CASE REPORT

An atypical case of neuroleptic malignant syndrome precipitated by valproate

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SUMMARY

Neuroleptic malignant syndrome (NMS) can be caused by various drugs. We report a case of a 60-year-old woman who presented with high-grade fever, muscular rigidity, tachycardia, tachypnoea and altered sensorium along with seizures. She had been taking olanzapine for the past 2 years for psychosis. For the last month valproate was added to her treatment. Her blood investigations revealed hyponatraemia and raised serum ammonia and creatinine phosphokinase (CPK) levels. In view of hyperthermia, muscular rigidity, autonomic disturbances, altered mental status and raised CPK, a diagnosis of NMS was made. Valproate could have probably precipitated NMS; although the patient was taking antipsychotics for a long time, it was only with the addition of valproate that she developed these symptoms. Raised serum ammonia levels also indicated the presence of valproate toxicity. Seizures were probably due to electrolyte disturbances. Offending drugs were withdrawn. The patient improved with treatment by dopamine agonist and other supportive treatments.

BACKGROUND

Neuroleptic malignant syndrome (NMS) is a well known potentially lethal complication of antipsychotics. It is a complication predominantly associated with typical antipsychotic agents. However, various other drugs have been implicated as a cause of NMS. Recently, there are few case reports which have shown that even atypical antipsychotics and antiepileptics can cause NMS. Valproate can precipitate NMS, especially when given concurrently with atypical antipsychotics. This case highlights the importance of maintaining a high index of suspicion in diagnosing NMS, especially in patients taking atypical antipsychotics and valproate. Timely diagnosis and adequate treatment of NMS can be life saving in such patients.

CASE PRESENTATION

A 60-year-old woman presented to our tertiary care hospital with a 2-day history of high-grade fever, recurrent vomiting and altered sensorium. Relatives also mentioned two episodes of generalised tonic clonic seizures. There was no history of seizures or head injury. The patient was a known case of psychosis and had been taking 10 mg olanzapine for the past 2 years. For the past month, 500 mg/day of valproate was added to the treatment by the treating psychiatrist because of her increased agitative behaviour. There was no history of any major medical or surgical illness.

On examination, the patient was febrile with a temperature of 101.6°F. She had tachycardia and tachypnoea. Her blood pressure at presentation was recorded to be 90/60mm Hg. Her tongue was dry and abdominal skin turgor was lost suggesting dehydration. She had pallor. There was no icterus. The patient was stuporous which was suggestive of diffuse dysfunction of cerebral cortex. There was no obvious cranial nerve palsy. Her pupils were small sized reacting to light. Motor system examination revealed lead-pipe rigidity in all four limbs implying basal ganglia involvement. Deep tendon reflexes were normal and plantars were bilateral extensors, suggesting pyramidal tract involvement.

INVESTIGATIONS

The routine blood investigations of the patient revealed mild anaemia with leukocytosis. Her serum sodium was low (121 mEq/L, normal value 135–150 mEq/L). Other serum electrolytes (potassium, magnesium and calcium) and renal functions were normal. Her liver function tests revealed normal bilirubin, alanine transaminase and aspartate transaminase but raised serum ammonia levels (97 mEq/L; normal value 4–47 μmol/L). Her serum creatinine phosphokinase (CPK) was found to be highly raised (26 226 IU/L; normal 24–170 IU/L). CT of the head and EEG were normal. Cerebrospinal fluid examination was normal. Chest radiogram, urine analysis and ultrasonography of the abdomen were performed to rule out the infectious cause for fever, and were found to be normal. Normal urine analysis, which included normal urinary osmolality, also ruled out syndrome of inappropriate antidiuretic hormone (SIADH) as a cause for hyponatraemia.

