American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2021; 22: e932374
DOI: 10.12659/AJCR.932374

Received: 2021.03.24
Accepted: 2021.05.01
Available online: 2021.06.11
Published: 2021.07.20

A Report of 2 Infant Siblings with Progressive Intrahepatic Familial Cholestasis Type 1 and a Novel Homozygous Mutation in the ATP8B1 Gene Treated with Partial External Biliary Diversion and Liver Transplant

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Conflict of interest: None declared

Case series
Patients: Male • Male / (siblings)
Final Diagnosis: Progressive intrahepatic familial cholestasis type 1 (PFIC-1)
Symptoms: Jaundice
Medication: —
Clinical Procedure: —
Specialty: Transplantology

Objective: Unusual clinical course

Background: Current treatment options for progressive intrahepatic familial cholestasis type 1 (PFIC-1) comprise ursodeoxycholic acid (UDCA), partial external biliary diversion (PEBD), and liver transplantation (LTx). The role and timing of LTx in PFIC-1 remains debated. We present 2 case reports of male siblings with PFIC-1 who benefited from different treatments.

Case Report: Both siblings harbored a homozygous truncating mutation in *ATP8B1* characteristic for PFIC-1 and both underwent PEBD after unsuccessful UDCA treatment at the age of 7 and 5 months, respectively. The older brother, after initial improvement of symptoms, developed severe pruritus, cholestasis, and diarrhea 9 months after PEBD and underwent LTx at the age of 16 months. Chronic diarrhea and abnormal transaminases activity appeared soon after transplantation. A liver biopsy was performed 3 months after LTx and showed severe macrovesicular steatosis (95%). Sixteen months after LTx, total biliary diversion was performed, with rapid relief from diarrhea and significant regression of graft steatosis by <30%.

In his brother we observed persistent severe pruritus and cholestasis after PEBD, but we decided to postpone LTx due to lack of a living related donor and risk of graft steatosis. Eight months after PEBD, bilirubin and bile acids significantly decreased and pruritus disappeared completely. Currently, in 5-year follow-up, liver function is stable and he has no pruritus.

Conclusions: The good effect of PEBD may be delayed in PFIC-1, even in severe mutation; thus, the decision to perform LTx should be made cautiously. Total biliary diversion is an efficient procedure in case of persistent symptoms after LTx and can reverse graft steatosis in children with PFIC-1.

Keywords: Biliary Tract Surgical Procedures • Cholestasis • Transplants

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/932374

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Background

Progressive familial intrahepatic cholestasis type 1 (PFIC-1) is an autosomal recessive disorder caused by biallelic pathogenic variants in the *ATP8B1* gene encoding FIC1 protein acting as aminophospholipid flippase, transferring phosphatidylserine from the external to cytoplasmic membrane leaflet. However, precise mechanisms of liver injury in PFIC-1 still remain to be determined [1,2]. Patients typically present with jaundice and severe pruritus in the first months of life. Unlike PFIC-2, PFIC-1 is multiorgan disorder due to the broad tissue distribution of FIC1 expression [1,2]. Extrahepatic symptoms, such as diarrhea, pancreatitis, deafness, and poor growth may persist, develop, or aggravate after liver transplantation (LTx) [3-9]. Moreover, the presence of steatohepatitis progressing to cirrhosis and the need for re-transplantation may be observed after LTx [3-6]. Patients with end-stage liver disease, severe pruritus, or severe growth retardation are liver transplant candidates, whereas partial external or internal diversion (PEBD/PIBD) or ileal exclusion (IE) should be considered in cases without cirrhosis [10-16]. Recent advances allowed determination of the genetic background with varying phenotypical presentation in the PFIC-1 population. We present 2 case reports of male siblings with genetically confirmed PFIC-1 who underwent PEBD with different outcomes. Both patients harbored the extremely rare 2097+2T>C homozygous mutation in *ATP8B1*. Parental informed consent was obtained before all performed diagnostic tests and data collection.

