Citrullinemia type I and hypertrophic pyloric stenosis in a 1-month old male infant

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Abstract

Citrullinemia type I (CTLN1) is an inherited urea cycle disorder, now included in most newborn screening panels in the US and Europe. Due to argininosuccinate synthetase deficiency, CTLN1 can lead to recurrent hyperammonemic crisis that may result in permanent neurological sequelae. Vomiting in patients with urea cycle disorders may either be the result or cause of acute hyperammonemia, particularly if due to an illness that leads to catabolism. Therefore, age-appropriate common etiologies of vomiting must be considered when evaluating these patients. We present a 1-month old male infant with CTLN1 who had a 1-week history of vomiting and was discovered to have hypertrophic pyloric stenosis. This is the first documented case of an infant with CTLN1 who was later diagnosed with hypertrophic pyloric stenosis, and only the second case of concomitant disease.

Introduction

Citrullinemia type I (CTLN1 or citrullinemia, classic; OMIM 215700) is an autosomal recessive urea cycle disorder that results from argininosuccinate synthetase deficiency. The classic neonatal-onset type usually presents within the first week of life with feeding difficulty, somnolence, vomiting and possible coma and stroke due to profound hyperammonemia, which may be greater than 1000 μmol/L (normal: <50 μmol/L). Quantitative plasma amino acid analysis is often diagnostic, demonstrating elevated citrulline and glutamine, low arginine and absence of argininosuccinic acid.3

Although vomiting in these patients is often a sign of elevated ammonia levels during times of metabolic stress, other more common pediatric etiologies may cause vomiting before the development of hyperammonemia. In this report, we describe a 1-month old male infant with CTLN1, diagnosed at 4 days of age and treated with L-arginine, sodium phenylbutyrate and protein restriction, who presented with vomiting, normal ammonia level and newly-discovered hypertrophic pyloric stenosis on abdominal ultrasound. A review of current medical literature reveals only one prior case report of a patient with suspected citrullinemia and pyloric stenosis.2

Case Report

A 1-month old male infant with CTLN1 presented to the biochemical genetics clinic with 1-week of vomiting and weight loss. The diagnosis of CTLN1 had been made at 4 days of age after he presented with hyperammonemic coma.

He was born at term by vaginal delivery to a primigravid Japanese mother and a Caucasian father. Prenatal and family histories were unremarkable. APGAR scores were 8 and 9 and the patient was discharged after 24 h with mild feeding difficulty, which continued at home. At 4 days old, the infant presented with lethargy, hypothermia, seizure, hemodynamic instability and hyperammonemia to greater than 1000 μmol/L. He required prolonged intensive care admission with dialysis and mechanical ventilation. Given high suspicion for urea cycle disorder, the patient was treated with IV sodium phenylacetate, sodium benzoate and L-arginine. During admission, plasma amino acids were consistent with a diagnosis of CTLN1 and newborn screening returned positive with elevated citrulline. Two known mutations for CTLN1 were identified on ASST gene sequencing: a heterozygous exon 7 mutation c.421-2A>G and a heterozygous exon 8 mutation c.539G>A (p.Ser180Asn). The infant was discharged home at 17 days of age with protein-restricted nasogastric tube feeds, L-arginine and sodium phenylbutyrate.

At approximately 3 weeks of age, the patient was twice evaluated at an outside hospital for lethargy and emesis. Ammonia level was normal at both visits and labs revealed mild transaminases and elevated total bilirubin to 3.4 mg/dL. Both times, the infant improved with IV hydration and was discharged home with reflux precautions. However, he was seen 4 days later at the genetics clinic and parents reported non-projectile vomiting for 1 week. Further history revealed that the nasogastric tube had been accidentally removed prior to onset of emesis, and thereafter replaced by parents with reported home nurse confirmation of positioning. In the clinic, the infant was vigorous but diffusely mottled with a weight loss of 0.12 kg in the last 2 weeks. Nasogastric tube placement was again confirmed and the patient was admitted to the inpatient genetics service for further management.

