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CASE REPORT

A fructose-intolerant patient with acute liver injury: Not only the active ingredient, but also excipients matter

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Clinical Pearls

- **Unique Features of the Case:** The patient's cholestatic liver injury was caused by undiagnosed hereditary fructose intolerance (aldolase B mutation). Symptoms worsened by fructose-containing medications resolved after switching to fructose-free treatment.
- **Primary Lesson for Clinicians:** Clinicians should consider hereditary fructose intolerance in unexplained liver injury, especially with a lifelong aversion to sweets or fruit. A thorough review of both diet and medications for hidden fructose excipients is essential, as their removal leads to rapid recovery.

ABSTRACT

We report the case of an 18-year-old female with cholestatic hepatopathy of unknown origin, presenting with therapy-resistant jaundice and pruritus following oral contraceptive use and gastrointestinal infections. In another hospital, drug-induced autoimmune hepatitis (DILI-AIH) was suspected, and corticosteroid therapy was initiated but remained unresponsive. Initiation of colestyramine led to a worsening of symptoms and increasing liver transaminases. After referral to our centre, a mini-laparoscopic liver biopsy was performed, and histopathology revealed cholestatic DILI and mild fibrosis, with no signs of AIH. After a repeated precise history from the mother, a hereditary fructose intolerance was highly suggestive, and genetic testing confirmed a homozygous mutation in the aldolase B gene (A149P). Additionally, no pathogenic mutations in genes encoding bile acid and phospholipid transporters were detected. The treatment was adjusted to sugar-free colestyramine, leading to complete resolution of symptoms. In the management of hereditary fructose intolerance, not only dietary ingredients but also the supplements and medications may contain fructose excipients that could exacerbate and aggravate liver injuries.

Keywords: Acute liver injury, aldolase B, fructose, liver fibrosis.

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Introduction

Hereditary fructose intolerance (HFI) is a rare autosomal recessive disorder caused by mutations in the ALDOB gene encoding aldolase B, located on chromosome 9q22.3. This enzyme deficiency leads to the accumulation of fructose-1-phosphate, which inhibits gluconeogenesis. HFI is typically diagnosed in childhood, with common symptoms including vomiting, hypoglycemia, and faintness starting after weaning from breast milk. These symptoms often result in a natural avoidance of fructose-containing foods.[1] Herein, we present a case of multifactorial liver injury based on HFI diagnosed late in adulthood and the presence of non-pathogenic mutations in bile acid and phospholipid transporters, which predispose to cholestatic liver diseases.

