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Benign Recurrent Intrahepatic Cholestasis Triggered By Gram-Negative Rod Sepsis

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Abstract

Background: Benign recurrent intrahepatic cholestasis is a rare condition. People living with it experience episodes of cholestasis, during which the liver cells have a reduced possibility to release bile. Episodes of cholestasis can last from weeks to months. Between these episodes, patients are asymptomatic. Bacterial infections are one of the factors that can trigger the disease. **Case**: A 68-year-old patient presents to our Emergency Department with urosepsis due to Escherichia Coli, based on clinical and laboratory findings. The patient reported that he had frequent episodes of jaundice. The patient was diagnosed with benign recurrent intrahepatic cholestasis syndrome and sepsis by Escherichia Coli. This paper aims to draw the clinicians' attention about this syndrome which is very rare in clinical practice and especially in Albania.

Conclusion: An early diagnosis of BRIC will prevent over-investigation of the patient during subsequent attacks and allows the patient and his family to be given the reassurance and advice that they require. Clinical physicians should always suspect BRIC in patients with high levels of bilirubin and normal laboratory values and radiology findings.

Keywords: benign recurrent intrahepatic cholestasis, BRIC, sepsis, Escherichia Coli

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INTRODUCTION

Benign recurrent intrahepatic cholestasis (BRIC) is an autosomal recessive disorder characterized by recurrent, self-limited episodes of cholestasis that are manifested by pruritis, anorexia, fatigue, steatorrhea, and jaundice. During these episodes, the liver cells have a reduced ability to release bile. The disease is prescribed as intrahepatic cholestasis because the problems with bile release occur inside the liver (intrahepatic). Episodes of cholestasis can last from weeks to months, and the time between episodes, during which there are usually no symptoms, can vary from weeks to years (1-8).

Two forms of BRIC are classified based on the genetic cause of the condition. Both forms follow an autosomal recessive pattern of inheritance. Episodes generally begin in the late teens or early twenties and may be accompanied by jaundice, severe itching, a vague feeling of discomfort, and sometimes irritability, nausea, vomiting, and a lack of appetite (1,2,4,8). The factors like viral or bacterial infections, pregnancy, and oral contraceptives have been implicated as causative agents to the onset the cholestasis, but the mechanism remains unclear. E. coli is one of gram-negative bacilli that may cause urinary tract infections, and sepsis. For several months or years, patients can be asymptomatic (1,5,9,10).

Diagnosis of this rare condition is based on the anamnesis (at least 2-3 episodes of cholestasis), serum biochemistry (low to normal serum gamma-glutamyl transferase (GGT) activity and cholesterol, elevated serum of total bile acids, and high levels of conjugated bilirubin during episodes), cholangiography (showing normal intra- and extrahepatic bile ducts), liver histology (revealing intrahepatic cholestasis with normal liver structure) and immunohistochemical analysis (absent or reduced bile salt export pump (BSEP) staining in the majority of BRIC2 patients). Molecular genetic testing confirms the diagnosis and discriminates between subtypes (1,3,5,8).

The purpose of our paper is to present a case of this rare syndrome worldwide and especially in Albania.

CASE REPORT

A 69-year-old male presented with fever, fatigue, loss of appetite, and headache. The patient reported jaundice and dysuria symptoms. On physical examination, he had deep icterus with no signs of liver cell failure. He was alert and well-oriented. Hemodynamic parameters were as follows: blood pressure: 100/60 mmHg; cardiac pulse 105bit/min; respiratory rate 22/min; blood oxygen 98% and the temperature was 39.8°C. Laboratory findings revealed a sedimentation rate of 65 mm/hour, WBCc 14.4 x 103/μL, hemoglobin of 12.5 g/dL and platelet count of 185 x 103/μL. Total bilirubin was 19.96 mg/dL with a direct component of 17.45 mg/dL. The patient's blood urea nitrogen, creatinine, cholesterol, calcium, phosphorus, uric acid, Thyroid stimulating hormone, free Thyroxine, free Triiodothyronine, and serum electrolytes were all normal. Patient´s urine was dark.