DIFFERENTIAL DIAGNOSIS

We diagnosed the patient with NMS as it is the only condition by which all the clinical and laboratory findings could be explained. Other differential diagnoses which could be misdiagnosed were hyponatraemia, epileptic seizures and encephalitis. Valproate can cause SIADH, leading to hyponatraemia. Hyponatraemia can cause disturbance of consciousness but it could neither explain the high-grade fever and rigidity the patient was suffering from nor could it explain the highly raised levels of CPK. Epileptic seizures can lead to elevated CPK but such a high level of CPK cannot be explained alone on the basis of seizures. Encephalitis could be one possibility but the cerebrospinal fluid examination was completely normal

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and hence it was considered less likely. Also it could not explain the markedly raised CPK.

TREATMENT

The patient was started on intravenous fluids to restore hydration and electrolyte correction was given. Fever was controlled by continuous cold sponging and parenteral antipyretics. Olanzapine and valproate were withheld. The patient was started on levetiracetam for controlling seizures. Owing to non-availability of dantrolene sodium, the patient was started on pramipexole and lorazepam as definitive therapy for NMS.

OUTCOME AND FOLLOW-UP

The patient significantly showed improvement over the next 10 days. Her CPK levels drastically reduced to 731 IU/L after 10 days and further reduced to normal levels when repeated after discharge at 30 days. She was successfully discharged from the hospital and was advised a close follow-up with the psychiatrist for reappearance of psychotic symptoms and their management. Levetiracetam was continued for 3 months and then tapered off.

DISCUSSION

NMS is a well-known entity characterised by hyperthermia, muscular rigidity, autonomic dysregulation and altered mental status.[1] Associated features include tachycardia, hypertension and leukocytosis and laboratory evidence of rhabdomyolysis.[2] It is a potentially lethal complication, predominantly associated with typical antipsychotic agents. However, various other drugs including metoclopramide, tetrabenazine, benzodiazepine, some antidepressants and amphetamine have been implicated as a cause of NMS.[3] Recently, some case reports have shown that even atypical antipsychotics, namely olanzapine and quetiapine, can cause NMS.[1 4–6]

In general, typical antipsychotic drugs cause NMS due to their high antidopaminergic action (D2 receptor blockage). However, even an atypical antipsychotic with low potency antidopaminergic action can also cause NMS.[1] Also various other drugs without any known antidopaminergic action have been mentioned to cause NMS. Therefore, it is thought that there are factors other than the D2 receptor blockage that are responsible for the pathogenesis of NMS.[1]

Antiepileptic drugs namely carbamazepine,[7] oxcarbazepine[8] and lamotrigine[9] have also been related to NMS. However, valproate, another antiepileptic, on the contrary, has been used as a treatment option for NMS.[10] In our case, valproate seems to have precipitated NMS. The patient was taking antipsychotics for the past 2 years without any overt complications, and it was only with the addition of valproate in her treatment regimen that NMS precipitated. Also toxicity of valproate is well evident by the raised serum ammonia levels. So, if not a causative agent, valproate is at least a precipitating agent for NMS. Tanii *et al*[11] have reported the development of NMS in a patient on valproate treatment after the discontinuation of levomepromazine. Also it is worth noting that in many case reports mentioning atypical antipsychotics as a cause of NMS, the patients were concurrently taking valproate.[1 6 12]

CPK is a marker of rhabdomyolysis and is elevated in patients with NMS. However, the usual values of CPK range from 1000 to 10 000 IU/L. There are a few case reports mentioning very high elevation of CPK levels in NMS caused by atypical antipsychotics with valproate.[12 13] In our case also, CPK was very high. Seizures, in our case, which were probably due to hyponatraemia, may confound with elevated CPK. However, such a high level of CPK cannot be explained alone on the basis of seizures.

The aim of this case report is to highlight the importance of maintaining a high index of suspicion in diagnosing NMS, especially in patients taking atypical antipsychotics and valproate. Timely diagnosis and adequate treatment can be life saving.

Learning points

- Neuroleptic malignant syndrome (NMS) is caused not only by typical antipsychotics but also by atypical antipsychotics and antiepileptics.
- Concurrent treatment with atypical antipsychotics and valproate is a risk for the development of NMS.
- A high index of suspicion for NMS, especially in patients taking atypical antipsychotics and valproate, leading to timely diagnosis and adequate treatment can be life saving.

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Competing interests None.

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