Case Report

An 18-year-old patient was referred initially to an external clinic following oral contraceptive use and diverse infections. The patient complained of fatigue and pruritus on the hands and feet, which was treated with cetirizine. On physical examination, no other signs were noted apart from icterus and scratch marks related to pruritus. There was no history of substantial alcohol, drug, or herbal mixture intake. The total bilirubin was 4.6 mg/dL, direct bilirubin 3.76 mg/dL, indirect bilirubin 1.04 mg/dL, alanine transaminase (ALT) 253 U/L, aspartate transaminase (AST) 375 U/L, alkaline phosphatase (ALP) 129 U/L, and γ-glutamyl-transferase (GGT) 23 U/L. Serological tests for viral hepatitis, including hepatitis A, B, C, and E, were negative. Viral infections, including Epstein-Barr virus, cytomegalovirus, varicella-zoster virus, and adenovirus, were ruled out. The autoantibodies, including antinuclear antibody, anti-mitochondrial antibody, liver-kidney microsomal antibody, myeloperoxidase antibody, proteinase 3 antibody, and immunoglobulin G and M concentrations, were within the normal range. Hepatic magnetic resonance imaging and cholangiopancreatography revealed no sign of tumor, inflammation, or biliary obstruction. The liver biopsy showed signs of drug-induced liver injury (DILI) without signs of autoimmune hepatitis. Oral contraceptives, which she used over 6 months, and cetirizine, which was prescribed due to pruritus, were stopped immediately. Initially, steroid therapy resulted in a decrease in ALP and bilirubin levels. The patient was prescribed colestyramine and ursodeoxycholic acid and followed up in ambulatory settings. Due to worsening of the symptoms and increase in liver transaminases, including ALT and AST, the patient was referred to our tertiary care center. During the extended anamnesis, the patient and her mother reported experiencing nausea and vomiting after consuming fruits since childhood, which resulted in avoiding fructose-containing foods. There was no documented history of abnormal liver test results in childhood. Subsequently, we performed a mini-laparoscopic hepatic biopsy, which yielded macroscopically a cholestatic green liver without organomegaly (Fig. 1). Liver histology showed a DILI with cholestasis accompanied by mild fibrosis without signs of autoimmune hepatitis, which indicated a worsening of liver fibrosis. Subsequently, we checked the additives of the prescribed colestyramine and determined that the preparation contained sucrose and replaced it with a sugar-free preparation. We finally performed a genetic analysis, which confirmed a homozygous mutation for the aldolase B gene (A149P, homozygous) and mutations of bile acid and phospholipid transporters, which predispose to cholestatic liver diseases (ABCB4 c.504T>C and c.711A>T, homozygous; ABCB11 p.A44V, heterozygous; ABCB11 p.D482G, heterozygous). Following the therapeutic change to a sugar-free colestyramine, after 4 weeks the patient was presented in our outpatient clinic with complete regression of icterus and pruritus. The patient was referred to a dietician. The change in the liver transaminases over time is depicted in Figure 2. Informed consent was taken from the patient. We did not use any artificial intelligence–assisted technology in preparation of this case report.

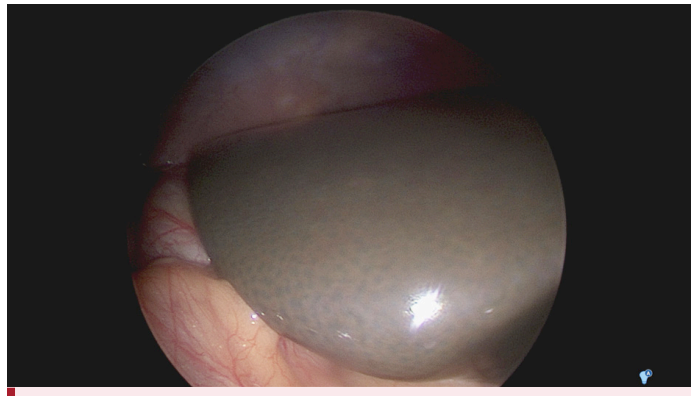
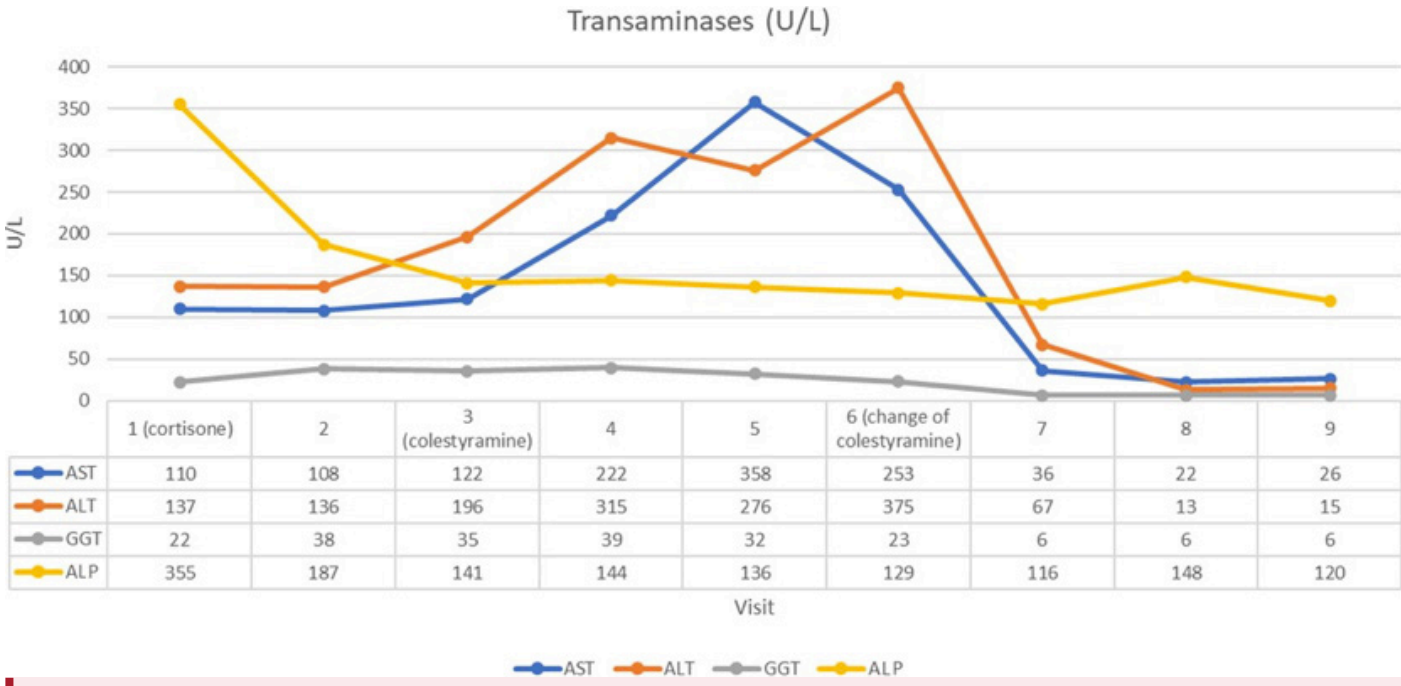


