Case Report

Insights of Clinical and Medical Images

Recurrent Hyperbilirubinemia - A Rare Case Of Benign Recurrent Intrahepatic Cholestasis - A Diagnostic Challenge

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1. Abstract

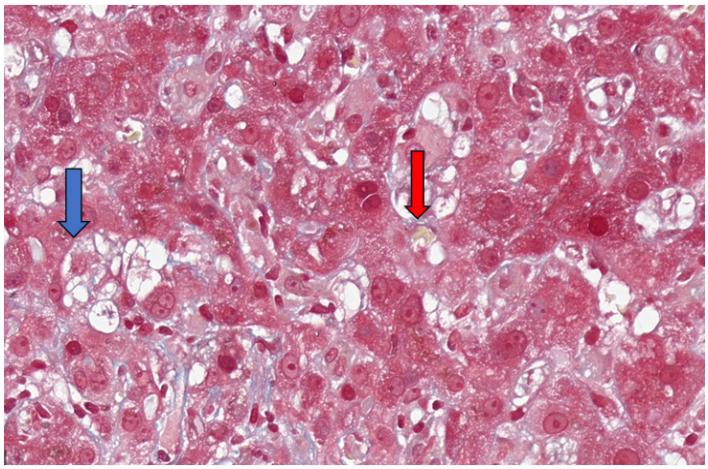
Benign recurrent intrahepatic cholestasis (BRIC) is a rare autosomal recessive disease with mutations in ATP8B1 or ABCB11 gene, characterized by repeated episodes of conjugated hyperbilirubinemia, jaundice, pruritus and general fatigue. Episodes last for weeks or months, followed by a complete clinical, biochemical, and histological remission period. We report the case of a young adult woman with heterozygote mutations in ABCB11 gene, who presented with recurrent jaundice and pruritis with negative diagnostic results for all possible etiologies and a liver biopsy that showed intrahepatic cholestasis without fibrosis. Patient improved on treatment with multiple plasmapheresis, but episodes are still repeating once to several times a year and has a pronounced impact on quality of life.

2. Case Report

19-year-old woman was hospitalised on 17.05.2013. with complaints of jaundice, pruritus, body rash, dark urine, and minor dyspeptic symptoms. Three weeks ago, a patient notes pharyngitis, a dry cough, a week later a rash has appeared on her arms, legs, and abdomen. Three days before inpatients, blood samples showed total bilirubin 107.8 µM/L, predominantly conjugated hyperbilirubinemia, ALT 95 U/L, AST 67 U/L. Patient denies other complaints, illnesses, allergies. No other medications and supplements were taken on daily basis, sexual contact was denied. Vaccination according to the mandatory vaccination calendar. Objectively patients' physical condition was moderate, the consciousness was clear, navigating in time, space, personality. Severe skin, sclera, and mucous jaundice. Maculopapular rash on arms, legs, and abdomen. Herpes labialis lesions. Lymph nodes unchanged. Abdomen was symmetrical, painless, liver along with rib arc, painless. Laboratory examination revealed leucocytosys 10.26 x 103/µL, changes in liver markers - total bilirubin 168.3 µM/L, conjugated bilirubin 129.1 µM/L, unconjugated bilirubin 39.2 µM/L, ALT 54 U/L, AST 44 U/L, alkaline phosphatase 105 U/L, alfa amylase 105 U/L, copper 27.9 µM/L, ceruloplasmin 0.315g/L which was within the limit of the norm. Negative serology for viral hepatitis, Epstein Barr virus, cytomegalovirus, HIV, and syphilis. The liver appeared normal on ultrasonography and magnetic resonance imaging with non - dilated intrahepatic and extrahepatic ducts, gallbladder also appeared normal with smooth walls and anechogenic fluid. Ultrasound-guided liver biopsy showed signs of acute hepatic injury with pericentrolobar and intracanalicular cholestasis. Portal fields were practically intact without acute injury or inflammatory cell infiltration, the tissue damage could be due to a toxic genesis.

The picture 1: Shows the liver fine needle biopsy in trichrome staining, with the blue arrow demonstrating hepatocyte hydropic changes and with the red arrow – cholestasis.

