

CASE REPORT

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Progressive familial intrahepatic cholestasis type 5 due to a novel mutation in the *NR1H4* gene

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Abstract

Progressive familial intrahepatic cholestasis type 5 is a rare cause of neonatal cholestasis with low-to-normal levels of gamma-glutamyl transpeptidase. It is caused by mutations in the *NR1H4* gene, which encodes farnesoid X receptor, an important transcription factor for bile formation. It also plays an essential role in biliary acid homeostasis. It is known to have a severe course with a rapid progression to end-stage liver failure. Very few cases have been reported worldwide.

The authors report the case of a 2-month-old female infant presenting with prolonged jaundice due to progressive familial intrahepatic cholestasis type 5. The laboratory assessment showed a normal level of gamma-glutamyl transpeptidase and an elevated rate of serum bilirubin, transaminase activity, bile acids, and alpha-fetoprotein. Whole-exome sequencing identified a novel homozygous pathologic variant in the *NR1H4* gene, described for the first time. At the age of 6 months, the patient died because of liver failure and disseminated intravascular coagulation.

In conclusion, this is the first Tunisian case report of PFIC type 5; the diagnosis was made based on a molecular study. The off-label use of ursodeoxycholic acid was ineffective.

Keywords PFIC 5, Jaundice, Cholestasis, Genetics, Infant

Introduction

Progressive familial intrahepatic cholestasis (PFIC) is a heterogeneous group of autosomal recessive disorders caused by defects in bile transport and/or secretion, resulting in intrahepatic cholestasis and progressive chronic liver disease. It is a rare condition, accounting for

12–13% of cholestatic disorders in neonates, infants, and children [1]. It has a broad phenotypic spectrum, ranging from benign recurrent jaundice to end-stage liver disease. Historically, three types of PFIC were described: type 1 (*ATP8B1* gene), type 2 (*ABCB11* gene), and type 3 (*ABCB4* gene). Recently, thanks to the advances in genetic sequencing, new types of this disease have been reported. To the best of our knowledge, 12 types of PFIC have so far been reported in the literature [2–4].

PFIC type 5 OMIM# 617049 is a rare inherited disorder, transmitted in an autosomal recessive manner, caused by *NR1H4* gene mutations, resulting in farnesoid X receptor (FXR) deficiency. The FXR, as the master regulator of biliary acid (BA) metabolism, regulates BA homeostasis,

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Table 1 Laboratory data of the patient

Age	9 weeks	13 weeks	15 weeks	17 weeks	21 weeks	23 weeks	25 weeks
Hemoglobin (g/dL)	11.1	7.2	10.7	7.9	8.4	7.4	6
White cell count (/mm ³)	8570	5490	10,030	11,970	17,110	8770	5810
Platelet count (/mm ³)	274,000	162,000	194,000	216,000	101,000	77,000	12,000
Total bilirubin (mmol/L)(NV < 17)	316	361	550	441	471		761
Direct bilirubin (mmol/L)(NV < 5)	175	187	467	248	260		378
ALT (U/L)	258	645	299	445	168		111
NV: 10–45							
AST (U/L)	452	898	383	478	233		234
NV: 10–45							
GGT (IU/L)	37	30			24		
NV: 10–80							
Alkaline phosphatase (U/L)	434	261		286			
NV: 100–230							
Glycemia (mmol/L)	5.06						1.65
Protein (g/L)	50	51			43		46
Albumin (g/L)	35.7	33.7					
Prothrombin rate (%)	54	55		34	27	20	9
Activated partial-thromboplastin time ratio	1.52			1.54	1.36	2.13	2.72
Factor V (%)				79	52		
NV: 70–100							
Bile Acids (μmol/L)	300.10						
NV < 10							
AFP (ng/mL)	121,000						
NV: 10–180							

ALT Alanine aminotransferase, AST Aspartate aminotransferase, GGT Gamma-glutamyl transpeptidase, AFP Alpha-fetoprotein, NV normal values

biliary BA secretion, and intestinal reabsorption [5]. It was first described in 4 patients from 2 unrelated families in 2016 [6]. To date, only ten additional infants with PFIC type 5 have been reported [7–12].

Herein, we report a two-month-old Tunisian infant presenting with cholestasis and liver failure due to a novel pathologic variant in the *NR1H4* gene OMIM#603826.

