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Case report

Clozapine versus other neuroleptics induced tardive dyskinesia in an elderly patient

Javed Ather Siddiqui, Shazia Farheen Qureshi, Khider Abdel Rahim

Abstract

Tardive dyskinesia (TD) is one of the most troublesome extrapyramidal side effects of neuroleptic medicine. The development of TD on clozapine, a second generation antipsychotics is rare. There are some case reports of TD induced or worsened by clozapine therapy, but clozapine still remains a viable treatment option for patients with antipsychotic induced TD as well as withdrawal dyskinesia. We report a case of 60 year old male patient with the diagnosis of schizophrenia for 25 years who developed TD, around one year after the initiation of clozapine therapy. Clozapine was replaced by amisulpride however it has to be reintroduced as psychotic symptoms continued. It was not clear if clozapine had a direct effect on inducing TD or it was the effect of prolonged exposure to previous antipsychotics. It is probable that clozapine may induce TD in rare cases; however treatment goals need to be balanced between symptom control and side effect management.

Key words

Clozapine, extrapyramidal side effect, neuroleptics, tardive dyskinesia

Introduction

Tardive dyskinesia (TD) is described as stereotypic, choreiform or athetoid involuntary repetitive and purposeless movements. It prominently affects head, neck, shoulders and trunk. TD was coined by Faurbye and colleagues in 1964; it has been associated with use of classical antipsychotics in treatment of schizophrenia since 1950s.[1]

The second generation antipsychotics are less associated with TD as compared to first generation antipsychotics because of their "atypical" effect on dopamine receptors.[2,3] The well-known risk factor for TD is age; and other than age, gender, race, neurological disease, high dose of antipsychotics, mood disorders, negative symptoms, alcohol and other drug use and diabetes mellitus and prolonged use of antipsychotics are also known to contribute towards development of TD.[4-6] There are some studies which suggest that atypical antipsychotics are less risky in terms of TD; but there are issues with comparators, which have used high doses of haloperidol in comparisons.[7,8] The prevalence of TD increases with increasing age, it is 29% in elderly patients receiving dopamine antagonist treatment for 3 months and 26-67% in patients undergoing long-term treatment.[9,10]

The criteria of TD is the symptoms must develop after at least 3 months of exposure to dopamine antagonist (or 1 month in patients with age 60 or more) or within 4 weeks of withdrawal from oral medication (or 8 weeks of withdrawal from depot medication) and should persist for at least 4 weeks after discontinuation of offending drug.[11]

Pathophysiology of TD is poorly elucidated. The different mechanisms postulated are; prolonged blockade of post synaptic dopamine receptor,[12,13] dopaminergic hypersensitivity,[14] gamma-aminobutyric acid (GABA) dysfunction,[15] cholinergic hypofunction and excitotoxicity.

In psychiatry commonest cause of TD is antipsychotics and other causes are antidepressants, anticholinergic, lithium.[16] Other medications that can cause TD are antiemetics, antiepileptics, calcium channel blockers, sympathomimetics and antiparkinsonians.[16]

Clozapine is a diabenzodiazepine derivative, is less likely to cause TD due to low affinity for striatal D2 receptors and to the inhibition of the presynaptic 5HT2A receptors;[17] and it may even ameliorate existing TD.[18]

Although there are many studies regarding the improvement of TD following introduction of clozapine; but few cases report a development or worsening of TD during clozapine treatment.[19] Clozapine has been reported to be effective in suppressing nearly 60 percent of TD syndrome especially those with dystonic features and considered as effective treatment for it.[20] Most of the reported dyskinesia seems to be related to the withdrawal of previous medications rather than the beginning of clozapine treatment.[21,22] TD is a group of disorders which are due to prolonged use of neuroleptics, occurring during on medication or shortly after cessation of medication.[23]

We report a case where TD was observed after around a year of starting clozapine. However the patient had prolonged use of other antipsychotic drugs for many years. The possibility of clozapine inducing TD and the contributing factor of other neuroleptic contributing to it are discussed.

