

World Journal of *Clinical Cases*

World J Clin Cases 2021 May 26; 9(15): 3487-3795



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The WJCC is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2020 Edition of Journal Citation Reports® cites the 2019 impact factor (IF) for WJCC as 1.013; IF without journal self cites: 0.991; Ranking: 120 among 165 journals in medicine, general and internal; and Quartile category: Q3. The WJCC's CiteScore for 2019 is 0.3 and Scopus CiteScore rank 2019: General Medicine is 394/529.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Ji-Hong Lin; Production Department Director: Xiang Li; Editorial Office Director: Jin-Lai Wang.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

May 26, 2021

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

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<https://www.wjgnet.com/bpg/gerinfo/240>

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<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Progressive familial intrahepatic cholestasis — farnesoid X receptor deficiency due to *NR1H4* mutation: A case report

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Author contributions: All authors contributed significantly to the preparation of the manuscript; Czubkowski P, Bull LN, Thompson RJ, Knisely AS, Jankowska I and Pawłowska J contributed to conception and design of the case presentation, acquisition of data and case description; Bull LN, Strautnieks S and Thompson RJ contributed to genetic studies; Knisely AS, Finegold M, Parsons P and Cielecka-Kuszyk J contributed to histopathological assessment; Czubkowski P, Bull LN, Thompson RJ and Knisely AS contributed to drafting the article and making critical revisions related to the content of the manuscript; All authors have read and approve the final manuscript.

Supported by National Institutes of Health, No. R01DK094828; and National Human Genome Research

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Abstract

BACKGROUND

Functioning farnesoid X receptor (FXR; encoded by *NR1H4*) is key to normal bile acid homeostasis. Biallelic mutations in *NR1H4* are reported in a few children with intrahepatic cholestasis. We describe a boy with progressive familial intrahepatic cholestasis and homozygous mutation in *NR1H4*.

CASE SUMMARY

A boy had severe neonatal cholestasis with moderate hypercholanemia and persistently elevated alpha-fetoprotein. Despite medical treatment, coagulopathy was uncontrollable, prompting liver transplantation at age 8 mo with incidental splenectomy. The patient experienced catch-up growth with good liver function and did not develop allograft steatosis. However, 1 year after transplant, he died from an acute infection, considered secondary to immunosuppression and

Institute, No. UM1 HG006493 and No. U24 HG008956.

Informed consent statement:

Parental consent was obtained for hospitalizations and all the procedures described in the manuscript.

Conflict-of-interest statement:

Dr. Thompson consults for Albireo, Mirum, GenerationBio, Alnylam, Qing Bile, Horizon, Sana, and Retrophin and has share options in Qing Bile and GenerationBio. Other authors report no conflicts of interest.

CARE Checklist (2016) statement:

The authors have read the CARE Checklist (2016) and the manuscript was prepared and revised according to the CARE Checklist (2016).

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Manuscript source: Unsolicited manuscript

Specialty type: Medicine, research and experimental

Country/Territory of origin: Poland

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: October 17, 2020

Peer-review started: October 17, 2020

First decision: November 3, 2020

asplenia. A homozygous protein-truncating mutation, c.547C > T, p.(Arg183Ter), was subsequently identified in *NR1H4*, and both parents were shown to be heterozygous carriers. Absence of FXR and of bile salt export pump expression was confirmed by immunostaining of explanted liver.

CONCLUSION

Severe cholestasis with persistently high alpha-fetoprotein and modest elevation of serum bile acid levels may suggest FXR deficiency. Some patients with FXR deficiency may not develop allograft steatosis and may respond well to liver transplantation.

Key Words: Neonatal cholestasis; Progressive familial intrahepatic cholestasis; Bile salt export pump; Liver transplantation; Alpha-fetoprotein; Case report

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Core Tip: Despite the central role farnesoid X receptor (FXR) plays in bile acid metabolism, only a few children with cholestasis and biallelic FXR deficiency have been reported, and that only recently. Using banked DNA from patients without previous successful genetic diagnosis, we have identified a child with a homozygous mutation predicted to truncate FXR prematurely. We describe his disease course before and after liver transplantation, accompanied by immunohistochemical studies. This report adds meaningfully to the available information regarding disease course and outcomes in patients with severe FXR deficiency. It highlights biochemical findings that may be characteristic of FXR deficiency.

