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Progressive familial intrahepatic cholestasis type 4: a case report

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Abstract

Background Progressive familial intrahepatic cholestasis is an autosomal recessive genetic disorder that manifests primarily with jaundice and pruritus and can progresses from persistent cholestasis to cirrhosis and late childhood liver failure. Classically, progressive familial intrahepatic cholestasis is classified into three subtypes: 1, 2, and 3 and results from a defect in a biliary protein responsible for bile formation and circulation in the liver. In the last decade and with the increased use of genetic testing, more types have been known.

Case presentation A 6-month-old Afrocentric boy presented with progressive jaundice and pruritus that started since the age of 2 months. He was thoroughly investigated to be finally diagnosed as progressive familial intrahepatic cholestasis type 4. A low-fat diet, ursodeoxycholic acid, fat-soluble vitamins, and cholestyramine were started. He showed initial improvement then had refractory pruritus and impaired quality of life. He underwent surgical biliary diversion at the age of 1 year with marked improvement of manifestations.

Conclusion Owing to the increased technology of genetic testing, more clinical subtypes of progressive familial intrahepatic cholestasis were diagnosed other than the classical three types. Surgical management using biliary diversion could be beneficial and delays or may even obviate the need for liver transplantation.

Keywords Pruritus, Progressive familial intrahepatic cholestasis, Case report

Introduction

Progressive familial intrahepatic cholestasis (PFIC) is a group of rare autosomal recessive genetic disorders involving defects in bile acid secretion or transport. There are a wide spectrum of manifestations ranging from neonatal cholestasis, recurrent cholestasis, refractory pruritus, growth failure, childhood liver failure, and portal hypertension to advanced end-stage liver disease [1, 2]. Classically, PFIC is classified into three subtypes: PFIC1, PFIC2, and PFIC3 according to the timing of their discovery. PFIC1 (Byler's disease) involves FIC1 deficiency due to mutations in the ATPase phospholipid transporting 8B1 (ATP8B1) gene. PFIC2, which is the most common subtype involves a defective or deficient severe bile salt export pump (BSEP) caused by a mutation in the ATP-binding cassette subfamily B member 11 (ABCB11) gene. PFIC3 is due to multidrug resistance protein 3 (MDR3) deficiency resulting from a mutation in the ABCB4 gene [3–5].

With the advancements in genetic analyses, newer subtypes are being discovered. PFIC4 was first reported in 1991 by Gumbiner *et al.* [6, 7]. In PFIC4, there is deficiency in a protein called tight junction protein 2 (TJP2) or zona occludens 2 due to mutation in the tight junction protein 2 (TJP2) gene. This results in reduced integrity of the canalicular membrane and reflux of bile acids into hepatocytes, with their

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deleterious effect in potentiating hepatocyte damage and cholestasis [7, 8]. TJP2 has a widespread expression, including the respiratory and central nervous systems [8].

Clinically, cases with PFIC4 can present with mild anicteric pruritus, recurrent cholestasis, or severe progressive liver disease [4, 8]. Extrahepatic manifestations in the form of neurological and respiratory symptoms can be present in these cases [7]. Similar to PFIC2, there is increased risk of progression to hepatocellular carcinoma (HCC) in PFIC4 [7, 9, 10]. Thus, early diagnosis, treatment, and close follow-up is mandatory.

Investigations in PFIC4 typically show elevated total and direct serum bilirubin with low to normal serum gamma glutamyl transferase (GGT). Liver enzymes are elevated in these cases as well as serum bile acids [7]. Liver histopathology classically reveals canalicular cholestasis along with a variable degree of fibrosis and giant cell transformation. Electron microscopy shows elongated tight junctions and a lack of the densest part of the zona occludens [11]. Molecular genetic diagnosis is considered the test of choice in diagnosing PFIC type as it is noninvasive unlike liver biopsy. This can be done using next-generation sequencing (NGS) [12]. Whole-exome (WES) or whole-genome (WGS) sequencing can be done in cases with negative targeted gene analysis.

Genetic counseling for parents is crucial as it is an autosomal recessive disorder. Nutritional management with providing adequate calories [125–140% of the recommended dietary allowances (RDA)], protein (2–3 g/kg daily), and a low-fat diet is crucial. Supplementation of medium-chain triglycerides (MCT) and fat-soluble vitamins is recommended [13]. Regular monitoring of growth parameters and nutritional deficiencies is important as those cases are liable for growth failure.

