CASE REPORT

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# Neuroleptic Malignant Syndrome Associated with Lithium Toxicity

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**ABSTRACT**

Neuroleptic Malignant Syndrome (NMS) is an idiosyncratic and potentially life-threatening reaction to neuroleptic drugs. Lithium is a first-line mood stabilizer used in the treatment and prophylaxis of bipolar disorder. There are several case reports of lithium-associated NMS, but only when it was given in combination with antipsychotics. Therefore, the possibility of NMS being secondary to the antipsychotics could not be ruled out in those cases. Here we present a case of lithium-induced NMS in a patient who was not being treated concomitantly with any other agent known to cause NMS. The patient, a 74-year-old female with a 30-year history of bipolar affective disorder, was admitted to the emergency room of the All India Institute of Medical Sciences, New Delhi, with history of high fever and generalized weakness for 10 days before the admission. NMS was established based the presence of three cardinal symptoms. She was started on intravenous fluids to correct her sodium levels slowly and requested to follow-up at the psychiatry clinic.

Neuroleptic Malignant Syndrome (NMS) is an idiosyncratic and potentially life-threatening reaction to neuroleptic drugs. It is usually characterized by hyperpyrexia, muscle rigidity, autonomic dysfunction, altered mental status, tremors, leukocytosis, and creatine kinase (CK) elevation.[1] Although its incidence has decreased in the last few decades due to the availability and increased use of the newer generation antipsychotics, NMS still represents a significant cause of morbidity and mortality in patients treated with antipsychotics. Its incidence is reported to be around 0.01–0.02%.[2]

NMS is mostly found associated with the use of traditional antipsychotics, but may also occur when atypical antipsychotics such as risperidone, olanzapine, and clozapine are used.[3–5] There are some cases of NMS associated with the use of non-neuroleptic drugs, like carbamazepine[6] and metoclopramide,[7] or drugs without known antidopaminergic activity, such as lithium.[8]

Lithium is a first-line mood stabilizer used in the treatment and prophylaxis of bipolar disorder. There are several case reports of lithium-associated NMS, but only in combination with antipsychotics.[9,10] Therefore, the possibility of NMS being secondary to the antipsychotics could not be ruled out in those cases. To the best of our knowledge, there are only two reports of isolated lithium-induced NMS.[11,12]

Here we present a case of lithium-induced NMS in a patient who was not being treated concomitantly with any other agents known to cause NMS.

## CASE REPORT

A 74-year-old female with a 30-year history of bipolar affective disorder and hypothyroidism was brought by her family members to the emergency department of the All India Institute of Medical Sciences, New Delhi. She presented with a 10-day history of high fever and generalized weakness. She was found to have rigidity in her limbs. According to her family, her oral intake had dramatically reduced in the preceding week. Four days before admission, her consciousness was affected. Her bipolar affective disorder corresponded to code 296.46 of Diagnostic and Statistical Manual of Mental Disorders (DSM) 5 and F31.7 of International Classification of Diseases (ICD) 10. She was on lithium 400 mg/d, valproate 500 mg/d and levothyroxine 100 µg/d tablets for the last two years with no change in dosage. Her family members denied any use of neuroleptics or other dopamine receptor-blocking agents, including antiemetics, by the patient. They also denied the possibility of medication overdose

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or any suicidal ideas expressed by the patient. The patient had no history of substance abuse or other medical or neurological illness and no family history of psychiatric illness.

On admission, the patient was disoriented and confused. There was history of fever, recorded by her family members. However, she was afebrile at the time of examination. Her blood pressure was 150/70 mmHg. Generalized rigidity was evident on examination. Blood counts showed marked leukocytosis (21.5 × $10^3$ /μL). Biochemistry revealed elevated CK levels (637 IU/L) and her serum sodium levels were low (107 mEq/L). Her serum lithium level was deranged (2.5 mEq/L; normal range = 0.6–1.2 mEq/L). As she did not have any clinical or biochemical features suggestive of valproate toxicity (tremors, ataxia, dysarthria, or deranged liver function tests), her serum valproate level was not measured. We did not perform an electroencephalogram (EEG) since we did not suspect non-convulsive status epilepticus.