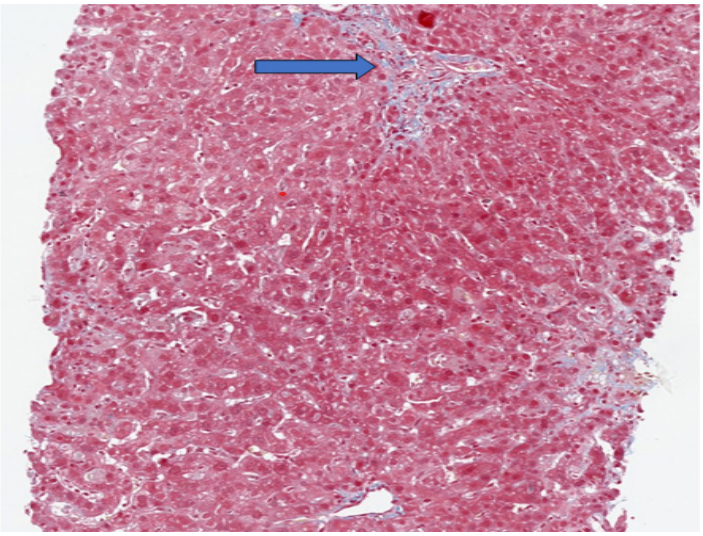
Picture 1: The liver fine needle biopsy, Trichrome staining



The picture 2: With the blue arrow demonstrates minimal fibrosis in portal field without inflammatory cell infiltration. Ophthalmologist

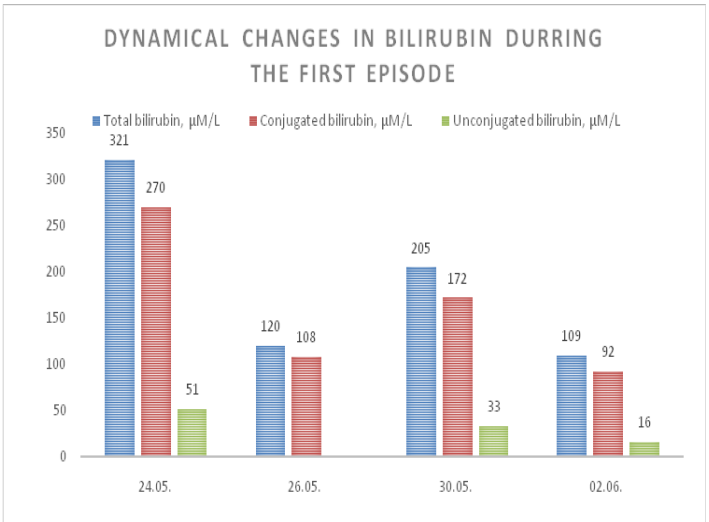
consultation – Kayser-Fleischer's rings have not been found.

Picture 2: The liver fine needle biopsy, Trichrome staining



The inpatient received Sol. NaCl 0.9% I/v, ursodeoxycholic acid 250 mg three times daily p/o, omeprazole 20 mg twice daily. Despite the treatment received, the patient's total bilirubin continued to increase. Repeated abdominal ultrasonography is performed to rule out the causes of post-hepatic jaundice, a slightly heterogeneous, oedematous structure of the left liver lobe with small double-duct structures is described, a small intrahepatic dilatation of the bile duct cannot be ruled out. The gallbladder is small. There are no free liquid collections. In localisation of the right ovary, a relatively large septal cystic structure 6.5 cm in diameter. The diagnosis is unclear. As jaundice increases despite previous therapy, a plasmapheresis procedure was performed, the total amount of fluid administered in 2250 ml. The patient tolerates it well. Positive dynamics are observed – total bilirubin starting to fall from 321 µM/L to 109 µM/L, jaundice and pruritus were reduced.

Picture 3: Dynamical changes in bilirubin during the first episode.



