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Neonatal Hereditary Fructose Intolerance: Diagnostic Misconceptions and the Role of Genomic Sequencing

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Abstract: Hereditary fructose intolerance (HFI) is a rare inborn error of metabolism due to deficiency of the enzyme aldolase B, preventing metabolism of fructose. Patients remain asymptomatic until exposed to fructose, sucrose, or sorbitol. HFI presenting as acute liver failure in the neonatal period is rare due to lack of exposure as breast milk and infant formulas are considered to be fructose free. Diagnosis can be delayed due to vague symptoms and lack of specific biomarkers. Recent advances in genetic testing have led to rapid diagnosis and favorable outcomes. We present the case of a formula-fed neonate who presented with acute liver failure where definitive diagnosis of HFI was made using expedited whole exome sequencing. Through this communication, we aim to bring attention to neonatal presentations of HFI from exposure to fructose in infant formulas and also highlight advances in rapid turnaround genomic testing in diagnosis.

Key Words: hereditary fructose intolerance, neonatal liver failure, whole exome sequencing

What Is Known

- Individuals with hereditary fructose intolerance (HFI) remain asymptomatic until exposed to fructose, sucrose, or sorbitol. Current medical training emphasizes clinical presentation at time of weaning from breast-feeding and initiation of table foods.
- Diagnosis of HFI in neonates is delayed due to absence of specific biomarkers and is established through genetic testing or liver biopsy.

What Is New

- Over-the-counter and prescribed infant formulas labeling of fructose content can be misleading for patients and providers.
- Nontargeted genetic testing, like whole exome sequencing, now allows for more rapid diagnosis of HFI in neonates, leading to earlier intervention and improved outcomes.

INTRODUCTION

Hereditary fructose intolerance (HFI) is a rare disease of metabolism typically seen among young children after exposure to fructose, sucrose, or sorbitol. An autosomal recessive disease, HFI stems from a genetic defect in the gene *ALDOB*, located on chromosome 9q31.1, resulting in deficiency in fructose bisphosphate aldolase B (or aldolase B for short), an enzyme critical in the pathway for metabolism of fructose (1). Without aldolase B, there is a buildup of the substrate fructose-1-phosphate (F1P) within the liver and kidney. Consequently, F1P cannot be cleaved into phosphotrioses resulting in inadequate glycolysis and gluconeogenesis. Because phosphate is trapped within F1P, phosphate pool depletion also occurs and cannot act as a substrate for hepatic glycogen phosphorylase leading to impaired glycogenolysis. In addition, F1P appears to have hepatotoxic and nephrotoxic effect at the cellular level resulting in intracellular precipitates, causing further organ damage. This clinically results in hypoglycemia, lethargy, and lactic acidosis. Significant liver dysfunction may occur leading to acute liver failure (ALF) and potential need for liver transplantation. Current medical training emphasizes typical presentation of HFI around the time of introduction of table foods containing fructose, sucrose, or sorbitol. However, recent addition of these sugars into over-the-counter and prescribed formulas seems to have resulted in an increasing number of neonatal presentations. Li et al (2) published 4 cases in formula-fed newborns, highlighting the effect of these additives in early clinical manifestations of HFI. In all 4 cases, patients presented with ALF and elevated serum alanine aminotransferase and aspartate aminotransferase levels. All 4 patients were genetically confirmed to have a homozygous variant of HFI, and all 4 cases clinically improved with transition to a formula free of fructose.

CASE REPORT

A 17-day-old infant who was referred to our emergency department with lethargy, low-grade fever, and poor feeding. He was noted to be in ALF with international normalized ratio of 11, elevated total bilirubin, aspartate aminotransferase, and alanine aminotransferase. He was also noted to have hypoglycemia, lactic acidosis but normal ammonia. He was born at full-term gestation, antenatal scans were normal, and there were no perinatal risk factors for infection. No history of hypoglycemic episodes in the immediate newborn period. There was no family history of metabolic or genetic disorders. He had 2 older siblings who were in good health. His physical exam was normal with no organomegaly or signs of chronic liver disease. Since birth, he was fed a routine over-the-counter infant formula. A work-up to rule out infection, hemophagocytic lymphohistiocytosis, and metabolic disorders as etiology for his ALF was inconclusive. His newborn screening was normal, decreasing the risk of galactosemia, fatty acid oxidation defects, early onset organic acidemias, and tyrosinemia. Urine organic acids testing was suggestive of markedly elevated alpha-ketoglutarate concerning for alpha-ketoglutarate

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dehydrogenase deficiency along with nonspecific elevation of lactic acid, pyruvic acid, para-hydroxyphenyl lactate, and para-hydroxyphenylpyruvate suggestive of acute liver dysfunction but not specific for any etiology. His infant formula was changed at the time of admission to a formula that was available in the hospital. He was empirically treated with acyclovir and intravenous antibiotics as per protocol for suspected neonatal sepsis. Blood, urine, and cerebral spinal fluid cultures were negative for bacterial and viral etiologies. Liver dysfunction improved slowly with over 5 days with normalization of liver synthetic function and resolution of lactic acidosis and hypoglycemia. The patient was discharged with follow-up arranged in a week.