Case report

A 60-year old, married male patient, diagnosed with schizophrenia was admitted to a chronic rehabilitation ward for 25 years. There was no significant past or family history of psychiatric illness. His medical history is unremarkable. He was treated with multiple typical and atypical antipsychotics. More recently these were chlorpromazine 500 mg per day which was changed to haloperidol up to 15 mg per day along with benztropine 2 mg once daily. He had anger outburst, irritability, hearing voices and persecutory delusions. In addition to this, he was also given sodium valproate 1000 mg per day and fluphenazine decanoate 25 mg IM two weekly last 4 years to control his psychosis. Above all treatments led to minimal response, so haloperidol was slowly tapered and stopped along with fluphenazine over two weeks. All routine investigations such as complete blood count, liver and kidney function tests and electrocardiogram were carried out as a pre-clozapine work up.

It was decided to start clozapine because symptoms were resistant with previous medications. The dose of clozapine was gradually titrated to 600 mg per day over a period of two months as per guidelines; and continued over a one year period. Patient had a significant improvement in his delusion and his aggression. One year after initiation of clozapine mild repetitive involuntary movement of jaw and both hands was observed. The abnormal movements continued and gradually worsened. His abnormal involuntary movement scale[24] (AIMS) score was 24. Patient was also assessed on Naranjo adverse drug reaction probability scale;[25] and the score was 6, suggestive of possible adverse drug reaction. Clozapine gradually tapered and stopped over a 2 months. He was commenced on amisulpride and increased up to 600 mg per day along with sodium valproate 1000 mg per day. Over a 5-6 months period revealed an improvement of his TD and its AIMS score came down to 14; but no improvement was observed in his psychosis; he continued remain deluded with frequent aggression. Clozapine was restarted. Amisulpiride was tapered and stopped. Clozapine was increased up to 300 mg within two months. Patient was improved in his psychosis and TD movements were greatly reduced.

Discussion

Tardive dyskinesia is an important clinical problem which has been shown to have a relationship with the dopamine hypersensitivity in basal ganglia. TD can be hard to diagnose and the symptoms might not appear until months or years after start of antipsychotics. TD can be prevented by early recognition and discontinua tion of the antipsychotic medication if this is clinically possible. Atypical antipsychotics like amisulpride and olanzapine have a reduced liability for inducing TD. Our patient did not have any dyskinetic movements until one year of initiation of clozapine when he developed dyskinesia of moderate severity. One of the reasons for worsening of TD in clozapine treated patients could be due to previous treatment with typical antipsychotics like haloperidol and long acting fluphenazine decanoate. Although rarely reported, there is a probability of clozapine inducing and worsening TD, which has been reported.[26,27] Other possible contributing factor in this case could be advanced age, exposure to high neuroleptic dose, long history of antipsychotic use and mood disorder.[5] Greater illness severity at baseline and poor response to typical antipsychotics are also reported to be predictors of risk of TD.[28] In this reported case the patient was an elderly male who had been exposed to multiple typical and atypical antipsychotics with high dosage and had a long history of antipsychotics use spanning more than 25 years, along with mood stabilizer. These risk factors may have increased the vulnerability of the patient towards development of TD.

Conclusion

This article suggests that long term treatment of neuroleptic medications may lead to TD even after change of antipsychotic drug to clozapine. Atypical antipsychotic drugs and clozapine may have decreased risk for TD, but it appears that they do not completely eliminate the risk. However, the prevalence of clozapine induced TD is very low, its severity is relatively mild, with no or mild self-reported discomfort; suggesting that clozapine should still be considered in patients with risk of TD. Based on the above it may be recommended that regular examination for TD should be performed in all patients taking antipsychotics including clozapine on a long-term basis.

Author information: Javed Ather Siddiqui, DPM, Psychiatrist javedsiddiqui2000@gmail.com; **Shazia Farheen Qureshi,** DPM, Psychiatrist shaziasiddiqui433@gmail.com; **Khider Abdel Rahim,** MD, Consultant Psychiatrist, chronic rehabilitation ward, drkabdelrahim@gmail.com; Mental Health Hospital, Taif, P.O. BOX. 2056, TAIF -21944 (KSA).

Correspondence: Javed Ather Siddiqui, Psychiatrist, Department of Psychiatry. Mental Health Hospital, Taif, P.O. BOX. 2056, Taif - 21944 (KSA), Email: javedsiddiqui2000@gmail.com

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