The patient is discharged with recommendations to continue ursodeoxycholic acid 250 mg three times a day orally and loratadine 10 mg once a day orally. Discharging diagnosis – reactive hepatitis. Liver markers return to normal within few weeks, there were no complaints. In December of the following year (2014), the woman is re-inpatient with complaints of fatigue, pruritus especially in the evenings, increasing jaundice, notes delay in the menstrual cycle and stronger menstruation. In blood biochemistry, hyperbilirubinemia with elevation of conjugated bilirubin, total bilirubin 66.7 µM/L, dynamically increases. ANA, c-ANCA, p-ANCA, AMA were negative, haptoglobin and alpha1 antitrypsin at normal levels, viral hepatitis markers and HIV antibodies negative. Fecal analyses do not find helminth eggs, intestinal protozoa and their cysts, the hidden blood test was negative. Abdominal ultrasonography is repeated, with no significant changes from previous ultrasonography. Duodenogastric bile reflux is found in fibrogastroscopy. No pathology is found on echocardiography. The patient is discharged with previous recommendations but is again hospitalized two weeks later with increasing jaundice, pruritus, dark urine, acholic feces. Total bilirubin 147.2 µM/L, ALT 34 U/L, AST 47 U/L, alpha amylase 93 U/L. The magnetic resonance imaging was performed in which no abnormal changes were seen.

There are no evidence of pre-hepatic or post-hepatic jaundice, no signs of Gilbert's disease, the course of the disease suggests genetically determined disorder of bilirubin elimination. The patient is discharged in a satisfactory condition with recommendations to continue ursodeoxycholic acid as before. Diagnosis at discharge – chronic non-differentiated hepatitis. Such episodes occur once to several times a year, as summarized in Table 1. In 2016 genetic analysis reject the presence of Rotor's syndrome. In 2016, the patient was hospitalized at another hospital with the same clinical symptoms as before. The patient was repeatedly extensively examined - ultrasonography and magnetic resonance imaging of the abdominal cavity, liver puncture biopsy in ultrasonography control, no changes in dynamics were detected. Diagnosis at discharge – undifferentiated hyperbilirubinemia.

Table 1: Summary of the follow-up of the disease

Date	Total bilirubin, µM/L	Symptoms	Therapy
05.2013.	168.3	Jaundice, severe pruritus, maculopapular rash, dark urine, abdominal discomfort	Ursodeoxycholic acid, Sol. NaCl 0.9%, omeprazole, 3 plasmapheresis
12.2014.	93.3	Fatigue, severe pruritus, jaundice, symptoms emerged after a delay in the menstrual cycle and stronger menstruation	Ursodeoxycholic acid, Sol. NaCl 0.9%

01.2015.	147.2	Increasing pruritus, jaundice, acholic feces	Ursodeoxycholic acid, Sol. NaCl 0.9%
01.2016.	185	Pruritus, jaundice, dark urine, acholic feces	Ursodeoxycholic acid, Sol. NaCl 0.9%, Suprastine
01.2016.	326.9	Fatigue, pruritus, jaundice	Ursodeoxycholic acid, 3 plasmapheresis ,colestyramine, Sol . NaCl 0.9%
11.2016.	517	Increasing pruritus, jaundice	Ursodeoxycholic acid, rifampin, Sol. NaCl 0.9%
06.2017.	458	Pruritus, jaundice	Ursodeoxycholic acid, 4 plasmapheresis, Sol . NaCl 0.9%
04.2018.	323.3	Increasing pruritus, jaundice, dark urine, acholic feces, symptoms emerged after a delay in the menstrual cycle	Ursodeoxycholic acid, 5 plasmapheresis, Sol. NaCl 0.9%
07.2019.	331.9	Increasing pruritus, jaundice, dark urine, acholic feces, insomnia, symptoms emerged afte r a delay in the menstrual cycle	Ursodeoxycholic acid, 6 plasmapheresis, Sol. NaCl 0.9%
08.2019.	367.2	Increasing pruritus, jaundice	Ursodeoxycholic acid, 7 plasmapheresis , Sol. NaCl 0.9%
10.2020.	383.2	Increasing jaundice	7 plasmapheresis
05.2021.	224.9	Increasing jaundice	8 plasmapheresis
06.2021.	162.3	Increasing jaundice	4 plasmapheresis
05.2022.	321	Jaundice, dark urine, acholic feces, insomnia, difficulty concentrating	Ursodeoxycholic acid, 6 plasmapheresis, Rifampin, Sol. NaCl 0.9%
12.2022.	418	Increasing pruritus, jaundice, dark urine, acholic feces, insomnia, difficulty concentrating, symptoms emerged after a delay in the menstrual cycle	Ursodeoxycholic acid, 6 plasmapheresis, Sol. NaCl 0.9%