Upon admission, labs were notable for the following (reference ranges within parentheses): potassium 5.1 mmol/L (3.5-5.5 mmol/L), chloride 100 mmol/L (100-113 mmol/L), bicarbonate 29 mmol/L, (22-26 mmol/L) ALT 44 IU/L (7-35 IU/L), alkaline phosphatase 440 IU/L (50-350 IU/L), total bilirubin 4.3 mg/dL, direct bilirubin 3.4 mg/dL, (0.0-0.3 mg/dL). Ammonia level was 59 μmol/L (11-60 μmol/L) and venous blood gas revealed pH 7.45, pCO2 of 42 mmHg and lactic acid level of 4.1 mmol/L (0.5-2.0 mmol/L). The infant was started on IV dextrose-containing fluids, sodium phenylacetate, sodium benzoate and L-arginine. Sepsis work-up with cerebrospinal fluid, blood and urine cultures did not yield a source of infection. Oral challenge without nasogastric tube resulted in continued emesis; therefore, an abdomi-
nal ultrasound was obtained. Results revealed hypertrophic pyloric stenosis (HPS) (Figure 1). Pediatric surgery was consulted and uncomplicated laparoscopic pyloromyotomy was performed on hospital day 2. On post-operative day 4, the infant was discharged home on continuous nasogastric tube feeds and ranitidine for peri-procedural gastritis. The patient has now undergone liver transplant, remains on low-dose L-arginine and is doing well at 11 months of age with age-appropriate neurocognitive parameters.

Discussion

CTLN1 is a rare autosomal recessive urea cycle disorder caused by argininosuccinate synthetase (ASS) deficiency due to mutations in the ASS1 gene. Decreased ASS production leads to failure of citrulline and aspartate to convert to argininosuccinate. This disruption in the urea cycle results in accumulation of ammonia from waste nitrogen, resulting in potentially life-threatening neurologic sequelae.

In the United States and Europe, routine newborn screening includes evaluation for distal urea cycle disorders, including citrullinemia and argininosuccinic acidemia. Diagnosis is confirmed by plasma amino acid levels, followed by ASS1 gene sequencing or enzymatic analysis. Children with CTLN1 receive maintenance treatment with L-arginine, sodium phenylbutyrate and strict protein-restricted diet in order to stop accumulation of ammonia, promote anabolism and prevent essential amino acid deficiencies. During intercurrent illness, emergency management with IV hydration, protein-restricted calories, IV arginine and nitrogen scavengers (sodium phenylacetate and sodium benzoate) are required to prevent hyperammonemia and neurologic damage. L-carnitine is also provided to prevent systemic hypocarnitinenia which may result from the use of acylating agents like sodium benzoate. If the hyperammonemia is severe, dialysis is required. Definitive long-term management may include liver transplantation and studies have shown promising results for survival and neurologic outcome.

Due to the devastating effects of recurrent hyperammonemia during times of stress, clinicians are often hyperaware of metabolic crisis in children with urea cycle disorders. When these children present with vomiting, a clinician’s first priority is to measure the ammonia level and evaluate for neurologic derangements. The patient must be assessed for acute infection and receive appropriate emergency care. However, age-appropriate common etiologies of vomiting should not be ignored given life-threatening consequences of persistent catabolism. The differential diagnosis for an infant with vomiting includes inborn errors of metabolism, as well as allergic, endocrinologic, infectious and structural causes, including HPS (Table 1). HPS has typical symptom-onset at 2-12 weeks of age with an estimated prevalence of 1-2 cases per 1000 infants and a 4:1 male predominance; however, prevalence may vary by maternal race/ethnicity and other complex epidemiologic factors.

In our 1-month-old male patient with CTLN1, early identification of pyloric stenosis led to a successful outcome with prevention of hyperammonemia due to vomiting and subsequent catabolism. There are a few points to note about our patient with regards to HPS. First, patients with HPS may develop jaundice and elevated bilirubin, a condition called icteropyloric syndrome that may have genetic correlates to Gilbert syndrome. Elevated total bilirubin in

Table 1. Etiologies of recurrent vomiting in infancy.

