Molecular Genetics and Metabolism xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Acute liver failure in neonates with undiagnosed hereditary fructose intolerance due to exposure from widely available infant formulas

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ARTICLE INFO

Keywords:
Hereditary fructose intolerance
Acute liver failure
Neonates
Infant formula
Diet

ABSTRACT

Hereditary fructose intolerance (HFI) is an autosomal recessive disorder caused by aldolase B (ADOLB) deficiency resulting in an inability to metabolize fructose. The toxic accumulation of intermediate fructose-1-phosphate causes multiple metabolic disturbances, including postprandial hypoglycemia, lactic acidosis, electrolyte disturbance, and liver/kidney dysfunction. The clinical presentation varies depending on the age of exposure and the load of fructose. Some common infant formulas contain fructose in various forms, such as sucrose, a disaccharide of fructose and glucose. Exposure to formula containing fructogenic compounds is an important, but often overlooked trigger for severe metabolic disturbances in HFI. Here we report four neonates with undiagnosed HFI, all caused by the common, homozygous mutation c.448G > C (p.A150P) in *ADOLB*, who developed life-threatening acute liver failure due to fructose-containing formulas. These cases underscore the importance of dietary history and consideration of HFI in cases of neonatal or infantile acute liver failure for prompt diagnosis and treatment of HFI.

1. Introduction

Hereditary fructose intolerance (HFI) (MIM 229600) is an autosomal recessive disorder caused by biallelic mutations in *ALDOB*, resulting in aldolase B deficiency. Individuals with HFI are unable to metabolize fructose, which leads to a toxic accumulation of fructose-1-phosphate (F-1-P) [1]. Excess F-1-P inhibits gluconeogenesis, glycogenolysis, and glycolysis, with resultant hypoglycemia, lactic acidosis, electrolyte disturbances, and cell toxicity to liver and kidney [1,2]. Clinical symptoms include nausea, vomiting, abdominal pain, and failure to thrive. If not recognized early, untreated HFI can lead to severe hepatic and renal dysfunction, seizures, coma and death [3].

Fructose is a naturally-occurring monosaccharide in fruits, honey and many vegetables. The classic presentation of HFI as an infant who presents around 6-months of life when fructose-containing foods, such as fruit, are first introduced into the diet [1]. However, any fructose source can precipitate symptoms. Sucrose and sorbitol are metabolized to fructose by hydrolysis and hepatic sorbitol dehydrogenase respectively [4,5]. Sucrose, sorbitol and many other fructogenic sweeteners are added to many processed foods for sweetness, including infant formula and over-the-counter (OTC) liquid medications [6,7], including widely available liquid preparations of acetaminophen, ibuprofen, and common cough syrups.

HFI is estimated to occur in 1 in 20,000 live births. Variable age of onset and severity of symptoms depends on when and how much fructose is introduced [1,2]. The relatively recent introduction of

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https://doi.org/10.1016/j.ymgme.2018.02.016
Received 22 December 2017; Received in revised form 23 February 2018; Accepted 23 February 2018

fructose and its antecedents to widely available commercial infant formulas has resulted in an alteration to the natural history of HFI and likely under-recognition of untreated HFI in neonates, with acute liver failure and potentially catastrophic consequences [3,8]. Yet, to our knowledge, this case series of four neonates is the largest report of HFI presenting with acute liver failure (ALF) after exposure to common infant formulas and emphasizes that HFI must be included on the differential diagnosis for acute neonatal or infantile hepatic failure.

2. Clinical summary

Here we present four cases of neonatal and early infantile acute liver failure (ALF) associated with multi-organ failure induced by sucrose-containing common infant formula in patients with undiagnosed HFI. All patients were appropriately grown, born at term after uncomplicated pregnancies and deliveries, and discharged within the first week of life. There was no known consanguinity. One patient had a family history of an older brother who died at day of life (DOL) 28 after a similar illness, though specific diagnosis was not known. Another patient had a maternal half-sister who required liver transplant for liver failure of unknown cause. Careful dietary history was obtained in all infants, though fructose exposure was unclear in two of the 4 cases due to unreliable history or unclear ingredient labeling, which delayed diagnosis. In all cases, newborn screen was normal and tyrosinemia type 1 was excluded based on negative urine succinylacetone (SA). Diagnosis was confirmed by *ALDOB* gene sequencing. All infants were homozygous for the common c.448G > C (p.A150P) pathogenic variant.

