## Case Report

# Aripiprazole induced Neuroleptic Malignant Syndrome : A Case Report

**Soumi Ghosh[1], Indranil Saha[2], Arijit Mondal[3]**

Neuroleptic Malignant Syndrome (NMS) is a life threatening adverse reaction to antipsychotics. It manifests as disorientation rigidity, fever and autonomic instability. NMS is commonly seen with first generation antipsychotics, and usually uncommon with atypical antipsychotics. A 20 years old female patient with the diagnosis of acute and transient psychotic disorder (ATPD) presented with characteristic features suggestive of NMS, following treatment with tablet aripiprazole 20 mg daily. The patient was diagnosed NMS, offending drug aripiprazole was immediately stopped, and rapid treatment with tablet bromocriptine and supportive care lead to recovery.

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Neuroleptic malignant syndrome (NMS) is an unpredictable, rare adverse reaction to antipsychotics. Characteristic features of NMS are rigidity, tremor, autonomic instability, fever, mental status change, leukocytosis, and elevated creatine kinase (CPK)[1]. NMS is encountered more with first generation antipsychotics (FGA) and is a rarity with second generation antipsychotics (SGA)[2].

Regarding the etio-pathogenesis of NMS, there are two hypothesis which may occur individually or together. First is Dopamine receptor blockade hypothesis: dopamine plays a important role in hypothalamic thermoregulation. Therefore, typical antipsychotics can cause dys-regulation of the dopamine mediated signalling on thermoregulatory centre by antagonising it[3]. Second is musculoskeletal fibre toxic hypothesis : it has postulated that massive entry of calcium ion in musculoskeletal fibre is the main factor behind sustained muscle contraction with rigidity and hyperthermia. This is supported by the evidence that dantrolene, which acts by a mechanism that decreses intracellular calcium concentration, is the effective treatment of neuroleptic malignant syndrome[4].

Here we are dealing with aripiprazole, which is being a atypical antipsychotic, is a partial agonist at dopamine receptors (mainly affinity for D2,D3), ie, it causes signal transduction from the receptor to be in the middle of somewhere between full output to no output (much less than an full agonist). So, according to the hypothesis of dopamine receptor blockade mechanism of NMS, it is quite unlike for atypical antipsychotics like aripiprazole to cause neuroleptic malignant syndrome[5].

Department of Phychiatry, IPGME&R and SSKM Hospital, Kolkata 700020

[1]MBBS, Postgraduate Trainee and Corresponding Author

[2]MBBS, MD, Associate Professor

[3]MBBS, MD, Senior Resident

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***Editor's Comment :***

- Neuroleptic Malignant Syndrome (NMS) is a rare fatal side effect of antipsychotic medication commonly with first generation(typical antipsychotics).
- Aripiprazole is a newer atypical antipsychotic which acts by modulation of dopaminergic system in brain.
- The uniquenes of this case report lies on the fact that NMS may occur with aripiprazole (very rarely)which can be explained by rapid dose escalation.

There are very few cases reported on this regarding this in the literature[6,7]. Here we present a case of NMS caused by aripiprazole in a young female having acute and transient psychotic disorder, thus focussing on NMS with the use of atypical antipsychotic aripiprazole.

## Case Report

A 20-year-old female with no significant past, personal and family history with well-adjusted premorbid personality presented with restlessness, aggressiveness, behavioral oddities, self-muttering, self-laughing without any apparent reason, and insomnia for past one week. She attended outpatient department (OPD), and a diagnosis of acute and transient psychotic disorder was made. She was advised aripiprazole 10 mg/day and lorazepam 2 mg/day. 3 days after starting medications, she presented to the OPD as her restlessness and aggressiveness did not subside significantly. Dose was increased to 20 mg of aripiprazole and 3mg of lorazepam daily. Four days later, the patient revisited the OPD with complaint of high fever, stiffness in all four limbs, and mutism. On examination, her consciousness was altered and she did not respond to commands. There was associated fluctuation of blood pressure. She was suspected to develop NMS and admitted. Her serum creatine kinase (CPK) level was 4068.25

IU/L The liver function tests were normal and the total leukocyte count was raised (15,200/mm$^3$) with

polymorphonuclear leukocytosis. Computed tomography of brain did not reveal any abnormality. Aripiprazole was stopped. Conservative management with Foley's catheterization, intravenous fluid, anti-pyretic, frequent monitoring of vitals and mental status was done. Tablet bromocriptine 5 mg/day in divided doses was started, which was gradually increased to 15 mg/day in divided doses. She also received tablet lorazepam 4 mg/day. After two weeks, the patient started to take food orally, walked on her own and rigidity decreased and had normal body temperature, suggesting significant improvement. Her serum CPK level gradually reduced to 127 IU/L after two weeks. Bromocriptine was slowly tapered down and stopped. On account of some residual psychotic behaviour, she was advised quetiapine 50 mg/day which was gradually escalated to 200 mg/day. She was then discharged in stable condition.

## Discussion

Second generation or atypical antipsychotic drugs, also known as Serotonin Dopamine Antagonists (SDA), are widely used for schizophrenia and schizoaffective disorder, mood disorder, dementia, autism spectrum disorder etc. The term atypical is used as these drugs differ in their side effect profile, most notably a lower risk of extra-pyramidal side effects (EPS)[8].

Aripiprazole is a dopamine (D2) antagonist, but can also act as partial D2 agonist. Partial D2 agonists compete at D2 receptors for endogenous dopamine, thereby producing a functional hypodopaminergic state. The absence of complete D2 blockade would be expected to minimize EPS[8].

A sharp escalation of antipsychotic dose is assumed to be the responsible for NMS by causing a massive and sudden down-regulation of dopamine receptors. This would be the possible mechanism in this patient too as there was rapid loading of aripiprazole to 20 mg/day. Symptoms subsided after holding the drug and along with supportive management. The causality of this adverse reaction was assessed by the Naranjo's Assessment Scale[9].

In our patient, there are clinical features and abnormal laboratory test results (serum CPK 4068.25 IU/L and total leucocyte count 15,200/mm$^3$) post exposure to the offending drug. Clinical features of our patient could not be explained on the basis of other disease or drugs. Stopping the drug produced significant clinical improvement. Considering the typical clinical features and laboratory abnormalities of NMS, a re-challenge with the drug was not required.

According the Naranjo's Assessment Scale, the probability score was '8' (probable). The severity of the adverse reaction was determined according to Hartwig *et al*[10]. This was life threatening adverse reaction and led to long hospital stay and required intensive observation and hence can be classified as 'severe'.

With rapid escalation of dose, NMS can occur with atypical antipsychotics such as aripiprazole. We should be more cautious particularly regarding dose adjustment in susceptible patients. A better understanding of this syndrome for prediction, early diagnosis and rapid intervention would be helpful in reducing fatalities.

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