<table>
<thead>
<tr>
<th>Endocrine</th>
<th>Gastro-intestinal (non-obstructive)</th>
<th>Inborn errors of metabolism</th>
<th>Infection</th>
<th>Neurologic</th>
<th>Obstruction</th>
<th>Renal</th>
<th>Toxins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital adrenal hyperplasia</td>
<td>Gastro-esophageal reflux</td>
<td>Fatty acid oxidation defects</td>
<td>Hepatitis</td>
<td>Brain tumor</td>
<td>Esophageal/intestinal atresia</td>
<td>Obstruction</td>
<td>Ingestion</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>Milk-protein allergy/enteritis</td>
<td>Inborn errors of carbohydrate metabolism</td>
<td>Meningitis/encephalitis</td>
<td>Head injury/child abuse</td>
<td>Hirschsprung disease</td>
<td>Uremia</td>
<td></td>
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<tr>
<td>Necrotizing enterocolitis</td>
<td>Organic acidemias</td>
<td>Otitis media</td>
<td>Hydrocephalus</td>
<td>Incarcerated hernia</td>
<td>Urinary tract infection/pyelonephritis</td>
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<tr>
<td>Overfeeding</td>
<td>Urea cycle disorders</td>
<td>Pneumonia</td>
<td>Intestinal malrotation +/- volvulus</td>
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<tr>
<td>Sepsis</td>
<td>Intussusception</td>
<td>Pyloric stenosis</td>
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Figure 1. A) Ultrasound images in this patient show a pyloric muscle length of 20 mm, and B) thickness of 5 mm consistent with the diagnosis of hypertrophic pyloric stenosis. During the dynamic study, no passage of fluid through the pyloric channel was seen.
our patient may have provided an earlier clue to HPS; however, there was predominance of direct bilirubin and HPS is more commonly associated with indirect hyperbilirubinemia. Second, our patient had a nasogastric tube at home that had been accidentally removed prior to onset of sustained emesis. Therefore, the nasogastric tube may have been inadvertently placed in a post-pyloric position, thereby delaying clinically significant emesis. Third, although patients with HPS are thought to present with significant hypokalemic hypochloremic metabolic alkalosis, growing studies reveal that the alkalosis and electrolyte derangements may not be as prevalent. On pre-operative admission, our patient was mildly alkalotic on venous blood gas with elevated bicarbonate level, but with normal chloride and potassium levels.

Finally, our patient was on 500 mg/kg/day of L-arginine for CTLN1 treatment, which may have also delayed diagnosis. L-arginine is converted into nitric oxide (NO) by means of neuronal nitric oxide synthase (NOS) in the gastrointestinal system, and NO is an inhibitory neurotransmitter that facilitates multiple gastrointestinal functions. Defects in neuronal NOS have been associated with multiple enteric neuropathies, and decreases in serum NO and tissue expression of neuronal NOS have been observed in patients with HPS. Therefore, exogenous L-arginine supplementation in our patient for management of CTLN1 may have slowed the development of HPS by increasing pyloric NO.

A review of the literature reveals only one prior case report of an infant who was diagnosed with citrullinemia after presenting with persistent vomiting and hyperammonemia, despite operative correction of pyloric stenosis. Details of this case are not available to confirm hypertrophy of the pylorus at surgery. However it is interesting to speculate a deficiency of NO related to low arginine levels as a possible explanation for the presenting pyloric stenosis in the previously reported case.

Conclusions

We present an unusual case of a male infant with CTLN1 and concomitant pyloric stenosis, who was born to non-consanguineous parents of different ethnicity. To our knowledge, this is the second documented case of pyloric stenosis in a patient with urea cycle disorder in the literature, and the first case where the diagnosis of HPS was confirmed with prior knowledge of a diagnosis of CTLN1. Increased awareness of common age-appropriate etiologies of vomiting in children with metabolic disorders may lead to earlier intervention and prevent significant morbidity and mortality.

References