Case presentation

A 2-month-old female baby was admitted for prolonged jaundice and failure to thrive. She was born at full term to consanguineous parents following an uneventful pregnancy. Her birth weight was 2900 g, length was 48 cm, and Apgar scores were 9/10 at 1/5 minutes, respectively. She was the second child of the couple, and there was no relevant family history, especially no history of liver diseases or deaths in infancy. She had developed jaundice since the age of 2 days, which was initially neglected by the parents. On physical examination, she had icterus and splenomegaly palpated 7 cm below the costal margin and no hepatomegaly. Her weight was 4.2 kg (10th percentile for age), her height was 59 cm (80th percentile), and she had normal head circumference (HC: 38 cm). The stool was partially discolored (bright yellow), and the urine was dark. An umbilical hernia was found, but the neurological examination was normal.

Blood tests showed hyperbilirubinemia with total bilirubin of 316 mmol/L (NV < 17 mmol/L) and direct

bilirubin of 175 mmol/L (NV < 5 mmol/L), aspartate transaminase (AST)/alanine transaminase (ALT) of 452/258 U/L (NV: 10–45 U/L), normal gamma-glutamyl transpeptidase (GGT) test of 37 U/L (NV: 10–80 U/L), serum bile acid of 300 μmol/L (NV: < 10 μmol/L), and an alpha-fetoprotein (AFP) level of 121,000 ng/ml (NV: 10–180 ng/ml) (Table 1). Negative urine screening for succinyl acetone excluded the diagnosis of tyrosinemia.

Infectious studies were positive for serum CMV IgM, and PCR (polymerase chain reaction) CMV in urine was positive. Fundoscopic examination did not show chorioretinitis. No brain CT scan was performed. Serology for other TORCH infections was negative. Besides fat-soluble vitamin supplementation, ursodeoxycholic acid (UDCA), and spironolactone, the infant received intravenous Ganciclovir for 3 weeks.

An abdominal ultrasound with Doppler showed splenomegaly and mild ascites with no signs of portal hypertension. Gallbladder and bile ducts were normal.

Weekly monitoring of the full blood count and liver function parameters was done during and after therapy (Table 1). Whole Exome Sequencing (WES) identified an extremely rare homozygous variant in the *NR1H4* gene (c.762 + 1G > A), and both parents were shown to be heterozygous carriers.

At the age of four months, the infant continued to have persistent cholestasis without pruritus and showed signs of hypocoagulability that did not respond to vitamin K,

and hypoglycemia that required continuous intravenous glucose infusion. The PELD (Pediatric End-Stage Liver Disease) score, which was initially estimated at 15, increased to 19 at the age of 4 months and then to 39 at 6 months. A liver transplantation was indicated, but it was impossible because of hypotrophy (weight of 4 kg at 4 months) and rapid worsening of her condition.

Moreover, her blood count revealed severe non-regenerative anemia (Hb level of 5.6 g/dL and reticulocyte count of 68000/mm³) because of repeated blood sampling, which required blood transfusion. During follow up, thrombocytopenia was associated with anemia; this may be attributed to hypersplenism and/or CMV infection. Bone marrow examination was not performed. At the age of 6 months, the patient died because of liver failure and disseminated intravascular coagulation.

Discussion

The loss of FXR function due to mutations in the *NR1H4* gene, located on chromosome 12q23, causes severe cholestasis and liver damage, resulting in a very rare form of PFIC (PFIC type 5) [2, 13]. Only 14 cases have so far been reported in the literature [6–12].

FXR is a nuclear receptor activated by bile acids (BAs). It plays an important role in BA's homeostasis and metabolic regulation [13, 14]. FXR protects the liver against BA accumulation by increasing bile salt export pump (BSEP) expression and suppressing further BA synthesis, which leads to a vicious cycle of ever-increasing BA in these cases. Consequently, FXR has a crucial role in avoiding BA's cytotoxicity and hepatic injury [9].

Features of this disease include neonatal onset of cholestasis, low-to-normal serum GGT, elevated bile acids, and high levels of AFP [6, 8, 9].

Elevated serum AFP is a part of the clinical features of the disease but it has not been demonstrated if the follow up levels of AFP would be a marker for improvement or progression. Positive serum CMV IgM and PCR CMV in urine, as seen in our patient, confirmed congenital CMV active infection, which may be responsible for accelerating the liver cell failure in our case. Surprisingly, no pruritus was noted in our case after the age of 4 months despite elevated bile acids.