Case Reports

Case 1

A 6-week-old boy was admitted to our hospital after an episode of prolonged subcutaneous bleeding after vaccination. He was born at term with weight of 2920 g, of healthy, unrelated parents. It was a second pregnancy after previous miscarriage at the 6th week of pregnancy. There was no family history of liver disease. At admission, the patient was jaundiced with subcutaneous hematoma at the site of vaccination. Spleen and liver were not enlarged and stools were yellow. Laboratory tests showed severe coagulopathy (INR was undetectable) and cholestasis with normal GGTP (**Table 1**). Vitamin K and blood plasma were transfused; UDCA (20 mg/kg/day) and vitamin supplementation (A, D, E, K) were started. After excluding other causes of cholestasis, PFIC-1 was confirmed genetically. Within the next months, the patient presented with poor growth and developed severe pruritus with rapid increase of serum bilirubin and bile acids. At the age of 7 months, partial external biliary diversion (PEBD) was performed. The liver biopsy showed changes consistent with PFIC1, with bland cholestasis, hepatocytic rosette formation around bile plugs, fibrosis, and normal bile ducts without ductular proliferation. After the initial disappearance of pruritus and normalization of serum bile acids, the cholestasis aggravated, and at the age of 16 months (8 months after PEBD), the patient underwent living related liver transplantation from his mother. Concurrently, the external stoma was removed. No surgical complications occurred in the post-transplant period, and standard immunosuppression with tacrolimus and mycofenolate mofetil (MMF) was started. Severe chronic diarrhea (5-7 liquid stools per day) appeared 1 month after transplantation. Repeated stool cultures and parasite examination were negative and there was no response to cholestyramine and MMF discontinuation (prednisone was introduced). Three months after LTx, due to abnormal transaminases activity, a liver biopsy was performed, which showed diffuse macrovesicular steatosis (95%) with no other changes (**Figure 1A**). Due to unremitting diarrhea and growth retardation 16 months after transplantation, total external biliary diversion (EBD) was performed a with previously described technique [8]. The distal part of the Roux loop was disconnected from the bowel tract and opened as a terminal jejunostomy. Liver biopsy at the time of EBD showed severe steatosis and moderate fibrosis (**Figure 1B**). After the surgery, rapid relief from diarrhea was observed and follow-up liver biopsies showed significant regression of steatosis and fibrosis (**Figure 1C, 1D**).

Five years after LTx, the patient has no diarrhea and his weight is between the 25th and 50th percentiles and his height is between the 10th and 25th percentiles. A clinical summary is presented in **Table 1**.

Case 2

The younger brother who was born at term after uncomplicated pregnancy developed cholestasis within the first 4 weeks after birth. Treatment with UDCA (20 mg/kg/day) was ineffective and during the next months the patient developed severe pruritus and coagulopathy (**Table 2**). PEBD was performed at the age of 5 months. Microscopic examination of the liver biopsy specimen revealed distortion of the normal architecture with severe fibrosis, giant cell transformation of the liver cells without steatosis, severe cholestasis, and rosette formation around the bile plugs, with non-specific mild inflammation. After initial transient improvement, the pruritus recurred and cholestatic parameters increased. Due to the lack of a living donor and stable liver function parameters, we decided to postpone the transplant decision. Meanwhile, the patient remained on UDCA and vitamin supplementation (A, D, E, K). Eight months after PEBD, bilirubin rapidly decreased to 2 mg/dl, bile acids concentration changed to 65 ng/ml, and pruritus disappeared completely. Afterwards, complete normalization of cholestatic parameters was observed. Currently, after 4-year follow-up, the patient presents with normal lab test results, itching occasionally (only when infected or tired), and growing well.

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Table 1. Patient 1. *ATP8B1* NM_005603.4: C.2097+2T>C.

