Case Report

Non-cirrhotic hyperammonemia in a newly diagnosed diabetic patient presenting in diabetic ketoacidosis

Robin George Manappallil[1], Pradeep Kumar[2], Blessy Josephine[3]

From [1]Consultant, Department of Internal Medicine, [2]Senior Consultant, Department of Gastroenterology, [3]Resident, Department of Internal Medicine, Baby Memorial Hospital, Kerala, India

Correspondence to: Dr. Robin George Manappallil, Department of Internal Medicine, Baby Memorial Hospital, Calicut, Kerala-673004, India. E-mail: drrobingeorgempl@gmail.com

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ABSTRACT

Hyperammonemia, a known cause of encephalopathy, is commonly seen in patients with liver disease. Non-cirrhotic hyperammonemia is an uncommon condition. Patients with uncontrolled diabetes can have elevated levels of ammonia. Diabetic ketoacidosis is a life-threatening complication in diabetes. This is a case of a middle-aged male who presented in encephalopathy. He was found to have diabetic ketoacidosis with hyperammonemia. Encephalopathy as a result of hyperammonemia in diabetes mellitus is a rare scenario.

Keywords: *Diabetic ketoacidosis, Diabetes mellitus, Encephalopathy, Hyperammonemia.*

Diabetes mellitus (DM) is a group of metabolic disorders that share the phenotype of hyperglycemia. Type 2 DM is a heterogeneous group of disorders characterized by insulin resistance, impaired insulin secretion and increased glucose production [1]. According to the WHO, the number of diabetic patients has increased from 108 million in 1980 to 422 million in 2014; and the global prevalence of diabetes among adults above the age of 18 years has risen from 4.7% in 1980 to 8.5% in 2014 [2]. India is regarded as the diabetic capital of the world, with the diabetic population expected to hit the mark of 69.9 million by 2025 and 80 million by 2030 [3].

Diabetic ketoacidosis (DKA) is an acute severe life-threatening complication of DM [1]. Diabetic patients tend to have altered protein metabolism due to abnormal glucose homeostasis resulting in hyperammonemia. Hyperammonemia is a metabolic disturbance where the levels of ammonia are elevated in the blood. This can be toxic to the brain. Encephalopathy due to hyperammonemia in a newly diagnosed diabetic patient presenting in DKA is a rare scenario.

CASE REPORT

A 52-year-old male was brought to the Emergency department with 2 days history of delirium. He also complained of fatigue, polyuria, and polydipsia for the past 2 weeks and constipation for 1 week. He was not a known case of any comorbid condition and was not on any regular medications. There was no history of any substance abuse.

On examination, he was disoriented and dehydrated. His heart rate was 110/ minute (regular), blood pressure 90/60 mmHg, respiratory rate of 24/ minute with saturation 94% (room air). His systemic examinations were normal and there were no signs of meningeal irritation.

His complete blood counts, electrolytes, calcium, thyroid stimulating hormone (TSH), thyroid peroxidase antibody and liver functions were normal. Renal functions were deranged (urea 92 mg/dL, creatinine 3.12 mg/dL). Random blood glucose was 442 mg/dL and HbA1c 14.4%. Urine ketone was positive (5+) and arterial blood gas analysis showed acidosis (pH 7.21, pO_2 95mmHg, pCO_2 29 mmHg, HCO_3 11 mEq/L). Serum amylase was mildly elevated (110 U/L) but lipase was normal (90 U/L). Fasting lipid profile had high density lipoprotein (HDL) of 42 mg/dL, low density lipoprotein (LDL) of 140 mg/dL, very low density lipoprotein (VLDL) of 32 mg/dL and triglycerides of 255 mg/dL. Electrocardiogram (ECG) showed sinus tachycardia. Echocardiography, ultrasound abdomen and computed tomography (CT) scan of the brain were normal. Cerebrospinal fluid analysis (CSF) was also normal.

Ryle's tube aspirate contained only food particles. He was managed with insulin and intravenous fluids as per the DKA treatment protocol. His vitals and renal parameters normalized. Blood glucose levels were maintained between 110 to 140 mg/dL. Though the patient became oriented, he continued to be drowsy. His plasma ammonium levels were elevated (97 µmol/L). He was given lactulose enema followed by lactulose syrup (15 ml) at night. Within 2 days, his sensorium became normal following normalization of ammonia levels (30 µmol/L) and was discharged on premix insulin analogs. On review after 2 weeks, he was asymptomatic, with fasting and postprandial blood glucose levels of 118 mg/dL and 157 mg/dL respectively, and plasma ammonia of 27 µmol/L.

DISCUSSION

In humans, ammonia is produced by the bacterial hydrolysis of intestinal urea and other nitrogenous compounds, the purine nucleotide cycle, the transamination of amino acid in skeletal muscle and other metabolic processes that take place in the liver and kidneys. Hyperammonemia can lead to neurological disorders when excess ammonia crosses the blood-brain barrier [4]. The primary cause for hyperammonemia is a congenital defect in enzymes of the urea cycle such as deficiencies of ornithine argininosuccinate lyase and transcarbamoylase. Secondary hyperammonemia is commonly seen in patients with liver disease leading to portosystemic encephalopathy. It can also occur in disorders like Reye's syndrome, infection in a neurogenic bladder and ureterosigmoidostomy [5-7]. Drugs like cyanide, valproic acid, carbamazepine and iron, in toxic amounts, can disrupt mitochondrial pathways, thereby causing secondary hyperammonemia [8,9]. Chemotherapeutic agents like cyclophosphamide, 5-fluorouracil, cytarabine, vincristine, etoposide, L-asparaginase can cause non-cirrhotic hyperammonemia. Acute leukemia, multiple myeloma, and solid organ tumors can also have hyperammonemia as a rare complication [10-12]. Non-cirrhotic hyperammonemia has also been reported in cases of gastric bypass surgery [13].

Insulin increases the rate of protein synthesis and decreases the rate of protein degradation. Hence, insulin resistance or deficiency can lead to increased protein catabolism. Moreover, the slow transit constipation can facilitate increased absorption of ammonia into the mesenteric blood supply which is sufficient enough to overwhelm the hepatic excretory pathway [6,14]. In some patients, hyperinsulinemia has been associated with hyperammonemia. The increase in intracellular fat in the liver and skeletal muscles, which occurs in association with insulin resistance, can lead to a mitochondrial defect in substrate oxidation; thereby resulting in decreased mitochondrial density and mitochondrial copy number. This, in turn, can impair the urea cycle and cause hyperammonemia [15].

The diagnosis of non-cirrhotic hyperammonemia can be challenging, requiring a high level of suspicion. It should be considered when other causes like liver failure, azotemia, stroke, electrolyte imbalance, and thyroid disorders have been ruled out. A delay in recognition can lead to complications like encephalopathy.

CONCLUSION

Hyperammonemia is a common metabolic disorder in patients with liver disease but non-cirrhotic causes are uncommon. Hyperammonemia leading to encephalopathy is an uncommon complication in DM. This may be due to factors like high protein catabolism, slow transit of bowel contents, insulin resistance, infections, and mitochondrial dysfunction.

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