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*Case Report*

# A Rare Cause of Hepatosteatosis in a Breast-Fed Infant: Hereditary Fructose Intolerance

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**Abstract** Hereditary fructose intolerance (HFI) is an autosomal recessive disease caused by a mutation in the *ALDOB* gene. Nausea, vomiting, abdominal pain, hypoglycaemia, hypertransaminasaemia and hepatosteatosis are observed after fructose intake. Symptoms usually occur after complementary feeding. Fructose is known to cause of non-alcoholic fatty liver disease (NAFLD). In studies of fructose-related hepatosteatosis have associated with obesity, dyslipidemia and insulin resistance, mostly as a result of high fructose intake. Although the pathogenesis of HFI is unclear, it is a rare cause of early-onset hepatosteatosis. Here, we report a 4-month-old infant with NAFLD who was diagnosed with HFI by detecting 'p.A105P and p.A175D compound heterozygous mutation' in the *ALDOB* gene. Our case was diagnosed with asymptomatic hepatomegaly and hepatosteatosis in the early period before complementary feeding. In this report, it was emphasized that HFI should be kept in mind in asymptomatic infants presenting with hepatosteatosis, even if they are breastfed.

**Key words** *ALDOB gene; Hepatosteatosis; Hereditary fructose intolerance*

## Introduction

Hereditary fructose intolerance (HFI) is an autosomal recessive disease caused by the mutation of *ALDOB* gene. The prevalence of the disease is 1:18000-1:31000, and the age of onset and severity of symptoms vary in relation to fructose consumption.[1] Although the disease is commonly diagnosed in infants around 6 months of age, acute liver failure (ALF) has been reported in the neonatal period when exposed to sucrose-containing formula.[2] However, some adult cases remain undiagnosed for many years due to voluntary avoidance of sweet foods.

HFI symptoms (vomiting, growth retardation, abdominal distension, jaundice, etc.) usually occur with the initiation of complementary feeding. In addition, metabolic changes such as hypoglycaemia, hyperuricaemia, metabolic acidosis, hypophosphataemia and hyperalaninaemia can be observed.[3] While diet regulation without fructose, sucrose and sorbitol with early diagnosis is associated with good prognosis, delayed diagnosis causes increased mortality due to liver and kidney failure.

It is known that fructose consumption causes fatty liver. Although the pathogenesis has not been clarified, hepatosteatosis can also be seen in HFI.[4] However, our case was only breast-fed and had no fructose consumption according to the information obtained from the parents. In this report, it was thought that hepatosteatosis may have started in the intrauterine period or that maternal fructose consumption may have an effect on hepatosteatosis in infancy.

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## Case Report

A four-month-old male patient was admitted to our clinic with hepatomegaly and moderate (grade 2) hepatosteatosis. In the past medical history; vaccines were age-appropriate (hepatitis B, BCG, Tetanus, Diphtheria, Pertussis, Haemophilus Influenzae type b, Pneumococcal Conjugate, Polio). Rotavirus vaccine was not administered. No supplement/drug use. The baby was exclusively breastfed up to 4 months and did not have any symptoms such as vomiting, poor feeding or weakness. When the maternal diet during pregnancy and breastfeeding was questioned, excessive fructose intake was not detected. In the family history, there were Turkish parents who were not consanguineous, but his uncle diagnosed with hepatosteatosis (unknown aetiology) at age of 25. On physical examination, body weight: 7700 gr (50-75 percentile), height: 64 cm (25-50 percentile), hepatomegaly 3-4 cm below the right costal margin. Other system examinations were normal.

In biochemical parameters, hypertransaminasemia [alanine aminotransferase (ALT): 107 U/L (0-45), aspartate aminotransferase (AST): 115 U/L (0-35)] and hyperuricaemia [uric acid: 8 mg/dL (2.6-7.2)] were detected. Complete blood count, coagulation parameters, ferritin, alpha fetoprotein, lipid profile, blood glucose and blood gas analysis were normal. Kidney function tests, electrolytes were in the normal range and no urinalysis abnormality. Abdominal ultrasonography revealed hepatomegaly and hepatosteatosis. [Liver is 99 mm (normal for age: 92 mm), the parenchymal echo was increased by grade 2]. Metabolic screening tests (tandem mass, urine-plasma amino acids, urine organic acids, lactate, ammonia), eye examination and echocardiography were normal.