In 2018, complaints about jaundice and pruritus after starting menstruation, which have been with severe pain syndrome, additionally had vomiting and epigastric pain before being hospitalized. Upon occurrence, total bilirubin 323.3 μM/L. Repeated abdominal ultrasonography - without dynamics, without abnormal changes. Positive dynamics after five plasmapheresis - total bilirubin 159.5 μM/L. Genetic analyses are performed using polymerase chain reaction (PCR) and gene sequencing confirming the diagnosis of benign recurrent intrahepatic cholestasis type 2 with heterozygote mutations in the ABCB11 gene. Patient has been hospitalized 7 more times by 2022. with the typical clinical symptoms. In all cases, positive dynamics following plasma exchange and plasma absorption procedures with special absorbent BS330 are observed.

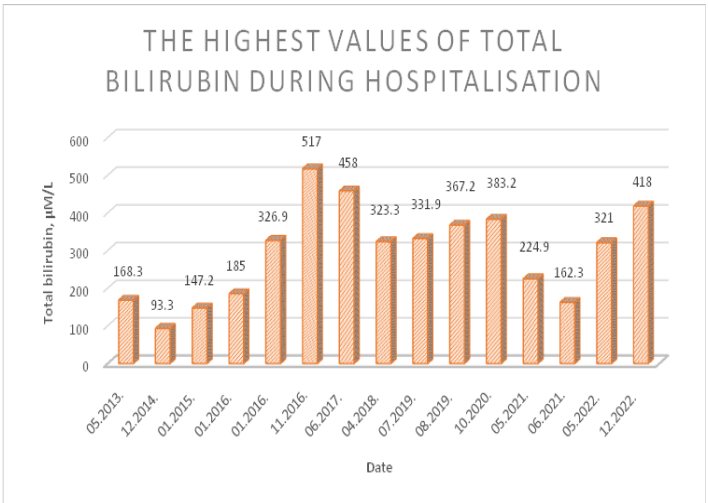
3. Discussion

Benign recurrent intrahepatic cholestasis (BRIC) is an autosomal recessive disease with mutations in genes encoding hepatocyte bile duct membrane proteins -- familial intrahepatic cholestasis protein 1 (FIC1, gene ATP8B1) and bile salt export pump (BSEP, gene ABCB11) [1]. ABCB11 mutations may be inherited or occur in de novo, most commonly in homogeneous form, but other mutations in heterozygous form are also observed in approximately 30% of patients [2]. However, cases with heterozygous changes are also described in the literature, but much less common. Most often, the first episode of cholestasis occurs before the second decade but may vary from infant age to middle age. The literature cites some triggers as oral contraceptives, infections, and pregnancy, and it is thought that consuming supplements in young men who engage in bodybuilding could be a trigger for cholestasis. The episodes are characterised by intermittent jaundice, pruritus, dark urine and acholic feces. There may be accompanying abdominal pain, fever, and general fatigue. Variations and severity of clinical manifestations are strongly individual. Cholestatic episodes can take a couple of months and can intervene with clinical remission periods [1]. The frequency of episodes varies from a few episodes per year to one episode per decade [3]. Laboratory examination shows hyperbilirubinaemia with elevation of direct bilirubin and cholestasis without liver injury[3].

Liver biopsy performed during hyperbilirubinaemia shows centrilobar cholestasis, very rarely inflammatory cell infiltration in the portal fields, liver histology is normal during remission. Although the disease may adversely affect a patient's quality of life, it does not cause progressive liver damage and, unlike progressive familial intrahepatic cholestasis, does not cause liver failure [1]. The clinical diagnosis of BRIC requires three criteria: at least two episodes of jaundice with symptom-free periods lasting several months to years; laboratory changes that show intrahepatic cholestasis with increased gamma-glutamyl transferase (GGT) and bilirubin; severe pruritus and normal intrahepatic and extrahepatic bile ducts in cholangiography [4]. It is thought that gene mutations in ATP8B1 and ABCB11 should be called BRIC1 and BRIC2 respectively. There are clinical differences between the two subtypes, e.g. in BRIC1 a frequent extrahepatic manifestation is acute pancreatitis, which is not observed in