	6 weeks of age	4 months of age	7 months of age		7 days after PEBD	1 month after PEBD	3 months after PEBD	6 months after PEBD	8 months after PEBD
Weight (kg) [percentile]	4.5 [10-25c]	5.6 [3c]	6.67 [<3c]		6.77 [<3c]	6.8 [<3c]	7.8 [3-10c]	9.1 [25c]	9.3 [10-25c]
Height (cm) [percentile]	57 [25c]	59 [<3c]	62 [<3c]		62 [<3c]	63 [<3c]	73 [25-50c]	74 [10c]	75 [3-10c]
Diarrhea	–	–	–		–	–	–	–	–
Pruritus*	–	+++	++++		++	–	–	+	++++
TB (mg/dl)	8.84	1.82	14.89		5.47	0.87	10.91	10.29	10.84
DB (mg/dl)	3.84	1.58	12.63	**PEBD**	5.04	ND	9.82	9.41	9.89
BA (mmol/l)	94.5	278	395		25.1	7	196	189.5	90.2
ALT (U/l)	24	49	49		37	20	44	57	60
AST (U/l)	57	70	126		88	47	73	86	112
GGTP (U/l)	27	23	39		52	14	15	16	16
Albumin (g/l)	3.77	ND	3.72		ND	ND	4.16	4.03	3.19
INR	ND	1.34	1.41		1.36	ND	1.03	0.92	0.98

		3 months after LTx	6 months after LTx		4 months	7 months	5 years after LTX
Weight (kg) [percentile]		9.5 [3-10c]	9.5 [<3c]		13.7 [25c]	14.4 [25-50c]	21 [25-50c]
Height (cm) [percentile]		78 [3c]	80 [<3c]		91 [3c]	92 [3c]	114.2 [10-25c]
Diarrhea		++++	+++++		Relief from diarrhoea		
Pruritus*		–	–		–	–	–
TB (mg/dl)		0.33	0.31		0.73	0.61	0.88
DB (mg/dl)	**LTx**	0.18	0.16	**EBD**	0.31	0.29	0.41
BA (mmol/l)		31.1	17		3.2	3.4	3.2
ALT (U/l)		135	175		65	70	57
AST (U/l)		116	143		69	80	83
GGTP (U/l)		64	67		62	72	105
Albumin (g/l)		3.79	3.26		4.1	3.9	3.88
INR		1.17	1.13		1.31	1.64	1.26

Albumin: N 38-54 g/l; ALT: N <60 U/l; AST: N <84 U/l; BA: N <10 umol/; DSB: N <0.5 mg/dl; GGTP: N <200 U/l (till 3 months); INR: N 0.8-1.2; TSB: N <1.0/dl; * according Whitington [14].