At his follow-up appointment, he was again found to have evidence of recurring liver synthetic dysfunction with hypoglycemia and lactic acidosis.

MOLECULAR INVESTIGATION AND RESULTS

Expedited whole exome sequencing (WES) test was ordered with a suspicion for mitochondrial disorder. WES results, which were made available in 5 days, established the diagnosis of HFI. The neonate was found to have 2 heterozygous, pathogenic alterations to the *ALDOB* gene (maternal nucleotide c.448G>C resulting in substitution of a proline for an alanine or p.Ala150Pro and paternal c.324+2T>A) (3). Infant formula was immediately changed to a fructose-free formula with rapid resolution of lactic acidosis and normalization of liver synthetic function.

DISCUSSION

HFI is a disease typically presenting in infancy when a breastfed or formula-fed patient begins to transition to a diet containing fructose and sucrose. However, recent literature has revealed introduction of additives into over-the-counter and prescribed formulas, most notably fructose and sucrose compounds, which may be leading to earlier presentation of disease within neonates. In our review of literature, it is difficult to pinpoint exactly when these were introduced into formulas but, as early as 2005, there had been a consolidated effort from international pediatric societies warning of their incorporation (4). Numerous studies have acknowledged the difficulty in diagnosing HFI in neonates due to provider assumption or training emphasizing the lack of exposure to fructose/sucrose in early life (5,6). Typical presenting signs and symptoms (nausea, vomiting, abdominal distress, and failure to thrive) and laboratory abnormalities (lactic acidemia, hypoglycemia, and electrolyte abnormalities) are frequently seen in other, more prevalent disease processes during this time period, often leading to late or incorrect initial diagnosis. Currently, there are no specific biomarkers to definitively diagnose HFI. A detailed feeding history may reveal a corresponding pattern of clinical deterioration and improvement, but this correlation is typically more obvious in older children. In our case, only on retrospective review of our patient's feeding history, did we realize that episodes of liver dysfunction correlated with exposure to infant formulas with fructo-oligosaccharides and galacto-oligosaccharides (Fig. 1).

The dramatic and rapid clinical changes caused by these sugar additives in our patient highlights a problem posed by vague and misleading product labeling, namely the inability to easily identify the presence of these additives in formulas. A 2015 study attempted to determine sugar content, via gas chromatography, in commonly found neonate and infant formulas and foods (7). Results showed many formulas contained large amounts of sugar product despite having labels stating that was little or no fructose within them. Formulas with the highest sugar content were typically lactose-free formulas. Some formula ingredients only defined the presence of sugar but did not clarify which types (Table 1). Vague labeling of some compounds only creates more confusion. Due to the need to determine a fructose-/sucrose-free formula for treatment of our patient, we evaluated several brands of formulas for sugar additives but, as

