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ACUTE PRESENTATION AND MANAGEMENT OF THE ENCEPHALOPATHIC CHILD WITH AN UNDIAGNOSED INBORN ERROR OF METABOLISM

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☐ **Abstract—Background: Inborn errors of metabolism (IEM) commonly present in infancy and, less commonly, later in life. Case Report: This case describes an IEM, specifically, ornithine transcarbamylase deficiency, in a previously healthy 7-year-old boy who presented to an emergency department with vomiting for approximately 24 h prior to admission. The child became progressively encephalopathic while in the emergency department, but an ammonia level was not obtained until several hours after admission. Irreversible brain damage with cerebral edema was already present at time of diagnosis, leading to death. Why Should an Emergency Physician Be Aware of This?: This case emphasizes that acute hyperammonemia can rapidly cause irreversible neurological damage and, in the case of a newly encephalopathic pediatric patient, ammonia levels should be evaluated early to facilitate proper diagnostic tests and treatment.** © **2018 Elsevier Inc. All rights reserved.**

☐ **Keywords—inborn error of metabolism; hyperammonemia; ornithine transcarbamylase deficiency; urea cycle disorder; late-onset OTC deficiency; encephalopathy**

INTRODUCTION

A previously healthy child presenting with vomiting and altered mental status as a manifestation of an inborn error of metabolism (IEM) can be a clinical conundrum for first-line providers and result in a fatal outcome. Immediate consideration of an IEM and resuscitation are paramount because interventions are time-sensitive.

Ornithine transcarbamylase (OTC) deficiency is an IEM and the most common urea cycle disorder. When inherited as a mild variant, OTC remains asymptomatic and undiagnosed until faced with an environmental stressor such as meals rich in protein or involuntary fasting (often caused by infection), which leads to catabolism and digestion of endogenous protein (1).

Vomiting is a common, inconspicuous symptom in children. However, vomiting associated with acute neurological deterioration should prompt obtaining an ammonia level and, if hyperammonemia is present, lead to rapid treatment to decrease ammonia and stop the patient's catabolic state (2,3). We present a case of an undiagnosed IEM and review its symptoms, pathophysiology, diagnosis, and treatment.

CASE REPORT

A previously healthy 7-year-old boy developed a vomiting illness approximately 24 h prior to presentation, which resulted in poor oral intake. He became lethargic over several hours and was taken to an emergency department (ED) due to vomiting and altered mental status. In the ED, he initially responded appropriately to commands but progressively worsened with confusion and agitation. His siblings had the same gastrointestinal symptoms without neurological symptoms. Physical examination in the ED was most notable for altered mental status and delirium, with additional findings of tachycardia and mild abdominal tenderness. He was afebrile with

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heart rate was in the low 100s, saturating in the 90s on room air, and normotensive.

The diagnostic work-up in the ED included a comprehensive metabolic panel that showed a mild transaminitis and mildly elevated prothrombin time and partial thromboplastin time. His electrolytes and a capillary blood gas were within normal limits. Head and abdominal computed tomography scans, as well as a lumbar puncture, were also normal. The patient received normal saline boluses for a total of 30 mL/kg; no medications were given. The initial differential diagnostic list included appendicitis, hepatic failure, volvulus, viral gastroenteritis, and meningitis. His neurological status progressively declined over a 5-h period at the referring ED, which prompted transfer to a tertiary children's hospital.

Upon arrival to the children's hospital ED, the patient had a Glasgow Coma Scale score of 5, without response to speech or pain, and clonus of the feet bilaterally and hypertonicity of the lower extremities. Due to his neurological status, he was emergently intubated. A repeat head computed tomography scan was normal. He was then admitted to the pediatric intensive care unit. His pH was normal at 7.4. Serum ammonia, drawn 7 h after presentation, was 374 μmol/L (normal range 21–50 umol/L). The patient had elevated lactate and ketones suggestive of a catabolic state. These studies suggested a urea cycle disorder. Additional studies, which resulted later, were consistent with OTC deficiency, including high orotic acid levels from urine organic acid panel and elevated alanine, and glutamine from plasma amino acids (Table 1).

