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The debut of benign recurrent intrahepatic cholestasis in acute hepatitis A

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Abstract

Background. *Benign recurrent intrahepatic cholestasis is a rare inherited disorder characterized by recurrent episodes of severe hyperbilirubinemia and pruritus that resolve spontaneously. However, attacks of cholestasis may persist for several months and in some cases be associated with frequent recurrences, which may be grounds for liver transplantation.*

Objective. *To present a clinical case of debut benign recurrent intrahepatic cholestasis following acute hepatitis A.*

Results. *A 30-year-old patient was admitted at the Liver Transplantation Center of Moscow Regional Research and Clinical Institute n.a. M.F. Vladimirskiy for a prolonged episode of intrahepatic cholestasis with severe coagulopathy after acute hepatitis A. Total bilirubin was elevated up to 835 μmol/L and INR was 3.6. The manifestations of vitamin K-associated coagulopathy were controlled after the first dose of parenteral menadione sodium bisulfite. Glucocorticosteroids, ursodeoxycholic acid and plasmapheresis turned ineffective in the treatment of*

hyperbilirubinemia. Due to long-persisting cholestasis resistant to conservative therapy, the patient was considered for inclusion to the liver transplant waiting list. However, spontaneous resolution of the cholestatic episode was achieved at 5 months after the onset of manifestations. Benign recurrent intrahepatic cholestasis type 2 was diagnosed on the basis of the specific clinical signs, laboratory blood tests and genetic testing.

Conclusion. *The present Case Report shows a long-lasting episode of cholestasis with severe coagulopathy in acute hepatitis A in a patient with benign recurrent intrahepatic cholestasis with subsequent spontaneous resolution of the clinical symptoms at 5 months after their manifestation onset. Therefore, the differential diagnosis of benign recurrent intrahepatic cholestasis should be considered prior to liver transplantation in patients with intrahepatic cholestasis.*

Keywords: benign recurrent intrahepatic cholestasis, liver transplantation, intrahepatic cholestasis

Conflict of interests Authors declare no conflict of interest

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ALT, alanine aminotransferase
AST, aspartate aminotransferase
LB, liver biopsy
ULN, upper limit of normal
ICP, intrahepatic cholestasis of pregnancy
GGTP, γ-glutamyl transpeptidase
HCC, hepatocellular carcinoma
BRIC, benign recurrent intrahepatic cholestasis
COCs, combination oral contraceptives
DILI, drug-induced liver injury

INR, International Normalized Ratio
MRCP, magnetic resonance cholangiopancreatography
PFIC, progressive familial intrahepatic cholestasis
FFP, fresh frozen plasma
UDCA, ursodeoxycholic acid
US, ultrasound examination
CCC, cholangiocellular carcinoma
LPAC syndrome, low-phospholipid associated cholelithiasis syndrome

Introduction

Benign recurrent intrahepatic cholestasis (BRIC) is a rare autosomal recessive disorder characterized by recurrent episodes of severe hyperbilirubinemia and pruritus with low or normal serum γ-glutamyl transpeptidase (GGTP) activity. A rare occurrence of this disorder places it in the group of orphan disorders. The first attacks may be mistakenly assessed as acute hepatitis or progressive familial intrahepatic cholestasis (PFIC). In most cases, BRIC does not lead to fibrosis or hepatocellular failure, and all clinical and laboratory signs of cholestasis resolve spontaneously. However, attacks may persist from two weeks to several months and in some cases are debilitating, which may become a reason for liver transplantation. Rare cases of identifying and following the patients with BRIC complicate a timely diagnosis and the selection of adequate treatment tactics.

The objective was to present a Case report on the debut of benign recurrent intrahepatic cholestasis in a 30-year-old man with acute hepatitis A.

Case Report

Patient Ch., 30 years old as it was known from the medical history, was born a healthy child, grew and developed normally; the patient's

sister was diagnosed with intrahepatic cholestasis of pregnancy (ICP) in the third trimester, which was completely stopped after delivery.

