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Management of Ornithine Carbamoyltransferase Deficiency with Underlying Hyperammonia Hyperinsulinemia Syndrome

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Female, 66
Final Diagnosis: Ornithine carbamoyltransferase deficency with underlying hyperammonia hyperinsulinemia syndrome
Symptoms: Seizure
Medication: —
Clinical Procedure: —
Specialty: General and Internal Medicine

Objective: Rare co-existance of disease or pathology

Background: The urea cycle converts amino acids to urea and is excreted by the kidneys. Ornithine carbamoyltransferase (OTC) deficiency is a rare X-linked urea cycle disorder which results in hyperammonemia. Diagnosis is made based on a clinical presentation of poor feeding, hypotonia, biochemical profile, and genetic testing. Another genetic cause for hyperammonemia is hyperammonia hyperinsulinemia (HAHI) syndrome. A mutation coding for glutamate dehydrogenase (GDH) results in increased alpha-keto glutarate and ATP, triggering the secretion of pancreatic insulin. However, unlike OTC deficiency, these patients are asymptomatic but do have symptoms of hypoglycemia. The purpose of this article is to present the case of a 66-year-old woman with an unusual late-onset of OTC deficiency compounded with an underlying HAHI syndrome with co-disease management.

Case Report: A 66-year-old female with a history significant for transient ischemic attack (TIA) and urea cycle disorder was admitted for new adverse symptoms. Further evaluation revealed hyperammonemia and hypoglycemia. Despite standard previous treatment for her underlying urea cycle disorder, high ammonia levels and hypoglycemia persisted. The contradicting values with continued hypoglycemia regardless of dextrose treatment was suspicious for underlying HAHI. Further genetic testing during her admission revealed a deletion in GLUD-1 gene concurrent with diagnosis of HAHI. After co-diagnosis was established, effective management required medications for both disorders in concordance with dietary restriction.

Conclusions: This is an extremely rare case of OTC deficiency, with a vague presentation in an elderly female. Exploring compounding genetic disorders in the presence of one that is already established and early recognition are crucial for prompt diagnosis and management.

MeSH Keywords: Diazoxide • Hyperammonemia • Hyperinsulinism • Hypoglycemia • Ornithine Carbamoyltransferase Deficiency Disease • Urea Cycle Disorders, Inborn

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/914416

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Background

Ornithine carbamoyltransferase (OTC) deficiency is a rare X-linked metabolic disorder and is thus seen less often in females. OTC is one of the 6 enzymes in the urea cycle that breaks down and removes nitrogen from the body. The deficiency of this enzyme leads to the accumulation of ammonia in circulation, ultimately resulting in encephalopathy. Initial symptoms are usually seen at birth and include refusal to eat, poor latch, vomiting, progressive lethargy, and irritability. The disorder may rapidly progress to seizures, hypotonia, hepatomegaly, and respiratory abnormalities at a later stage [1]. HAHI syndrome is the deficiency of another enzyme, GDH, resulting in an increase of ammonia by-products but remaining asymptomatic, and increased insulin secretion resulting in symptoms of hypoglycemia such as dizziness, sweating, confusion, and blurred vision.

In this report, we present an unusual case of late-onset of OTC deficiency with an underlying HAHI syndrome, and discuss the co-disease management.

Case Report

We report a case of a 66-year-old female with a history of prior TIA and a 10-year history of a urea cycle disorder. Her urea cycle disorder was first diagnosed 10 years prior due to elevations of amino acids detected on urinalysis. Subsequent genetic testing was conducted via polymerase chain reaction gene sequencing, and she was found to have a deletion on the OTC coding gene. This confirmed the suspicion for OTC deficiency. She was initially admitted to hospital in 2016 due to confusion, gait disturbance, and facial droop. Evaluation for stroke was negative and brain MRI demonstrated no acute changes. She was found to have brain toxicity secondary to increased ammonia level with resultant encephalopathy. Clinical presentation can be highly variable and with episodic symptoms. Initial signs of hepatic encephalopathy (HE) may be inversion of sleep pattern, mild confusion, lethargy, and personality changes. There may be asterixis. However, HE can develop into somnolence, disorientation, marked confusion, and even coma. If left untreated, it may lead to intracranial hypertension, seizures, and death [2].