Treatment consisted of calories in the form of intralipids and intravenous glucose, with continuous insulin to halt the catabolic process. In addition, the patient received sodium phenylacetate and sodium benzoate to

Table 1. Initial Diagnostic Studies in Suspected Inborn Errors of Metabolism

Diagnostic Study	OTC Deficiency Normal/Abnormal	Differential Diagnosis if Abnormal
Blood gas	Normal	Mitochondrial disorders Fatty acid oxidation defects Organic acidemias
Serum ammonia level	Elevated	Urea cycle defects Organic acidemias Fatty acid oxidation defects Carbohydrate disorders Glycogen storage disease
Serum electrolytes	Normal	Glycogen storage disease Mitochondrial disorders Carbohydrate disorders Organic acidemias
Serum glucose	Normal	Carbohydrate disorders Fatty acid oxidation defects Endocrinopathies
Blood urea nitrogen (BUN)	Low	Urea cycle defects Poor eating (from any reason)
Liver function tests	Normal or mildly elevated	Carbohydrate disorders Glycogen storage disease Mitochondrial disorders Urea cycle defects Aminoacidopathies
Serum lactate	Normal	Glycogen storage disease Fatty acid oxidation defects Mitochondrial disorders Carbohydrate disorders
Serum total and direct bilirubin	Normal	Carbohydrate disorders Mitochondrial disorders
Serum uric acid	Normal	Glycogen storage disease
Plasma amino acids, quantitative	Abnormal	Aminoacidopathies Urea cycle defects
Plasma acylcarnitine profile	Normal	Organic acidemias Fatty acid oxidation defects
Complete blood cell (CBC) count	Normal	Organic acidemias
Urinalysis	Normal	Ketotic hypoglycemia
Urine organic acids, including orotic acid	Abnormal	Urea cycle defects Organic acidemias
Serum ketones	Normal	Ketotic hypoglycemia Mitochondrial disorders Organic acidemias Glycogen storage disease

OTC = ornithine transcarbamylase.

normalize ammonia levels, and dialysis was initiated to enhance elimination of ammonia. However, the child remained unconscious despite normalized ammonia levels. He developed clinical evidence of cerebral edema herniation over the next 24 h and progressed to brain death, which was confirmed with two examinations 12 h apart per our institution's protocol. The patient's family elected to pursue organ donation after brain death was confirmed.

Notably, after the diagnosis of a urea cycle disorder, further review of the history indicated subtle clues for a possible IEM. One maternal uncle died unexpectedly in his fifties after an injection of steroids and two male cousins of the mother died in their 20s for unknown reasons. The mother also described that the patient had recurrent abdominal pain and vomiting after brief fasting and ate several snacks daily to mitigate such symptoms. His primary care physician had performed a limited work-up in the absence of symptoms without yielding any diagnosis to explain the reason for recurrent vomiting. The family was eventually connected to a large pedigree of male patients with late-onset OTC deficiency through common ancestors (4).

DISCUSSION

This patient had a late presentation of OTC deficiency with an ultimately fatal outcome. Though OTC deficiency and other IEMs commonly present in the neonatal period or infancy, some may present at any age. Outside of the neonatal period, IEMs are low on the differential diagnosis list during ED evaluations because they are rare and have nonspecific symptoms that can mimic other illnesses. Common differential diagnoses include encephalitis, infection, ingestions, mild traumatic brain injury, liver failure, and electrolyte disturbances. However, emergency medicine practitioners are often the first providers to face these patients in metabolic crises. Recognizing the presentation of the acutely symptomatic child with a potential IEM and concomitant awareness of the diagnostic studies and treatment options for such diseases offers significant potential to prevent morbidity and mortality (5).

Pathophysiology and Hyperammonemia Production

OTC deficiency is the most common urea cycle disorder and has an X-linked inheritance pattern. In unaffected individuals, the urea cycle removes nitrogen from the blood stream in the form of urea. In patients with a urea cycle disorder, a defect in one of five enzymes blocks the urea cycle and removal of nitrogen, which leads to the accumulation of ammonia, a neurotoxic substance (6,7).