After exclusion of other causes of hepatomegaly and hypertransaminasaemia, such as infectious/toxic/autoimmune, liver biopsy and genetic testing remained for further investigation. Whole exome sequencing (WES) was performed to identify possible rare genetic causes of infantile hepatosteatosis. Genomic DNA was extracted from peripheral blood of patient and WES was performed using the next generation sequencing method. All detected variants (pathogenic, likely pathogenic, and VUS) were evaluated using the QCI interpreter, ClinVar, VarSome, and 'in-silico' prediction programs based on the patient's clinical information. Variant classification was identified according to ACMG (American College of Medical Genetics) guidelines. The result of genetic analysis was reported as '*ALDOB* gene c.448 G>C (p.A105P) and c.524 C>A (p.A175D) compound heterozygous mutation'. These detected mutations are defined as pathogens in the ClinVar and HGMD databases.

Since the age-of-diagnosis of our patient was 6 months, it allowed us to regulate a diet without fructose, sucrose and sorbitol before complementary feeding. Therefore, he was followed up without symptoms such as hypoglycaemic attack and vomiting. Our patient is now 18 months old and his development is normal. In the follow-up of the asymptomatic patient, grade 1 hepatosteatosis and mild transaminase elevation (ALT: 70 U/L, AST: 65 U/L) were observed.

## Discussion

Nonalcoholic fatty liver disease (NAFLD) is a disease often associated with obesity and insulin resistance, characterised by >5% fat accumulation in the liver in the absence of alcohol intake. Although NAFLD is most common in adolescents, it is less frequently in under 10 years of age. Especially in infants and children younger than 3 years with fatty liver; genetic/metabolic, syndromic and systemic causes should be investigated such as mitochondrial hepatopathies, disorders of fatty acid metabolism, urea cycle and carbohydrate (HFI, galactosemia), tyrosinemia type 1, cystic fibrosis, Niemann-Pick diseases type C.[5]

Literature on fructose and NAFLD are often associated with dietary fructose intake. In studies on the role of fructose in the development of hepatosteatosis, it has been stated that the prosteatotic effect observed in hypercaloric fructose intake may possibly be related to weight gain. On the other hand, numerous studies clearly demonstrate that fructose has lipogenic effect. Fructose intake increases plasma triglyceride levels and high fructose diets contribute to the development of NAFLD by inducing hepatic de nova lipogenesis.[6]

Relevant to the pathogenesis of hepatosteatosis in HFI, an association between hepatic fat deposition and inhibition of AMP-activated protein kinase (AMPK) has been suggested. AMPK is a protein regulated by posttranslational modifications such as phosphorylation and competes with ATP. Fructose-1-phosphate accumulation due to aldolase B deficiency in HFI patients results in a decrease in free inorganic phosphate. This decrease in cellular inorganic phosphate reserve activates the enzyme AMP deaminase. AMP deaminase activation

may lead to decrease in fatty acids β-oxidation by inhibiting AMPK. In this way, fatty acids will accumulate in the liver as triglycerides and cause hepatosteatosis.[7]

In the literature, data about the effect of maternal fructose consumption during pregnancy on fetal intrauterine development and postnatal diseases are limited. In a study on pigs, increased of free fatty acid, uric acid and triglyceride levels was found with increased maternal fructose fetal exposure compared to the control group. The same study showed that increased fructose intake during pregnancy can change maternal metabolic functions and milk composition.[8] Also, in a study on fructose transmission during lactation, maternal high-fructose intake was shown that increased breast milk fructose concentrations.[9] Since hepatosteatosis was observed in our case although he was exclusively breastfed, maternal diet was questioned during intrauterine and lactation period before genetic analysis. Rare genetic causes of hepatosteatosis were evaluated due to lack of maternal excessive fructose consumption.

The diagnosis of HFI is based on metabolic disturbances and clinical findings following fructose, sucrose or sorbitol containing food intake. The fructose tolerance test is not recommended, because it could result life threatening adverse metabolic effects. In clinically suspected patients the diagnosis is confirmed by molecular analysis of *ALDOB* gene. Detection of aldolase B activity deficiency by liver biopsy is less preferred because it is an invasive procedure.[10] In our case, the diagnosis of HFI was determined by WES.

In conclusion, metabolic diseases should be considered in the aetiology of children with hepatosteatosis in infancy. In this manuscript, a breastfed infant who presented with hepatosteatosis and diagnosed to have HFI is reported. In this way, our patient had the chance to be treated before the onset of the catastrophic metabolic decompensation. Although symptoms usually occur with fructose intake in the diet, HFI should also be kept in mind in only-breastfed cases with hepatosteatosis in infancy.

## Conflict of Interest

The authors have indicated they have no potential conflicts of interest to disclose.

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