She presented 2 years later with complaints of hallucinations, worsening ataxia with resultant fall, abdominal pain, and lower-extremity lymphedema. Initial workup showed elevated ammonia level of 97 mcg/dL with hypoglycemia and a drop in hemoglobin from 10 to 8 g/dL. After admission, she became hypotensive and started to seize. She was given 1 dose of 0.5 mg Lorazepam; her blood pressure of 99/45 mmHg did not improve with normal saline bolus and she was therefore transferred to the Intensive Care Unit (ICU). On the unit, her blood pressure improved with 500 cc albumin and she became responsive. In the past, typically used as standard treatment for OTC deficiency, Raviciti (glycerol phenylbutyrate) was used in this patient to manage elevated ammonia levels. At this point, the previous regimen of Raviciti 1.1 g/mL and lactulose was re-started for hyperammonemia and she was placed on vasopressors. She remained in the ICU for nosocomial pneumonia, secondary septic shock, and sequential worsening of her respiratory status, resulting in intubation and requiring vasopressor support.

Her ammonia levels fluctuated throughout her hospitalization, between 50 and 170 mcg/dL, as did her mental status and glucose levels. Upon her initial lab work, the management of balancing her elevated ammonia levels and persistent low glucose levels ranging from 40 to 54 mg/dL was difficult at best. Attempts in achieving euglycemic state with a normal range of ammonia levels were made with trials of various glucose fractioned solutions such as D5, D10, and D20 in combination with normal saline. At this point, we explored different possibilities for potential causes of persistent hypoglycemia in the presence of hyperammonianemia. The superimposed syndrome of hyperammonia hyperinsulinemia (HAHI) causes an elevation of alpha-keto glutarate and an ammonia by-product, due to a mutation in a mitochondrial matrix enzyme that is responsible for the oxidation of glutamate. The elevation of alpha-keto glutarate results in subsequent elevated ATP that leads to an uncontrolled release of insulin from the pancreatic B cells. Patients with this syndrome are found to be asymptomatic from the elevated ammonia by-products; however, they do experience symptoms of persistent hypoglycemia [3]. The causative agent for her resultant fluctuating mental status was debated as being due to the hepatic encephalopathy, hypoglycemia, or a combination of both. At this point, genetic testing was performed and confirmed the hypothesis of the superimposed syndrome. She was positive for a mutation of the GLUD-1 gene encoding for the mitochondrial matrix enzyme, with elevated alpha-keto glutarate on repeat urinalysis.

After trial and error, we found that with the continuation of a balanced treatment with dextrose 20 infusion 500 mL/hr, Raviciti, and a low-protein restricted diet with the goal of keeping her at normal ammonia and euglycemic level, her mentation improved. Intensive management by registered dieticians with training and experience with metabolic disorders is crucial in this process.

Discussion

OTC deficiency usually presents in childhood or infancy; therefore, our patient must likely have a partial of the disease or be a carrier. OTC deficiency, being an X-linked disorder,

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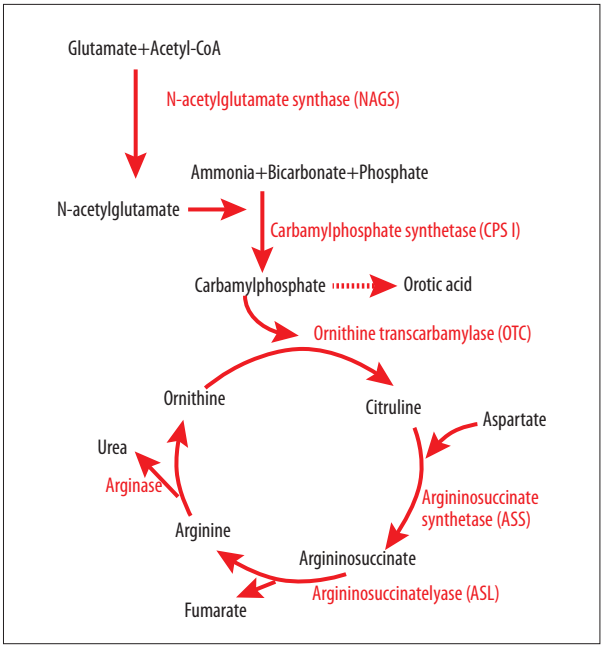