Ammonia is removed by conversion in the liver to urea, which is then excreted in urine. Ammonia escaping urea synthesis is conjugated with glutamate to generate glutamine, thus elevating glutamine in all urea cycle defects (2). Existing evidence suggests that ammonia alters several amino acid pathways and neurotransmitter systems, cerebral energy metabolism, nitric oxide synthesis, and signal transduction pathways (8).

Hyperammonemia can be caused by other IEMs, such as organic acidemias or fatty acid oxidation defects (5). In these cases, other abnormalities (such as metabolic acidosis or hypoglycemia, neither of which are typically seen in urea cycle defects) can suggest the correct diagnosis. The diagnosis of a urea cycle defect is confirmed by plasma amino acids that show increased glutamine and altered levels of citrulline.

Clinical Presentation and Diagnostic Work-up

Patients with IEM are typically morphologically normal and can be asymptomatic for long periods of time. A metabolic crisis occurs with exposure to a large exogenous protein load or a hypercatabolic state (infections, fasting, corticosteroids, pregnancy, gastrointestinal bleed, or surgery). Symptoms in patients with metabolic disorders may be nonspecific, such as vomiting, but they can also include recurrent decompensation with fasting or illness, unusual body odor, failure to thrive, jaundice, hepatomegaly, fatigue, lethargy or coma, unexplained hemorrhage or stroke, developmental regression, abnormal motor function, tremors, weakness, ataxia, seizures, and chronic movement disorders (9). In urea cycle defects, patients may also describe inability to fast or a tendency to avoid meat (10).

Regardless of age or history, clinical symptoms without an apparent explanation should prompt further investigation for IEMs (Table 1). Obtaining an ammonia level immediately is crucial in patients with altered mental status of unclear cause, as the first-line provider needs to intervene as soon as possible to reduce ammonia levels. The sample, when drawn, should be placed directly on ice and run within 1 h (11). Falsely elevated plasma ammonia levels can be due to hemolysis, increased sample temperature, and delays in processing the sample (12).

Although the results of plasma amino acids and urine organic acids will not become available prior to the patient being transferred from the ED, they are vital to the diagnostic work-up and may be abnormal only during a metabolic crisis. Therefore, we recommend obtaining these laboratory tests upon presentation.

Treatment

All urea cycle defects and other IEM with hyperammonemia are managed similarly in the acute phase while the diagnosis is pending. Early treatment steps can mitigate the potentially fatal neurological outcomes. There is far

less risk associated with the implementation of treatment than the consequences of not treating. The following are treatment guidelines for hyperammonemia/suspected IEM (2,5,6,9,13–15):

1. Stop protein intake to suppress toxic metabolite production and restrict nitrogen intake.
2. Stop catabolism and promote anabolism by providing calories:
   a. Infusion of high-concentration dextrose solution at 1.5 times the normal maintenance rate:
      i. D10 with peripheral intravenous (i.v.) access (keeping in mind that 1.5 maintenance of D10 provides only 51 kcal/kg).
      ii. D20 with central venous access.
   b. Intralipid (20%) infusion at 3–5 g/kg/day i.v. if there is no suspicion of a fatty acid oxidation defect.
   c. When/if glucose > 160 mg/dL, give 0.1 units/kg of insulin followed by an insulin infusion at 0.1 units/kg/h i.v. to promote anabolism.
3. Facilitate removal of ammonia through alternate pathways by providing medications that bind nitrogen byproducts prior to ammonia production and allow for urinary excretion:
   a. Sodium phenylacetate and sodium benzoate i.v. with a loading dose of 2.5 mL/kg over 90–120 min followed by a maintenance infusion of 2.5 mL/kg over 24 h.
   b. Sodium phenylbutyrate or glycerol phenylbutyrate 450–600 mg/kg/day (maximum dose 20 g/day) enterally divided into three doses and administered every 8 h.
4. Provide i.v. arginine (200 mg/kg/day divided into four doses) to resume protein synthesis and prevent catabolism.
5. In cases of refractory hyperammonemia or encephalopathy, initiate continuous renal replacement therapy or hemodialysis.

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

Hyperammonemia can be indicative of an undiagnosed IEM and should be considered in an acutely encephalopathic patient, regardless of the cause. Early recognition of hyperammonemia facilitates proper diagnostic tests and treatment. Management should aim to stop catabolism, lower ammonia, and prevent cerebral edema.

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