

Sodium Taurocolate Cotransporting Polypeptide Mutation Associated Transaminase Elevation

Sodyum Taurokolat Taşıyan Polipeptit Mutasyonuna Bağlı Transaminaz Yüksekliği

Zeynep Begüm ERENŞOY KARAGÜL¹, Coskun Firat ÖZKEÇECİ², Melike ARSLAN²,
Edibe Gözde BAŞARAN², Yasin Maruf ERGEN², Necati BALAM²

¹Department of Child Health and Diseases, Gülhane Training and Research Hospital, Ankara, Türkiye

²Department of Pediatric Gastroenterology, Gülhane Training and Research Hospital, Ankara, Türkiye



ABSTRACT

Familial hypercholanemia-2 is a condition caused by mutations in the human solute carrier family 10 member 1 (SLC10A1) gene, which results in the inability to transport conjugated bile salts from plasma to hepatocytes. This is due to the sodium taurocolate cotransport polypeptide encoded by the gene being affected. Although the gene was first described in 1994, there is limited knowledge on the clinical features of the disease. In the few reported cases, both clinical and laboratory findings have varied. We reported a twelve-year-old girl was diagnosed with familial hypercholanemia-2 through a whole gene exome sequencing study. She was brought in with asymptomatic hypertransaminasemia, and after comprehensive studies on etiology failed to detect the cause, genetic testing was done. The patient had no clinically abnormal findings but had hypercholanemia (bile acid level 81.9 µmol/L) (fasting < 10 µmol/L, postprandial < 15 µmol/L) and hypertransaminasemia in laboratory examinations.

It is believed that the disease can present with a wide range of phenotypes, and laboratory findings may differ between patients depending on the underlying genetic mutation or mechanisms that have not yet been identified. Therefore, it is recommended to expand diagnostic genetic examinations in patients with hypertransaminasemia whose cause cannot be determined.

Key Words: Bile acids and salts, Cholestasis, Hypercholanemia, Sodium taurocolate cotransporting polypeptide

ÖZ

Ailesel hiperkolanemi-2, SLC10A1 genindeki mutasyonların neden olduğu, konjuge safra tuzlarının plazmadan hepatositlere taşınmasındaki bozukluk ile sonuçlanan bir durumdur. Bunun nedeni, etkilenen gen tarafından kodlanan sodyum taurokolat kotransport polipeptididir. Gen ilk olarak 1994 yılında tanımlanmış olmasına rağmen hastalığın klinik özelliklerine ilişkin bilgiler sınırlıdır. Bildirilen birkaç vakada da hem klinik hem de laboratuvar bulguları farklılık göstermiştir. Bu yazımızda; tüm ekzon dizi analizi çalışmasıyla; ailesel hiperkolanemi-2 tanısı alan on iki yaşında bir kız hastayı sunuyoruz. Asemptomatik hipertransaminazemi nedeniyle getirilen hastaya, etiyolojye yönelik kapsamlı çalışmalar sonucunda nedenin belirlenememesi üzerine genetik temelli tanı testleri yapıldı. Klinik olarak asemptomatik olan hastanın, laboratuvar incelemelerinde hiperkolanemi (safra asidi düzeyi 81.9 µmol/L) (açlık < 10 µmol/L, tokluk < 15 µmol/L) ve hipertransaminazemi mevcuttu.

Hastalığın çok çeşitli fenotiplerle ortaya çıkabileceği ve altta yatan genetik mutasyon veya henüz tanımlanamayan mekanizmalara bağlı olarak laboratuvar bulgularının hastalar arasında farklılık gösterebileceği düşünülmektedir. Bu nedenle nedeni belirlenemeyen hipertransaminazemili hastalarda tanısız genetik incelemelerin yaygınlaştırılması önerilmektedir.