Figure 1. Urea cycle pathway.

is predominant in males. Of symptomatic female carries, only 20% exhibit mild symptoms, as opposed to the full-blown presentation seen in this case [4]. OTC deficiency is the most common form of urea cycle disorder. Because OTCD symptoms are nonspecific, it can easily be mistaken for general digestive system infection or other neurological diseases. In addition, treatment and prognosis of OTCD and these other diseases are largely different; therefore, early diagnosis is particularly important to guide treatment and prognosis [5]. The liver is the only site of the complete urea cycle in the body, consisting of 9 enzymes that participate in the breakdown of protein to amino acids, depicted in Figure 1. Any disruption of the enzymes results in the accumulation of ammonia and predecessor by-products of enzymatic reactions [6].

Our patient had a late, vague initial presentation, with multiple hospitalizations due to seizures and TIA-like symptoms attributed to underlying primary neurological disorders. The target for this intervention was found to the balance between a low-protein restricted diet and a maximum dose of Raviciti (1.1 g/mL) 5 mL 3 times per day. She was placed on an infusion of D20 500 mL/h to maintain euglycemia, and received bolus feedings for calorie and glucose supplementation. Attempts to wean her off of the dextrose solution resulted in persistent hypoglycemia. At this point, we explored the possibility of superimposed syndrome of hyperammonia hyperinsulinemia (HAHI). HAHI is a congenital condition resulting from a mis-sense amino acid substitution on the GLUD1 gene that codes for glutamate dehydrogenase (GDH), a mitochondrial matrix enzyme. The mutation causes an inability to oxidize glutamate, resulting in alpha-ketoglutarate and an ammonia by-product. The increase of alpha-ketoglutarate causes an increase of ATP, influx of calcium, and subsequent depolarization triggering the secretion of insulin from the pancreatic beta cells. However, unlike OTC deficiency, despite having elevated ammonia levels, these patients do not have related encephalopathic symptoms, but do suffer from symptoms of hypoglycemia due to the hyperinsulinemia. These symptoms, such as dizziness, altered mental status, and blurry vision, were seen in the patient due to persistent hypoglycemia [7]. Her recorded glucose levels fluctuated throughout her admission, but remained less than 50 mg/dL, ranging from 33 to 49 mg/d. This supported the postulation of HAHI and OTC deficiency in conjunction. Genetic testing was performed and confirmed the hypothesis with a positive result of a mutation of GLUD-1 with decreased levels of GDH and elevated alpha-ketoglutarate on repeat urinalysis. Diazoxide is a commonly used medication, and is often the first-line treatment for pediatric HAHI patients. This medication accts on the potassium-ATP channels in pancreatic beta cells, inhibiting the release of insulin and subsequent hypoglycemia. We found that this therapeutic intervention, in addition to the simultaneous use of D20 infusion and Raviciti 5 mL 3 times a day, prevents recurrent hypoglycemia and hyperammonemia, while allowing for adequate nutrition.

Conclusions

Although OTC disorder is rare, this case illustrates the importance of early recognition as well as exploration of possible simultaneous genetic disorders. After an established OTC deficiency diagnosis, the continuous hypoglycemia despite dextrose treatment prompted further workup to explore an underlying endocrine abnormality – HAHI syndrome. Early recognition of both disorders is critical to early institution of appropriate therapy and prevention of complications such as recurrent encephalopathy, seizures, ataxia, and tertiary sequelae (e.g., falls resulting in bleeding or fractures, prolonged immobility, and muscle wasting).

Conflicts of interest

None.

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