



Case Report

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Chronic elevated liver enzymes with ABCB11 mutation in healthy adult twin males: A case report

Auda Fares¹, Thomas Landmann², Christoph charisius²

¹ Department of Geriatric Medicine, St. Willibrord-Spital Emmerich/Rees - Germany

² Christoph charisius: Hausaerztliche Gemeinschaftspraxis, Pulheim- Germany

Abstract

We present a diagnostically challenging case of 30-year-old twin males with chronic elevated liver enzymes (GGT) without history of hepato-biliary diseases. Genetic study disclosed mutations in gene ABCB11 and liver histopathology shows only scanty fatty change without evidence of fibrosis or malignancy. Liver enzymes level successfully return to normal in 2 months following ursodeoxycholic acid (UDCA) therapy.

Keywords: ABCB11, Bile acid synthesis defect, congenital, Cholestasis, Progressive familial intrahepatic.

INTRODUCTION

Mild elevations in levels of the hepatobiliary enzymes—alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyltransferase (GGT), and alkaline phosphatase (ALP) are commonly discovered in asymptomatic patients in primary care. The most common cause of elevated levels of hepatobiliary enzymes is non-alcoholic fatty liver disease, which can affect up to 30 percent of the population. Other common causes include alcoholic liver disease, medication-associated liver injury, viral hepatitis (hepatitis B and C), and hemochromatosis. Less common causes include α_1 -antitrypsin deficiency, autoimmune hepatitis, Wilson disease and Cholestatic Liver Diseases. Extrahepatic conditions (e.g., thyroid disorders, celiac disease, hemolysis, muscle disorders) can also cause elevated liver transaminase levels^[1]. However, the accidental finding of raised levels of hepatobiliary enzymes may need to extensive investigations of the liver in apparently healthy people. In this paper, we present a rare case of chronic elevated liver enzymes and BSEP mutation in healthy adult twin males with a good response to ursodexychoic acid therapy. Unfortunately, only one patient has agreed to continue with differential diagnostic procedure (MRCP, Liver biopsy) and recommended therapy.

CASE REPORT

A 30-year-old white identical twin males non-smoker with an unremarkable past medical history. Both patients presented for evaluation of chronic mild elevations in serum levels of Gamma-glutamyltransferase (GGT). They denied nausea, vomiting, diarrhoea or abdominal pain. They also denied alcohol, tobacco, and illicit drug use or exposure to hepatitis. Family history revealed an identical twin with same findings. The parents and grandparents had a negative history of hepato-biliary diseases.

Physical Examination

(Patient No. 1) revealed a well-developed, well-nourished man, in no acute distress. He has no evidence of scleral icterus. He has no evidence of supraclavicular, cervical, or axillary adenopathy bilaterally, his mucous membranes are moist. His lungs are clear to auscultation bilaterally and heart is regular rate and rhythm. He has no evidence of spinal tenderness. His abdomen is soft and nontender without evidence of hepatosplenomegaly. His extremities are without clubbing, cyanosis, or edema. Neurologically, he is alert and oriented.

Physical examination finding for the patient No. 2 are same as identical twin brother.

*Corresponding author:

Dr. Auda Fares

Department of Geriatric
Medicine, St. Willibrord-Spital
Emmerich/Rees- Germany

Email: audafares[at]yahoo.com

Laboratory findings for the patient No. 1 is shown in Table (1).

Magnetic resonance cholangiopancreatography (MRCP) revealed 3 stones (diameter 4–5mm) in the infundibulum and one polyps measuring 11mm in the fundus of the gallbladder.

Table 1: Laboratory results before and after therapy

Parameter	Normal values	Before therapy	After 2 months treated with UDCA 500 mg
Hemoglobin (g/L)	13.5–17.5	16.1	15.8
Leukocyte count (×10 ⁹ /L)	4–10	4.7	4.0
Erythrocyte count (×10 ¹² /L)	4.2–5.8	5.18	5.11
Platelet count (×10 ⁹ /L)	150–400	305	255
Gamma GT(IU/L)	0-60	141	38
Alanine aminotransferase (IU/L)	0–50	61	62
Aspartate aminotransferase (IU/L)	0–50	39	25
Alkaline phosphatase(IU/L)	40-130	133	117
Bilirubin mg/dl	0-1.2	0.45	0.53
Cholesterol mg/dl	0-200	241	210

Laboratory and image findings for the patient No. 2

Investigations showed a haemoglobin of 15.5 g/dl, normal total and differential white blood cell counts, serum bilirubin of 0.8 mg/dl, alkaline phosphatase of 125 IU/L(normal 40-130 IU/L)), gamma glutamyltransferase (GGT) of 157 IU/L (normal = 0- 60IU/L), aspartate aminotransferase (AST) of 26 (IU/L) and alanine aminotransferase (ALT) of 58 (IU/L) (normal 0- 50 IU/L) respectively, Cholesterol of 191 mg/dl (normal 0-200 mg/dl).

Abdominal US for patients No. 2 showed a 2- hyperechoic lesion in the segment V measuring 10x 8 mm and in segment VI measures 7x8 mm. At contrast-enhanced Ultrasound the lesion shows homogeneous enhancement in the arterial phase.

Both patient were negative for Anti-double-strand DNA antibodies, Anti-cyclic Citrullinated Peptide, C-reactive protein, Perinuclear -Antineutrophil cytoplasmic antibodies (P-ANCA), Cytoplasmic antineutrophil cytoplasmic antibodies(C-ANCA), Liver kidney microsomal type 1 antibody 1 (LKM1), Antimitochondrial M2 Antibody (AMA-M2), Anti-Smooth Muscle Antibody (ASMA), hepatitis B surface antigen (HBsAg), anti-hepatitis B core-IgG (anti-HBc,-IgG), antibodies to hepatitis C virus -IgG(anti HCV-IgG), IgM antibodies to hepatitis A virus (IgM anti HAV). IgG antibodies to hepatitis A virus (Anti-HAV-IgG) was Positive

The genetic sequence analysis for the patient and his identical twin brother showed a homozygous polymorphism mutation in ABCB11 (V444A).

