lithium and hence its potential side effects may serve to reduce the risk of recurrence of NMS.[6] Nevertheless, vigilance in monitoring for NMS is imperative in this given clinical context.

This case proposes that lithium-induced NDI may increase the vulnerability for NMS. Patients with lithium-induced NDI are at an increased risk of dehydration, especially if adequate water homeostasis is not maintained. A medical condition can further exacerbate this. In a patient on lithium, we suggest that practitioners actively inquire on the polyuria-polydipsia complex, and remain vigilant about the monitoring of sodium levels and serum and urine osmolality. Serum lithium should also be maintained on the lower end of the therapeutic range, avoiding episodes of toxicity, and psychoeducation needs to be given regarding water intake, to avoid dehydration or overhydration. Lithium is best avoided in a patient with NDI and NMS unless absolutely necessary, after a risk-benefit analysis is performed.

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The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Neuroleptic Malignant Syndrome with Low Dose Lithium, Without Concomitant Antipsychotics

To the Editor,

Neuroleptic malignant syndrome (NMS) is a rare, life-threatening condition characterized by fever, rigidity, increased creatine phosphokinase (CPK) level, tachycardia, diaphoresis, blood pressure changes, leukocytosis, and altered mental status.[1] NMS is almost always associated with the use of antipsychotics, especially first-generation antipsychotics and high dose or parenteral administration, but there are also reports of NMS with atypical antipsychotics.[2] Very rarely, NMS may be associated with drugs that do not act predominantly on dopamine; an example to this is lithium, especially in the context of toxicity[3] and rarely with lithium-induced nephrogenic diabetes insipidus (NDI).[4] We describe a case of NMS associated with lithium at serum levels well within the therapeutic range and without NDI.

Case Report

The patient was a 52-year-old male with a 16-year history of bipolar disorder and a 3-month history of systemic hypertension, dyslipidemia, and ischemic stroke. He had been receiving oral haloperidol (10 mg/day) and olanzapine (2.5 mg/day) from a mental hospital for at least two to three years, and possibly 10 years. While on the above medications, he had presented to the treating hospital with acute mania and was given parenteral haloperidol (5 mg), oral lithium (600 mg/day), olanzapine, and lorazepam. There was no history of recent treatment with a depot antipsychotic. Two days later, he developed altered consciousness. There was no improvement across a week after withholding lithium and antipsychotics, and he was referred to our tertiary hospital.

On examination, he was conscious but disoriented to time, place, and person. He was restless. He had tachypnea, tachycardia, fever, sweating, and fluctuating blood pressure but no rigidity. Laboratory investigations were generally within normal limits: the total leukocyte

count was 9800/mm³ and serum lithium was 0.2 mEq/L. Importantly, serum CPK was 1228 (reference level, 25–192) IU/L. A diagnosis of NMS was made, based on the presence of two major and four minor Levenson's criteria of NMS.

Lithium and the antipsychotic drugs were stopped, and he was treated with Tab. bromocriptine 15 mg/day, Tab. sodium valproate 400 mg/day, and Tab. lorazepam 4 mg/day along with supportive measures. Bromocriptine was tapered and stopped when the CPK level decreased to 357 IU/L. Twelve days after stopping lithium and antipsychotics, the CPK level was 249 IU/L; NMS had also resolved clinically within a week of stopping the drugs.

Sodium valproate was uptitrated to 1 g/day. Plasma ammonia was checked because of continued restlessness, and the level was found raised (133 µmol/L; lab range, 16–66 µmol/L). Valproate was therefore stopped, and lithium (450 mg/day) was reintroduced 17 days after its discontinuation. No antipsychotics were started.

Five days after lithium reinitiation, fever (100.4° F), sweating, restlessness, tachycardia, tachypnoea, and tremors recurred; however, there was again no rigidity. The total leukocyte count was 13,300/mm³, and serum CPK was 5073 IU/L. The serum lithium level was 0.3 mEq/L, and there were no clinical signs specific to lithium toxicity. Meningitis and encephalitis were ruled out clinically by the physician. It appeared that there was a recurrence of NMS. MRI of the brain revealed gliosis of left parietal and occipital lobes and diffuse parenchymal atrophy, consistent with old cerebrovascular accident. No fresh changes were noted. Chest X-ray, electrocardiogram, abdominal ultrasonography, and other investigations identified no relevant abnormalities, and a presumptive diagnosis of lithium-related NMS was made. Two major and four minor Levenson's criteria were fulfilled.

Lithium was again stopped, and bromocriptine was resumed. The CPK level dropped to 2700 within a day. The NMS attenuated, and serum CPK progressively fell to 160 IU/L across 10 days.

He was discharged in a relatively stable condition on clonazepam 3 mg/day. However, three weeks later, he required readmission for relapse into mania. He was successfully managed with clozapine and valproate; there was no recurrence of NMS.

On a final note: the patient had been receiving aspirin (150 mg/day), atorvastatin (20 mg/day), and amlodipine (5 mg/day) as part of his medical and neurological management. These drugs were continued throughout the period of NMS and thereafter.