Anahtar Kelimeler: Safra asitleri ve tuzları, Kolestaz, Hiperkolanemi, Sodyum taurokolat birlikte taşınan polipeptit



0009-0008-5638-8928 : ERENŞOY KARAGÜL ZB
0000-0002-3954-6428 : ÖZKEÇECİ CF
0000-0002-0107-4699 : ARSLAN M
0000-0003-3165-3234 : BAŞARAN EG
0000-0002-3689-6852 : ERGEN YM
0000-0001-8665-5611 : BALAM N

Conflict of Interest / Çıkar Çatışması: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Financial Disclosure / Finansal Destek: The authors declared that this case has received no financial support.

Confirmation / Onay: The written consent was received from the patient who was presented in this study.

How to cite / Atıf Yazım Şekli : Erensoy Karagül ZB, Özkeçeci CF, Arslan M, Başaran EG, Ergen YM and Balam N. Sodium Taurocolate Cotransporting Polypeptide Mutation Associated Transaminase Elevation. Turkish J Pediatr Dis 2024;

Correspondence Address / Yazışma Adresi :

Zeynep Begüm ERENŞOY KARAGÜL

Department of Child Health and Diseases,
Gülhane Training and Research Hospital, Ankara, Türkiye
E-posta: begumerensoy@gmail.com

Received / Geliş tarihi : 09.01.2024

Accepted / Kabul Tarihi : 04.03.2024

Online published : 13.05.2024

Elektronik yayın tarihi

DOI: 10.12956/tchd.1416503

INTRODUCTION

Familial hypercholanemia-2 (FHCA2) is a rare condition that affects the way bile salts are transported into the liver. It is caused by a mutation in the human SLC10A1 gene, which codes for the Sodium taurocholate cotransporting polypeptide (NTCP) protein (1). The disease has a genetic basis and is usually found in people with homozygous or compound heterozygous mutations in this gene. However, there is limited knowledge about the disease's symptoms and characteristics. The reported cases show different clinical presentations. In this article, we present and discuss a pediatric patient who was diagnosed with familial hypercholanemia type 2 after being examined for hypertransaminasemia.

CASE REPORT

A 12-year-old girl complained about abdominal pain and fatigue in May 2017 and was taken to the pediatrics outpatient clinic. During examination, it was discovered that her ALT (alanine transaminase) was 78 U/L (normal range: 10-60 U/L) and AST (aspartate transaminase) was 44 U/L (normal range: 10-55 U/L). A follow-up examination conducted one week later revealed that her ALT had increased to 192 U/L, while her AST had increased to 93 U/L. As a result, she was referred to the pediatric gastroenterology outpatient clinic for further examination. The patient had no history of liver disease or any other specific medical conditions, and there was no such condition in her family medical history. Her height was 158 cm (75-90 percentile) and her weight was 50 kg (75-90 percentile). There were no pathological findings during the abdominal and other system examinations. During laboratory examinations, the patient's hemoglobin level was measured at 13.2 g/dl (10.3-14.9 g/dl), white blood cell count level was 7900/mm³, and platelet level was 380.000/mm³. The patient's INR (international normalized ratio) was 1 (0.8-1.2). In routine biochemistry examinations, total bilirubin measured at 0.6 mg/dl (0.2-1.3mg/dl), while direct bilirubin level was 0.13 mg/dl (0-0.2mg/dl), and gamma glutamyl transferase level was 80 U/L (5-55 U/L). In the lipid profile, total cholesterol was 179 mg/dl (<170mg/dl), low-density lipoprotein cholesterol was 121mg/dl (<110mg/dl), high-density lipoprotein cholesterol was 41mg/dl (40-85mg/dl), and triglycerides measured at 83 mg/dl (30-130 mg/dl). In examinations for the etiology of hypertransaminasemia, viral hepatitis markers were detected as follows: HBsAg (hepatitis B surface antigen) nonreactive, anti HIV (human immunodeficiency virus) nonreactive, anti HBs reactive (861.7mIU/mL), and anti HCV (hepatitis C virus) nonreactive. Ceruloplasmin measured at 0.31g/L (20-63 mg/dl), while 24-hour urine copper was 15 µg (<40 µg). No Kayser-Fleischer ring was detected in the eye examination. Anti-tissue transglutaminase IgA and IgG were negative. TSH (thyroid stimulating hormone) measured at 1.1mIU/MI, T4 measured at