Pruritus is the most devastating manifestation in PFIC. It can affect the quality of life. Local skin emollients, ursodeoxycholic acid (UDCA), cholestyramine, antihistamines, rifampicin, naltrexone, and sertraline are used to control pruritus [14]. Some cases respond well to these medications. Others can have deterioration in liver status or refractory itching despite drug therapy, necessitating biliary diversion or liver transplantation [15].

Biliary diversion (BD) procedures aim at the diversion of bile from the intestine, reducing the reabsorption of bile through enterohepatic circulation [16]. This reduces the accumulation of bile acids. BD has good results in the alleviation of refractory pruritus in PFIC1 and 2 [17]. Its role in the newer variants of PFIC is not yet well known. We report a case with PFIC4 who had refractory pruritus for which he underwent surgical biliary diversion.

Case report

A 6-month-old Afrocentric boy presented to our institute with a 3-month history of progressive generalized jaundice and persistent pruritus. History revealed that the parents were cousins. No family history of cholestasis or hepatic disease was reported. On clinical examination, the patient was markedly icteric and pale. His growth parameters were affected; weight −1.8 standard deviation (SD), length −1.5 SD, and mid upper arm circumference 12 cm, despite being within the normal range at birth (weight 0.7 SD and length 0.9 SD). He had marked hepatomegaly, but no splenomegaly or ascites. He had scratch marks allover his body, especially around in his face. His urine was dark.

His investigations showed direct hyperbilirubinemia along with elevation of liver enzymes and serum bile acids. On the other hand, gamma-glutamyl transpeptidase (GGT), serum albumin, and coagulation profiles were within normal ranges (Table 1). At this stage, biliary atresia and other causes of obstructive jaundice in this age group such as PFIC, Alagille syndrome, and inspissated bile syndrome were considered. Percutaneous ultrasound (US)-guided liver biopsy revealed marked pseudoglandular transformation of almost all of the hepatocytes with canalicular cholestasis, florid ductular proliferation, and mild ductopenia (Fig. 1A and B). Thus, PFIC was the prime consideration.

The patient was on nutritional management with adequate calories and proteins in addition to MCT. He was on high doses of vitamin D (2000 units/day) based on his serum vitamin D level. He also received the recommended daily doses of vitamins A and E. UDCA dose was escalated according to clinical and laboratory findings. Cholestyramine was added in maximum doses with initial control of pruritus, then became nonbeneficial.

Table 1 Laboratory results of the patient

Parameter	Value	Reference value
Serum bilirubin	9.18 mg/dl	0.2–1.3 mg/dl
Direct bilirubin	8.55 mg/dl	< 0.3 mg/dl
Indirect bilirubin	0.63 mg/dl	0.2–0.8 mg/dl
Gamma-glutamyl transpeptidase (GGT)	55 U/L	10–71 U/L
Alanine transaminase (ALT)	131 U/L	4–36 U/L
Aspartate aminotransaminase (ALT)	200 U/L	8–33 U/L
Albumin	4.1 g/dl	3.5–5.5 g/dl
Coagulation profile		
Prothrombin time	13 seconds	10–13 seconds
Partial thromboplastin time	32 seconds	25–35 seconds
International normalized ratio (INR)	1	1.1 or below
Total serum bile acids (TSBA)	219 µmol/L	< 10 µmol/L