Figure 1. Cholestatic green liver detected in mini-laparoscopic examination.

Discussion

In the case report, we presented a young female with multifactorial liver injury due to the presence of HFI and non-pathogenic mutations in bile acid and phospholipid transporters, predisposing to cholestatic liver disease. The patient did not report any similar cholestasis episodes previously due to a strict self-avoidance of fructose and no history of medication use, which resulted in a late diagnosis in adulthood. The acute injury was caused by oral contraceptives, gastrointestinal infections, cetirizine, and exacerbated with the unfortunate treatment of pruritus with sorbitol-containing excipients of colestyramine. In Figure 3, we depicted the liver histopathology indicating the deficient aldolase B expression with less staining compared to the normal liver. To the best of our knowledge, this is the first laparoscopic and histological visualization of the liver in a patient with hereditary fructose intolerance and severe cholestasis.

A fructose-restricted diet constitutes the backbone of HFI. Besides, medications should also be strictly chosen to avoid sucrose and sorbitol.[2] In the literature, there are reported cases of fatal outcomes following the infusion of fructose-containing solutions after an appendectomy or abortion in otherwise healthy young adults.[3,4] Therefore, fructose-containing solutions are abandoned due to the lethal complications and absence of reported advantages over glucose.[3] To prevent such exposures, mobile applications have been proposed to help identify and eliminate foods and medications containing intolerable ingredients, and they should be encouraged.[5]



	1 (cortisone)	2	3 (colestyramine)	4	5	6 (change of colestyramine)	7	8	9
AST	110	108	122	222	358	253	36	22	26
ALT	137	136	196	315	276	375	67	13	15
GGT	22	38	35	39	32	23	6	6	6
ALP	355	187	141	144	136	129	116	148	120

Figure 2. Change of liver transaminases during the visits.

