A Case of Atypical Adult Presentation of Urea Cycle Disorder

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ABSTRACT

Introduction: Urea cycle disorders are metabolic disorders of nitrogenous waste substances due to either complete or partial deficiency of enzymes. Hyperammonemia associated with urea cycle disorders should be addressed immediately in the acute setting, as it can cause irreversible neurological injury or death.

Case Presentation: We report the case of a 48-year-old woman who presented with lethargy, weakness, and altered mental status following prolonged nausea and vomiting despite an esophageal dilatation procedure 3 weeks prior. Further investigation with assistance from the genetics consult team revealed a partial enzyme deficiency associated with urea cycle disorder.

Discussion: Although many cases of urea cycle disorder present in neonates 24 to 48 hours following birth, a delayed presentation may be observed in female carriers with partial activity of any urea cycle enzyme leading to ammonia buildup. This is the result of stress-related events that form a catabolic state involving protein breakdown within the body that trigger increased ammonia levels.

Conclusion: A diagnosis of urea cycle disorder should be suspected in patients who have had a recent stressor with progressive lethargy and confusion associated with hyperammonemia, so that treatment may begin with intravenous sodium benzoate and phenylacetate initially and hemodialysis at 8 hours if ammonia levels do not decrease to avoid permanent neurologic damage.

INTRODUCTION

Urea cycle disorders are inborn errors of metabolism that can present rarely for the first time in adulthood. They are treatable but life-threatening causes of metabolic encephalopathy that are underrecognized and underreported. Here we present a case of urea cycle disorder precipitated by poor oral intake and recent infection.

CASE PRESENTATION

A 48-year-old woman with a past medical history of asthma, peptic ulcer disease, fibromyalgia, depression, migraine headaches, and pulmonary embolism presented to the Emergency Department with lethargy, gait disturbance, and weakness. Upon admission, her vitals were stable except for tachycardia. On exam, she was lethargic with dry mucous membrane. The rest of the physical exam was unremarkable. Initial laboratory results demonstrated high ammonia level (more than 400s) and anion gap metabolic acidosis (refer to Table). Other workup, including computed tomographic scan, lumbar puncture, toxicology tests, and liver function test, was normal. The patient was intubated and admitted to the intensive care unit (ICU) for altered mental status and impending respiratory failure. Upon questioning, her husband reported a history of refractory nausea and vomiting associated with poor oral intake for the past 3 weeks. The patient had an esophagogastroduodenoscopy that showed gastric ulcer and esophageal stricture, which resulted in a dilatation procedure but did not improve her symptoms.

A record review revealed that the patient was admitted to the same hospital 6 years prior with altered mental status and unexplained hyperammonemia. She had extensive workup to rule out

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all possible causes, including infection, vasculitis, drugs, toxins, and alcohol. She had quickly recovered from the illness with supportive care and indicated that she thought the episode was precipitated by a viral illness and new dietary program that she had started. Based on clinical improvement with intravenous sodium benzoate, she was referred to a genetics clinic but was lost to follow-up.

During this ICU stay, the patient was treated with sodium phenylacetate, sodium benzoate, arginine replacement, and dextrose 10%-0.45% saline, as recommended by the genetics consult team for possible urea cycle disorder. She also was treated with intravenous antibiotics for pneumonia that developed during her hospital stay. Following treatment, our patient exhibited improvement in mental status and ammonia levels. On day 7, she was transferred out to the medicine floor in stable condition and was discharged home on day 10 with a plan for outpatient follow-up. She underwent genetic testing to investigate the defective urea cycle enzyme; post discharge results showed negative N-acetylglutamate synthase and ornithine transcarbamylase deficiency, but a positive carbamoyl phosphate synthetase deficiency.

Table. Laboratory Study Results of Patient With Urea Cycle Disorder on Admission and 1 Day After Treatment With Intravenous Sodium Benzoate and Phenylacetate

Lab	On Admission	1 Day After	Reference Range
Glucose	96	159	65-99 mg/dL
Ammonia	406	29	11-51 umol/L
Bicarbonate	8	11	22-29 mmol/L
Anion gap	31	17	10-18 mmol/L
Urine ketones	2+	Negative	Negative
AST	13	19	11-33 unit/L
ALT	11	15	6-37 unit/L
Albumin	4.4	3.5	3.8-5.0 g/dL
Alkaline phosphatase	80	68	35-104 unit/L
Barbiturates screen	Negative	N/A	Negative
Benzodiazipine screen	Negative	N/A	Negative
Tricyclic antidepressant screen	Negative	N/A	Negative
Ethanol	<0.01	N/A	<0.01 g/dL
Methanol	<10	N/A	<10 mg/dL
	pH 7.27	pH 7.32	7.35-7.45
Arterial blood gas	pCO2 26	pCO2 23	35-45 mmHg
	pO2 179	pO2 177	80-104 mmHg
	HCO3 12	HCO3 12	21-28 mmol/L
Lactic acid	2.3	2.3	0.5-2.0 mmol/L