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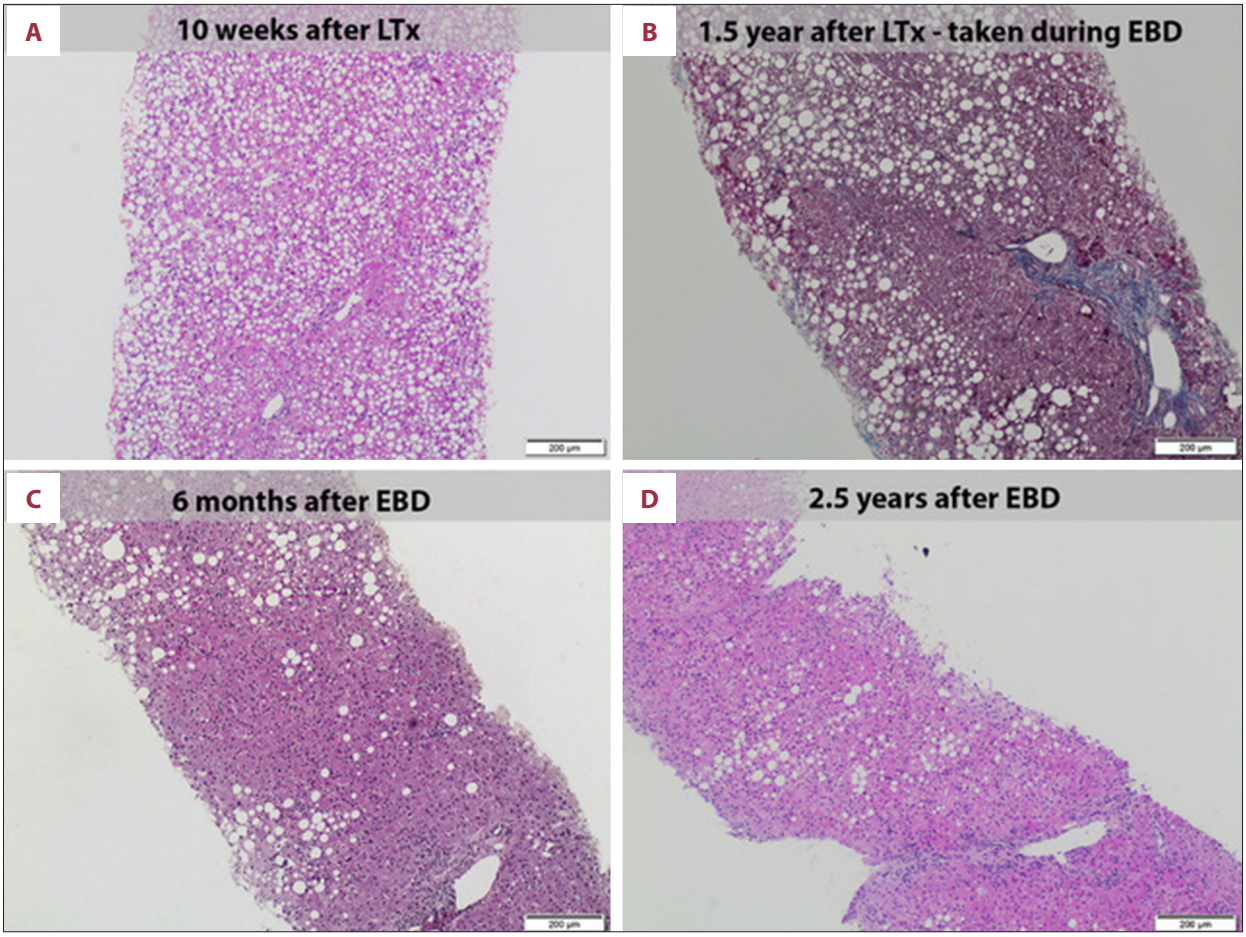

Figure 1. Liver biopsies after LTx – Case 1. (**A**) Mixed macro- and microvesicular steatosis (95%) and portal tract without fibrosis, without ductular proliferation (H&E staining). (**B**) Mixed macro- and microvesicular steatosis (70%), portal and periportal fibrosis without ductular proliferation (Azan staining). (**C**) Mixed macro- and microvesicular steatosis (40%), portal tract without fibrosis, without ductular proliferation, mild inflammatory infiltrates (H&E staining). (**D**) Mixed macro- and microvesicular steatosis (30%), fibrous septa, and mild inflammatory filtrates (H&E staining).

Discussion

We presented 2 case reports of male siblings, sharing the same homozygous mutation in *ATP8B1,* who underwent different treatment. One patient unexpectedly improved after initial failure of PEBD and avoided liver transplantation. The other developed recurrence of symptoms after LTx successfully treated with EBD. These observations shed new light on the disease course in homozygous, possibly protein-truncating, mutations, which are thought to result in severe phenotype and progressive liver injury. Also, it may suggest phenotypic differences between individuals sharing the same genetic background.

PFIC-1 is an inherited disorder leading to progressive liver damage, severe pruritus, and diarrhea, significantly influencing survival and quality of life [1,2]. Current medical treatment options are limited to administration of ursodeoxycholic acid, nutrition support with fat-soluble vitamin supplementation, and anti-pruritus agents of varying effectiveness, like rifampicin, cholestyramine or ondansetron [1,2,10-17]. Moreover, neither of the above seems to affect the primary disease process. Over the last decades, surgical techniques causing disruption of the enterohepatic circulation have been employed and they remain the mainstay of primary treatment in PFIC. They include partial or total external biliary diversion, internal biliary diversion, and liver transplantation [6-16,18-19].

