lisinopril 5 mg, atorvastatin 40 mg, omeprazole 30 mg, and a variable insulin regimen.

The patient was hospitalized because of auditory hallucinations, persecutory delusions, and depression with suicidal thoughts. Cognition was intact and there was no history of head injury or other new ailment. His physical and neurological examinations were unremarkable. Vital signs, a metabolic profile, a complete blood count, urinalysis, and an electrocardiogram were within normal ranges. Other than aripiprazole and clozapine dosage adjustments, his home-medications remained unchanged.

On the day after admission, the aripiprazole dose was increased to 20 mg/day; subsequently, this medication was increased to 30 mg. The patient remained psychotic through day seven, leading to an aripiprazole dose decrease to 15 mg and its discontinuation by day 14. Clozapine was gradually titrated upward to 850 mg by day 17. The following morning, the patient became confused and agitated. Disorientation was overtly observed, along with impaired short-term memory, inappropriate speech, and a disheveled appearance. A repeated neurological examination was unremarkable, with no extremity tremors or muscular stiffness. Afebrile, his vital signs remained normal. A repeat of all the previous laboratory studies was fully normal. There was no

assay of creatinine phosphokinase (CPK) or clozapine level performed.

On day 19, clozapine was reduced to 600 mg/day dose and agitation managed by as-needed lorazepam and haloperidol injections. The next day, his delirium resolved, but psychotic symptoms persisted. Therefore, paliperidone 6 mg/day was added to his regimen on day 22, and increased to 9 mg by day 24. Over the next week, he improved dramatically. Psychotic symptoms resolved, hygiene improved, and he was discharged in stable condition.

3. Discussion

A possible case of a clozapine-induced delirium occurred after a dosage increase. Although his physical examination and laboratory tests remained normal, a clozapine-version of a neuroleptic malignant syndrome (NMS) could not be ruled out. CPK levels were not measured. Although muscular rigidity and a high CPK concentration are common in NMS, cognitive changes including delirium, autonomic instability, or fever, can be the only presentation (3). In this case report, vital signs remained stable and there was no evidence for an infection. A subclinical seizure has not been ruled out and electroencephalography was not performed, but his normal neurological examination and past history renders that less likely.

Delirium is an under-recognized potential adverse effect of clozapine therapy. Pharmaceutically-induced causes for delirium are common, and several case reports of clozapine-induced delirium are documented (4,5), possibly related to anticholinergic properties (6). Encephalopathy risk escalates with rapid dosage increases, high dose therapies, and when the patient takes many medications. The presented case evidences this clinical picture. Caution is advised during clozapine administration, especially at the beginning of treatment, when restarting clozapine after a period of discontinuation (5), with dose escalations unrelated to the medication dose (2), and for people receiving polypharmacy.

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