Patent refers that he had similar episodes of jaundice in the past. He remind us that the first episode of jaundice occurred at the age of fifteen-twenty years old, which resolved spontaneously within a month, and the second episode occurred four years later, which also resolved in six weeks. Since then patient reported having repeated episodes of jaundice once every two-three years. He reported no family history of cholestasis or liver disease. Serologic tests for viral hepatitis (HAV, HBV, and HCV), Adenovirus, Cytomegalovirus, Ebstein-Barr virus, and Leptospirosis were all negative. He was also negative for Anti-nuclear antibody, Anti-mitochondrial antibody, Anti-smooth muscle antibody, Anti-soluble liver antigen, Anti myeloperoxidase antibody, Anti-proteinase 3, and Anti-liver kidney microsome-1 antibody. On the other hand, the Wilson disease was excluded. Based on ultrasonography and magnetic resonance cholangiography there were neither gallstones nor intrahepatic or extrahepatic bile duct obstruction. Bile ducts were normal. Spleen and liver were of normal size and there were no ascites or other abdominal abnormalities. The procalcitonin on the first day was 2,5ng/dl (range 0.5-2) and after two days it became 0,2 ng/dl. Blood culture and urine culture test resulted positive for Escherichia Coli. The patient was treated with Piperacillin/Tazobactam 4,5g three times per day and Gentamicin two times a day for seven days. He reported that he was hospitalized in Italy, in 2018 for toxic dysmetabolic hepatopathy with hepatosteatosis, where he was diagnosed with BRIC1 (Table 1).

Table 1. Patient follow-up in the last four years

Exams/Years	2018	May 2019	September 2019	May 2022
ALT	49 U/L	32 U/L	23 U/L	168 U/L
GGT	38 UI/L	33,66 UI/L	55 UI/L	50 UI/L
ALP	80 UI/L	79 UI/L	81 UI/L	79 UI/L
AST	28 U/L	47 U/L	19 U/L	124 U/L
Total Bilirubin	8,02 mg/dl	8,85 mg/dl	9,10 mg/dl	19,96 mg/dl
Direct Bilirubin	6,58 mg/dl	7,84 mg/dl	6,55 mg/dl	17,45 mg/dl
Indirect Bilirubin	1.44 mg/dl	1,01 mg/dl	2.55 mg/dl	2,51 mg/dl

The patient was followed up for more than six months and the level of bilirubin lowered to 3.2 mg/dl in December 2022 and then to 1.2 mg/dl on January 2023.

DISCUSSION

BRIC was first described by Summerskill and Walshe in 1959 (1,3,4,6-8,11). Two forms of BRIC are classified based on the genetic cause of the condition. BRIC1 is caused by mutations in the ATP8B1 gene and BRIC2 is caused by mutations in the ABCB11 gene. Both follow an autosomal recessive pattern of inheritance. Clinically, these forms are very similar. BRIC1 is allelic to Progressive familial intrahepatic cholestasis (PFIC) and is caused by mutations in the ATP8B1 gene which provides instructions for

making a protein that helps to control the distribution of certain fats in the membranes of liver cells. This function likely plays a role in maintaining an appropriate balance of bile acids. This process, known as bile acid homeostasis, is critical for the normal secretion of bile and the proper functioning of liver cells. The imbalance of bile acids leads to the signs and symptoms of BRIC1. BRIC2 is allelic to PFIC2 and is caused by mutations in the ABCB11 gene. The disease-causing mutations in BRIC are generally missense mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition (1,3,4,8). Some people with BRIC have no family history of the disorder. In our case, the six children of the patient have normal levels of bilirubin. Also, his parents didn't refer having the same condition, and neither did his sister nor brother. We also verified our diagnosis with genetic analysis and concluded at was BRIC type 1. Occasionally ALT and AST levels may be markedly elevated but usually, there is only a mild elevation. In our case, in the last four years, that we have the blood tests documented, there were no elevated hepatic enzymes (Tab. 1) (4,8). The factors that trigger episodes of BRIC can be infections, pregnancy or unknown (1,4,6,12). In this case our patient was diagnosed with sepsis caused by Escherichia Coli. E. coli is one of the major gram-negative bacilli which may cause, urinary tract infections, and sepsis. The mechanisms of the infection are well known nowadays (13). Infection with this gram-negative pathogen is common in elderly people, but what does specifically this case is BRIC syndrome, which was the first case in our experience.

CONCLUSION

An early diagnosis of BRIC will prevent over-investigation of the patient during subsequent attacks and allows the patient and his family to be given the reassurance and advice that they require. Clinical physicians should always suspect BRIC in patients with high levels of bilirubin and normal laboratory values and radiology findings.

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