0.91ng/dl, IgG measured at 1227mg/dl (579-1610), and IgA measured at 182mg/dl (27-198). ANA (antinuclear antibody), anti-dsDNA (double-stranded DNA antibody), AMA (anti-mitochondrial antibody), ASMA (anti-smooth muscle antibody), LKM (liver kidney microsomal antibody) results were negative. Metabolic evaluation tests were within normal limits. AFP (Alpha fetoprotein) level was measured at 10ng/ml (0-14ng/ml), and alpha-1 antitrypsin level was measured at 100 mg/dl (90-200mg/dl). Bile acid level was detected as 81.9 µmol/L (0-10µmol/L). The patient underwent a whole abdominal ultrasonographic examination in radiological examinations, which turned out to be normal. However, during follow-up in July 2019, the patient's AST and ALT levels increased to 117 and 229, respectively, after a liver biopsy. During the biopsy, few lymphocytes were observed scattered individually in the liver tissue, along with minimal reactive changes in hepatocytes. However, there was no evidence of portal inflammation, bile duct damage, or iron/bile/alpha 1 antitrypsin, which could have suggested a chronic hepatic process. As the liver biopsy did not provide any clear diagnostic findings, a whole exome sequencing was conducted. The genetic study identified a homozygous mutation in the SLC10A1 gene, which encodes the NTCP protein associated with FHCA-2. No other mutation was detected during the genetic examination.

DISCUSSION

Liver transaminases are enzymes that are present in low levels in the plasma. In children, elevated levels of these enzymes can be caused by various reasons. Bile salts play a crucial role in digesting fats in the small intestine. They are formed when cholesterol undergoes enzymatic steps in the liver. The transport of conjugated bile salts from the plasma into the hepatocyte is carried out by the main carrier protein known as sodium taurocholate cotransporting polypeptide. On the other hand, the non-sodium-dependent bile salt transporter is responsible for the transport of unconjugated bile salts to the hepatocyte. This protein belongs to the SLC10A1 solute carrier family and provides uptake from the basolateral membrane by cotransporting two Na⁺ molecules for every one bile salt from the basolateral membrane (2). This process is crucial for enterohepatic circulation. NTCP deficiency is a condition that needs to be identified early as it can cause damage to hepatocytes and bile ducts. The first case of NTCP deficiency was reported in 2015 by Vaz et al.(3). The patient had clinical hypotonia, growth retardation and motor delay with significant hypercholanemia. However, the patient had no clinical pruritus or jaundice, and their serum bilirubin and bile acid levels were normal, and their liver functions were unaffected. In another study by Tan et al. (4), two monozygotic female twin cases with transient neonatal cholestasis that resolved at seven months of age were presented. It was reported that NTCP deficiency may cause transient neonatal cholestasis in early infancy. Dong and