In early April 2023, at the age of 30, he first noted the appearance of yellowness of the skin and sclera with a simultaneous increase in body temperature to 39°C. The patient took no alcoholic beverages, medications, nor dietary supplements, which excluded the toxic genesis of liver damage. He was admitted at the Department of Internal Medicine at the local hospital. The blood test showed increased levels of total bilirubin to 161 μmol/L, alanine aminotransferase (ALT) to 1003 U/L and aspartate aminotransferase (AST) to 308 U/L. The test for the viral hepatitis markers revealed anti-HAV IgM; tests for HCV RNA and HBsAg were negative. Ultrasound examination of the abdominal organs revealed hepatomegaly, the gallbladder wall thickening. The patient was transferred to the Unit for Infectious Diseases. Against the administered infusion therapy, a gradual increase in total bilirubin to 600 μmol/L was achieved (both fractions, direct bilirubin being 320 μmol/L); the international normalized ratio (INR) of 3.6 indicated the development of coagulopathy. Since the end of April 2023, oral prednisolone 80 mg per day, ursodeoxycholic acid (UDCA) 750 mg per day, transfusions of fresh frozen plasma (FFP) were administered. During therapy, total bilirubin and coagulogram parameters remained unchanged. Magnetic resonance imaging on 07.05.2023 revealed no signs of pathology of the abdominal organs and retroperitoneal space. HAV RNA from 11.05.2023 was not detected.

Due to lingering hyperbilirubinemia, the patient was transferred to the Moscow Regional Research and Clinical Institute n.a. M.F. Vladimirskiy on 18.05.2023. At examination on admission, no other abnormalities were revealed except for yellowness of the skin and sclera.

Laboratory blood tests of 19.05.2023 showed the following: hemoglobin 123 g/L, leukocytosis $15x10^9$/L without band shift (assessed

as distributive leukocytosis against the administered glucocorticosteroid therapy), platelets 448x10^9/L, coagulopathy with INR 3.47, prothrombin time 40.4 sec, total bilirubin 720 μmol/L (direct bilirubin 414 μmol/L), GGTP 29 U/L, alkaline phosphatase 174 U/L (higher than normal, the norm being up to 120 U/L), cholesterol 5.2 mmol/L, albumin 36 g/L, creatinine 82 μmol/L, urea 6.4 mmol/L. The levels of immunoglobulins A, M and G were normal; electrophoresis of blood serum proteins revealed no abnormalities in the α1, α2 and γ fractions.

To exclude Wilson-Konovalov disease, the level of ceruloplasmin, daily urinary copper excretion rates, and Kayser-Fleischer rings were investigated; no abnormalities were found. Investigations for autoimmune liver diseases were conducted; neither smooth muscle antibodies, anti-liver-kidney microsome antibodies, antineutrophil cytoplasmic antibodies, nor antimitochondria antibodies were found.

Repeated abdominal ultrasound examination showed no signs of portal or biliary hypertension. No free fluid in the abdominal cavity was found.

The administered therapy included UDCA at a dose of 1000 mg, menadione sodium bisulfite (a water-soluble analogue of vitamin K) 2 ml (10 mg/mL) per day; a dose reduction of prednisolone was initiated with subsequent complete withdrawal.

On the 2nd day from the start of menadione sodium bisulfite administration, the coagulogram parameters were normalized: INR 1.0, prothrombin by Quick 106%, prothrombin time 10.9 sec. The total bilirubin level continued to increase to 835 μmol/L (direct bilirubin being 428 μmol/L), with normal values of GGTP equal 31 U/L, and alkaline phosphatase of 162 U/L.

Due to increasing hyperbilirubinemia, a decision was made to use extracorporeal detoxification methods. The patient underwent two plasmapheresis sessions (07.06.2023 and 09.06.2023) with the removal of

2300 ml of plasma and replacement with solutions of 20% albumin, FFP and crystalloids. A short-term decrease in the level of total bilirubin to 626 μmol/L was noted, with the return to the previous values (789 μmol/L) 3 days after the last session.

