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*Case Report*

# Byler's disease in a young child (own clinical observation)

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## ABSTRACT

Bailer's disease is an ultra-rare (orphan) pathology associated with a deficiency of the membrane enzyme responsible for the transport of fat-soluble compounds and bile acids through the tubular membrane of the hepatocyte, as a result of which they accumulate in liver cells and have a damaging effect on them, being triggering factors of apoptosis. A clinical case of diagnosis of progressive familial cholestasis in a child aged 2 months with genetic verification of the diagnosis and successful treatment, including liver transplantation, is presented. Two mutations in the heterozygous state were identified: the previously described pathogenic mutation CM033442 and a previously undescribed mutation in the PGM1 gene.

**Keywords:** Progressive familial intrahepatic cholestasis, Byler's disease, Cholestasis, Children

## INTRODUCTION

Byler's disease can be classified as a rare cause of non-obstructive forms of cholestasis, it accounts for no more than 13% of cases. The modern name of the disease/Byler syndrome is progressive familial intrahepatic cholestasis or (PFIC).[1,2] At present, three types of diseases have an autosomal recessive type of inheritance, manifest cholestasis and, as a rule, lead to the formation of cirrhosis of the liver already in the 1st year of life. The frequency of pathology in different countries ranges from 1/50,000 to 1/100. The clinical picture of all three types is similar and includes conjugated hyperbilirubinemia, manifested by jaundice with an olive (greenish) tinge as well as a change in the colour of faeces and urine. A typical symptom is skin itching, significantly disrupting the well-being of patients with hepatomegaly.[3] Fibrosis and cirrhosis of the liver, hepatic cell insufficiency and portal hypertension develop rapidly.[4]

## CASE REPORT

A clinical case is presented demonstrating the classic course of PFIC with the development of severe liver damage that required liver transplantation, which we observed from the age of 2 months.

The girl D. was hospitalised in a children's clinical hospital at the age of 2 months and 9 days at the direction of a district paediatrician for detected hepatosplenomegaly and hyperbilirubinemia. The mother is 28 years old, was observed for mitral valve prolapse and rare supraventricular extrasystole. The father of the child, as well as the brothers and sisters of the mother and father are healthy. The parents are not related by blood. Pregnancy II proceeded with bronchitis at 30 weeks, childbirth II, urgent and physiological. At birth, the weight is 3020 g, the body length

is 50 cm, the head circumference is 34 cm and the Apgar score is 7/8 points. Vaccinated against tuberculosis and viral hepatitis. She was discharged from the maternity hospital for 4 days of life in a satisfactory condition. The hemoglobin level was 192 g/l of total bilirubin 190 mmol/l. At the age of 1.5 months, due to the preservation of jaundice, a biochemical blood test was performed: total bilirubin −126.6 mmol/l, direct bilirubin −68.5 mmol/l, ALT −98 units/l and AST −62 units/l. There was an increase in the liver by 3 cm from the edge of the costal arch, the spleen by 4 cm. Physical development is below average and harmonious (weight −4650 g, height −54 cm).

## DISCUSSION

Neuropsychic development corresponded to age. The skin and sclera are yellowish with an olive tinge. Urine is intensely coloured. The stool is slightly discoloured. At the first stage, a differential diagnosis was made between biliary atresia, hepatitis and haemolytic anaemia. The hemoglobin level was 95-83 g/l. The level of total bilirubin was 332 mmol/l, direct 71.0 mmol/l, ALT −165 units/l, AST − 286 units/l, total protein −42.9 g/l, fibrinogen −0.89 g/l, γ-GTP −65.0 units/l and alkaline phosphatase −1590 units/l. Haemolytic anaemia was ruled out by a double negative Coombs test. Methods of serology and PCR revealed intrauterine cytomegalovirus infection: IgG −26 units/ml, IgG avidity −74.46% (high) and blood test for hepatitis B and C negative. During an MRI of the abdominal cavity, the heterogeneous structure of the liver was determined, and the gallbladder was not visualised, which did not allow to exclude the diagnosis of biliary atresia. Given the high level of conjugated bilirubin, in the absence of an increase in γ-GTP, PFIC (Byler's disease) was suspected. Before the diagnosis was clarified, the child received ursodeoxycholic acid, ganciclovir intravenously and fat-soluble vitamins. At the age of 2 months and 19 days, the girl was hospitalised in surgical department No. 2 of the Russian Children's Clinical Hospital to exclude biliary atresia. A tandem mass spectrometric study was conducted in the laboratory of the Moscow Medical and Genetic Research Centre (head – Doctor of Medical Sciences E.Yu.) and hereditary amino acid pathology, organic aciduria and defects of mitochondrial β-oxidation were excluded from the study. The level of α-fetoprotein in the blood was 5333 IU/ml (the norm is up to 100 IU/ml). The laboratory of selective screening of the medical genetic research centre conducted a study of bile acids in urine using high-performance liquid chromatography in combination with tandem mass spectrometry (HPLC-MS/MS). The changes characteristic of the cholestasis syndrome was revealed. At the age of 4 months, 47 genes were analysed by targeted sequencing: changes in the nucleotide sequence in the gene POLG: NM 002693: exzon3:c. G803C: p G2680A in the heterozygous state were revealed. This replacement is described in the database as pathogenic SM033442. A pathogenic mutation was found in the PGM1 gene: NM 002633: in exon 9: c.1376 1377 del: pF459 fs in a heterozygous state. This mutation is not described in the human mutation database; however, it can be pathogenic with a high probability since it leads to a shift in the reading frame and premature termination of protein translation.

