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Case Report

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When a normal newborn screen is not normal

Pooja D Utamsingh[1]; Susan A Gutierrez[1]; Laura Victoria Chamorro Dauer[3]; Courtney Premer[2]*

[1]Jackson Memorial Hospital, Department of Pediatrics, Miami, Florida, USA.

[2]University of Miami Miller School of Medicine, Miami, Florida, USA.

[3]Department of Pediatrics, University of Miami Miller School of Medicine/Jackson Memorial Holtz Children's Hospital, Florida, USA.

***Corresponding Author: Courtney Premer**

McGaw Medical Center of Northwestern University, 211 E Ontario Street, Suite 200, Chicago, IL 60611, USA.

Tel: 312-694-7000;

Email: courtney.premer-barragan@northwestern.edu

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Abstract

Introduction: Ornithine Transcarbamylase (OTC) deficiency-an X-linked disorder-is the most common urea cycle defect in infancy and often presents with elevated ammonia.

Case presentation: A 2-month-old with a normal newborn screen presented with feeding difficulties. The patient was incorrectly diagnosed with gastroesophageal reflux, which at 4 months progressed to recurrent vomiting. At 5 months he developed status epilepticus, was found to have an ammonia level >500 micromol/L, and genetic testing revealed OTC deficiency.

Conclusion: Despite a normal newborn screen, unusual infant presentations need to be approached with a broad differential in order to prevent deleterious outcomes.

Keywords: OTC; Ornithine transcarbamylase deficiency; Urea cycle; Urea cycle disorder; Newborn screen.

Case presentation

A four-month-old infant is brought to the emergency department for recurrent non-bloody, non-bilious emesis for the past three days described as projectile and formula-colored. He has been fussy with decreased appetite. His mother reports no fever, diarrhea, constipation, bloody stools, or changes in urine output. He has no cough, congestion, or rash. He is exclusively formula fed with Enfamil Gentlease four ounces every four hours. He is cared for during the day by his mother and lives in a rural region of Florida.

The child was born full term to a mother with gestational diabetes controlled by diet. He has no history of UTI, congenital anomalies, or abdominal surgeries. He had a normal newborn screen at birth was normal. His vaccinations are up to date.

Physical exam reveals an overall well-appearing infant with vitals within normal limits and a weight of 5.06 kg, down from 5.22 kg on a prior ER visit. He is active with a strong cry. He has a normal abdominal exam, normal bowel sounds, no distension, no abdominal masses, and no tenderness. He has normal strength, reflexes, tone, and a flat fontanelle. His capillary refill is 2-3 seconds, with normal skin turgor. Testes are normal and he is uncircumcised.

Laboratory values are significant for an elevated BUN/Cr ratio of 38.1 (normal values 7-25), elevated AST of 85 U/L (13-65), elevated ALT of 80 U/L (12-42), with a bilirubin of 0.4 mg/dL (0-1.1). Sodium, potassium, chloride are all within normal limits. The anion gap is normal at 10 with a bicarbonate of 26 mmol/L(17-29) and a normal glucose of 101. White blood cell count is 12.3 x 10^3/uL (5-15 x10^3 u/L), with a hemoglobin of 14.2

g/dL (10-14.5), and mild thrombocytosis of 414 x 10^3 u/L (150-350 x 10^3). C-reactive protein and erythrocyte sedimentation rate are <0.5 mg/dL, (0-0.9) and 3 mm/h (1-20) respectively. Electrolytes are normal, with the exception of an elevated BUN/Cr ratio indicative of pre-renal causes such as dehydration. Liver enzymes are also mildly elevated.

Pyloric ultrasound shows no evidence of pyloric stenosis. Abdominal sonogram shows a homogenous texture liver, with no lesions, gallstones, or sludge, and no evidence of intussusception. Pelvic ultrasound is normal. Abdominal x-ray shows a non-obstructive gas pattern.

He is given intravenous fluids, ondansetron and ranitidine and discharged home with a diagnosis of viral gastroenteritis.

Three days later, he returns with persistent emesis. At the time it is noted that weight-for-length Z-score has decreased by 1.77 over the past four months and he is admitted for further workup and management of failure to thrive. A nasoduodenal tube is placed for enteral feeds.

He continues to have emesis and a nasogastric tube is placed to possible gastric irritation from the large coil of the nasoduodenal tube. During this time, an upper gastrointestinal study is performed without significant findings. He initially improves, but after 10 days, is found to be restless. He grimaces with small amounts of feeds and the recurrent emesis has returned. 15 days into hospitalization, his mother notes abnormal movements during sleep and noisy breathing. He develops respiratory distress and decreased level of consciousness, requiring intubation. Subsequently, he has a seizure that progresses to status epilepticus. A metabolic team is called immediately and he is found to have an ammonia >500.

Infectious and genetic etiologies of vomiting and elevated liver enzymes are considered. He has an unremarkable urinalysis. Viral, bacterial, and parasitic stool studies are negative. Alpha-1-antitrypsin level is normal. Hepatitis A, hepatitis B, hepatitis C, EBV testing are performed and are all negative.