Citation: Czubkowski P, Thompson RJ, Jankowska I, Knisely AS, Finegold M, Parsons P, Cielecka-Kuszyk J, Strautnieks S, Pawłowska J, Bull LN. Progressive familial intrahepatic cholestasis — farnesoid X receptor deficiency due to *NR1H4* mutation: A case report. *World J Clin Cases* 2021; 9(15): 3631-3636

URL: <https://www.wjgnet.com/2307-8960/full/v9/i15/3631.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v9.i15.3631>

INTRODUCTION

A key function of the farnesoid X receptor (FXR) is maintenance of physiologic bile acid (BA) pool size. FXR activation by BA within terminal-ileum enterocytes triggers production of fibroblast growth factor 19, which in turn suppresses hepatocellular synthesis of BA. In addition, FXR protects against intrahepatocytic BA accumulation by increasing bile salt export pump (BSEP) expression and by suppressing both uptake of BA from plasma *via* Na⁺-taurocholate cotransporting polypeptide and synthesis of BA *via* sterol-27 hydroxylase[1].

NR1H4 encodes FXR. Biallelic mutation in *NR1H4* is a rare cause of intrahepatic cholestasis. Eight such children have been reported, three of whom underwent liver transplantation (LT)[2-4]. We describe a patient with FXR deficiency, due to biallelic mutation in *NR1H4*, who presented with neonatal cholestasis that progressed to end-stage liver disease successfully treated by LT.

CASE PRESENTATION

Chief complaints

Neonate presented with rapidly progressing cholestatic jaundice.

History of present illness

Jaundice was observed from the second postnatal day. Phototherapy was given. At age 5 wk, deepening jaundice and pale stools were noted. He was hospitalized at age 6 wk and transferred to Children's Memorial Health Institute at age 7 wk.

Revised: December 16, 2020**Accepted:** February 24, 2021**Article in press:** February 24, 2021**Published online:** May 26, 2021**P-Reviewer:** Mrzljak A**S-Editor:** Gao CC**L-Editor:** Filipodia**P-Editor:** Li JH

History of past illness

The patient had an otherwise unremarkable medical history.

Personal and family history

A boy was born at term, weighing 4.1 kg (93rd percentile), to parents without known consanguinity. Pregnancy and spontaneous vaginal delivery were uncomplicated. A brother aged 5 years was healthy; however, two maternal uncles had died as neonates for unknown reasons.

Physical examination

At transfer, he was jaundiced but otherwise well [5.8 kg (77th percentile)]. Motor development was normal. Stools varied from pale to bright yellow. The liver and spleen were palpable, respectively 3 cm and 2 cm below the costal margin. A left iridial coloboma and a right inguinal hernia were found.

Laboratory examinations

Conjugated hyperbilirubinemia accompanied elevated serum transaminase activity (Table 1). Serum BA and alpha-fetoprotein (AFP) levels were elevated. Serum gamma-glutamyl transpeptidase activity was normal. Hypocoagulability did not respond to vitamin K. Persistent hypoglycemia required intravenous glucose. Investigation for metabolic disorders yielded no diagnosis.

Imaging examinations

A normal gallbladder and non-dilated bile ducts were visible on sonography; the left lobe of the liver was enlarged. Splenomegaly was confirmed. After 3 d of phenobarbital, hepatobiliary scintigraphy found decreased and patchy isotope uptake by the liver and substantially decreased, but detectable, excretion into the bowel. A type 2 atrial septal defect (assessed as clinically unimportant) and a butterfly vertebra were noted.