Since the cause of cholestasis remained unclear, the patient examination was continued. Esophagogastroduodenoscopy revealed no pathology, the large duodenal papilla was unchanged.

Magnetic resonance cholangiopancreatography (MRCP) was performed. The bile duct structure variant was as follows: absent right lobar duct (trifurcation), the accessory bile duct flowing into the cystic duct. There were no signs of biliary hypertension, cholecystocholedocholithiasis, or space-occupying lesions. According to literature data, the described variant of the biliary tree anatomy occurs in the general population in 0.58% of cases and has no clinical significance [1].

In order to clarify the diagnosis, a liver puncture biopsy was performed on 13.06.2023. The results of the morphological study revealed protein dystrophy of hepatocytes, expansion of the portal tracts due to fibrosis and mild inflammatory infiltration that does not destroy the border plate. In some portal tracts, the bile ducts are poorly visible (ductopenia), and pronounced intracanalicular and intracellular cholestasis is observed in the lobules. According to the Knodell score, the histological activity index and fibrosis index were I – 0; II – 4; III – 1; IV – 1.

Due to the isolated increase in total bilirubin by values of both fractions with GGTP values being normal, in the absence of hepatic encephalopathy and other laboratory signs of liver dysfunction (normal coagulogram and albumin values), and the presence of an episode of ICP in a sister, the BRIC diagnosis was assumed. A possible reliable assay to confirm the diagnosis is molecular genetic testing.

Stable condition and the absence of hepatocellular failure signs in isolated hyperbilirubinemia allowed the patient to be discharged from the hospital on June 14, 2023, with subsequent active outpatient follow-up by a physician of the Transplantation Department from the Moscow Regional Research and Clinical Institute n.a. M.F. Vladimirskiy. Upon discharge, it was recommended to take the UDCA medications at a dose of 750 mg per day, menadione sodium bisulfite 1 ml intramuscularly once a week, as well as laboratory monitoring of liver function tests once a week.

According to the results of laboratory blood tests, a week after discharge, a decrease in the level of total bilirubin to 493 μmol/L was noted, other parameters showed no significant dynamics. Subsequently, a progressive decrease in the level of total bilirubin was observed from 188 μmol/L 6 weeks after discharge, to 86 μmol/L after 9 weeks, 44 μmol/L after 3 months, and to 50 μmol/L after 5 months.

In February 2024, the screening for hereditary diseases associated with cholestasis syndrome using the massive parallel sequencing method was performed in Academician N.P. Bochkov Medical Genetic Research Center. As a result, a previously described pathogenic (HGMD_ID CS042529) nucleotide sequence variant was identified in the splice donor site, intron 18 of the ABCB11 gene (chr2:169820715 C>T) in a heterozygous state leading to a nucleotide substitution (NM_003742.4: c.2178+1G>A). The identified nucleotide sequence variant was registered in the control sample of the Genome Aggregation Database (gnomAD v2.1.1) with an allele frequency of 0.00054%. Pathogenicity prediction algorithms for splice_ai, mmsplice, squirls, spip assessed this variant as likely pathogenic. According to ACMG criteria, this variant is pathogenic (PVS1, PM3, PM2, PP5).

The results of the genetic test confirmed the diagnosis of BRIC type 2.

At the time of writing the paper, with the most recent blood test of 16.02.2024 showing total bilirubin being 47.7 μmol/L, ALT 17.1 U/L, AST 16.3 U/L, GGTP 11 U/L, alkaline phosphatase 65 U/L, INR 0.98, prothrombin 89%, the patient does not have any subjective manifestations of the disease. He leads an active lifestyle. He has not received therapy for 3 months (Figure).