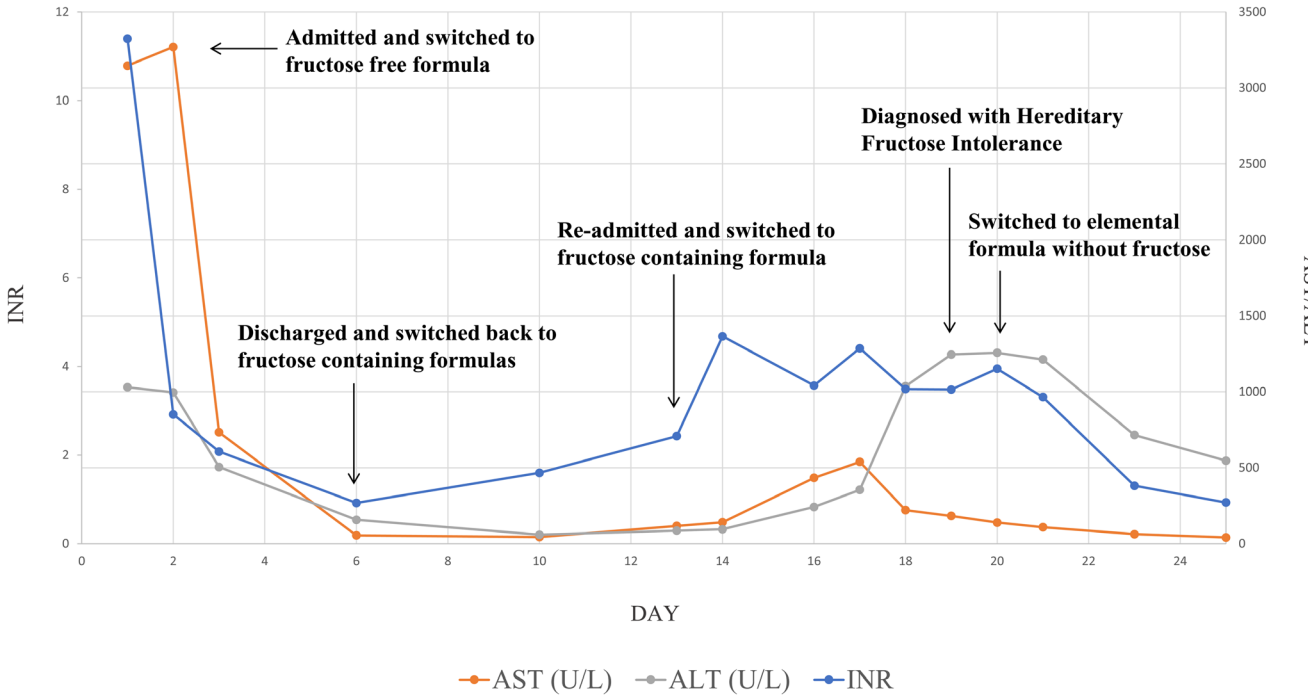

FIGURE 1. INR, AST, and ALT during formula changes. ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio.

TABLE 1. Additives within over-the-counter and prescribed infant formulas

Formula	Fructo-oligosaccharide	Galacto-oligosaccharide	Lactose	Corn syrup solid/ corn maltodextrin	Other
Abbott Elecare				+	
Enfamil A.R.		+	+		
Enfamil Gentlease			+	+	
Enfamil Infant		+	+		
Gerber Good Start		+	+		
Gerber Good Start Soothe			+	+	
Mead Johnson Nutramigen				+	
Mead Johnson PurAmino				+	
Nutricia Neocate				+	
Parent's Choice	+			+	
Parent's Choice Advantage	+		+		
Parent's Choice Gentle				+	
Parent's Choice Organic	+			+	
Similac Advance		+			
Similac Alimentum					+*
Similac For Spit-Up		+		+	
Similac Neosure			+	+	
Similac PM 60/40			+		
Similac Pro		+	+		
Similac Pro Advance	+		+		
Similac Pro Sensitive	+				
Similac Pro-Total Comfort	+			+	
Similac Sensitive		+			
Similac Soy Isomil	+			+	
Similac Special Care 20			+	+	
Similac Total Comfort		+		+	
Up&Up Advantage	+		+		
Up&Up Gentle				+	
Up&Up Infant	+	+	+		
Up&Up Sensitivity	+			+	

A.R. = anti-regurgitation.
*Ingredient listed as "sugar."

previously mentioned, found the process challenging for some formulas due to the vague descriptions present on ingredient labels. After further research, using resources from the American Society of Parental and Enteral Nutrition (ASPEN), we created a consolidated table (Table 1) listing the sugar additives found in commonly used over-the-counter and prescribed formulas (8). We share this resource with the hope that it may be helpful in the clinical treatment of future **of** infants with HFI.

Detection of biallelic, pathogenic variants of *ALDOB* on molecular genetic testing or deficient hepatic fructose 1-phosphate aldolase activity on liver biopsy is required for definitive diagnosis (9). Due to size concerns in a neonate, molecular testing is preferred over liver biopsy to avoid potential adverse effects associated with a liver biopsy. A lack of definitive biomarkers to diagnose HFI and nonspecific biomarkers that indicate liver dysfunction, often times lead to misdiagnosis (10–12). In our case, definitive diagnosis was made with WES in 5 days, which allowed prompt, targeted therapy. Turnaround time in standard WES, a previous downside to this method of diagnosis, has dropped dramatically with recent advances in molecular genetic testing (13,14). In fact, there have been numerous studies that have utilized WES with rapid turnaround times ranging from less than 24 hours to 8 days. We believe that advances in genetic testing, especially rapid WES, can decrease nonspecific and potentially harmful testing, initiate treatment sooner and ultimately improve outcomes. In fact, children's hospitals have begun to implement rapid genomic testing projects within their critical care units to identify children in which diagnosis of a genetic disease may alter crucial clinical management (15,16). In addition to improving outcomes, WES cost analysis has been well studied and found that early use, in particular, can decrease costs compared with the standard diagnostic pathway (17,18). Even as the technology for WES improves, new genetic tools have emerged such as whole genome sequencing and next generation sequencing, which can not only examine exons but introns, short copy variants, single-nucleotide variants, and mitochondrial variants as well as provide more targeted, precise diagnostic tools (19,20).

Physicians should be trained to consider HFI in the differential diagnosis of ALF in neonates. Our case and available literature support the use of genomic testing with rapid turnaround times in making definitive diagnosis in neonates with severe disease. Finally, labeling of infant formulas need to be transparent to identify fructose and sucrose additives.

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J.L. drafted and edited the article. J.A. and N.K. edited and supervised the article.

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