The examination made it possible to formulate the final clinical diagnosis: PFIC type I (Byler's disease). By the age of 5 months, the child's condition had negative dynamics, which was manifested by an increase in the liver + 5 cm, spleen + 5 cm below the costal edge, there was an expansion of subcutaneous veins on the anterior abdominal wall, jaundice of the skin and sclera persisted. Indicators of physical development and nutritional status decreased, direct hyperbilirubinemia, cytolysis syndrome and hypoproteinemia persisted [Figures 1-3]. Taking into account

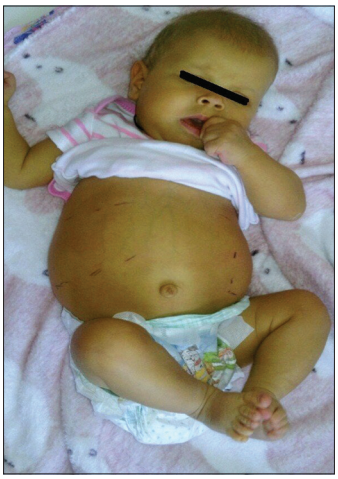

**Figure 1:** Ictericity of the skin with an olive shade.

**Figure 2:** Abdominal enlargement due to splenic and hepatomegaly.

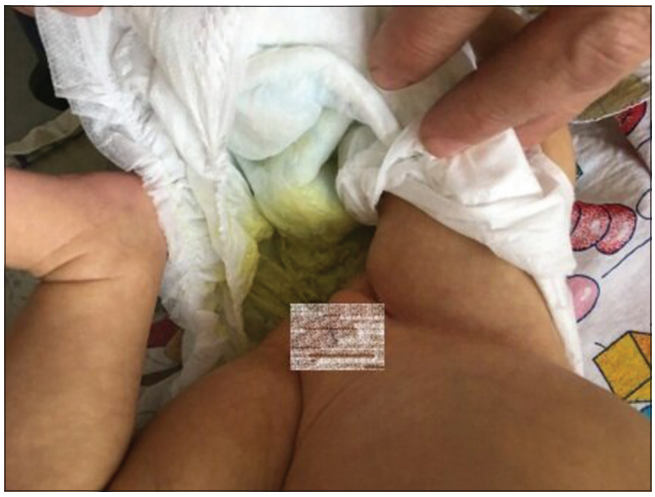

**Figure 3:** Discoloured faeces.

the progressive course of liver disease with the development of cirrhosis and hepatic cell insufficiency, on 26 February, 18, at the age of 6.5 months (that is, 1.5 months after diagnosis), a corresponding operation was performed at the Academician V.I. Shumakov National Medical Centre for transplantation and artificial organs. A fragment of the mother's liver was used for transplantation. In the postoperative period, the child received tacrolimus, methylprednisolone, valacyclovir, ursodeoxycholic acid, famotidine, fat-soluble vitamins, dipyridamole and cotrimoxazole. The patient's condition quickly stabilised: Jaundice disappeared after 3 days, the spleen decreased and the biochemical parameters of liver blood approached normal by the 2nd week after surgery. At present, the girl at the age of 4 years has normal physical and neuropsychic development: weight 17 kg and height 99 cm continue to receive immunosuppressive therapy with tacrolimus. The results of general clinical and biochemical blood tests are normal.

## CONCLUSIONS

The presented clinical case demonstrates the possibility of nosological diagnosis of a rare hereditary pathology manifested by such a common syndrome of neonatal hyperbilirubinemia. To confirm the diagnosis, a genetic study was conducted, the results of which made it possible to diagnose Byler's disease. However, the role of the two mutations found in the heterozygous state has not been fully determined. The first mutation in the POLG: NM 002693 gene is described in the database as pathogenic CM033442. The second, in the gene PGM1:NM 002633, is not described in the database but is probably pathogenic.

Attention should also be paid to the detection of active cytomegalovirus infection in the child, which required specific therapy. As noted in some sources, CMV infection is often found in newborns with the cholestatic syndrome, which can complicate diagnosis and treatment. Timely liver transplantation provided the patient with a favourable outcome. It is obvious that for many cases of unspecified hyperbilirubinemia of newborns (both 'transient' and persistent), there are genetic syndromes, timely diagnosis of which will allow to correctly determine the prognosis of the disease and prescribe effective therapy on time.

### Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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### Conflicts of interest

There are no conflicts of interest.

## REFERENCES

1. Jankowska I, Socha P. Progressive familial intrahepatic cholestasis and inborn errors of bile acid synthesis. Clin Res Hepatol Gastroenterol 2012;36:271-4.
2. Kaganov BS, Strokova TV, Machula IV, Kamenets EA, Zakharova EY. The case of Byler's syndrome. Exp Clin Gastroenterol 2012;1:43-8.
3. Polyak ME, Metelin AV, Koroteeva NA, Lurie YE, Kim EF, Zaklyazminskaya E. The case of DNA diagnostics and medical genetic counseling of progressive familial intrahepatic cholestasis Type II Klin. and experiment, hir. J Acad B V Petrovsky 2015;13:36-41.
4. Varma S, Revencu N, Stephenne X, Scheers I, Smets F, Beleza-Meireles A. *et al*. Retargeting of bile salt export pump and favorable outcome in children with progressive familial intrahepatic cholestasis Type 2. Hepatology 2015;62:198-206.

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