Type 3 of progressive familial intrahepatic cholestasis (PFIC-3): Case report

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Abstract

Progressive familial intrahepatic cholestasis (PFIC) is an abnormality in the formation and secretion of bile components and bile acids.We present a case of a 6-years-old female with Type 3 of PFIC which was confirmed via detecting pathogenic variants in the ABCB4 gene.

Type 3 of progressive familial intrahepatic cholestasis (PFIC-3): Case report

Abstract

Progressive familial intrahepatic cholestasis (PFIC) is an abnormality in the formation and secretion of bile components and bile acids, which present in infancy and early childhood as signs of growth failure and vitamin K deficiency. We present a case of a 6-years-old female who complained of yellow discoloration of the sclera and skin and abdominal distension. Her history revealed tiredness, mild abdominal pain, itching, frequent bleeding, and epistaxis. At first, hepatic cirrhosis was the diagnosis, but the abdominal ultrasound revealed hypoechoic lesions with the normal bile duct. The diagnosis of PFIC-3 was confirmed via detecting pathogenic variants in the ABCB4 gene. Progressive Familial Intrahepatic Cholestasis type 3 is an extremely rare case in the literature, which we can add to the other reported cases previously.

Keywords

Progressive familial intrahepatic cholestasis, Type 3, ABCB4 gene, vitamin K deficiency, Case report

Introduction

Progressive familial intrahepatic cholestasis (PFIC) is a heterogeneous group of genetic autosomal recessive disorders which cause defects in the formation and secretion of bile components and bile acids [1]. Progressive Familial Intrahepatic Cholestasis consists of five different variant forms numbered 1 through 5 based on the gene involved [2]. Most of these disorders present in infancy and early childhood as signs of growth failure vitamin K deficiency (i.e., easy bruising, epistaxis, coagulopathies) due to impaired vitamin K absorption and progressive liver disease leading to cirrhosis before adulthood [1. 2].

Progressive Familial Intrahepatic Cholestasis type 3 is an autosomal recessive disorder arising from mutations in the ATP-binding cassette subfamily B member 4 (ABCB4) gene located on chromosome 7 [3]. This gene encodes multidrug resistance protein-3 (MDR3). This 12-domain transmembrane plasmalemmal translocator actively transports phosphatidylcholine from the inner to the outer canalicular membrane to neutralize bile salts and prevent injury to biliary epithelial and bile canaliculi [4].

The PFIC-3 patients are homozygous or compound heterozygous for ABCB4 pathogenic variants; however, monoallelic ABCB4 variants may also result in cholestatic liver disease [5]. Genetic testing confirms the diagnosis of PFIC syndromes for all types, and immunostaining can confirm the diagnosis of PFIC types 2 and 3 [6. 7].

There were no approved pharmacological treatment options to treat PFIC that may lead to symptom relief or even limit the disease progression. Ultimately, liver failure would be the definitive result and may indicate a need for liver transplantation [6].

Case report

A 6 years old girl presented to the internal medicine clinic in King Saud medical city due to yellow discoloration of the sclera and skin and abdominal distension. The parents reported that their child has recently complained of tiredness, mild abdominal pain, itching, frequent bleeding, and epistaxis. Her parents have noticed the abdominal distension earlier. However, they have not sought any medical consultation until they noticed the yellow discoloration of the skin and mucous membranes at four. She was diagnosed with hepatic cirrhosis of unknown etiology at the time. Her family history was unremarkable, but the parents have mentioned that they were second-degree relatives.

The physical examination revealed a yellow discoloration of the skin sclera and the mucous membranes, failure to thrive, hepatosplenomegaly, moderate ascites, and ecchymosis in both legs.

Her vital signs were normal, and the physical examination was otherwise normal.

The abdominal ultrasonography examination reported that the liver was of average size measuring 11.5 cm coarse parenchymal echo pattern, with multiple small variable sizes ill-defined hypoechoic lesions (Fig. 1), the gallbladder had a thick wall yet no stones or biliary sludge were seen inside (Fig. 2), and splenomegaly was also reported. The examination was otherwise normal. The complete blood count test revealed mild normocytic normochromic anemia, mild leukopenia, and neutropenia, Thrombocytopenia, as hemoglobin levels were 11.2 g/dl (normal g/dl), hematocrit of 32.0 percent (normal percent), mean corpuscular volume of white blood cell count 4.47 10ˆ3/ul (normal 10ˆ3/ul), platelet count of 92 10ˆ3/ul. Other laboratory tests revealed elevated serum AST of 223 U/L (normal $<$ 40 U/L), ALT of 115 U/L (normal $<$ 50 U/L), and total bilirubin levels of 4.14 mg/dl (normal 0.2-1.3 mg/dl), alkaline phosphatase levels of 647 U/L (normal 38 - 126 U/L) whereas serum GGT was not measured. Thyroid-stimulating hormone was also measured and revealed a serum level of 6.54 mIU/l (normal 0.465-4.68 mIU/L), the measurement of endomysial autoantibodies was positive. Other laboratory tests were in the normal range. The diagnosis of PFIC-3 was confirmed via detecting pathogenic variants in the ABCB4 gene. The patient has been listed as a candidate for liver transplantation, as the patient showed signs of portal hypertension in ultrasonography examination after a one-year follow-up.