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase

DISCUSSION

Urea cycle disorders are metabolic disorders leading to buildup of nitrogenous waste substances due to either complete or partial deficiency of urea cycle enzymes which may include carbamoyl phosphate synthetase I (CPS1), ornithine transcarbamylase (OTC), argininosuccinic acid synthetase (ASS1), argininosuccinic acid lyase (ASL), arginase (ARG1), and/or a cofactor-producing enzyme N-acetyl glutamate synthetase (NAGS), or 2 amino acid transporters: ornithine translocase (ORNT1) and/or citrin. Accumulation of ammonia most commonly occurs because of severe deficiency or total absence of CPS1, OTC, ASS1 and ASL, or NAGS, and presents in neonates within the first 24 to 48 hours of life with failure to feed and somnolence initially with progression to lethargy and coma. These neurologic symptoms, through the proposed mechanism of ammonia-induced brain injury resulting from increased ammonia levels, lead to increased glutamine, which precipitates cerebral edema because of the osmotic effects of increased glutamine levels within the astrocytes.[1]

Although approximately 33% of urea cycle disorder cases present during the neonatal period (ie, < 30 days of life), a delayed presentation is typically observed in childhood. In patients with partial OTC deficiency or with partial activity of all urea cycle enzymes, the likelihood for a delayed presentation depends on the deficient urea cycle enzyme.[2] For female patients with OTC deficiency, 29% initially present with symptoms after 12 years of age, with a median age of presentation at 10 years. If the deficient enzyme is CPS1 or ASS1, the initial age of presentation decreases to a median age of 11 months, with 24% and 16% presenting after the age of 12, respectively.[3]

Patients with a delayed presentation often are symptomatic only when specific situations trigger increased ammonia levels. These scenarios commonly include an increased protein load from a new diet or a systemic catabolic state as a result of illness, pregnancy, surgery, or fasting.[4] Clinical presentation of patients with partial or atypical urea cycle enzyme deficiency typically demonstrate decreased levels of consciousness, altered mental status, vomiting, a seizure disorder, sleep disorders, or psychiatric illness. In our patient, her lack of a consistent diet due to vomiting led to a state of starvation, likely triggering a catabolic state involving protein breakdown and thus hyperammonemia. In other patients, however, a new vegetarian diet low in protein may lead to catabolism of peripheral proteins resulting in hyperammonemia in addition to poor growth, development, and nutritional deficiencies. Diets high in protein also may result in hyperammonemia as a result of gastrointestinal tract processes, which break down consumed proteins into usable amino acids.

In our patient, hyperammonemia and ketonuria, in combination with her clinical presentation of altered mental status, suggest that she was experiencing symptoms consistent with a urea cycle disorder. Urea cycle disorder typically presents with normal blood pH and anion gap, but the cause of this patient's increased anion gap metabolic acidosis may be a result of poor oral intake and concomitant infection. *Staphylococcus aureus* was isolated in bronchoalveolar lavage obtained on the day following her admission.[5] In fact, this infection, in addition to her poor oral intake, also may have contributed to her urea cycle disorder exacerbation.

In the acute setting, diagnosis for patients experiencing hyperammonemia due to urea cycle disorder is considered when the plasma ammonia level is greater than 100-150 umolL. The recommended method of initial treatment includes intravenous (IV) sodium benzoate and phenylacetate with follow-up treatment with hemodialysis at 8 hours if ammonia levels do not decrease.[7] A newer 2016 protocol, however, suggests a different approach based on the patient's presenting ammonia level. For patients above the limit of normal, but less than 250 umol/L, it was suggested they stop with protein intake and IV glucose be administered to prevent onset of a catabolic state. Nitrogen scavengers, such as IV sodium benzoate and phenylacetate, were suggested to be used within the ammonia levels of 150 and 250 umol/L.[6] At levels above 250 umol/L, use of hemodialysis or continuous renal replacement therapy were advised instead of peritoneal dialysis due to a lower rate of clearance observed with peritoneal dialysis.[7]

Long-term management for patients with suspected or confirmed partial urea cycle enzyme deficiency should include avoiding activities that contribute to increased catabolic activity (ie, diets with too much or too little protein content) and monitoring fasting ammonia and plasma amino acid levels. For patients who cannot receive the recommended protein amounts due to abnormally high ammonia and/or amino acid levels, nitrogen scavenging drugs should be titrated accordingly. In patients planning to undergo surgery, the recommendations regarding the amount of sodium benzoate, phenylacetate, and protein within the diet vary based on the surgery.[8]

CONCLUSIONS

Prompt diagnosis and treatment is crucial to prevent and reduce the development of permanent neurologic sequelae from hyperammonemia, though current recommendations for altered mental status workup in adults do not incorporate urea cycle disorder as it rarely presents after 24 to 48 hours following birth. A diagnosis of urea cycle disorders should be suspected in patients who had a recent stressor or multiple stressors with progressive lethargy and confusion associated with hyperammonemia.[9] Long-term management in patients with partial urea cycle disorder focuses on providing adequate nutritional content with monitoring of plasma ammonia levels during known events that create catabolic conditions within the body.

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