Further diagnostic work-up

Percutaneous liver-biopsy (age 9 wk) found moderate fibrosis, mild inflammation and ductular proliferation; immunostaining for BSEP was unavailable. At age 12 wk, open cholangiography was performed and found a normal biliary tree; wedge liver biopsy revealed changes like those seen previously.

FINAL DIAGNOSIS

Archived patient DNA underwent sequencing of a panel of cholestasis-associated genes (*ATP8B1*, *ABCB11*, *ABCB4*, *TJP2*, *JAG1*, *NOTCH2*, *BAAT*) with no diagnostic variants found. These results were confirmed when patient DNA then underwent whole-exome sequencing. However, homozygosity was found for c.547C > T, p.(Arg183Ter), a nonsense mutation in *NR1H4*. Sanger sequencing confirmed homozygosity for this variant in the patient and heterozygosity in each parent. Immunostaining revealed absence of BSEP (Figure 1B) and of nuclear marking for FXR (Figure 1C). Gamma-glutamyl transpeptidase expression was present but very abnormal (Figure 1D).

TREATMENT

Vitamin supplementation and ursodeoxycholic acid (20 mg/kg per d) were initiated. Icterus and hypercholanemia worsened and the patient required repeated intravenous vitamin K. At age 8 mo [8.4 kg (40th percentile)], uncontrollable coagulopathy prompted maternal-donor LT, with splenectomy due to substantial splenomegaly. Histopathologic evaluation revealed marked hepatocellular and canalicular cholestasis with steatosis and micronodular cirrhosis (Figure 1A). Dysplasia and malignancy were not found.

Table 1 Summary of laboratory data

Serum analyte	Reference range	Age 7 wk (presentation)	Age 22 wk (before liver transplantation)
Hematocrit (%)	33.0-39.0	29.2	29.6
Hemoglobin (g/dL)	10.5-13.5	10.1	10.1
White-cell count (per mm ³)	6.0-17.5	9.1	11.4
Platelet count (per mm ³)	150-400	184	154
Total bilirubin (mg/dL)	0.0-1.0	9.4	23.8
Direct bilirubin (mg/dL)	0.0-0.4	7.3	14.0
ALT (U/L)	10-55	170	224
AST (U/L)	10-55	260	456
GGT (U/L)	10-80	35	41
Alkaline phosphatase (U/L)	15-350	331	356
Bile acids (mol/L)	0-11	69	157
Cholesterol (mg/dL)	80-170	228	220
Triglycerides (mg/dL)	50-150	136	137
Creatine kinase (U/L)	60-400	30	
Activated partial-thromboplastin time (s)	21-33	49	59
Prothrombin time (s)	10-13	17	20
International normalized ratio	< 1.2	1.50	2.03
D-dimer	< 500	138	274
Fibrinogen	150-400	200	174
Factor V (%)	70-140	70.4	-
Factor VII (%)	70-120	36.9	-
Ammonia (g/dL)	12-48	178	243
Glucose (mg%)	70-110	55	30
Creatinine (mg/dL)	0.3-1.0	0.2	0.2
Protein (g/L)	60-83	45	55
Albumin (g/L)	33-50	25	34
Globulin (g/L)	26-41	7	14
Immunoglobulin G (mg/dL)	231-1411	713	-
Immunoglobulin A (mg/dL)	0-83	21	-
Immunoglobulin M (mg/dL)	0-145	79	-
¹ Alpha-fetoprotein (IU/mL)		358000	230000
Vitamin A (ng/mL)	200-800	165	-
Vitamin E (g/mL)	3.8-16.0	8.4	-
25OHD ₃ (ng/mL)	11-54	26	-

¹Alpha-fetoprotein normal values according to age: Premature 95000-175000; term newborn 13000-83000; 2 wk-1 mo 20-19000; 3 mo 10-180; 8 mo 0-10. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transpeptidase.

OUTCOME AND FOLLOW-UP

There were no surgical issues after LT. Immunosuppression included tacrolimus and corticosteroids, with trimethoprim/sulfamethoxazole prophylaxis. Vaccination against meningococcus infection was unavailable. His course after LT was unremarkable for 12 mo, apart from transaminitis (cytomegalovirus infection, resolved with ganciclovir).