BRIC2, where cholelithiasis is a frequent clinical manifestation [3]. At the moment there is no specific treatment option, symptomatic therapy is used, most often ursodeoxycholic acid, which greatly reduces pruritus. However, other options for reducing symptoms are also described, such as rifampin, cholestyramine, plasmapheresis, which in some cases produce positive dynamics, and endoscopic nazobiliary drainage can be performed in patients who do not respond to the above-mentioned treatment [4]. Liver transplantation is not considered as the disease is not progressive [3]. In cases where patients are hospitalised with an episode of jaundice, exams are carried out to help differentiate between the most common causes of pre-hepatic, hepatic and post-hepatic jaundice, such as haemolysis, viral or toxic hepatitis, choledocholitiasis or other obstructive biliary diseases. In this case, the patient was excluded from all common pathologies, as well as autoimmune hepatitis, Wilson's disease, primary sclerosing cholangitis and primary biliary cholangitis, which further suggested rarer diseases, especially when conjugated episodes of hyperbilirubinemia were repeated and no other abnormal findings were found.

Picture 4: The highest values of total bilirubin during hospitalisation



In the conclusion of a liver biopsy, the pathologist suspected drug-induced hepatitis, most likely after the patient's age, could be caused by oral contraceptives, but in this case the patient does not take them. Histologic finding is very similar to drug-induced liver damage, especially estrogen, anabolic steroid and parenteral nutrition, which also produces intrahepatic cholestasis [1]. Therefore, patients with jaundice should be carefully asked about the use of various drugs and also supplements. Jaundice due to intrahepatic cholestasis is also described as a paraneoplastic phenomenon in patients with lymphoma and Stauffer's syndrome. In Hodgkin's lymphoma, two clinical syndromes are described: idiopathic cholestasis and vanishing bile duct syndrome, but both manifestations are very rare [5]. Stauffer's syndrome, on the other hand, is a paraneoplastic phenomenon associated with renal cell carcinoma, but jaundice is very rare in syndrome and only a few cases are reported in literature [6]. In this case, the patient was extensively examined and there is no suspicion of lymphoma or other malignancy. In literature, homozygous gene mutations and additional heterozygous mutations in other cholestasis-related genes are most commonly described. Which is interesting in this case, there was only one detected heterozygous mutation in ABCB11 and no other heterozygous changes were found.

A similar case has been described in a 27-year-old woman for whom the first episode of cholestasis has started after pregnancy and genetic analyses show heterozygous changes in ABCB11, NPH4 and A1ATD genes, which are also associated with bile elimination disorders, the authors of the clinical case believe that multiple heterozygous changes determine the severity of the clinical manifestations of the patient concerned [7]. Perhaps in this particular case, repeated genetic analyses should be carried out that would test for even rarer mutations in the genes responsible for the formation and elimination of bile salts. The disease does not have a progressive nature, which is also objectively assessed by fibroelastography (grade F0-F1), but results in a marked deterioration in quality of life, again in this particular case the patient developed depression. A number of treatment options were tried during treatment, such as ursodeoxycholic acid, which did not produce positive dynamics during the first time of hospitalisation, but later gave some improvement in symptoms. Rifampin therapy was also used, but there are no data on the effect. The best therapeutic effect was given directly by plasma exchange (PEX) and plasma absorption perfusion (PAP) with BS330 absorbent. The molecular absorption recirculating system (MARS) is also used to correct hyperbilirubinaemia, but in a 2017 study comparing the effectiveness of all three methods to reduce hyperbilirubinaemia, it was MARS that performed slightly worse, so PAP, the most cost - and time-effective, is nominated as the first choice therapy, and MARS is recommended as a choice for patients with kidney disease [8].

4. Summary

BRIC is an autosomal recessive disease with mutations in genes encoding hepatocyte bile duct membrane proteins most commonly in homogenous form, only 30% of cases have multiple heterozygous changes. The case demonstrates unusual example of BRIC with heterozygous mutations in only one hepatocyte bile duct membrane protein encoding gene and explicit clinical symptoms. It is believed that multiple heterozygous changes determine the severity of the clinical manifestations of the patient concerned, but this example proves otherwise.

5. Conclusions

BRIC is a rear disease, to label a rare disease, practically all causes of pre-hepatic, hepatic and post-hepatic jaundice should be considered. Only after numerous episodes of relapses and remissions it could be asserted that this disease has a recurring pattern. Although there is currently no specific treatment available to prevent recurrence, the disease does not progress and has a benign course.

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