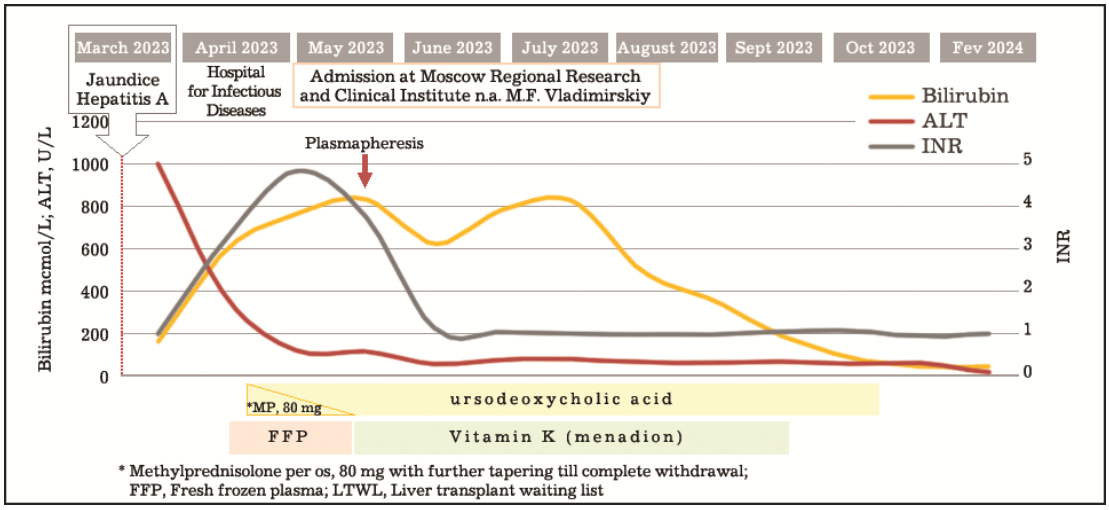

Figure. Dynamics of laboratory parameters during therapy

Discussion

A group of genetically heterogeneous autosomal recessive cholestatic diseases caused by defects of hepatobiliary transporters is represented by BRIC types 1 and 2, PFIC (12 types), ICP and other rare diseases. Hereditary predisposition also plays an important role in the development of drug-induced intrahepatic cholestasis [2].

BRIC is defined as a mild form of PFIC. The prevalence of the disease is unknown. However, it is believed to be less common than PFIC, which has an incidence of 1/50,000–1/100,000 [3].

BRIC was first described in 1959 by W. Summerskill and J. Walsh in 2 patients from the UK [4]. The characteristic features of the disease

are recurrent episodes of cholestasis, occurring with severe hyperbilirubinemia and skin itching, which resolve spontaneously without the development of progressive liver disease. Skin itching may be absent in a quarter of patients with BRIC. Other common symptoms include general weakness, nausea, vomiting, steatorrhea, decreased appetite, and weight loss. Fever, arthralgia, headache, urticaria and dermatophytosis on the background of erythematous rash are rarely observed. In the case of a protracted course, coagulopathy and hemorrhagic complications may be observed due to malabsorption of vitamin K. Laboratory tests of blood serum show a significant increase in the level of total bilirubin and bile acids, while an important distinguishing feature of BRIC and other forms of familial intrahepatic cholestasis is the level of GGTP, which remains normal or is minimally elevated [5, 6].

Attacks may persist for several months to 2 years, on average 32 weeks, and resolve spontaneously without the development of fibrosis or hepatocellular failure. Laboratory parameters of liver tests during the asymptomatic period are within normal values. If for PFIC, the manifestation in infancy or early childhood with the progression to end-stage liver disease in the second decade of life is typical, then the average age of the first episode in BRIC is 14 years. However, the range of disease onset can vary from 3 months to 48 years [7].

Due to the recurrent nature of the BRIC course, possible triggers of cholestasis episodes are of great interest. According to the literature, in 40% of cases, the provoking factor cannot be determined. The main triggers of cholestasis episodes were infectious diseases (mainly viral) in 54.3% of cases, pregnancy or the use of combined oral contraceptives (COCs) in 30%, drug therapy in 10%, and other causes in 5.7%. There was a correlation found between BRIC episodes and the use of the following drugs: tetracycline, acetaminophen, amoxicillin-clavulanic

acid, cefuroxime, erythromycin, and sulfonamides. Other rare triggers include vaccination and hyperthyroidism [8].