In contrast to other forms of PFIC, an *NR1H4*-related disorder consistently manifests with early-onset of vitamin K-independent coagulopathy, which seems to be disproportionate to the severity of liver disease [6, 8, 9]. FXR is also involved in the regulation of coagulation factor synthesis by transactivating fibrinogen and kininogen genes. Thus, the FXR mutation leads to the development of vitamin K independent, early-onset coagulopathy, well before liver failure sets in [6]. Our patient had a persistent low prothrombin time despite parenteral vitamin K supplementation.

FXR is a receptor expressed not only in the liver but also in the intestine. Its deficiency may cause intestinal disorders such as pathogenic bacteria proliferation and cancers [15]. Our patient did not show gastrointestinal symptoms, which suggests heterogeneity in the expression of extrahepatic FXR deficiency.

The diagnosis was confirmed by genetic analysis; whole-exome sequencing revealed a novel homozygous pathogenic variant (NM_001206993.2:c.762+1G>A) in the *NR1H4* gene, which is an extremely rare variant in the general population, and it is most likely responsible for an adverse effect on FXR function. It affects the consensus site of the donor splice site of intron 4 of the gene. The parents were heterozygous for this variant. To the best of our knowledge, this variant has not been previously described in the literature and does not exist in the gnomAD databases. For the 14 patients with PFIC5 reported in the literature, nine patients had a homozygous genotype [6, 8–10], and five had a compound heterozygous genotype [7, 11, 12]. In total, 15 different variants were detected.

Genetic analyses allow families to receive specific genetic counseling and risk estimation for future offspring. This genetic counseling was performed for the couple, which could prevent the recurrence of this serious pathology in their third child; if the mutation is identified in the fetus at 14 weeks of gestation, the parents will have to decide on the voluntary termination of pregnancy.

To date, there is no specific treatment for PFIC type 5. Medical management aims to correct vitamin deficiencies and control pruritus and complications, such as ascites [2, 14]. UDCA is contraindicated in neonatal cholestasis and was not effective in our studied case. UDCA is transformed into lithocholic acid, and both are known to be hepatotoxic. UDCA was neither effective nor safe in a large Egyptian cohort of neonates and infants with cholestasis [16]. We did not assess the lithocholic acid in our case, and we are not aware of the contribution of UDCA hepatotoxicity to the course of her disease.

Due to the rapid progression of hepatic dysfunction, an early liver transplantation (LT) is mostly required [2, 14]. Patients with PFIC 5 had a significantly worse prognosis due to a more rapid progression [8, 12]. All patients without LT died, and survival with a native liver has not been observed.

Conclusion

This is the first case of PFIC 5 reported in Tunisia. We emphasize that in case of severe early onset of cholestasis with normal GGT and persistently elevated AFP, the diagnosis of PFIC type 5 should be considered, and thus genetic sequencing should be conducted. In our case, the use of ursodeoxycholic acid was ineffective and was probably associated with the mortality of the infant.

Abbreviations

AFP	alpha-fetoprotein
APGAR	Activity, Pulse, Grimace, Appearance, Respiration
BA	biliary acid
BSEP	bile salt export pump
CMV	cytomegalovirus
FXR	farnesoid X receptor
GGT	gamma-glutamyl transpeptidase
gnomAD	the genome Aggregation database
HC	head circumference
LT	liver transplantation
NV	normal value
PCR	polymerase chain reaction
PELD	pediatric end-stage liver disease
PFIC	progressive familial intrahepatic cholestasis
UDCA	ursodeoxycholic acid
WES	whole-exome sequencing

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Authors' contributions

All authors contributed equally to this manuscript.

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Data availability

The mutation reported in this paper is a new variant and studies are underway for functional analysis. We hereby declare that this paper doesn't contain data deposited in a database. The authors declare that all datasets supporting the findings, used, and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The parents signed a free and informed consent form for genetic tests, which were performed for the patient and the parents. The Ethics Committee of the Faculty of Medicine of Sfax, Tunisia, approved this study.

Consent for publication

Informed written consent was obtained from the parents of the patient for the publication of the paper and all information within it. The proof of consent can be requested at any time.

Competing interests

The authors declare no competing interests.

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