2.1. Case 1

A full term male first presented at 6 weeks of age for failure to thrive [weight 2.85 kg (< 1st centile)], and frequent emesis. He had been fed by Gerber® Good Start® Soy (containing sucrose) since 2 weeks of age. Initial chemistries showed mild elevation of transaminases. He continued on home formula in hospital and developed hematemesis and hematochezia secondary to a severe coagulopathy and acute liver failure, complicated by acute renal insufficiency and respiratory failure requiring mechanical ventilation. He had a high anion gap metabolic acidosis, lactic acidosis, hypoglycemia and direct hyperbilirubinemia (Table 1). Physical examination showed a palpable liver 2.5 cm below the costal margin. Based on his clinical presentation and the dietary exposure to the high concentration of sucrose in Gerber Good Start Soy, HFI was suspected. He was switched to fructose-free formula upon transferring to the ICU. By day 4, his PT/APTT/INR normalized; at day 12, transaminases were normal. Thin layer chromatography analysis of a residual urine specimen collected at the time of admission identified large amounts of fructose. Of note, as part of his initial work up, transferrin isoform was ordered for screening congenital disorders of glycosylation, which showed abnormality as seen in CDG type I, but normalized after his liver function recovered. The patient remained hospitalized for 2 weeks and experienced feeding difficulty requiring NG tube feeding for about 4 months after discharge. At 2 years of age, he has normal growth and development with good dietary compliance.

2.2. Case 2

A Caucasian male infant presented to the emergency room due to emesis and ecchymosis at DOL 16. He had begun using Similac Sensitive ("sugar"-sucrose containing formula) on DOL7. Laboratory evaluation revealed hypoglycemia, acute transaminitis, coagulopathy, indirect hyperbilirubinemia and lactic acidosis with normal bicarbonate (HCO_3 23 mmol/L) (Table 1). Physical examination showed two bruises on his lower extremities and no hepatomegaly. After admission, his liver function quickly improved while exclusively on intravenous fluids. Family history was significant for the death of an older brother at 28 days of life after a similar illness. Liver biopsy in the older brother suggested an "unknown genetic disorder similar to galactosemia". Given the possibility of galactosemia in the deceased brother, he was started on Isomil, a soy-based formula initially. Surprisingly, his coagulopathy worsened. It was noted that Isomil contains 10% sucrose, and HFI was suspected. He was immediately switched to a fructose/sucrose-free formula and recovered quickly and was discharged 2 weeks later without complications.

2.3. Case 3

A full term African-American girl was admitted at DOL 38 for the evaluation of a self-resolving episode of apparently acholic stools between DOL 11 and 22. Her foster mother recalled that the patient had a faint yellowish skin tone on her inner thighs and abdomen during the time that she had the "white stools". In retrospect, the episode of apparently acholic stools coincided with a change to Similac Sensitive ("sugar"-sucrose containing formula). Family history was significant for a sister (paternity not established) who had a liver transplant at age 4 years for presumed biliary atresia, though the diagnosis could not be confirmed. Because of the social circumstances, no addition information is available regarding this sibling.

Physical examination showed a palpable liver 3 cm below the costal margin At the time of admission her diet was reported as Similac Advance (contains lactose but no fructogenic sugars) with no known exposure to fructose or solid foods, so HFI was considered unlikely. She had positive urine reducing substances, so was placed on a galactose free formula Isomil Advance (contains sucrose, labeled "sugar") while waiting repeat GALT enzyme activity. During hospitalization, she had several episodes of pre-prandial hypoglycemia (blood glucose as low as 37 mg/dL, usually 2 to 3 h after the last feeding), with low serum insulin on several occasions. Liver disease progressed (Table 1); liver biopsy was markedly abnormal, but non-specific without evidence of bile duct paucity. Repeat GALT activity and red blood cell gal-1-phosphate were normal, so the galactose free diet was stopped and she was started on Pregestimil (sucrose and fructose free). Her symptoms immediately began to improve on the fructose free diet, with normalization of AST, ALT, and PT/APTT within 5 days, and normalization of bilirubin within one week. Rapid whole exome sequencing under an IRB approved research protocol in a clinical laboratory showed homozygosity for c.448G > C (p.A150P) variant in *ADOLB*. No other deleterious variants were identified. She remains well with normal growth and development at 2 years of age.

2.4. Case 4

A term male presented with emesis on DOL9. He was exclusively fed with Similac Sensitive (contains sucrose, but only labeled "sugar") since birth. Laboratory evaluation showed severe coagulopathy, transaminitis and anion gap acidosis. Lactate and ammonia were normal. Given his critical status, he was made NPO and rapidly improved with intravenous dextrose and blood products support. Urine culture grew pan-sensitive enterococcus; and infectious etiology was considered most likely. A thorough evaluation was unrevealing and the patient was discharged at three weeks of age with home diet of Similac Sensitive.

One week later, carbohydrate deficient transferrin (CDT) resulted with an abnormal pattern consistent with CDG-type I. When the medical team called the family with this result, the mother reported the patient was lethargic, pale and feeding poorly. He was thus re-admitted, now at age 4-weeks and with severe lactic acidosis and coagulopathy (Table 1). Again, coagulopathy and acidosis rapidly improved with blood products and IV-dextrose. Liver biopsy showed severe macrovesicular steatosis (90%), pericellular fibrosis and bridging fibrosis. Given the rapid improvement with only IV support and positive CDT, HFI was considered and *ALDOB* sequencing confirmed the diagnosis. Confirming the presence of sucrose in the Similac Sensitive required a call to the formula manufacturer to discover "sugar" was composed of a