Genetic studies have revealed a relationship between the disease and pathogenic variants of the ATP 8 B 1 and ABCB 11genes, each of which encodes hepatocanalicular bile acid transporters [8]. Mutations in ATP8B1 gene are associated with the development of type 1 BRIC. ATP8B1 deficiency in hepatocytes induces a loss of aminophospholipids on the cytoplasmic surface of the canalicular membrane, which contributes to the destabilization of the canalicular membrane in terms of the effect of hydrophobic bile acids and disruption of the function of membrane transporters. This results in the accumulation of bile acids in hepatocytes and a compensatory increase in the concentration of cholesterol in bile. Changes in the biochemical composition of bile worsen its rheological properties, which contributes to the development of hepatocellular cholestasis. At the same time, the accumulation of bile acids in hepatocytes leads to their damage [9, 10].

BRIC type 2 is caused by a mutation in ABCB11 gene, which encodes the ATP-dependent bile salt export pump protein (BSEP) [11]. It is a liver-specific ATP-binding protein that transports conjugated bile salts from the hepatocyte into the bile canaliculi against the concentration gradient. An impaired BSEP function reduces the secretion of bile salts, leading to a decreased bile flow and the accumulation of bile acids inside hepatocyte with subsequent hepatocellular damage [12].

While the ABCB11 gene is expressed only in the liver and is often associated with the development of cholelithiasis and hepatobiliary neoplasms (hepatocellular carcinoma (HCC) and cholangiocarcinoma), the ATP8B1 gene is also detected in other organs, which explains extrahepatic manifestations of the disease, such as pancreatitis, diarrhea, and sensorineural hearing loss [8].

Mutations in the ATP8B1 and ABCB11 genes can phenotypically manifest as more severe forms of cholestatic diseases: PFIC types 1 and 2, respectively, ICP and drug-induced liver injury (DILI). The best studied subtypes of familial intrahepatic cholestasis are presented in the Table [13, 14].

Table. Characteristic features of best-studied familial intrahepatic cholestasis subtypes

Gene	Possible clinical phenotypes/symptoms	Diagnostic features
ATP8B1	BRIC 1, PFIC 1 Possible extrahepatic manifestations (diarrhea, pancreatitis, sensorineural hearing loss)	Increased serum bile acids Normal GGTP level LB: intracanalicular bile sludge
ABCB11	BRIC 2, PFIC 2, DILI, ICP or cholestasis while using COCs Cholelithiasis Risk of HCC and CCC	Increased serum bile acids Normal GGTP level Often increased ALT ≥ 5 ULN LB: giant cell hepatitis, bile filaments
ABCB4	PFIC 3, ICP, DILI, isolated increase in GGTP, LPAC syndrome	Increased serum bile acids Increased GGTP levels LB: ductule proliferation

Notes: CCC, cholangiocellular carcinoma; ULN, upper limit of normal; LB, liver biopsy; LPAC, low-phospholipid associated cholelithiasis

When performing a liver puncture biopsy during an episode of cholestasis, the most characteristic features of BRIC are centrilobular cholestasis, the presence of bile deposits in the tubules, in hepatocytes, and Kupffer cells. Less common are hepatocyte degeneration, necrosis in the pericentral zone, lobular and portal infiltration with the inclusion of mononuclear cells and eosinophils, and proliferation of cholangioli. In the asymptomatic period, the histological examination of the liver biopsy gives normal results [15].