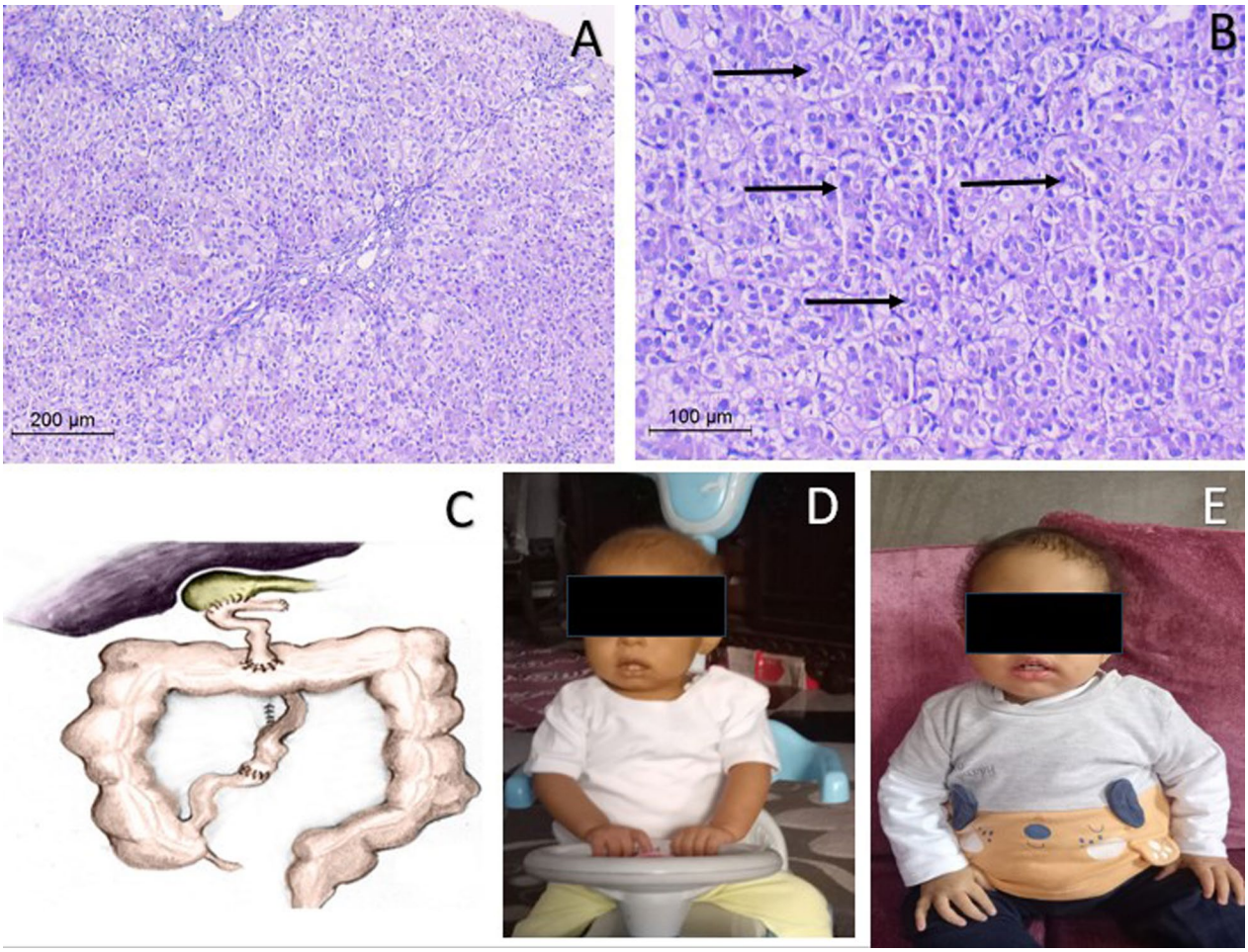

Fig. 1 **A**, **B** Prominent pseudoglandular transformation and canalicular cholestasis (arrows). Hematoxylin and eosin stain (**A** ×100, **B** ×200). **C** Diagrammatic illustration of the operation performed. **D**, **E** Marked improvement of jaundice and growth

Whole-exome sequencing was done to detect the exact genetic mutation. A homozygous pathogenic variant in TJP2 was identified, which was consistent with the diagnosis of progressive familial intrahepatic cholestasis type 4 (OMIM: 615878). The patient continued on his nutritional and medical management till 1 year of age; however, he still had growth failure and worsening of pruritus with evident scarring and impaired quality of life.

The patient was scheduled for partial internal diversion. On exploration, the gallbladder was found to be dilated with thickened wall. A 15-cm-long jejeunal segment was isolated with its blood supply, 40 cm from the duodenojejunal junction, and passed retrocoloic for anastomosis with the gallbladder. The proximal stump was closed and side-to-side jejunocolic anastomosis was done, while the distal end was anastomosed with the transverse colon in an end-to-side fashion. Restoration of the bowel continuity was done by end-to-end jejunojejunal anastomosis (Fig. 1C).

Postoperatively, the patient was doing well after 18 months of follow-up with marked drop in the level of total and direct bilirubin, improvement in the growth pattern (weight 0.9 SD, length 0.5 SD) and relief of pruritus (Fig. 1D, E).