Discussion

There are isolated reports of NMS associated with lithium combined with antipsychotics[5,6] and NMS associated with lithium toxicity.[7] Reports of NMS with lithium monotherapy are very rare; in a case report of lithium-induced NMS,[3] the serum lithium level was 1.5 mEq/L, which is above the therapeutic range. Our patient first developed NMS while on haloperidol and lithium, and we considered it to be haloperidol-induced NMS because haloperidol is one of the commonest antipsychotics associated with NMS. However, 22 days later, when lithium was reintroduced without concomitant antipsychotics, our patient developed NMS again, and the NMS resolved after discontinuing lithium. The score on Naranjo Adverse Drug Reaction Probability Scale was 6, indicating probable causality with lithium.[8] Our high index of suspicion, early detection, and prompt withdrawal of lithium prevented further clinical deterioration.

Could the second instance of NMS have been a relapse of the first, and, if so, might both have been related to haloperidol, which may have a long half-life in some individuals, particularly during long-term treatment? This is possible but unlikely. There was an interval of at least 10 days when the patient did not have NMS and was not on treatment for NMS. If the second instance of NMS had been a prolongation of the first, it would have emerged much earlier, within a few days of stopping bromocriptine. Furthermore, the CPK response to lithium rechallenge was higher than during the first instance of NMS, and the CPK level dropped by half, one day after lithium was again discontinued.

As far as we could ascertain, the patient had not received lithium before nor had he experienced NMS earlier. Our report indicates that lithium monotherapy at even subtherapeutic serum levels may very rarely be associated with NMS. We speculate that the recent stroke was a predisposing factor, as preexisting brain damage may be a risk factor for lithium-related neurotoxic effects with serum lithium within the therapeutic range.[9]

On a final note, we suggest that NMS be defined by the spectrum concept[10] or using a broad definition in order to ensure early detection, especially when it develops with drugs that are not typically associated with the disorder and when not all the classical symptoms (e.g., rigidity, in our patient) are present.

The only reported case of lithium monotherapy causing NMS was at a higher dose of 900 mg and at a supratherapeutic level of 1.5 mEq/L, in a 72-year-old female.[3] Our case report is unique in that this is perhaps the first published report of lithium without concomitant antipsychotics and at a subtherapeutic dose and level being associated with NMS.

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Diabetes Insipidus Induced by Oral Olanzapine at Therapeutic Dose

Sir,

Diabetes insipidus (DI) is characterized by the passage of excess amounts of dilute urine. In central DI, antidiuretic hormone (ADH) is deficient; in nephrogenic DI, there is decreased response of the kidneys to ADH.[1] Hypovolemia, dehydration, and electrolyte imbalance can occur as complications of DI. In addition to various congenital and acquired causes, several drugs have been implicated in the etiology of DI. Lithium, foscarnet, and clozapine are the most common drugs implicated in drug-induced DI.[2] With olanzapine, drug-induced DI is relatively rare and is reported in the literature as case reports. Olanzapine-induced DI has been reported to occur primarily in the context of overdose.[3,4] Here, we describe the clinical manifestations and outcome of a patient who developed olanzapine-induced DI at a therapeutic dose.

A 35-year-old male was admitted to the psychiatry ward with diagnoses of alcohol dependence syndrome, alcohol-induced psychotic disorder, recurrent depressive disorder, nicotine dependence syndrome, acute on chronic pancreatitis, seizure disorder, and bilateral varicose veins. He was treated with lorazepam, thiamine, and multivitamins parenterally (changed to oral formulations after five days) and levetiracetam and pancreatin-dimethicone combination orally. As auditory and visual hallucinations persisted after the resolution of alcohol withdrawal symptoms, he was started on oral olanzapine at 2.5 mg per day. The dose was titrated to 10 mg per day over one week. With the initiation of olanzapine, the frequency and intensity of hallucinations significantly reduced over the next few days. Ten days after initiating olanzapine, he reported increased urine output and nocturia. He also reported increased thirst and excessive consumption of water. An input-output chart was maintained, which showed that his urine output was 4000–5000 ml/day. Further investigations revealed that his urine osmolality was 100 mosmol/kg (reference range—200–1200 mosmol/kg) and serum osmolality was 289 mosmol/kg (reference range—275–300 mosmol/kg). The presence of polyuria, decreased urine osmolality, and normal plasma osmolality favored the diagnosis of DI in this patient. Blood investigations did not show any electrolyte imbalance (serum sodium level was 140 mEq/L), and the blood sugar levels were in the normal range. In the absence of recent trauma, surgery, neurological symptoms/signs (headache, vomiting, or visual field defects), and other urinary symptoms, a diagnosis of drug-induced DI was considered. Among the medications the patient was taking, olanzapine was considered the most likely causative agent based on the temporal relationship and the existence of previous reports. A score of 7 was obtained on the Naranjo adverse drug reaction probability scale,[5] indicating that olanzapine was a "probable" cause of DI in this patient. Olanzapine was stopped, and over the next five days, the urine output became normal (average of 2800 ml per day), and other symptoms, namely nocturia and excessive thirst, also subsided. The patient was not started on any other antipsychotic as he did not have a relapse of psychotic symptoms after discontinuation of olanzapine.

Various causes for DI were considered and ruled out based on the clinical picture. Both central and nephrogenic DI can be congenital in origin. The onset of symptoms in the fourth decade was a strong pointer against a congenital cause in this patient. Acquired forms of central DI can occur due to trauma, surgery,