The patient is stabilized and transferred to the pediatric intensive care unit of a tertiary care center. Here, an evaluation for metabolic disorders is pursued and reveals low citrulline, low arginine, high alanine, and high glutamine levels. These findings are suggestive of OTC deficiency. With this knowledge, whole genome sequencing is performed and a variant (c.386G>A, p. Arg129His) in the Ornithine Transcarbamylase (OTC) gene is found. After his diagnosis, genetic testing is performed on the patient's mother and she is found to have a hemizygous variant of OTC deficiency.

Discussion

Ornithine transcarbamylase deficiency is a rare X-linked defect that often presents in infancy [1]. It is the most common urea cycle defect and commonly presents as a severe neonatal-onset disease in the first two to three days of life in the homozygous variant [1]. Patients with OTC deficiency develop vomiting and seizures that may rapidly progress to coma due to hyperammonemic encephalopathy[1]. Ornithine transcarbamylase is an enzyme that breaks down and removes nitrogen in the urea cycle by catalyzing the formation of citrulline from ornithine. Lack of this enzyme results in an increase in ornithine and inhibition of the urea cycle, leading to excessive nitrogen accumulation in the form of ammonia. Ammonia is a neurotoxin that affects multiple aspects of the central nervous system [1].

Males are more commonly affected due to its X-linked nature, but partial OTC deficiency (hemizygous variant) can also occur, which is more commonly found in females than males and typically presents as a post-neonatal onset disease [2]. Liver transplantation is curative as the OTC enzyme is produced by the liver. Affected children typically require liver transplantation by the age of six months. The decision to pursue liver transplantation is dependent on episodes of hyperammonemia [3].

OTC deficiency is screened by testing amino acids citrulline, arginine, alanine, and glutamine [3]. Citrulline levels in OTC deficiency are usually in the single digits with glutamine levels usually >800. Only six states In the United States screen for OTC deficiency. These are California, Connecticut, Florida, Massachusetts, New Hampshire, and Tennessee. Each state has a different screening cutoff for each of these amino acid levels. Quick recognition is imperative as neurologic abnormalities and impaired cognitive function are significantly correlated with the duration of hyperammonemia and encephalopathy [4].

Treatment/management

For acute phases of metabolic disorders with hyperammonemia, treatment should be directed towards rapid lowering of plasma ammonia to less than 80 mL. A patient whose ammonia is 200 micromol/L or higher should be started on dialysis for rapid lowering of ammonia to a safer level [5]. Other options to lower ammonia include ammonia scavenger therapy such as nitrogen scavengers and citrulline supplementation. These options, however, lower ammonia at a slower rate [3]. Long-term treatment consists of restricting dietary protein intake, maintaining hydration, minimizing catabolism, using nitrogen scavengers, promoting growth and preventing hyperammonemic episodes. Liver transplantation is the most effective means of preventing further crises and neurodevelopmental deterioration and should be considered in patients who fail to respond to medical therapy [3,4].

Patient course

Due to the complex patient presentation, a multidisciplinary treatment approach was utilized. The clinical geneticists and nutritionists managed the patient's hyperammonemia and guided treatment to prevent further hyperammonemic episodes. Specifically, rapid lowering of plasma ammonia levels to less than 200 micromol/L was achieved with the ammonia scavenger, glycerol phenylbutyrate (0.6 mL, Q8H) in order to lower the ammonia. When ammonia levels were critically elevated, renal replacement therapy was administered. Reversal of catabolism was achieved through strict diet which included citrulline supplementation to increase nitrogen clearance through the urea cycle. The neurologists managed the patients' infantile spasms, which were suspected to be secondary to neurologic damage from prior hyperammonemic episodes. The patient received ACTH therapy with a 14-day course of ACTH (24 units, q12h) followed by a 15 day taper. Additionally, our patient was treated with Baclofen (5 mg, Q8H) for spasticity, and levetiracetam (250 mg, Q12H), Topiramate (60 mg, Q12H), clonazepam (0.0625 mg, BID) and PRN Lorazepam for seizures.

Currently, our patient continues to be followed closely by genetics for management of OTC deficiency including dietary management to prevent further hyperammonemic crises. He is followed by neurology for management of seizures and spasticity. He has a global developmental delay with his most recent brain imaging (CT) demonstrating stable diffuse cortical volume loss with ex-vacuo ventricular dilatation. Although liver transplantation is the gold standard for preventing hyperammonemia and neurodevelopmental deterioration [5], our patient is currently not a candidate. Palliative care is closely involved and his family has been connected to hospice services for additional support.

Conclusion

Early diagnosis of inborn errors of metabolism is crucial to prevent irreversible cognitive complications. A metabolic disorder should be considered in the setting of intractable vomiting, even with a normal newborn screen. Newborn screening practices vary by state and the newborn screen has a lower likelihood of picking up the heterozygous variant of OTC, compared to the homozygous variant. An ammonia level is an excellent screening test if a metabolic disorder is suspected [6]. Initial treatment for OTC deficiency focuses on hydration, removing nitrogen from the body, minimizing catabolism, and stimulating anabolism in order for nitrogen uptake to increase [7].

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