Unmasking Hereditary Fructose intolerance through growth chart in an infant

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ABSTRACT

Hereditary Fructose Intolerance (HFI) is a rare autosomal recessive disorder caused by a deficiency of aldolase B, an enzyme essential for fructose metabolism. It often presents in infancy after the introduction of complementary feeding and is frequently underdiagnosed due to nonspecific symptoms. We report a case of a 7-month-old male infant with recurrent vomiting, poor feeding, and failure to thrive. Laboratory investigations revealed elevated transaminases, hypertriglyceridemia, low HDL, and hyperuricemia, while abdominal ultrasound showed hepatomegaly with fatty changes. Clinical suspicion of a metabolic liver disorder prompted genetic testing, which confirmed HFI through identification of a homozygous pathogenic variant (c.469C>T, p.Gln157Ter) in the *ALDOB* gene. Elimination of fructose, sucrose, and sorbitol from the diet led to rapid clinical improvement, including cessation of vomiting within 24 hours and significant weight gain. This case underscores the importance of growth chart monitoring and detailed dietary history in suspecting HFI, especially in resource limited settings

KEY WORDS

Hereditary Fructose Intolerance, case report, infant, growth charts.

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INTRODUCTION

Hereditary Fructose Intolerance (HFI) is a rare autosomal recessive metabolic disorder caused by mutations in the ALDOB gene, leading to a deficiency of aldolase B—an essential enzyme in fructose metabolism.1 In the absence of this enzyme, ingestion of fructose, sucrose, or sorbitol results in the toxic accumulation of fructose-1-phosphate, which disrupts hepatic and renal metabolism.1 HFI typically presents after the introduction of complementary foods and may manifest with jaundice, hepatomegaly, vomiting, lethargy, irritability, convulsions, and failure to thrive.1 The estimated incidence of HFI is 1 in 20,000 live births, making it an uncommon but important consideration in pediatric practice.2

Despite being a treatable condition, HFI often goes undiagnosed or misdiagnosed due to the non-specific nature of early symptoms, lack of specific biomarkers, and limited access to genetic testing in low-resource settings. In busy outpatient departments, HFI is often misdiagnosed as food allergies, lactose intolerance, or other nutritional issues.3

We report a case of a 7-month-old infant who presented with recurrent vomiting and failure to thrive, initially managed symptomatically without definitive diagnosis. This report highlights the role of growth chart assessment in the early detection of rare metabolic conditions and the importance of considering HFI in infants with unexplained gastrointestinal and hepatic symptoms. We hereby report this as per CARE guidelines.4

CASE PRESENTATION:

A 7-month-old male infant presented to the outpatient department with a one-week history of multiple episodes of vomiting and poor feeding. The child had a history of recurrent vomiting since early infancy, for which he had been evaluated multiple times at a local hospital and managed conservatively without definitive diagnosis. He was passing urine and stools normally, and there was no history of fever, or other systemic symptoms.

Weaning was started at 1 month of age with lito (a locally prepared cereal-based food) mixed with honey due to lack of awareness regarding exclusive breastfeeding practice. Since then, the infant had continued to receive home-based complementary foods along with breastfeeding. Birth weight was 2.5 kg (5th centile) and development was age appropriate.

There was no history of consanguinity. The first sibling had a history of failure to thrive, with no improvement despite a three-month admission to a nutritional rehabilitation center. She died at three years of age following a sudden deterioration, the cause of which remained unknown. The second sibling, a 7-year-old girl, was healthy and had no such history. The index case was appropriately immunized as per the Expanded Programme on Immunization (EPI) schedule of Nepal up to 14 weeks of age.

Physical Examination

On examination, the child was irritable but responsive. There was no pallor, icterus, or clinical dehydration. Anterior fontanelle was open and at level. On anthropometric examination, the body weight, length and occipitofrontal circumference was below 5th centile. These findings confirmed failure to thrive.

Abdominal examination revealed a soft, non-tender abdomen and liver palpable below the right costal margin.The cardiovascular, respiratory, or neurological examinations were within normal physiological limits.

On examination, the child was irritable but responsive. There were no signs of pallor, icterus, or dehydration. The anterior fontanelle was open and at level. On anthropometric assessment body weight, length, and occipitofrontal circumference were all below the 5th percentile for age, consistent with failure to thrive.

Abdominal examination demonstrated a soft, non-tender abdomen, with the liver palpable just below the right costal margin, suggestive of mild hepatomegaly. The cardiovascular, respiratory, and neurological examinations were within normal physiological limits.

Investigations

Initial laboratory evaluation showed a complete blood count (CBC) within normal limits, with a hemoglobin level of 12 g/dL. Random blood glucose (RBS) was measured at 83 mg/dL. Liver function tests (LFTs) revealed elevated transaminases, with ALT at 147 U/L and AST at 261 U/L, while alkaline phosphatase was 279 IU/L. Total bilirubin was slightly elevated at 2.0 mg/dL, with a conjugated bilirubin level of 0.3 mg/dL. Thyroid function tests (TFTs) were normal, with a thyroid-stimulating hormone (TSH) level of 2.61 µIU/mL. Renal function tests (RFTs) were within normal limits. The serum triglyceride was 244 mg/dL, showed hypertriglyceridemia, low HDL cholesterol at 28 mg/dL, and mildly elevated serum uric acid at 6.0 mg/dL. Coagulation profile was normal, with a prothrombin time (PT) of 12 seconds and international normalized ratio (INR) of 1.09.