Discussion

PFIC type 4 represents a new entity of PFIC that evolved after the advances in genetic testing. The exact incidence of PFIC4 is not well known due to the limited number of studies, which are mostly case reports or small case series [7]. PFIC1 and PFIC 2 usually occur in early infancy and are caused by a mutation in the ATP8B1 and ABCB11 genes, respectively. They are characterized by having a normal level of GGT, compared to PFIC3, that occurs in adolescents due to a mutation in the ABCB4 gene and has high GGT levels [1, 2]. In PFIC4, there is a mutation in the TJP2 gene, which is a member of the membrane-associated guanylate kinase homolog family, located

on the long arm of chromosome 9. It encodes a protein called tight junction protein 2 (TJP2). This encoded protein is an integral component of the tight junction barrier in epithelial and endothelial cells, which are crucial for proper assembly of tight junctions. Deficiency of TJP2 protein results in reduced integrity of the canalicular membrane and reflux of bile acids through the intercellular spaces into the hepatocytes, causing liver damage and progressive cholestasis [8, 18]. All homozygous mutations cause deficient TJP2 protein and complete loss of function. Missense and frame deletion lead to milder disease due to residual TJP2 protein expression [19, 20].

Medical treatment for PFIC4 using UDCA (10–30 mg/kg/day), fat-soluble vitamins, MCT, and cholestyramine (240–400 mg/kg/day) can be effective in some cases [14, 21]. Surgery is indicated if there is intractable pruritus despite optimum treatment. Other indications include failure to thrive and nutritional deficiencies. Sambrotta *et al.* reported 12 cases with PFIC4; 9 cases (75%) required liver transplantation (LT) while 2 had portal hypertension [19]. On the other hand, Zhang *et al.* reported 7 cases and none of them required LT; all of them responded well to medical treatment [20].

Biliary diversion in PFIC is indicated for children who do not yet have advanced fibrosis or liver cirrhosis. [15] Regardless of the adopted technique, the main aim is to interfere with enterohepatic recirculation of bile salt leading to bile salt pool depletion; hence, pruritus decreases and the progression to cirrhosis is delayed. This can be achieved either by anastomosis of the biliary tract to the outside skin using a jejunal loop as a conduit as a stoma (external drainage) or to the intestines (internal drainage). The latter has now gained ground and can be performed by anastomosing the gall bladder via a jejunal (cholecystojejunocolic), ileal (cholecystojejunocolic), appendix (cholecystoappendicocolic) conduit to the colon or directly between gall bladder and antireflux loop of colon (cholecystocolocolic anastomosis) [22].

Concerning biliary diversion surgeries, a meta-analysis yielded a 60% incidence of pruritus relief and only a 27% need for liver transplantation [23]. They also found that partial internal biliary diversion using a chole-cystojejunocolic approach has lower complications and liver transplantation requirement than partial extrabiliary diversion using appendix or jejunum [23].

Conclusions

Owing to the advances in genetic testing, more clinical subtypes of PFIC have been diagnosed, other than the classical three types. Surgical management using biliary diversion could be beneficial and could delay or even obviate the need for liver transplantation. The CARE Checklist has been completed by the authors for this case report, attached as supplementary material.

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Author contributions
M. Abokandil, M. Abdelgawad, and S. Waheeb made and confirmed the diagnosis, provided the details of the case, and contributed to the design of the report. M. Abdelhady provided the pathological diagnosis. W. Zaghloul, M. Mansy, and M. Kotb drafted the manuscript. All authors read and approved the final version of the manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Written informed consent was obtained from the patient for publication of the details of her medical case and any accompanying images. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Consent for publication
Written informed consent was obtained from the patient's legal guardian for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests.