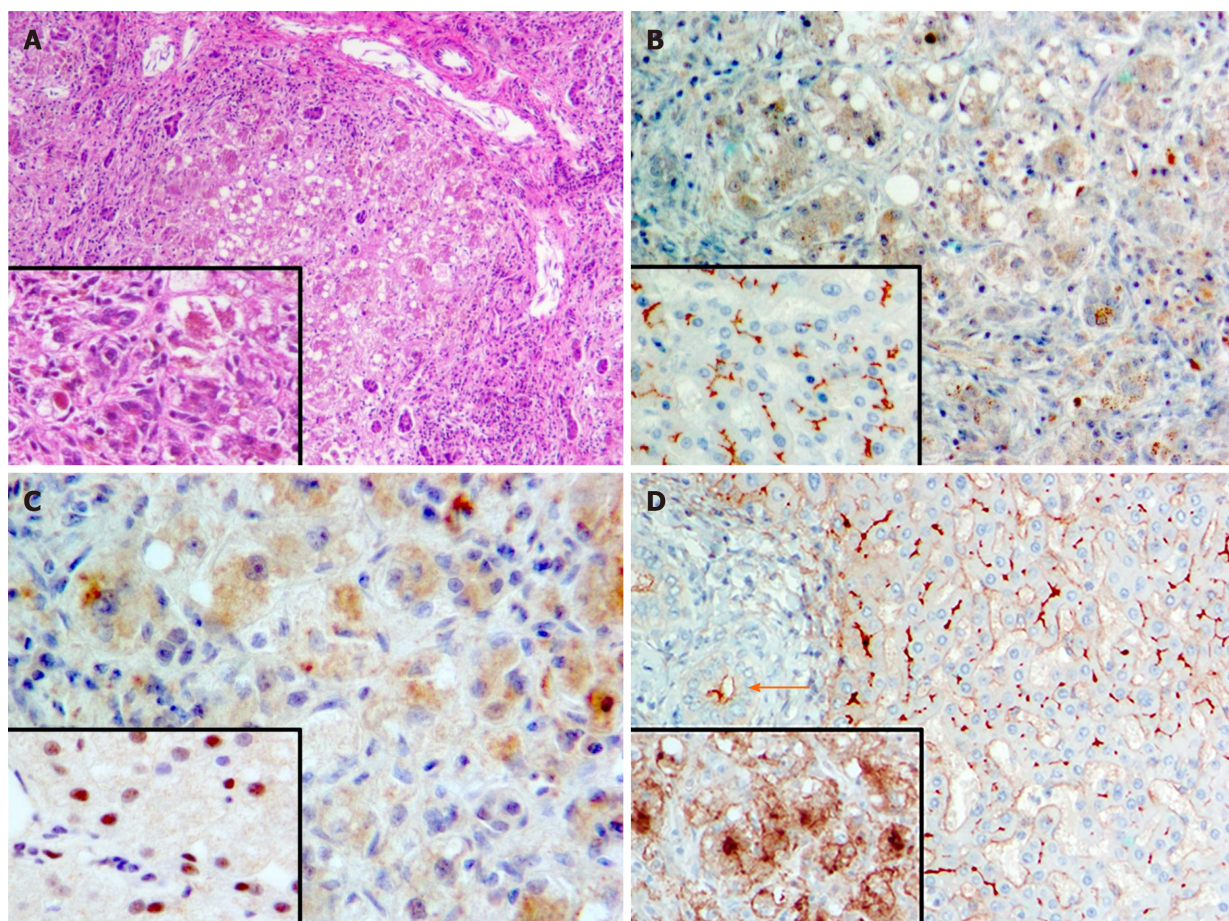


Figure 1 Histopathologic findings, explanted liver and controls. A: Fibrosis and nodularity with steatosis and substantial lobular disarray, explanted liver. Pronounced cholestasis spares portal tracts. Hematoxylin & eosin; main image 100 ×, inset 200 × original magnifications; B: Bile salt export pump expression in normal liver ("control") and explanted liver. No expression in explanted liver (main image); the pigment seen is bile. Control (inset), crisp expression along an unremarkable bile-canalculus network. Anti-bile salt export pump antibody (Santa Cruz Biotechnology, Dallas, TX, United States; sc-74500)/hematoxylin; both main image and inset 200 × original magnifications; C: Farnesoid X receptor expression in normal liver ("control") and explanted liver. No expression in explanted liver (main image); the pigment seen is bile. Control (inset), nuclear expression evident in most hepatocytes. Anti-farnesoid X receptor antibody (Santa Cruz Biotechnology; sc-25309)/hematoxylin; both main image and inset 400 × original magnifications; D: Gamma-glutamyl transpeptidase expression in normal liver ("control") and explanted liver. Control (main image), crisp expression at apices of cholangiocytes (arrow) and along an unremarkable bile-canalculus network, with faint perisinusoidal staining. Explanted liver (inset), blurred marking at severely distorted canalicular network with pronounced cytoplasmic and basolateral staining, abnormalities that reflect the extent of hepatocellular injury and disarray. Anti-gamma-glutamyl transpeptidase 1 (Abnova, Taipei, Taiwan; H00002678-M01)/hematoxylin; both main image and inset 200 × original magnifications.

His weight recovered [75th percentile (age 19 mo) 11 mo after LT]. At age 20 mo, vomiting and fever required hospital admission elsewhere. He was assessed as in good condition, but within 12 h he died with disseminated intravascular coagulation and multiorgan failure. No micro-organisms were cultured. Necropsy found hemorrhagic adrenal necrosis. The liver was unremarkable. The heart contained a few foci of remote intramyocardial arterial thrombosis, with dystrophic mineralization.

DISCUSSION

