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LETTER TO THE EDITOR

Neuroleptic malignant syndrome occurring with amisulpride after lithium toxicity in a patient

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Dear Editor,

Lithium has a narrow therapeutic range, making the risk of intoxication significant (1). Neuroleptic malignant syndrome (NMS), another psychiatric emergency, is an idiosyncratic drug reaction that typically occurs with antidopaminergic medications (2). This report presents a patient whose symptoms of lithium neurotoxicity resolved with hemodialysis, but who subsequently developed NMS following the introduction of low-dose amisulpride for worsening psychotic symptoms.

A 44-year-old female patient was admitted to the emergency department with recent-onset insomnia, ataxia, incoherent speech, and agitation. She had a 23-year history of schizoaffective disorder and had lived with cerebral palsy since birth. Over the years, she had been treated with various combinations of selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), bupropion, lithium, valproate, lamotrigine, topiramate, olanzapine, quetiapine, risperidone, amisulpride, central anticholinergics, and benzodiazepines. Her most stable period, lasting four years, was achieved with a regimen including lithium (1200 mg/day), lamotrigine (150 mg/day), venlafaxine (150 mg/day), amisulpride (100 mg/day), and biperiden (4 mg/day).

On admission, her body temperature was 38°C, blood pressure 142/89 mmHg, and pulse 120/min. She was disoriented but showed no signs of meningeal irritation. Neurological examination revealed spasticity in both lower extremities, as well as dysmetria and dysdiadochokinesis in the upper extremities, along with ataxia. Cranial computed tomography, brain magnetic resonance imaging, lumbar puncture, complete blood count, renal, liver, and thyroid function tests, plasma lithium level, creatine kinase (CK), and culture studies were performed. No abnormalities were detected except for leukocytosis and an elevated plasma lithium level of 1.94 mmol/L. Electrocardiography revealed only sinus tachycardia. A diagnosis of lithium intoxication was made. All psychotropic medications except lamotrigine were discontinued, and hemodialysis was initiated. After three sessions, her neuropsychiatric symptoms resolved. However, muscle strength in her lower extremities declined from 3/5 to 2/5. While she had previously been able to walk with a cane, following the intoxication she required a wheelchair. She was discharged on the fourth day with lamotrigine at 150 mg/day. Three weeks later, she presented with auditory hallucinations, persecutory delusions, irritability, and suicidal thoughts. Venlafaxine 150 mg/day and amisulpride 100 mg/day were reintroduced. Within one week, she developed disorientation, diaphoresis, and lead-pipe rigidity. Her temperature rose to 39.7°C, pulse was 122/min, blood pressure 151/96 mmHg, and respiratory rate 24/min. Given these symptoms and a recent history of lithium neurotoxicity, NMS was

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diagnosed. Laboratory findings revealed hypokalemia, hypernatremia, leukocytosis with a left shift, and acute kidney injury consistent with NMS. CK levels rose to 1,720 U/L during follow-up. Electrocardiography showed sinus tachycardia with frequent ventricular bigeminy. She was transferred to the intensive care unit (ICU), all medications were discontinued, and treatment was initiated with intravenous saline and lorazepam at 6 mg/day. Her symptoms gradually improved over 19 days. Upon stabilization, she was maintained on lamotrigine 25 mg/day and valproate 1,000 mg/day. However, the patient experienced persistent loss of walking ability as a sequela of NMS. Approximately two months after resolution of NMS, she developed insomnia and psychosis-like symptoms, for which quetiapine 25 mg/day was initiated. Unfortunately, within three days of starting quetiapine, her alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels increased nearly 14-fold, indicating drug-induced toxic hepatitis. Quetiapine was immediately discontinued, and liver enzyme levels returned rapidly to the normal range. Given her history of poor response to many psychotropic medications, the treatment team adopted a harm-reduction approach using a combination of lamotrigine and valproate, alongside intensive psychosocial interventions, which successfully stabilized her condition.

In the differential diagnosis, serotonin syndrome (SS) was considered due to concurrent venlafaxine use. However, the absence of mydriasis, dry mucosa and skin, hyperreflexia, clonus, and myoclonus, along with the severity of the course and the presence of residual symptoms, made SS unlikely. The case did not meet Hunter criteria for serotonin syndrome (3). In contrast, the patient met all major and six minor criteria for NMS according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), as well as all diagnostic criteria outlined by Levenson (2).

Although NMS is more frequently associated with first-generation antipsychotics, atypical presentations, characterized by milder hyperthermia, rigidity, and CK elevation, have also been documented with second-generation antipsychotics such as amisulpride (2). To date, 11 cases of amisulpride-induced NMS have been reported in the literature (4–14). Upon review, most resembled typical NMS. CK elevation was observed in 82% of cases, with 70% showing levels above 1000 U/L (mean: 5187 U/L). Rigidity was reported in 73%, and NMS developed within two weeks of amisulpride initiation in 66.7% (n=6), with all patients recovering within four weeks, similar to cases involving typical antipsychotics (2). Despite the use of a low dose of amisulpride, our case demonstrated classical features of NMS, including lead-pipe rigidity, a fever of 39.7°C, and CK levels exceeding 1000 U/L. Although medications such as bromocriptine, dantrolene, and amantadine are used in severe cases of NMS, supportive therapy with benzodiazepines may be sufficient for milder presentations (2). In this case, which showed classical NMS symptoms without extreme CK elevation, treatment with benzodiazepines and supportive care alone led to full recovery.

The combined use of lithium and antipsychotics is known to increase the risk of NMS (15). Several mechanisms may explain this interaction: lithium reduces dopamine release into the synaptic cleft (15), suppresses the mRNA expression of tyrosine hydroxylase (16), and inhibits tyrosine reuptake (17), thereby impairing dopamine synthesis. Additionally, chronic lithium exposure reduces the number of dopamine receptors (18). In our patient, urine osmolality remained low (1002–1008 mOsm/L), indicating impaired renal concentrating capacity. Since amisulpride is renally excreted, lithium-induced nephrogenic diabetes insipidus may have hindered its elimination, leading to elevated plasma levels. Furthermore, the presence of cerebral palsy may have increased her vulnerability to NMS. Prior to lithium intoxication, the patient's only motor deficit related to cerebral palsy was in the bilateral lower extremities, with muscle strength graded at 3/5. Following the intoxication, paraparesis developed in the same limbs (2/5), and after the NMS episode, the patient became paraplegic. This progression suggests that brain regions responsible for lower extremity motor function may have been particularly susceptible, possibly due to pre-existing damage from cerebral palsy (CP). However, the key precipitating factor was likely the interaction between amisulpride and residual lithium effects.

In clinical practice, caution is warranted when prescribing renally excreted medications such as lithium and amisulpride concurrently, as this combination may increase the risk of life-threatening psychiatric emergencies. If their concomitant use becomes necessary, close monitoring for lithium-induced nephropathy is essential. In addition to routine assessments of serum lithium levels and kidney function, more detailed indicators, such as urinary densitometry, urinary sodium, and urinary albumin, may facilitate early detection and intervention (1).

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