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Long-term outcomes of six patients after partial internal biliary diversion for progressive familial intrahepatic cholestasis

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ABSTRACT

Background: Partial internal biliary diversion (PIBD) is an alternative approach for the treatment of devastating pruritus in patients with progressive familial intrahepatic cholestasis (PFIC). In these patients quality of life can be improved and progression of liver disease can be delayed while waiting for liver transplantation. The aim of our study was to evaluate six patients with PFIC who have undergone PIBD in long-term follow-up.
Methods: Retrospective review of the records of six patients who underwent PIBD for PFIC between 2008 and 2010 was conducted to evaluate age, growth, clinical and laboratory studies for long-term outcome.
Results: Serum postoperative bile acid levels were reduced from a mean 340.1 μmol/L (range 851–105) preoperatively to a mean of 96.3 μmol/L at postoperative fifth year. The difference between pre- and postoperative bile acid levels was statistically significant ($p = 0.018$). AST decreased from 79.1 U/L (range 43–150 U/L) to 64.6 U/L (range 18–172 U/L), ALT decreased from 102.8 U/L (range 35-270 U/L) to 84.6 U/L and total bilirubin decreased from 2.9 μmol/L (range 0.35–6.4 μmol/L) to 1.53 μmol/L (range 0.3–2.4). Again, the decrease in total bilirubin levels was significant ($p = 0.043$). Pruritus was diminished from a mean of +4 (range 4–4) preoperatively to a mean of +2 (4–0). One patient who underwent liver transplantation owing to relapsing pruritus died from postoperative sepsis in the early postoperative period at the fifth year after PBID. Five symptom-free patients have not required liver transplantation at a mean period of 6.1 ± 0.83 years (5.1–7.0 years) follow-up.
Conclusion: PBID is an effective surgical procedure in the long-term and can delay the need for liver transplantation in children with PFIC by reducing jaundice and pruritus.

Progressive familial intrahepatic cholestasis (PFIC) is a rare genetic disease that disrupts the ability of the hepatocyte to transport bile salts into the biliary canaliculi [1]. PFIC type 1, also known as the Byler's disease, is caused by a mutation in the ATP8B1 gene that encodes bile salt exporter pump expression on the hepatocytes [2]. A defect in this pump results in the accumulation of bile salts in the hepatocytes, causing progressive liver damage with cirrhosis and finally ending with the need for liver transplantation [3]. There are other forms of PFIC, all causing intrahepatic cholestasis associated with severe pruritus. The main presentation of the disease is intractable pruritus in children. If left untreated, these children die before reaching adolescence. Partially internal biliary diversion (PIBD), through a cholecystojejunocolonic anastomosis, is a novel surgical approach for these patients as recently described [4]. The early results of PBID were encouraging, with the disappearance of pruritus, improvement in growth and normalization of laboratory findings. However, the relative infrequency of PFIC caused a scarcity in the literature regarding the long-term outcome of PIBD for PFIC.

1. Patients and methods

Six children (2 girls, 4 boys) who underwent PIBD between 2008 and 2010 were retrospectively analyzed. No patients had any other surgical intervention previously.

1.1. Patient characteristics

Diagnosis was made according to the existence of pruritus, early onset of cholestasis, typical biochemical, laboratory findings, and the exclusion of other cholestatic diseases [5]. All other causes of cholestasis such as biliary atresia, Alagille syndrome, α-1 antitrypsin deficiency, cystic fibrosis, sclerosing cholangitis, and primary bile acid synthase defects were excluded. Low gamma glutamyl transpeptidase (GGT), high bile acids levels and severe pruritus existed in all the patients for both PFIC type1 and type 2. The diagnosis was confirmed by genetic analysis in three of the patients. One of these patients had heterozygote mutations in ATP8B1, ABCB11 and ABCB4 gene analysis. The patient was harboring a novel mutation in both alleles as in the study of Davit-Spraul et al. [6]. The other two had homozygote mutation in ABCB11 gene analysis (PFIC type 2). The rest of three patients' diagnosis was based on

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Table 1
Clinical features of the patients.

Case no	Gender	Signs and symptoms	Liver biopsy	Age at diagnosis (years)	Grade of pruritus	Age at surgery (years)
1	M	Jaundice, pruritus, hepatomegaly	Moderate fibrosis	2	+4	5
2	M	Jaundice, pruritus, hepatomegaly	Mild fibrosis	1	+4	4
3	F	Jaundice, pruritus, hepatomegaly	Moderate fibrosis	1.5	+4	4
4	F	Jaundice, pruritus	Cirrhosis with degenerative changes owing to intrahepatic cholestasis, giant cell hepatitis	0.5	+4	3
5	M	Jaundice, pruritus, hepatomegaly	Mild fibrosis	2	+4	5
6	M	Jaundice, pruritus, hepatomegaly	Moderate fibrosis	2	+4	2

liver histology; two of them who had mild cholestasis and periportal fibrosis on liver biopsy were regarded as type 1, whereas one patient with giant cell hepatitis with periportal fibrosis was regarded as like type 2 as in the study of Ramachandran et al. [7]. Diarrhea was among the initial symptoms in the two PFIC type 1 patient.