Ultrasound of the abdomen showed hepatomegaly with fatty changes, raising suspicion of metabolic liver disease.

The clinical picture of failure to thrive with hepatomegaly, steatosis, and dyslipidemia, in the absence of infectious or structural causes, raised suspicion of an inborn error of metabolism, with a clinical suspicion of hereditary fructose

intolerance (HFI). Genetic testing (clinical exome analysis) confirmed the diagnosis of hereditary fructose intolerance, with a homozygous pathogenic variant c.469C>T (p.Gln157Ter) in the ALDOB gene.

Management and Follow-Up

A fructose-, sucrose-, and sorbitol-free elimination diet was initiated, comprising breast milk, moong dal jaulo (green gram and rice porridge), and homemade lito (prepared without added sugars). Within 24 hours of dietary modification, vomiting ceased. The child showed an 800-gram weight gain over one month, indicating a marked clinical improvement.

At a 6-month follow-up, liver enzyme levels had normalized (AST: 49 U/L, ALT: 30 U/L), and the child's weight had improved from below -3 SD to -2 SD on the WHO growth chart.

DISCUSSION:

We reported a case of a child with HFI who presented with persistent vomiting, initially misattributed to gastroesophageal reflux and milk protein allergy; definitive diagnosis was delayed until targeted gene testing of the ALDOB gene was done confirming the diagnosis.

HFI is a rare but serious metabolic disorder that can present subtly in infancy and is often under recognized in routine outpatient practice. Deficiency of fructose-1,6-bisphosphate aldolase is a severe condition of infants that appears with the ingestion of fructose-containing food and is caused by a deficiency of fructose aldolase B activity in the liver, kidney, and intestine. The enzyme catalyzes the hydrolysis of fructose- 1,6-bisphosphate into triose phosphate and glyceraldehyde phosphate. The same enzyme also hydrolyzes fructose-1-phosphate. Deficiency of this enzyme activity causes a rapid accumulation of fructose-1-phosphate and initiates severe toxic symptoms when exposed to fructose.1

Patients with HFI are asymptomatic until fructose or sucrose is ingested. Symptoms may occur early in life, soon after birth if foods or formulas containing these sugars are introduced into the diet.1 In our case, the infant exhibited nonspecific symptoms after complementary feeding was started. This led to multiple healthcare encounters without a definitive diagnosis. These clinical features are common and often initially attributed to benign conditions such as viral gastroenteritis, lactose intolerance, or inadequate feeding practices.5 However, the persistence of symptoms and anthropometric faltering raised concern for a chronic underlying etiology. The elevated liver enzymes, hepatomegaly with fatty infiltration on ultrasound, and dyslipidemia with hyperuricemia were all consistent with metabolic liver disease.

Suspicion of the enzyme deficiency in HFI is fostered by the presence of a reducing substance in the urine during an episode. The fructose challenge, although an effective method of diagnosis, causes a rapid fall, first of serum phosphate and then of blood glucose, and a subsequent increase in uric acid and magnesium. Because of high risks to the patient who can become acutely ill after the oral tolerance test, it should not be performed.1 These test was not be performed in our case, as the patient visited multiple outpatient departments and was not admitted. The growth chart is often the first visible indicator of chronic disease in the outpatient, and its consistent documentation can prompt earlier, more targeted evaluation.6 The family history of unexplained sibling death with failure to thrive also supports the genetic basis of the diagnosis.

The diagnosis was ultimately confirmed through clinical exome sequencing, which identified a homozygous pathogenic variant (c.469C>T, p.Gln157Ter) in the ALDOB gene, one of the known mutations associated with HFI. Due to its rarity, high cost and limited availability of genetic testing, many cases of HFI go unrecognized, leading to progressive liver injury, which can significantly increase morbidity and mortality.7

Treatment consists of the complete elimination of all sources of sucrose, fructose, and sorbitol from the diet. It may be difficult because these sugars are widely used additives, found even in most medicinal preparations. With treatment, liver and kidney dysfunction improves, and catch-up in growth is common. Intellectual development is usually unimpaired. As the patient matures, symptoms become milder even after fructose ingestion; the long-term prognosis is good.1 In our case, the patient had normalization of liver enzymes and substantial improvement in growth parameters. Patients with HFI and their families often face difficulties in navigating daily life due to poor food labeling, limited awareness of the condition among healthcare providers, and unclear guidance on which foods and medications are safe or harmful that complicate disease management.8

Only a limited number of cases have been documented in the literature. Solano et al. reported a 4-year-old girl with recurrent hypoglycemia and aversion to fruits, who was initially misdiagnosed despite extensive workups. She was ultimately diagnosed with HFI through gene panel testing, identifying biallelic pathogenic variants in the ALDOB gene. Her symptoms resolved with dietary fructose restriction.9 Lozzo et. al. reported another patient with unrecognized hereditary fructose intolerance in which chronic gastrointestinal complaints, low body weight, and unexplained food avoidance were addressed as manifestations of an eating disorder during adolescence.10

CONCLUSION:

HFI presents a significant diagnostic challenge, particularly in low-resource settings where genetic testing is not readily accessible. The successful identification and management of this case underscore the importance of clinical suspicion, careful growth monitoring, and detailed dietary history in guiding timely diagnosis and intervention.

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