Discussion

PFIC-3 is an autosomal recessive disease. This is a rare case of PFIC-3, which results from consanguineous parents. The parents are second-degree relatives with no clinical signs of PFIC-3. Neither the mother nor the patient had reported jaundice in the post gestation period. The patient's siblings are unaffected but were recommended for carrier testing.

PFIC-3 usually manifests in later childhood or young adulthood. Unlike type 1 and type 2, PFIC-3 has a later onset and slower prognosis [8]. In our case, signs of splenomegaly appeared in the infancy period, but jaundice was delayed until four years of age. Occasional ascites and leg pigmentations have been noted after. Coagulation profile abnormalities are coherent with obstructive chronic liver disease. Infections with Salmonella typhi or Brucella were excluded. Serology testing for Hepatitis B and C were also negative.

A variant of uncertain significance has been detected in the PC gene, which is associated with pyruvate carboxylate deficiency. Although the clinical picture is not adequately consistent with severe types of pyruvate carboxylate deficiency, episodic types cannot be excluded. Thus, further genetic counseling may be required.

Symptomatic treatment involving Ursodeoxycholic acid was ordered. The patient is beginning to show signs of portal hypertension. She is on the list for liver transplantation, and it's expected to be fully curable.

A similar case has been described by Zhang et al. [9] in which PFIC-3 is combined with biliary atresia. A 4-month-old female presented with severe jaundice, pruritus, and pale stool for 20 days. Abnormally strong echoes near the portal area, an abnormally small gallbladder with an irregularly stiff wall, and splenomegaly were identified on abdominal ultrasound. Blood tests showed elevated liver enzymes as well. Kasai portoenterostomy was enough to relieve clinical symptoms and improve blood tests. To compare with our Case, this patient presented at a younger age, with more complicated symptoms due to biliary atresia, and eventually required the Kasai procedure. Similar ultrasound features and elevated liver blood tests were observed. The diagnosis was confirmed by genetic testing of the ABCB4 gene as well.

Additionally, Lipiński et al. have reported four cases of PFIC-3 [10]. The mean age was 7. Only two of them presented with pruritus, and all of them had splenomegaly. All of them established chronic cholestatic liver disease of unknown etiology, which was the key to order genetic counseling. Several novel variants have been identified. They concluded that the clinical phenotype of PFIC-3 could be variable, and the diagnosis of PFIC-3 is difficult because some PFIC-3 patients initially presented with no jaundice. Fortunately, in our case, our patient's main complaint was jaundice, which helped faster diagnosis.

Conclusion :

Children with jaundice, and elevated liver enzymes, with unknown etiology, should always be considered for genetic testing. Although PFIC-3 is not widely common, we recommend that consanguineous parents should undergo genetic counseling before conceiving.

References:

1 - Goubran, M., Aderibigbe, A., Jacquemin, E. et al. Case report: progressive familial intrahepatic cholestasis type 3 with compound heterozygous ABCB4 variants diagnosed 15 years after liver transplantation. BMC Med Genet 21, 238 (2020). https://doi.org/10.1186/s12881-020-01173-0

2 - Davit-Spraul, A., Gonzales, E., Baussan, C. et al. Progressive familial intrahepatic cholestasis. Orphanet J Rare Dis 4, 1 (2009). https://doi.org/10.1186/1750-1172-4-1

3 - de Vree J, et al. Mutations in the MDR3 gene cause progressive familial intrahepatic cholestasis. Proc Natl Acad Sci U S A. 1998;95(1):282 7. https://doi.org/10.1073/pnas.95.1.282

4 - De Masi R, et al. Progressive familial intrahepatic cholestasis type-3 and multiple sclerosis: lessons from comorbidity. Annals of Clinical and Translational Neurology 6: 2347-2350, No. 11, Nov 2019. Available from: URL: http://doi.org/10.1002/acn3.50883

5- Patryk Lipiński, Elżbieta Ciara, Dorota Jurkiewicz, Rafał Płoski, Marta Wawrzynowicz-Syczewska, Joanna Pawłowska, Irena Jankowska: Progressive familial intrahepatic cholestasis type 3: Report of four clinical cases, novel ABCB4 variants and long-term follow-up, Annals of Hepatology, Volume 25, 2021, 100342, ISSN 1665-2681, https://doi.org/10.1016/j.aohep.2021.100342

6- Alastair Baker, Nanda Kerkar, Lora Todorova, Binita M. Kamath, Roderick H.J. Houwen: Systematic review of progressive familial intrahepatic cholestasis, Clinics and Research in Hepatology and Gastroenterology, Volume 43, Issue 1, 2019, Pages 20-36, ISSN 2210-7401, https://doi.org/10.1016/j.clinre.2018.07.010

