Neuroleptic malignant syndrome in cycloserine-induced psychosis

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ABSTRACT

A 33-year-old multidrug-resistant tuberculosis female patient diagnosed as cycloserine-induced psychosis developed several neuroleptic side effects such as extrapyramidal reaction, neuroleptic malignant syndrome, and drug-induced parkinsonism while she was being treated with initially haloperidol and then olanzapine over a period of 2 months. Patient’s antipsychotic medications were withdrawn, and treatment with bromocriptine showed prompt recovery. The multiple neurological adverse effects which the patient developed had implications on the management of the complications as well as her illness.

KEY WORDS: Cycloserine, multidrug-resistant tuberculosis, neuroleptic malignant syndrome, parkinsonism

Introduction

Neuroleptic malignant syndrome (NMS) is a life-threatening adverse reaction caused both by typical and atypical antipsychotics. It is characterized by changes in the level of consciousness, muscle rigidity, fever, mutism, dysphagia, autonomic instability and laboratory evidence of rhabdomyolysis, and myoglobinuria. The cause for NMS is probably a hypodopaminergic state that disrupts heat regulation with other neurotransmitters such as serotonin, noradrenaline, acetylcholine, and gamma aminobutyric acid also being implicated.[1] Cases of NMS have been reported with both typical and atypical antipsychotics with dehydration, hyponatremia, use of restraints and intramuscular injections being the most frequently reported risk factors.[1,2]

We report a case of multidrug-resistant tuberculosis (TB) who developed cycloserine-induced psychosis with resultant neurological complications of extra pyramidal reactions, NMS and drug-induced parkinsonism on typical and atypical antipsychotics during cross titration, with the difficulties in management.

Case Report

A 33-year-old married female was referred from the TB hospital for an acute onset of symptoms of not eating, talking or responding to verbal commands with tremulousness of whole body. The patient was a diagnosed case of multidrug-resistant TB on CAT IV AKT (kanamycin 500 mg, levofloxacin 750 mg, ethionamide 500 mg, cycloserine 750 mg, and pyridoxine 100 mg) since 4 months. After 1 month of starting AKT, the patient showed a change in behavior of becoming irritable, refusing to take her medications and having delusions of infidelity against her husband. There were no other hallucinations or delusions. The patient was referred to a local psychiatrist who diagnosed her as suffering from cycloserine-induced psychosis and advised the physician to stop cycloserine. The patient was then started on tab olanzapine (5 mg) which was increased to 30 mg in 15 days. Tab haloperidol (1.5 mg) and tab trihexyphenidyl (2 mg) were added after 2 weeks of being on tab olanzapine as the patient’s aggressive behavior was uncontrolled though her suspiciousness towards her husband had reduced. The patient developed tremulousness and dystonic reactions within 2 days of adding the above medications for which her olanzapine was then reduced and gradually stopped over 1 week as it was in high doses. After the extra pyramidal symptoms had subsided, the dose of haloperidol was gradually increased to 10 mg with trihexyphenidyl at 4 mg over 10 days, as the patient still remained aggressive though her delusions had now abated. However, the next day patient came with severe akathisia and whole body tremulousness as a side effect of the typical antipsychotic medication. This time haloperidol was reduced to 5 mg, and olanzapine was restarted at 5 mg and increased to 10 mg with cross titration done gradually over 10 days. The patient was on the above medications for 2 weeks after which she presented first time to us with a sudden onset of dysphagia, mutism, and rigidity. She did not have any history of fever, diaphoresis, convulsions or autonomic...
fluctuations. Higher function examination revealed her to be in altered sensorium, apathetic, unresponsive to oral commands with cogwheel rigidity.

The patient was considered to be in NMS, and all her psychotropic medications were stopped. Her laboratory investigations revealed elevated serum creatine phosphokinase kinase (CPK) 1650 IU, white blood cell - 12,000/mm², blood urea nitrogen - 10 mg/dl, serum creatinine - 1.2 mg/dl and urine for myoglobin was positive. Other blood parameters such as hemogram, erythrocyte sedimentation rate, electrolytes, cerebrospinal fluid examination, and liver function test were normal. Her magnetic resonance imaging brain showed mild ventricular dilatation. Medical and neurological references also confirmed the diagnosis and the patient was started on tab bromocriptine 7.5 mg/day in divided doses and later increased to 10 mg/day after 2 days. She was given intravenous fluids to maintain hydration and was later put on ryles tube (nasogastric) feeds as she still complained of dysphagia. All her vital parameters were monitored and within 2 weeks, the patient improved with a reduction in the rigidity and tremulousness. She started accepting oral feeds and was ambulatory. Serum CPK levels reduced to 190 IU/l by day 16 and her urine for myoglobins became negative after which tab bromocriptine was tapered and stopped.

During her inpatient stay, no behavioral problems or delusions were present, hence antipsychotics were not considered. However, it was noticed that though she was ambulatory, the patient had difficulty in getting up from sitting position and would have coarse truncal tremors with a short festinant gait. This time, the neurologist considered an additional problem of drug-induced Parkinsonism and started her on tab amantadine 100 mg bid with tab trihexyphenidyl 2 mg bid. The patient improved in her symptoms over the following 10 days and is still maintained on the same with a regular follow-up.

Discussion

The incidence of NMS varies from 0.5% to 3% in those on typical neuroleptics and is about 0.01–0.02% in those on atypical antipsychotics.41 Caroff et al.42 claimed that lack of muscle rigidity and temperature above 38°C was more commonly seen in NMS with atypical antipsychotics. As our patient had developed psychotic features within a month of being on cycloserine, a drug known to cause psychosis she was diagnosed to be having cycloserine induced psychosis by the psychiatrist. As per diagnostic and statistical manual of mental disorders in drug-induced psychosis, the symptoms should develop soon after exposure to medication and there should be presence of one or both delusions or hallucinations which conformed to the clinical picture of our patient. An attempt to control the behavior and the disturbed thought processes with both typical and atypical antipsychotics led to several neuroleptic-induced extrapyramidal reactions, akathisia as well as dystonic reactions in our patient which were seen either with increasing the doses or cross titration of both typical and atypical drugs. Despite an attempt by the psychiatrist to titrate the doses of the offending drugs, the patient also developed NMS. An elevated CPK which is often due to myonecrosis secondary to intense muscle contracture leading to acute myoglobinuric renal failure confirmed the diagnosis.

Several risk factors like high neuroleptic doses, rapid dose titration, dehydration, malnutrition, infection, organic brain disease etc., could lead to NMS of which a few were also seen in our patient. The pathogenesis of muscle rigidity in NMS is usually attributed to the dopamine receptor blockade resulting in impaired temperature regulation and autonomic changes.13 The drug treatment for NMS should continue for 2–3 weeks until symptoms remit along with the cessation of the neuroleptic trigger with supportive therapy. Our patient additionally also developed drug-induced parkinsonism which remitted with amantadine. Extra pyramidal syndrome has been reported in three-fourth of cases of atypical neuroleptic-induced NMS, which also corroborates with our findings. In this case, all the adverse drug reactions were assessed as “certain” with high level of causality by WHO Uppsala monitoring center criteria for case causality assessment43 and were identified as “probable” level of causality based on Naranjo’s Algorithm,44 with a score of five.

Neuroleptic malignant syndrome, a serious disorder with variable presentations, should be identified early so as to prevent NMS related mortality. The presence of only one NMS symptom should be sufficient for the clinicians to consider NMS as a differential diagnosis in patients on antipsychotics. Using lower potency agents, a lower initial dose, avoidance of polypharmacy help prevent the occurrence of life-threatening adverse effects due to this and similar drugs.

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