In 2004, V. Luketic and M. Schiffman proposed diagnostic criteria for BRIC [5]:

- a history of several episodes of cholestasis separated by an asymptomatic period lasting for at least 6 months;
- absence of biliary hypertension according to MRCP data;
- absence of factors (for example, alcohol, medications, pregnancy, autoimmune cholestatic liver diseases, viral hepatitis, etc.) that provoke the cholestasis development;
- laboratory signs of intrahepatic cholestasis (increased bilirubin due to the conjugated fraction);
- normal level or minimal increase in GGTP;
- centrilobular cholestasis according to liver biopsy data.

In our described clinical case, the patient had the following characteristic features of BRIC: the disease onset in adulthood against the presence of acute hepatitis A, absent biliary hypertension according to imaging studies, isolated increase in total bilirubin for both fractions against normal GGTP values, vitamin K-associated coagulopathy, relatively benign course of cholestasis (absent hepatic encephalopathy, hypoproteinemia, the resolution of coagulopathy in response to therapy), prevalence of intracanalicular cholestasis with preserved liver tissue morphology. It was also noted that the patient's sister had an episode of ICP.

Because episodes of BRIC resolve spontaneously, the treatment should aim at relieving symptoms and preventing complications. There is currently no specific treatment that can completely prevent attacks.

In patients with BRIC during a long course of cholestasis attack, steatorrhea with significant weight loss and vitamin K-associated coagulopathy may occur. The main methods of correcting these conditions are a low-fat diet (less than 20 g/day), supplementation with

short-chain fatty acids and high doses of fat-soluble vitamins. In case of significant coagulopathy (INR> 2.5), parenteral administration of vitamin K preparations is possible [16].

The most common symptom of cholestasis attacks is skin itching. The use of statins, corticosteroids, UDCA, cholestyramine, and opioid receptor antagonists is usually ineffective [17].

Reduction of skin itching and reduction in the length of cholestasis episodes have been described in patients with BRIC taking rifampicin. The initial dose is 150 mg per day, if there is no effect and in good tolerance, the dose can be increased to the maximum 600 mg per day. However, in 12% of patients after 2–3 months of therapy, the drug-induced hepatitis with hepatocellular failure syndrome was recorded [18–20].

In case when therapeutic methods turn ineffective, it is possible to use extracorporeal detoxification methods, such as plasmapheresis or albumin-mediated hemodiafiltration (MARS) [6, 21].

Temporary endoscopic nasobiliary drainage may also be used to reduce episodes of cholestasis in order to eliminate excess bile acids from the enterohepatic circulation. The resolution of cholestasis attacks within a few days after nasobiliary drainage in patients with BRIC has been reported [22, 23].

Liver transplantation in patients with BRIC is not recommended because there are neither progressive forms of liver disease, nor hepatocellular insufficiency. However, the literature describes a case of persistent skin itching in a patient with BRIC, which required continuous plasmapheresis for 4 years. A significant decrease in quality of life required orthotopic liver transplantation [24].

Conclusions

In our reported clinical case, a lengthy episode of cholestasis in a 30-year-old man after acute hepatitis A served as an indication for admission at the Liver Transplantation Center. Based on the specific clinical presentation, laboratory blood test data, and morphological examination results, as well as genetic testing, the patient was diagnosed with benign recurrent intrahepatic cholestasis type 2. The episode of cholestasis with severe jaundice proceeded without skin itching. Treatment was aimed at eliminating hyperbilirubinemia. We did not note a significant effect from the use of glucocorticosteroids and ursodeoxycholic acid. Two plasmapheresis sessions conducted were accompanied by a short-term decrease in the bilirubin level. It is difficult to assess the effect of this procedure for further resolution of the cholestasis episode. Laboratory manifestations of vitamin K-associated coagulopathy were coped with after the first parenteral administration of menadione sodium bisulfite. During dynamic observation, the resolution of the cholestasis episode was achieved 5 months after its manifestation.

In conclusion we can state that clinicians' awareness of the clinical features of benign recurrent intrahepatic cholestasis course and screening the patients on the waiting list for this pathological condition are essential for timely diagnosis of the disease. This will help to identify those patients who can avoid liver transplantation and get the most benefit from alternative therapies.

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