their team have presented clinical and histopathological data of 13 patients with NTCP deficiency (5). Eight patients experienced visible jaundice and twelve patients had hyperbilirubinemia. Mild chronic inflammation was observed in all eleven patients who underwent biopsy. The researchers concluded that diagnosing NTCP deficiency is crucial, as it can result in both hepatocellular and biliary histological involvement. In another study, Zou et al.(6) reported a patient with NTCP deficiency who experienced self-limiting conjugated bilirubin elevation. Additionally, Lin et al. (7) reported that they discovered NTCP deficiency in three patients with cholestatic liver disease as a result of citrine deficiency. Despite the cholestasis symptoms improving with appropriate treatment, their hypercholanemia persisted. It seems that our patient didn't exhibit any noticeable symptoms but was found to have high liver enzyme levels without high bilirubin levels. The patient did not exhibit the typical symptoms of hypotonia, growth retardation, motor delay, itching, jaundice or transient cholestasis in the neonatal period that have been reported in other cases. This highlights that NTCP deficiency in childhood can occur without any noticeable clinical symptoms. After examining the lab results, it was found that our patient did not have high bilirubin levels, which are often present in reported cases. It was also noted that plasma bile acid levels varied between patients. In our patient, bile acid levels were significantly elevated at $81.9\mu\text{mol/L}$ ($<10\mu\text{mol/L}$), which is over eight times higher than normal. The diagnosis was made based on the laboratory results which showed elevated levels of transaminases. It has been observed in the literature that there are no cases of asymptomatic hypertransaminasemia patients who have been examined and diagnosed. Therefore, the case we are presenting here is a valuable addition to the literature as a new presentation of NTCP deficiency (5). In our patient, the liver biopsy showed sparse lymphocytes scattered singly in the parenchyma and minimal reactive changes in hepatocytes. It has been reported in the literature that almost all NTCP patients have minimal chronic inflammation findings in liver biopsy. The biopsy findings in our case are partially similar to the results reported in the literature, thus supporting the knowledge that histopathologically mild changes are observed in the liver in NTCP deficiency. We examined all possible causes of hypertransaminasemia in our patient and ruled out other causes. The diagnosis was made by detecting a homozygous mutation in the SLC10A1 gene in the whole exome sequencing.

CONCLUSION

Our research shows that NTCP plays a crucial role in maintaining bile salt balance, and its deficiency can cause persistent hypercholanemia in children. The findings suggest that the disease can manifest in different ways and laboratory results may vary among patients. It is believed that these differences might be due to genetic mutations or other unidentified factors. More comprehensive research is needed to determine the

long-term effects of this newly discovered genetic disease on bile acid transport. Additionally, genetic testing should be expanded to diagnose patients with hypertransaminasemia of unknown origin.

REFERENCES

1. Deng M, Mao M, Guo L, Chen FP, Wen WR, Song YZ. Clinical and molecular study of a pediatric patient with sodium taurocholate cotransporting polypeptide deficiency. *Exp Ther Med* 2016;12:3294-300.
2. Stieger B. The role of the sodium-taurocholate cotransporting polypeptide (NTCP) and of the bile salt export pump (BSEP) in physiology and pathophysiology of bile formation. *Handb Exp Pharmacol* 2011;201:205-59.
3. Vaz FM, Paulusma CC, Huidekoper H, et al. Sodium taurocholate cotransporting polypeptide (SLC10A1) deficiency: conjugated hypercholanemia without a clear clinical phenotype. *Hepatology* 2015;61:260-7.
4. Tan HJ, Deng M, Qiu JW, Wu JF, Song YZ. Monozygotic Twins Suffering From Sodium Taurocholate Cotransporting Polypeptide Deficiency: A Case Report. *Front Pediatr* 2018;6:354.
5. Dong C, Zhang BP, Wang H, Xu H, Zhang C, Cai ZS, et al. Clinical and histopathologic features of sodium taurocholate cotransporting polypeptide deficiency in pediatric patients. *Medicine (Baltimore)* 2019;98:e17305.
6. Zou TT, Zhu Y, Wan CM, Liao Q. Clinical features of sodium-taurocholate cotransporting polypeptide deficiency in pediatric patients: case series and literature review. *Transl Pediatr* 2021;10:1045-54.
7. Lin H, Qiu JW, Rauf YM, Lin GZ, Liu R, Deng LJ, et al. Sodium Taurocholate Cotransporting Polypeptide (NTCP) Deficiency Hidden Behind Citrin Deficiency in Early Infancy: A Report of Three Cases. *Front Genet* 2019;10:1108.