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References

1. Bull LN, Thompson RJ. Progressive familial intrahepatic cholestasis. Clin Liver Dis. 2018;22(4):657–69.
2. Srivastava A. Progressive familial intrahepatic cholestasis. J Clin Exp Hepatol. 2014;4(1):25–36.
3. Baker A, Kerkar N, Todorova L, Kamath BM, Houwen RHJ. Systematic review of progressive familial intrahepatic cholestasis. Clin Res Hepatol Gastroenterol. 2019;43(1):20–36.
4. Sharma A, Poddar U, Agnihotry S, Phadke SR, Yachha SK, Aggarwal R. Spectrum of genomic variations in Indian patients with progressive familial intrahepatic cholestasis. BMC Gastroenterol. 2018;18(1):1–10.
5. Pawlikowska L, Strautnieks S, Jankowska I, Czubkowski P, Emerick K, Antoniou A, *et al*. Differences in presentation and progression between severe FIC1 and BSEP deficiencies. J Hepatol. 2010;53(1):170–8.
6. Gumbiner B, Lowenkopf T, Apatira D. Identification of a 160-kDa polypeptide that binds to the tight junction protein ZO-1. Proc Natl Acad Sci U S A. 1991;88:3460–4.
7. Vinayagamoorthy V, Srivastava A, Sarma MS. Newer variants of progressive familial intrahepatic cholestasis. World J Hepatol. 2021;13(12):2024.
8. Sambrotta M, Thompson RJ. Mutations in TJP2, encoding zona occludens 2, and liver disease. Tissue Barriers. 2015;3: e1026537.
9. Vij M, Shanmugam NP, Reddy MS, Sankaranarayanan S, Rela M. Paediatric hepatocellular carcinoma in tight junction protein 2 (TJP2) deficiency. Virchows Arch. 2017;471:679–83.
10. Wei CS, Becher N, Friis JB, Ott P, Vogel I, Grønbæk H. New tight junction protein 2 variant causing progressive familial intrahepatic cholestasis type 4 in adults: a case report. World J Gastroenterol. 2020;26:550–61.

11. Gomez-Ospina N, Potter CJ, Xiao R, Manickam K, Kim MS, Kim KH, *et al*. Mutations in the nuclear bile acid receptor FXR cause progressive familial intrahepatic cholestasis. Nat Commun. 2016;7:10713.
12. Togawa T, Sugiura T, Ito K, Endo T, Aoyama K, Ohashi K, *et al*. Molecular genetic dissection and neonatal/infantile intrahepatic cholestasis using targeted next-generation sequencing. J Pediatr. 2016;171:171-7.e1.
13. Lane E, Murray KF. Neonatal cholestasis. Pediatr Clin N Am. 2017;64:621–39.
14. Thébaut A, Debray D, Gonzales E. An update on the physiopathology and therapeutic management of cholestatic pruritus in children. Clin Res Hepatol Gastroenterol. 2018;42:103–9.
15. Wang KS, Tiao G, Bass LM, Hertel PM, Mogul D, Kerkar N, *et al*. Analysis of surgical interruption of the enterohepatic circulation as a treatment for pediatric cholestasis. Hepatology. 2017;65(5):1645–54.
16. Lemoine C, Superina R. Surgical diversion of enterohepatic circulation in pediatric cholestasis. Semin Pediatr Surg. 2020;29: 150946.
17. Verkade HJ, Thompson RJ, Arnell H, Fischler B, Gillberg PG, Mattsson JP, *et al*. Systematic review and meta-analysis: partial external biliary diversion in progressive familial intrahepatic cholestasis. J Pediatr Gastroenterol Nutr. 2020;71:176–83.
18. Mirza N, Bharadwaj R, Malhotra S, Sibal A. Progressive familial intrahepatic cholestasis type 4 in an Indian child: presentation, initial course and novel compound heterozygous mutation. BMJ Case Rep. 2020;13: e234193.
19. Sambrotta M, Strautnieks S, Papouli E, Rushton P, Clark BE, Parry DA, *et al*. Mutations in TJP2 cause progressive cholestatic liver disease. Nat Genet. 2014;46:326–8.
20. Zhang J, Liu LL, Gong JY, Hao CZ, Qiu YL, Lu Y, *et al*. TJP2 hepatobiliary disorders: novel variants and clinical diversity. Hum Mutat. 2020;41:502–11.
21. Alam S, Lal BB. Recent updates on progressive familial intrahepatic cholestasis types 1, 2 and 3: outcome and therapeutic strategies. World J Hepatol. 2022;14(1):98.
22. Gunaydin M, Bozkurter Cil AT. Progressive familial intrahepatic cholestasis: diagnosis, management, and treatment. Hepat Med. 2018;10:95–104.
23. Bolia R, Goel AD, Sharma V, Srivastava A. Biliary diversion in progressive familial intrahepatic cholestasis: a systematic review and meta-analysis. Expert Rev Gastroenterol Hepatol. 2022;16:163–72.

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