The fundamental role of FXR in BA homeostasis is consistent with the severity of liver disease associated with its absence. Our patient had substantially impaired liver function from presentation at Children's Memorial Health Institute onward (hypoglycemia; coagulopathy unresponsive to parenteral vitamin K). These disease manifestations overlap with those in the children in whom FXR deficiency was first reported[2]. Coagulopathy is common in cholestasis. Initially, however, it usually responds to vitamin K. In FXR deficiency, vitamin K does not correct the clotting, which seems disproportionate to the severity of liver disease. This may reflect direct involvement of FXR in regulating-clotting factor production[5]. Serum BA elevations in our patient and in one previously described FXR-deficient patient for whom serum

BA were reported[2] were modest compared with those in patients with similarly severe cholestasis and BSEP deficiency. This difference may reflect failure of FXR-mediated down-regulation of Na⁺-taurocholate cotransporting polypeptide in FXR deficiency, with consequent unabated hepatocellular uptake of BA[6].

High AFP levels are found in hepatocellular carcinoma and, during early infancy, in severe early-onset cholestasis. As seen in our patient and others, persistently elevated AFP values in the absence of hepatocellular carcinoma may be a feature of *NR1H4* disease[2-4]. This may complicate monitoring for hepatocellular carcinoma development.

Two siblings who underwent LT for FXR deficiency developed mild allograft steatosis, ascribed provisionally to disrupted ileal control of enterohepatic BA homeostasis[2]. The third transplanted patient had stable graft function, and no steatosis in post-transplant liver biopsies in the first 2 years. Our patient had no allograft steatosis, good graft function and no evidence of gastrointestinal disease. These observations suggest heterogeneity in compensation for extrahepatic FXR deficiency. We consider our patient's death (sepsis, adrenal haemorrhage; predisposed by immunosuppression and lack of spleen) to be independent of *NR1H4* mutation.

CONCLUSION

FXR deficiency due to *NR1H4* mutation is a rare cause of neonatal cholestasis. Severe cholestasis with persistently high AFP and modestly elevated serum BA levels may suggest FXR deficiency.

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