DISCUSSION

Bile salt export pump (BSEP, ABC11) is a protein located in the canalicular membrane of hepatocytes, are responsible for the elimination of unconjugated and conjugated bile acids/salts from hepatocyte into the bile. When the bile salts are not transported to the canaliculi there is no bile flow and the bile salts accumulate in the hepatocytes causing severe liver damage ^[2].

Mutations of BSEP are associated with cholestatic liver diseases of varying severity including progressive familial intrahepatic cholestasis type 2 (PFIC2), benign recurrent intrahepatic cholestasis type 2 (BRIC2), and intrahepatic cholestasis of pregnancy (ICP) and risk for drug-induced cholestasis (DC) ^[3]. BSEP mutations have also been described in children with hepatocellular carcinoma ^[4].

Percutaneous liver biopsy revealed scanty fatty degeneration of the liver parenchymal cells without evidence of inflammation, fibrosis, or malignancy.

PFIC2 usually appear in the first months of life. Main clinical manifestations include cholestasis, pruritus and jaundice. PFIC2 patients usually develop fibrosis and end-stage liver disease before adulthood. Serum gamma- glutamyltransferase (GGT) activity is normal in PFIC2 patients ^[5].

Benign recurrent intrahepatic cholestasis (BRIC) is a rare genetic disorder characterized by intermittent episodes of intrahepatic cholestasis, generally without progression to chronic liver damage. In a large series of patients the age of presentation varied from 1 to 59 years and duration of icteric phase was also variable lasting from weeks to months ^[6,7]. BRIC can be differentiated from PFIC on the basis of the disease course and liver histology. Moreover, a variety of statistical models and genetic models have demonstrated that the BSEP mutations may play an important role in the process of Primary biliary cirrhosis (PBC). Primary biliary cirrhosis (PBC) is a chronic autoimmune liver disease that leads to progressive cholestasis and often end-stage liver disease. The diagnosis of PBC is based on the presence of at least 2 of 3 key criteria including a persistently elevated serum alkaline phosphatase, the presence of serum AMAs, and liver histology consistent with PBC ^[8].

Our patients presented none of the typical findings of BRIC, PFIC, or even PBC, having only high serum GGT, and one of them (patient No. 1) has mild hypercholesterolemia, gallbladder polyp with gallbladder stones, along with BSEP mutation. However, Researchers suggest that the clinical phenotypes of PFIC2, BRIC2, may directly correlate with the amount of mature protein that is expressed at the cell surface. The patient was started on ursodeoxycholic acid. One of our patient's serum cholesterol levels and liver enzymes returned to normal in 2 months following ursodeoxycholic acid (UDCA) therapy. The patient on follow up since 3 years after starting therapy, there was no evidence of hepato-biliary diseases development. Ursodeoxycholic acid (UCDA) has recently been shown to improve serum liver chemistries in patients with various liver diseases. The beneficial effects of UDCA include promoting bile flow, reducing hepatic inflammation, preventing apoptosis, and maintaining mitochondrial integrity ^[9].

The possible connection between cholesterol and ABCB11 is controversial. In a large population-based study in China, a Positive association was observed between the ABCB11 and serum lipid. Enhanced canalicular expression of ABCB11 resulted in a marked increase of both bile flow and biliary lipid secretion ^[10]. However, the specific roles of ABCB11 in regulating the hepatobiliary lipid metabolism remain poorly understood. Several studies reveal that bile

acids are signalling molecules that activate several nuclear receptors and regulate many physiological pathways and processes to maintain bile acid and cholesterol homeostasis. Analysis of orphan receptor expression patterns in enterohepatic tissues identified bile acids as ligands for farnesoid X receptor (FXR) ^[11]. FXR is a key regulator of bile salt and cholesterol homeostasis. Another appearance is a high risk of developing cholelithiasis. The cholelithiasis is probably due to the low bile salt concentration in the canaliculi because of the malfunction of BSEP, resulting in a relatively high concentration of cholesterol. Furthermore, a major "gallstone locus" termed Lith 1 has been identified on mouse chromosome 2, which co-localizes to the chromosomal mapping position of Abcb11 ^[12].

Elevation serum liver enzymes level along with BSEP mutation might predispose to the development of hepatic disorders such as acquired forms of intrahepatic cholestasis. A crucial question raised by our case is whether serum liver enzymes elevation with BSEP mutation in adult patient is a new form of PFIC2 or BRIC2 syndrome or a risk factor for the development of hepatic disorder such as acquired forms of intrahepatic cholestasis. Future studies should investigate whether this association is causal or has clinical utility in the prediction of the presence or incidence of cholestatic liver diseases. If this is confirmed, further consideration should be given to measures that reduce the serum liver enzymes levels as a means of preventing cholestasis in persons with elevated levels.

CONCLUSION

Our finding, suggest that patients who are present with chronic elevation of transaminases of unexplained etiology should be evaluated for BSEP mutation, as the possibility of such a diagnosis is latent. Ursodeoxycholic acid (UDCA) therapy for asymptomatic patients with BSEP mutation could have a beneficial role in the prevent development of hepato-biliary diseases. However, further studies investigating these mutations may enrich the knowledge of the ABCB11 gene, and may therefore be beneficial to the personalized management of individual patients in the future.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Conflicts of interests

All authors have no conflict of interests.

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