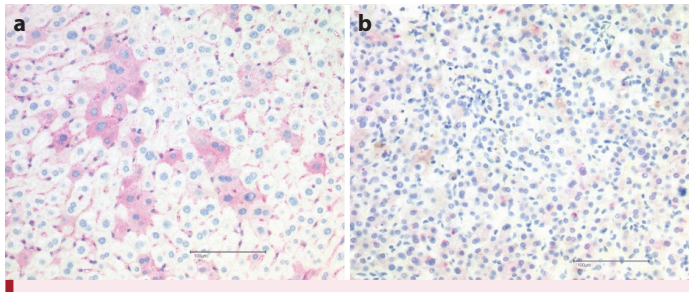


Figure 3. Comparison of normal liver tissue with the patient with aldolase B deficiency. **(a)** Normal liver **(b)** Patient with aldolase B deficiency.

Moreover, strict adherence to a diet that eliminates fructose, sucrose, and sorbitol (FSS) is linked to an excellent prognosis and a normal life expectancy.[6] Also in our case, cessation of fructose-containing medications resulted in immediate improvement of the liver injury. On the other hand, in some cases, small amounts of fructose consumption—less than 40 mg/kg/day or 1.5 g/day—seemed to be tolerable.[7] Furthermore, in an Italian cohort with long-term follow-up over 10 years, even minimal fructose exposure was associated with hepatic steatosis on liver ultrasound (93%). Elevated transaminase levels were reported in 75% of the patients. There was no sign of growth retardation.[7] Therefore, the safe level of fructose exposure remains controversial. Moreover, adhering to a strict diet can sometimes be challenging. As an alternative to the strict FSS diet, PF-06835919—an oral ketohexokinase inhibitor that suppresses hepatic fructose metabolism—was recently investigated in three patients with HFI. The authors administered different doses of fructose and observed a successful suppression of hepatic fructose metabolism.[8] Such a medical approach should certainly be investigated in clinical trials but represents a promising therapeutic option.

When fructose intolerance is suspected, it should be confirmed through genetic testing rather than histological confirmation via liver or kidney biopsy, due to the invasive nature of the latter.[9] A fructose tolerance test should be avoided due to a possible lethal complication. In our case, we performed mini-laparoscopy due to an atypical and prolonged period of liver injury, which began with the use of oral contraceptives and persisted with infections and cetirizine. Therefore, we had the opportunity to stain the liver tissue for aldolase B activity.

Here, aside from identifying aldolase B deficiency, we identified mutations in bile acid and phospholipid transporters that contribute to a predisposition for cholestatic liver disease. ABC transporters play a crucial role in transporting bile salts from hepatocytes to the bile canalicular lumen. Among these, ABCB11 has been linked to progressive familial intrahepatic cholestasis (PFIC) type 2—a condition characterized by severe cholestasis and intense pruritus. This disorder is marked by significantly elevated serum bile acids and normal serum γ-glutamyl-transferase activity. ABCB4 is known to be involved in a large spectrum of diseases, including PFIC type 3, intrahepatic cholestasis of pregnancy, low-phospholipid-associated cholelithiasis, and primary biliary cirrhosis.[10] Although we did not find any mutations indicating PFIC in our case, the heterozygous mutations may predispose to cholestatic liver disease following drug-induced liver injury.

In summary, this case represents a multifactorial liver injury with contributing factors including gastrointestinal infections, DILI associated with contraceptive use, and fructose ingestion in a patient with HFI. Consequently, attributing the liver injury to a single cause is challenging. However, we believe that the primary challenge was the undiagnosed HFI, which proved decisive for treatment decisions, particularly in the choice of medication.

Conclusion

In conclusion, the management of HFI includes lifetime monitoring and the engagement of medical and dietary counsellors, including hepatological follow-up. Not only the dietary ingredients, but also the supplements and medications, should be meticulously investigated.

Informed Consent: Informed consent was taken from the patient.

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