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Delirium Heralding Clozapine-Induced Myoclonus: An Uncommon Sequence of Side-Effects

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Abstract

There are few reports on clozapine induced myoclonus and delirium, co-occurring at a low dose of clozapine. A 63 year old male patient presented with persistent delusional disorder. Following failed trials of two antipsychotics, clozapine was started, along with modified ECT in view of high suicidality. Following this, the dose of clozapine was increased to 175mg/day. Three days after the ECT, the patient developed delirium, with routine blood investigations being normal. Delirium persisted even after clozapine was stopped. MRI was normal. The next day, the patient developed positive and negative myoclonus. A three-hour video EEG monitoring was done which showed bilateral frontal and temporal generalized epileptiform abnormalities with multifocal distal myoclonus noted during awake state. Patient was initiated on valproate as anti-epileptic and myoclonic jerks and delirium was found to have resolved completely over the next 24 hours. Clozapine was restarted and dose was gradually titrated to 150 mg. Myoclonus associated with cortical epileptiform discharges may have delirium as a presenting feature, which may occur even at low doses of clozapine, especially in the elderly Asian patients.

Keywords: Clozapine, Myoclonus, Delirium, Geriatric Psychiatry

INTRODUCTION

Clozapine is an antipsychotic working as a serotonin 5HT2A- dopamine D2 antagonist, used in treatment resistant schizophrenia.[1] Though it has a lower propensity to cause extrapyramidal symptoms, it is known to cause other neurological adverse effects such as myoclonus, seizures and delirium. Myoclonus is a rapid, involuntary jerky movement of the muscle which is seen in 2% of individuals on clozapine and is a harbinger of generalized tonic-clonic seizures.[2] EEG changes with clozapine have been attributed to its effect on GABA-A receptors, nicotinic acetylcholine receptor, NMDA receptors, 5-HT receptors and strychnine sensitised glycine receptors and is related to the dose of clozapine.[3] Delirium can develop independently, especially in the elderly who are on clozapine, due to its anticholinergic properties.[4] Here, we present a rare case of clozapine induced myoclonus with generalised epileptiform changes in the EEG with the presenting feature as delirium.

Case history:

A 63 year old married male patient, presented to the psychiatry outpatient department with two years history of a fixed belief that he had stomach cancer, which was accompanied by social withdrawal, decreased appetite and poor self-care. He had a significant weight loss of around 15 kgs in two years along with constipation. For the above complaints he had consulted multiple gastroenterologists and had

undergone blood investigations, upper GI endoscopy and CT abdomen which did not reveal any abdominal pathology. On mental status examination, he was noted to have hypochondriacal delusion with significant acting out behaviour and death wishes. A diagnosis of persistent delusional disorder was made and he was started on antipsychotic treatment. He was tried on risperidone 6 mg for a period of 6 weeks, on which he showed partial response. However, no improvement was noted on cross-tapering risperidone with olanzapine 20 mg.

Patient was brought for admission following an attempt of self-harm secondary to his hypochondriacal delusion. Baseline PANSS score was 112. He was initiated on clozapine in view of failed trials of two antipsychotics. In view of active suicidal ideation for a period of four days, modified ECT was planned. Seizure activity was observed in the third session of ECT (on day 9 of admission) delivered for three seconds at 80 Hz. Mini mental status examination (MMSE) score post-ECT was 30. Over the next two days, the patient no longer reported suicidal ideation and had better interaction with family members. The dose of clozapine was 175 mg at this point of time. On day 12 of admission, patient had acute onset of disorientation, psychomotor agitation, hallucinations and disturbed sleep. The possibilities considered were post-ECT delirium and clozapine-induced delirium. Post-ECT delirium was ruled out as patient had received his last ECT three days ago and MMSE upto two days following the ECT showed no cognitive impairment. Considering the possibility of clozapine-induced delirium, clozapine was stopped. Leukocyte counts, renal function tests, electrolytes, liver function tests and urine routine examination were normal. Neurology consultation was sought in view of unresolved delirium. The possibility of limbic encephalitis was considered, in view of which MRI brain was done, which was normal.

The next day, the patient developed sudden, jerky involuntary movements involving distal muscles of upper limbs more than lower limbs. He was also found to have sudden buckling of knee when he attempted to walk. These symptoms pointed to the possibility of clozapine induced myoclonus. A three hour video EEG monitoring was done which showed bilateral frontal and temporal generalized epileptiform abnormalities with several multifocal distal myoclonus noted during awake state with EEG correlation. Patient was initiated on valproate as anti-epileptic and the dose was titrated to 1000 mg (18 mg/kg). Following this, the myoclonic jerks subsided and delirium was found to have resolved completely over the next 24 hours. Clozapine was restarted and dose was gradually titrated to 150 mg. Patient's symptoms improved over the next two weeks; he was no longer reporting suicidal thoughts or hypochondriacal delusion. PANSS scores had reduced to 52. He was discharged on clozapine 150 mg and valproate 1000 mg and was maintaining well on follow-up. Informed consent was obtained from the patient for the write-up of this case report.

Discussion:

Delirium is an under-recognized adverse effect of clozapine, generally attributed to its anticholinergic properties, the prevalence of which is 10%, especially in elderly patients.[5] It is noteworthy that in our case, while the differentials of delirium were being ruled out, it is the clinical picture that followed delirium that revealed the underlying etiology. Positive and negative myoclonus which correlated with bilateral frontal and temporal generalized epileptiform abnormalities on EEG pointed to a diagnosis of cortical variety of epileptic myoclonus in this case, the first manifestation of which was delirium. In previous studies, clinical improvement of myoclonus and diminished epileptiform abnormalities with valproic acid therapy also supported a cortical aetiology.[6]

Earlier reports have shown that clozapine-related seizures occur in a dose-dependent fashion, with seizure incidence rising to 4.4% when doses exceed 600 mg.[7] Though a previous report by Goyal et al shows generalised slowing on EEG at a dose of 100mg of clozapine, epileptiform discharges were still found to be at a mean dose of 306.25 mg.[3] Our case highlights that a dose as low as 175mg of clozapine may induce myoclonus and epileptiform changes on EEG. One explanation can be that in most studies which have looked into the doses of clozapine associated with seizures and myoclonus, the subjects were mostly of Caucasian descent. It has been shown that in Asian population, plasma clozapine levels were higher with a given dose of clozapine, when compared to Caucasian patients.[8] These patients have

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also been found to show clinical improvement with lower doses of clozapine, which is consistent with the observation in this case, where the patient responded to a dose of 150 mg.

Conclusion:

Myoclonus associated with cortical epileptiform discharges may have delirium as a presenting feature especially in the elderly and may occur even at low doses of clozapine. Early recognition and treatment with antiepileptics can lead to resolution of myoclonic seizures and delirium.

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