The pruritus was present in all six patients. The degree of pruritus was (+4) according to the scale described by Whitington and Whitington et al. [8] in all of the patients preoperatively. All of the patients underwent PIBD with the diagnosis of PFIC. The mean age of the patients at the time of the operation was 3.83 ± 1.17 years (range 2–5 years). The clinical features of the children are listed in Table 1. Serum bile acids, aspartate amino transferase (AST), alanine aminotransferase (ALT) and bilirubin levels were measured preoperatively. Preoperatory liver biopsies were also evaluated.

1.2. Surgical technique

All six patients received partial internal biliary diversion as described by Gun et al. [4]. Postoperatively, the patients were inserted nasogastric tubes; Sefazoline 100 mg/kg/dose was given as antibiotic therapy. Early postoperative recovery was uneventful in all patients. In only one of our patients had bile salt induced diarrhea occurred postoperatively in response to medical therapy with cholestyramine. The patients used ursodeoxycholic acid (10–30 mg/kg) permanently.

1.3. Outcome assessment

Survival with own liver and morbidities were evaluated. Serum bile acids, AST, ALT, and bilirubins were monitored. The degree of pruritus was reevaluated according to the scale by Whitington and Whitington et al. [9]. The height and weight gain of the patients were followed. Height and weight z scores were recorded at the last follow-up of the patients. Abdominal ultrasonography was performed to evaluate the spleen size and liver perfusion.

1.4. Statistical analysis

Statistical analysis was performed by the SPSS 22.0 software package (Chicago, USA). Paired t-tests were used to compare preoperatory and postoperative fifth year laboratory findings. Statistical significance was defined as $p < 0.05$.

Table 2
Bile acid values and pruritus score of each patient preoperatively and five years postoperatively.

Patients	Bile acids (μmol/L)		Pruritus	
	Preoperative	Postoperative	Preoperative	Postoperative
1	216	78	+4	+2
2	212	3.1	+4	+1
3	851	170.1	+4	+3
4	452	310	+4	+4
5	105	10	+4	+1
6	205	6.6	+4	+1
Mean	340.1	96.3	+4	+2

2. Results

The mean follow-up after PIBD was 6.1 ± 0.83 years (5.1–7.0 years). Bile acid and pruritus score of each patient are given in Table 2 preoperatively and five years postoperatively.

Table 3 shows the mean laboratory parameters at five years after surgery. Serum postoperative bile acid concentrations were reduced from a mean 340.1 μmol/L (range 851–105) preoperatively to a mean of 96.3 μmol/L at the postoperative fifth year. This difference was statistically significant ($p = 0.018$). AST decreased from 79.1 U/L (range 43–150 U/L) to 64.6 U/L (range 18–172 U/L), ALT decreased from 102.8 U/L (range 35-270 U/L) and total bilirubin decreased from 2.9 μmol/L (range 0.35–6.4 μmol/L) to 1.53 μmol/L (range 0.3–2.4). Again, the decrease in total bilirubin levels was statistically significant ($p = 0.043$). Pruritus score also improved, decreasing from a mean of +4 (range 4–4) preoperatively to a mean of +2 (4–0).

The mean weight –z score of the patients was −1.02, and the mean height –z score of the patients was −2.22 preoperatively. The mean weight –z score of the patients was −0.65, while the mean height –z score of the patients was −1.52 postoperatively. The improvement in the height –z score was statistically significant (0.028). Table 4 presents the mean height z scores and mean weight z scores of patients preoperatively and five year postoperatively.

All patients survived with their own liver except one. This patient has died owing to postoperative sepsis after liver transplantation in another center at the fifth year of PIBD She is the one with jaundice occurring at birth; her onset of the disease is the earliest and her preoperatory liver biopsy revealed severe cirrhosis with degenerative changes. None of the remaining patients are candidates for liver transplantation in terms of liver failure or intractable pruritus. One patient who had been a candidate for liver transplantation was removed from the liver waiting list because of the amelioration in his liver status. None of the patients experienced long-term complications of PIBD, such as cholangitis, intestinal adhesions or electrolyte imbalance.

3. Discussion

PFIC type 1, also known as Byler's disease, is a very rare genetic disorder (1 per 50,000 to 1 per 100,000). The defect is in ATP8B1 gene encoding the FIC1 protein, causing impaired bile salt secretion. A similar but more rapidly progressive form of biliary transport defect, PFIC type 2 arises owing to defects in the canalicular bile salt export pump caused by mutation in ABCB11. PFIC 1 and PFIC 2 both present with intrahepatic cholestasis with normal serum GGT. The third form of the PFIC

Table 3
Mean values of laboratory parameters and pruritus scores preoperatively (preop) and at the postoperative fifth year (postop).

	Preop	Postop	p value
Bile acids (μmol/L)	340,1	96,3	0.018*
Total bilirubin (μmol/L)	2,9	1,53	0.043*
AST (U/L)	79,1	64,6	0.237
ALT (U/L)	102,8	84,6	0.06
Pruritus score	+4	+2	

* Statistically significant ($p < 0.05$).