7- Ulrich Beuers, Michael Trauner, Peter Jansen, Raoul Poupon, New paradigms in the treatment of hepatic cholestasis: From UDCA to FXR, PXR and beyond, Journal of Hepatology, Volume 62, Issue 1, Supplement, 2015, Pages S25-S37, ISSN 0168-8278, https://doi.org/10.1016/j.jhep.2015.02.023

8-Gunaydin, M., & Cil, A. T. B. (2018). Progressive familial intrahepatic cholestasis: diagnosis, management, and treatment. Hepatic Medicine : Evidence and Research, 10, 95. https://doi.org/10.2147/HMER.S137209

9- Zhang, B. P., Huang, Z. H., & Dong, C. (2019). Biliary atresia combined with progressive familial intrahepatic cholestasis type 3: A case report and review of the literature. Medicine, 98(19). https://doi.org/10.1097/MD.0000000000015593

10- Lipiński, P., Ciara, E., Jurkiewicz, D., Płoski, R., Wawrzynowicz-Syczewska, M., Pawłowska, J., & Jankowska, I. (2021). Progressive familial intrahepatic cholestasis type 3: Report of four clinical cases, novel ABCB4 variants and long-term follow-up. Annals of Hepatology, 25, 100342. https://doi.org/10.1016/J.AOHEP.2021.100342

Figure legends

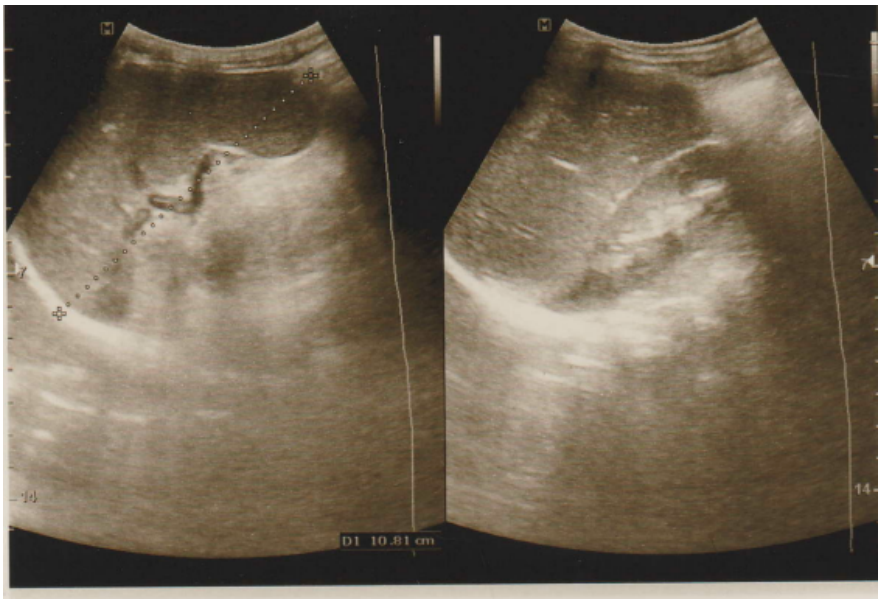

Figure 1 : Abdominal ultrasound revealed multiple small variable sizes ill-defined hypoechoic lesions

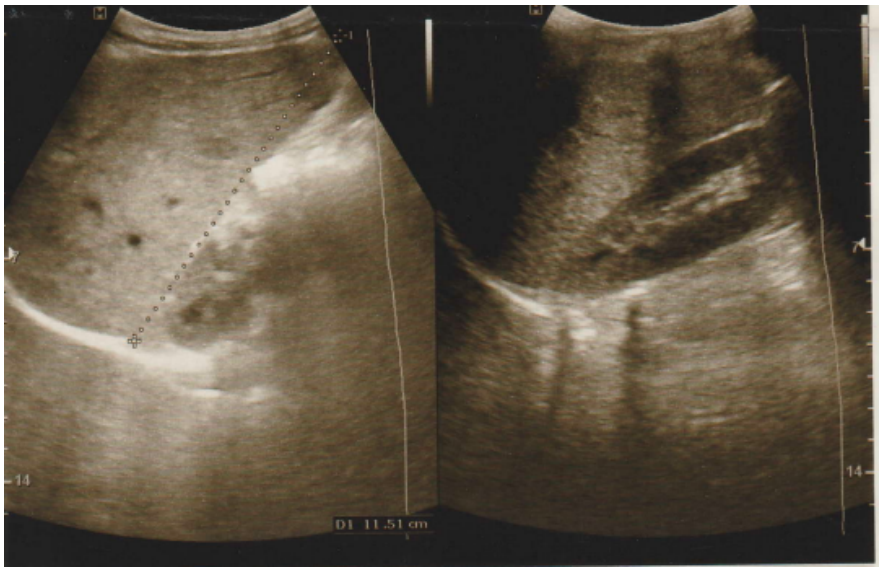

Figure 2 : Abdominal ultrasound revealed no stones or biliary sludge in gallbladder.