CLINICAL VIGNETTE

Altered Mental State in a Patient with Hyperammonemia and Ornithine Transcarbamylase Deficiency

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Case

A 64-year-old physically active male with coronary artery disease, type 2 diabetes mellitus, hypertension, and hyperlipidemia presented to the emergency room with recurrent altered mental status. He was recently discharged from the hospital a few days prior for new onset confusion, which improved with hydration, without further testing. One day prior to his current hospitalization, he became somnolent and confused again. His family reported the patient attempted home hydration, and denied any physical trauma, seizures, fever, chills, illicit drug or alcohol use.

The patient was recently diagnosed with poorly controlled type 2 diabetes with HgbA1c of 12 and started on semaglutide. He also started a low carbohydrate diet supplemented with whey protein shakes. Three days prior to his first episode of confusion, he underwent an outpatient coronary angiogram and was without food for a prolonged time. On further questioning, additional family history was notable for a biological brother with ornithine transcarbamylase deficiency diagnosed in his 40s and a mother who was confirmed to be a carrier. The patient and his children had not undergone genetic testing.

In the emergency room, brain imaging and basic lab testing including complete blood count, comprehensive metabolic panel and infectious testing were unremarkable. An ammonia level returned high at 218 umol/L. Liver ultrasound was unremarkable.

His high ammonia levels and family history of ornithine transcarbamylase deficiency raised concerns that he was acutely ill from the same genetic condition. Medical genetics was consulted, and the patient was started on dextrose-containing intravenous fluids, intravenous arginine, and low-protein diet. He had rapid improvement of hyperammonemia and his mental status returned to baseline.

Discussion

Ornithine transcarbamylase deficiency (OTCD) is a rare X-linked urea cycle disorder which disrupts the removal of ammonia waste produced from protein turnover. Complete OTCD results in neonatal onset of rapidly progressive metabolic encephalopathy.[1] However, due to many different possible mutations, hemizygous males and some heterozygous females can have partial enzyme deficiency and remain asymptomatic until as late as middle age.[2] Symptoms are typically due to ammonia accumulation that is triggered by an acute metabolic stressor, increased catabolic state, or increased demands on the urea cycle. Metabolic stressors include acute severe illness and trauma while an increased catabolic state can be seen intra/post-partum, after gastric bypass surgery, or from prolonged fasting. Acute gastrointestinal bleed, rapid weight loss, increased protein consumption including sport supplements, and certain medications including systemic corticosteroids, chemotherapy, and some anticonvulsants can increase demands on the urea cycle.[2]

Patients with late-onset can present with symptoms ranging from loss of appetite to recurrent vomiting to behavioral disturbances.[3] If not diagnosed and appropriately treated, a hyperammonemic crisis can become a life-threatening due to cerebral edema leading to seizures and elevated intracranial pressure.[3] Guidelines recommend checking serum ammonia level in individuals of any age presenting with acute unexplained encephalopathy or acute psychiatric illness, and OTCD should be considered if found to have an elevated serum ammonia level without evidence of liver dysfunction.[4,5]

Additional features that may hint at OTCD include family history, serum ammonia concentration >150 µmol/L with normal anion gap and normal serum glucose,[1] unexpectedly low serum BUN,[6] and respiratory alkalosis in an encephalopathic patient who is hyperventilating.[6] Definitive diagnosis of OTCD requires molecular testing and consistent biochemical features including elevated serum ammonia, elevated serum glutamine, low or normal serum citrulline, and elevated urine orotic acid.[6]

Acute management during a hyperammonemic crisis involves decreasing catabolism and rapidly lowering plasma ammonia level. High catabolic states should be reversed with dextrose-containing fluids. Patients should be started on a low protein diet or enteral nutrition with a low protein formulation if they are unable to tolerate an oral diet.[1] Patients should also be started on ammonia scavenger therapy with an intravenous mixture of sodium phenylacetate and sodium benzoate along with intravenous arginine to replete deficient urea cycle intermediates.[1,6] Hemodialysis should be initiated if plasma ammonia level exceeds 500 µmol/L and can be considered

when plasma ammonia level is ≥200 μmol/L or hyperammonemia does not improve with ammonia scavenger therapy.[4,6]

Given his age of presentation and family history, we suspected this patient has partial OTCD. His hyperammonemic crisis was triggered by a catabolic state caused by periods of fasting, protein loading, and semaglutide use which puts the body in a catabolic state. Semaglutide was subsequently discontinued, and the patient was started on oral ammonia scavenger therapy with sodium phenybutyrate and citrulline and counseled on maintaining a low protein diet. Medical genetic testing subsequently revealed a hemizygous OTC gene mutation, confirming a diagnosis of partial OTCD.

Conclusion

It is important to consider urea cycle disorders in the differential diagnosis patients with altered mental status and elevated ammonia levels. Hyperammonemic crises can be triggered by increases in the catabolic state and strain on the urea cycle. Prompt diagnosis and treatment with ammonia scavenger therapy is critical for recovery.

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