Confusion, Rigidity, and Elevated Creatine Phosphokinase: Atypical Neuroleptic Malignant Syndrome Possibly Associated With Clozapine and Sodium Valproate Use

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Neuroleptic malignant syndrome (NMS) is a rare medical emergency associated with antipsychotic use with an estimated mortality of 10%.[1] NMS is characterized by muscle rigidity, hyperthermia, autonomic instability, mental status changes, leukocytosis, and evidence of muscle injury (eg, elevated creatine kinase [CK] levels).[2] However, there are reports[3] of "atypical" presentations of NMS wherein symptoms of hyperthermia or muscle rigidity may be absent or develop more slowly with lesser intensity, which can make the diagnosis difficult, delayed, or missed. NMS with clozapine use has been reported with various atypical features.[4] Mood stabilizers like lithium and sodium valproate also can precipitate NMS. We report a case of atypical NMS associated with clozapine and sodium valproate.

Case Report

A 50-year-old man with a 25-year history of schizophrenia presented to a tertiary care hospital emergency department (ED) for an episode of mental status changes, tiredness, tremors, and reduced food intake. It was learned from the family that he was on regular medication prescribed from a government psychiatric hospital and was taking oral sodium valproate 500 mg/d and oral clozapine 50 mg/d. Although symptomatically better, he had developed difficulty in walking and rigidity for the last 3 months and had consulted a psychiatrist 2 days before presenting to the ED. Given the possibility of sodium valproate–induced extrapyramidal syndrome, the family was advised to stop the drug, and he was prescribed trihexyphenidyl 4 mg/d along with clozapine 50 mg/d. However, his symptoms gradually worsened. At the time of presentation to the ED, he was disoriented and had rigidity and tremors. There was no fever, blood pressure lability, tachypnea, sialorrhea, flushing, or skin pallor.

His laboratory investigations revealed an elevated creatine phosphokinase (CPK) level of 930 U/L. The medical workup revealed euvolemic hyponatremia, indicating a diagnosis of syndrome of inappropriate antidiuretic hormone (SIADH) secretion and aspiration pneumonia. Other investigations including full blood count, renal and liver function tests, C-reactive protein, cerebrospinal fluid evaluation including anti–*N*-methyl-D-aspartate antibodies, and urine examinations were within normal limits. A brain magnetic resonance imaging scan showed no significant intracranial acute pathology. Considering the patient's altered mental status, rigidity, tremor, and elevated CPK level, the possibility of atypical NMS was considered, and psychotropics were stopped. He was admitted to a medical ward and given intravenous fluids, and oral bromocriptine was started. He was also treated with hypertonic saline followed by tolvaptan and fluid restriction for SIADH. On the third day of admission, he developed tachypnea, tachycardia, and hypoxia, and aspiration pneumonia was diagnosed. He was shifted to the intensive care unit and ventilated. He also received intravenous cefoperazone sulbactam, steroids, oral levodopa, and vitamin D_3 supplementation, along with other supportive measures. His clinical condition gradually improved over a period of 1 week, and he was extubated. The repeated CPK level was found to be within normal limits. He was discharged on the tenth day of admission with a prescription of oral quetiapine 12.5 mg, if necessary, along with oral levodopa. He was conscious and oriented at the time of discharge with significant improvement in tremor and appetite but had difficulty walking due to persisting rigidity.

Discussion

In our case, a diagnosis of atypical NMS was made given the presence of muscle rigidity, mental status changes, and mild elevation in CK level; the absence of other organic conditions; and the improvement of symptoms following cessation of clozapine and sodium valproate. However, the clinical presentation of our case differs from the "typical" clozapine-associated NMS reported in the literature. A systematic review analyzing second-generation antipsychotics and neuroleptic malignant syndrome found that NMS associated with clozapine use has the following characteristics: fever as the initial symptom, lack of muscular

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rigidity and tremor, severe autonomic instability, and lower and delayed elevation of CK.[4] Our patient did not have fever or severe autonomic instability, but he did have severe rigidity and tremor. Use of the sodium valproate combination could have been an added risk factor in our case.

The atypicality of clozapine-associated NMS in our case also raises the possibility of a primary sodium valproate–induced NMS with clozapine use as an added risk factor. Verma et al[5] described the case of a 60-year-old woman taking olanzapine for the past 2 years for psychosis who experienced NMS after adding sodium valproate. Tanii et al[6] reported NMS associated with valproate use in a 37-year-old man with mental retardation and profound intellectual impairment. Another case of NMS associated with valproate use was reported in a 17-year-old male patient.[7] Moreover, atypical NMS (absence of hyperthermia) was also reported with sodium valproate use in the past, similar to our case.[8] The absence of hyperthermia in NMS associated with valproate use is thought to be due to the relative ineffectiveness of valproate to block the hypothalamic dopamine sites compared to antipsychotics.[8]

The concurrent use of clozapine and sodium valproate precipitated atypical NMS in our patient. Past reports[5,7] of NMS associated with atypical antipsychotic use also mentioned concurrent use of sodium valproate. However, the absence of fever and autonomic instability and the presence of severe rigidity favors a diagnosis of sodium valproate–induced atypical NMS in our case. Physicians should be aware of atypical presentations of NMS with the use of clozapine and sodium valproate so that they can diagnose and treat this life-threatening condition early for better prognosis.

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