Unlike in PFIC-2, LTx has significant limitations in PFIC-1 in which extrahepatic features like diarrhea, failure to thrive, or pancreas dysfunction can aggravate after transplantation. Moreover, patients often develop graft steatosis or steatohepatitis possibly progressing to cirrhosis with need of re-transplantation [3,5-10]. One of the possible responsible mechanisms could be decompensation of malfunctioning *ATP8B1* gene product after restoration of normal biliary secretion and intestinal bile flow, leading to the development of refractory

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Table 2. Patient 2. *ATP8B1* NM_005603.4: C.2097+2T>C.

	1 month of age	Before PEBD		1 month after PEBD	4 months after PEBD	6 months after PEBD	8 months after PEBD	1 year after PEBD	1.5 year after PEBD	3.5 years after PEBD
Weight (kg) [percentile]	4.49 [50c]	6.0 [10c]		6.6 [3-10c]	7.14 [3c]	7.32 [3c]	8.5 [3-10c]	8.9 [3-10c]	11.2 [25-50c]	16.5 [50-75c]
Height (cm) [percentile]	55 [50c]	64 [50c]		65 [10c]	70 [10-25c]	72 [10c]	72 [3c]	78 [10c]	79 [<3c]	97 [3-10c]
Pruritus (*)	–	++++		+/–	++++	++++	++	+	–	–
TB (mg/dl)	13.74	31.5		18.59	26.2	26.3	2.07	1.8	0.63	0.5
DB (mg/dl)	6.68	27.4		14.54	24.2	25.8	1.87	1.6	0.46	–
BA (mmol/l)	143	428.5	PEBD	–	145	332	65.9	58.7	8.1	7.2
ALT (U/l)	70	61		35	34	28	23	20	35	30
AST (U/L)	204	172		107	99	85	51	52	57	53
GGTP (U/l)	56	28		40	31	30	17	19	18	18
Albumin (g/l)	37.4	38		ND	ND	36.4	40.6	39.6	ND	40.4
INR	1.03	2.88		1.22	1.2	1.36	1.21	1.26	1.19	1.09

Albumin: N 38-54 g/l; ALT: N <60 U/l; AST: N <84 U/l; BA: N <10 umol/;, DSB: N <0.5 mg/dl; GGTP: N <200 U/l (till 3 months); INR: N 0.8-1.2; TSB: N <1,0 mg/dl; * according Whitington [14].

Table 3. Rescue procedure in PFIC 1 patients with diarrhea/steatosis after LTx.

Autor	Number of patients after LTx	First procedure	Age at LT	Number of pts with steatosis	Second procedure	Follow-up
Miyagawa-Hayashino A. [6]	11	LDLTx and Roux-en-Y anastomosis	1-18 years, median 4 years	8	1 pts transitional biliary diversion (due to bile leakage)	Improvement during procedure (diarrhea disappeared) but returned after biliary reconstruction
Usui M. [7]	1	LDLTx	1	1	Re-transplantation (4 y after first surgery) with EBD	10 months – without diarrhea
Nicastro E. [8]	1	LDLTx and Roux-en-Y anastomosis	3.years	1	EBD 28 months after LDLTx	6 months: – diarrhea disappeared and liver biopsy – improvement of steatosis
Alrabadi L.S. [9]	2	Cadaveric whole LTx with a Roux-en-Y -choledocho-jejunostomy	26 m	2	EBD 38 months post-LTx	6 months: resolution of macrovesicular steatosis (biopsy); improvement in diarrhea
		cadaveric donor LTx	7 y		EBD 39 months post-LTx	6 months: diarrhea improved, biopsy showed rare macrovesicular steatosis

EBD – external biliary diversion; LDLTx – living donor liver transplantation; LTx – liver transplantation.