Neuroimaging showed age-related cerebral and cerebellar atrophy. Physical examination of chest and abdomen was unremarkable and cerebrospinal fluid (CSF) analysis showed no abnormalities. Urine toxicology, blood, urine, and CSF cultures were negative. Her thyroid hormone levels were normal.

In light of the above findings, the possibility of sepsis was ruled out, and a diagnosis of NMS and lithium toxicity was made. NMS was diagnosed based on the presence of three defining symptoms: fever, muscle rigidity, and elevated CK. The diagnosis can also be made in the presence of two out of three of the aforementioned symptoms and at least two other supplementary symptoms, including tachycardia, abnormal blood pressure, tachypnea, altered consciousness, diaphoresis, or leukocytosis.[13]

The patient was shifted to the intensive care unit (ICU) and her psychotropics were discontinued. She was started on intravenous (IV) fluids to correct her sodium level slowly. With supportive management, her serum lithium levels, serum sodium levels, and serum CK levels normalized. She showed a gradual improvement in her mental status, had no problems with articulation, and was fully oriented after two weeks. Her vitals stabilized, and there was minimal rigidity at the time of discharge.

She was discharged on valproate 500 mg/d and levothyroxine 100 μg/d tablets and requested to attend the psychiatry clinic.

## DISCUSSION

Lithium is usually used as a first-line mood stabilizer in bipolar affective disorder with proven efficacy.[14] It has a narrow therapeutic index, and its toxicity varies from mild tremors to serious side-effects such as renal impairment, convulsions, and altered mental status. The concomitant administration of drugs such as antipsychotics, diuretics, non-steroidal anti-inflammatory drugs (NSAIDs), antiemetics or dopaminergic agents may result in lithium toxicity. Factors that increase the risk of lithium toxicity are dehydration, infection, and the presence of other medical condition. Prior to the onset of symptoms, the medical condition of our patient was satisfactory, and she was not on any medications other than lithium, valproate, and levothyroxine. There was no change in the medications or their doses in the last two years. Her family members reported that they ensured compliance to medications. They denied any possibility of overdose. Her thyroid status was also normal.

Serotonin syndrome was considered as one of the differential diagnosis. However, its possibility was considered very low owing to the absence of concomitant use of another serotonergic drug and symptoms suggestive of hyperserotonergic state (e.g., myoclonus, diarrhea).[15]

In this particular case, we suspected a possibility of dehydration induced lithium toxicity, which probably led to NMS. The patient's old age, which is an important risk factor for psychotropic neurotoxicity, might have contributed to her developing this complication. Another possibility is that she might have developed idiosyncratic and slowly progressive symptoms of NMS despite being on a stable lithium dose, and that could have led to decreased oral intake and subsequent lithium toxicity.

Lithium alters neurotransmitter activity and reduces the effects of dopamine by preventing the accumulation of cyclic adenosine monophosphate at the intracellular level.[16] Dopamine hypoactivity has been widely accepted as a hypothesis for the occurrence of NMS.[17] This might be the causal mechanism of NMS in our case.

There are few reports available that have described the association of valproate use with the appearance of NMS; however, in these cases, patients were also on antipsychotics.[18,19] To the best of our knowledge, no literature exists on the occurrence of

NMS with valproate monotherapy. Verma et al,[20] reported the development of NMS in a patient after the addition of valproate while he was maintained on olanzapine. NMS in that case could be attributed solely to olanzapine since NMS can occur even after prolonged use of antipsychotics.

## CONCLUSION

In our patient, lithium seemed to be the likely offending drug causing NMS. We recommend that treating physicians should remain cautious about the risk of NMS during lithium monotherapy.

*Disclosure*

The authors declared no conflicts of interest.

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