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Case Report

LOW DOSE CLOZAPINE INDUCED ACUTE AKATHISIA

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ABSTRACT
Akathisia is a feeling of subjective and objective restlessness. It is one of the most common and distressing neuroleptic induced extrapyramidal side effects so much so that the person might even attempt suicide due to the distress (Mathews *et al.*, 2005; Schulte, 1985). It is a very well recognized side effect of first generation antipsychotics but is usually overlooked by clinicians when it comes to second generation antipsychotics. Recent literature has shown that SGAs (second generation antipsychotics) also can cause akathisia highest being risperidone and least clozapine (Caroff *et al.*, 2011). Literature review shows few studies which have shown efficacy of clozapine in treatment of antipsychotic induced akathisia and other EPS (Poyurovsky, 2010). Very few studies discuss about clozapine induced akathisia and it is in higher doses above 100mg. Few case reports talk about nocturnal akathisia with clozapine (Sahoo and Ameen, 2007; Kariyakos *et al.*, 2005). Here, we are presenting a case of clozapine induced acute akathisia on low doses of clozapine.

Keywords: *Clozapine, Akathisia, SGAs*

INTRODUCTION
Akathisia consists of motor restlessness accompanied by subjective feelings of inner tension and discomfort, mainly in the limbs (Mathews *et al.*, 2005). Symptoms commonly seen are lower-limb movements, rocking from foot to foot, shuffling of legs, or swinging one leg over the other while sitting. In severe akathisia, patients may pace up and down or they may be unable to feel comfortable in any position, such as sitting, lying, or standing, for more than a few minutes. Trunk rolling and fidgeting movements of the upper limbs may also be seen (Mathews *et al.*, 2005).
Although, there are many possible hypotheses for pathophysiology of acute akathisia, none is completely satisfactory. So far most the most attractive hypothesis is dopamine receptor blockade mainly (D2) in the mesocortical and mesolimbic regions of the brain. It is unlikely that single neurotransmitter will explain all features; there is a complex interaction of several NTs (Mathews *et al.*, 2005). Responses to anti-cholinergics, and beta-adrenergic and serotonergic blockers, suggest a role for other neurotransmitters as well (Poyurovsky, 2010). Some exploratory reports of dopamine receptor polymorphisms in drug-induced akathisia are present other familial studies being done in cases of restless leg syndrome might help in explaining mechanisms (Mathews *et al.*, 2005).
Proposed treatment guidelines of akathisia includes decrease in dose of antipsychotic drug, switch over to a drug with lower propensity for akathisia, switch over to clozapine, use of anti akathisia medications: Beta blockers, benzodiazepines, 5HT-2A receptor antagonists, anticholinergics (mainly for patients with concurrent drug induced parkinsonism), amantadine or clonidine (Poyurovsky, 2010).
Clozapine as already mentioned is one of the treatment options for akathisia, and also other drug induced extrapyramidal symptoms either acute or chronic. As per current evidence clozapine has mainly D4 and 5HT-2A receptor antagonism and weak D2 antagonism this is the reason for its low propensity for EPS and how it helps in the treatment of drug induced EPS (Levin *et al.*, 1992; Spivak *et al.*, 1997; Hazari *et al.*, 2013).
In spite of the above mentioned facts there are few studies who have looked at occurrence of akathisia in SGAs and shown that though less when compared to FGAs akathisia does occur even with SGAs. Among SGAs risperidone, ziprasidone, aripiprazole have the highest risk, olanzapine intermediate risk and quetiapine and clozapine least risk (Poyurovsky, 2010). There are reports of cases who developed

akathisia on clozapine both acute and tardive and most of these cases were on doses between 150mg – 300mg (Chengappa *et al.*, 1994).

Here, we present a case of Paranoid Schizophrenia who developed acute akathisia with clozapine doses 50-75mg.

CASES

A 37 year old married female Mrs. J who was in contact with our hospital since the past 2 years she had initially presented to us with 2 years history of being withdrawn, 2nd person auditory hallucination running commentary type and derogatory type, delusions of reference and persecution, impaired sleep and appetite, past history k/c/o B/L Atypical Retinitis Pigmentosa, with a family H/O Retinitis pigmentosa in her father and three of her sister, pre morbidly fairly well adjusted, after detailed evaluation she was diagnosed with Paranoid Schizophrenia and as per ICD 10 classificatory system.

She had been initially tried on olanzapine upto 20mg, patient showed upto 50% improvement as per PANSS in positive symptoms but negative symptoms were persisting in view of these persisting symptoms patient was started on amisulpiride upto 300mg, it was also noted that patient was highly sensitive to antipsychotics and developed EPS at low doses of medications after 2-3 weeks of trial decision was taken to start the patient on clozapine.

The patient was admitted and after pre clozapine checkup started on clozapine with 12.5mg with this dose she showed around 50% improvement in both positive and negative symptoms. Patient was discharged on request and advised regarding getting regular blood counts. Patient came for regular weekly follow up and gradually over one month period dose increased to 75mg and psychotic symptoms showed 80-90% improvement.

After 2days of receiving this dose patient developed increased salivation, slurring of speech, restlessness not able to sit in one place continuously pacing around, feel like moving her legs continuously. Patient was admitted for further evaluation detailed history taken and MSE done anxiety symptoms and any anxiety disorders were r/o, restless leg syndrome r/o.

Abnormal involuntary movement scale (AIMS) was applied which showed score of 2 in lower limb movements. Barnes akathisia rating scale (BARS) showed marked akathisia.

The dose of clozapine was maintained at 75mg as patient had shown significant improvement with this dose and propranolol 40mg OD and clonazepam 0.5mg BD were started over a period of one week her akathisia improved upto 90% and she maintained improvement in psychotic symptoms. Patient was discharged on same doses of medications.

DISCUSSION

The index patient started showing significant improvement in psychotic symptoms with a small dose of clozapine 25mg, and also developed akathisia at a dose of 50-75mg. She also is a k/c/o of retinitis pigmentosa with a significant family history of the same as mentioned in the introduction this could be one of those cases of dopamine receptor polymorphism.

The usual protocol for drug induced akathisia is reducing dose of antipsychotic which was not done here weighing the risk benefit ratio and patient showed significant improvement on just add on anti akathisia drugs and is maintain well on further follow up, thus, it may be worthwhile to first try add on medications rather than reducing antipsychotic dose which might worsen the psychotic symptoms especially in resistant schizophrenia.

Thirdly, and the most important thing is that though studies show that SGAs and especially clozapine has a low incidence of akathisia it is important to be watchful for these features as we know akathisia is one of the most distressing EPS. Co-relation between akathisia, depressive symptoms and impulsiveness may account for suicidal and violent behavior in patients with akathisia.

Conclusion

In conclusion as per our study and current literature akathisia with clozapine is known and clinicians should be watchful for it and unlike other antipsychotics developing akathisia on clozapine, low dose

could be more dependent on patient factors like receptor polymorphism, other genetic factors and this area needs further research.

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