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diarrhea and graft steatosis [6,8,10,17]. The steatosis seen after LTx in FIC1 deficiency could be a manifestation of altered signalling in the gut-liver axis and microbiota aberrations, although clear mechanisms remain unknown. Interestingly, post-transplant steatosis is usually associated with chronic refractory diarrhea, and *ATP8B1* mutations appear to affect sites of more functional importance in patients with post-transplant steatosis, which suggests greater protein dysfunction at sites of secretion and absorption in the body, including the intestine and pancreas [6].

Medical symptomatic treatment options for protracted diarrhea are limited. Some authors described a good effect of bile adsorptive resin therapy, but that was not satisfactory in our patients [4,17]. Several subsequent reports showed outstanding outcomes of post-transplant biliary diversion, with relief of diarrhea and regression of liver steatosis (**Table 3**). Some authors described good results of internal biliary diversion used preemptively at the time of LT as a stoma-free procedure to prevent postoperative graft steatosis or as a next step after PEBD [9,18].

Bull et al analyzed 42 PFIC-1 patients, and reported no difference in the frequency of clinically important poor outcomes of PEBD between FIC1 and BSEP patients, but found a greater proportion of BSEP-other compared to FIC1 patients who progressed to cirrhosis [10].

Squires et al [19] reported 8 patients with PFIC after PEBD and follow-up after 32 months on average (range, 15-65 months). They observed that total bilirubin levels dropped below 2 mg/dL in all patients by 8 months after PEBD (itching improved after PEBD within 3 months in all patients). Despite observed overall clinical improvement after PEBD, the authors reported recurrent transient episodes of cholestasis, often in combination with both worsening pruritus and declining vitamin levels.

Our patients harbored the homozygous state of a very rare mutation (2097+2T>C) causing in-frame deletion and subsequent protein truncation. Only 1 case was previously reported with the same mutation, who received cadaveric liver transplant at 5.5 years, followed by diarrhea exacerbation requiring parenteral nutrition, appearance of liver steatosis and no catch-up of stature growth [5] Diarrhea control was gained with cholestyramine. Ten years after LTx, there is persistent graft steatosis, slight lobular fibrosis, and portal fibrosis. Heterozygous variants of this mutation were reported twice previously and tend to have milder phenotype not leading to liver transplantation [1,19].

The delayed and sustained effect of PEBD observed in our patient with PFIC-1 is unclear. One of the possible explanations may be some interplay among overall bile acid pool, FXR expression, function of ASBT (apical sodium-dependent bile acid transporter), and microbiota alterations. Hypothetically, cholestasis develops presumably because of both enhanced ileal uptake of bile salts via upregulation of the apical sodium-dependent bile acid transporter and diminished canalicular secretion of bile salts secondary to downregulation of the bile salt excretory pump [2,20]. How biliary diversion affects these pathways could be a key to development of targeted medical treatment.

Our findings should be interpreted with caution due to some methodological limitations resulting mainly from retrospective chart review.

Conclusions

In conclusion, a good effect of PEBD may occur with delay in PFIC-1, even in severe mutations; thus, the decision to perform LTx should be made cautiously. Post-transplant diarrhea and graft steatosis are reversible by biliary diversion. A combination of concurrent LTx and biliary diversion may be considered individually in PFIC-1 patients.

Conflict of Interest

None.

Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

Abbreviations

PFIC- 1 – progressive intrahepatic familial cholestasis type 1; **UDCA** – ursodeoxycholic acid; **PEBD** – partial external biliary diversion; **LTx** – liver transplantation; **PIBD** – partial internal biliary diversion; **IE** – ileal exclusion; **INR** – international normalized ratio; **GGTP** – gamma glutamyl transpeptidase; **MMF** – mycophenolic acid; **EBD** – external biliary diversion; **ALT** – alanine aminotransferase; **AST** – aspartate aminotransferase; **BA** – bile acids; **DSB** – direct serum bilirubin; **LDLT** – living donor liver transplantation; **N** – normal value; **ND** – not determined; **TIBD** – total internal biliary diversion; **TSB** – total serum bilirubin.

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