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Total biliary diversion as a treatment option for patients with progressive familial intrahepatic cholestasis and Alagille syndrome

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ABSTRACT

Background: Progressive familial intrahepatic cholestasis (PFIC) with low gamma-glutamyl transpeptidase (GGT) and Alagille syndrome are associated with persistent cholestasis and severe pruritus. Various types of biliary diversion have been used to reduce this pruritus and prevent liver dysfunction. We report our experience concerning the efficacy and safety of total biliary diversion (TBD) as an additional treatment option.
Methods: TBD was performed in four PFIC patients and one patient with Alagille syndrome, and was accomplished by anastomosing a jejunal segment to the choledochal duct terminating as an end stoma, or by disconnecting the choledochal duct after previous cholecystojejunocutaneostomy.
Results: TBD resulted in a marked improvement of symptoms and biochemical parameters in all PFIC patients. Despite relief of pruritus, cholestasis persisted in the Alagille patient. During 5–15 years of follow-up, no clinical signs of fat malabsorption such as diarrhea or weight loss were encountered. However, to maintain adequate levels of fat-soluble vitamins, especially of vitamin K, substantial supplementation was necessary.
Conclusions: Total biliary diversion can be a useful surgical treatment option for patients with low-GGT PFIC and possibly also Alagille syndrome, when partial biliary diversion is insufficient. It can be performed without inducing clinical signs of fat malabsorption although individualized supplementation of fat-soluble vitamins with careful monitoring is warranted.

Partial biliary diversion (PBD) is currently regarded as the therapy of first choice for patients with progressive familial intrahepatic cholestasis (PFIC) associated with a low serum gamma-glutamyl transpeptidase (GGT) [1–5]. This group comprises both PFIC type I (ATP8B1 deficiency) and PFIC type II (ABCB11 deficiency) [4]. In some patients with Alagille syndrome with severe cholestasis and pruritus, refractory to pharmacological therapy, PBD has also been effective [2,6]. All types of PBD, of which partial external biliary diversion (PEBD) by cholecystojejunostomy is used most frequently, intend to lower the accumulation of bile acids by a substantial reduction of the enterohepatic circulation of these compounds [7]. As PEBD leaves the common bile duct intact, a small fraction of the bile is still excreted into the duodenum [8]. Reabsorption of these bile salts in the terminal ileum might contribute to sustained cholestasis and associated pruritus in some patients with a PEBD. We hypothesized that complete abrogation of bile flow to the gastrointestinal tract by total biliary diversion (TBD) could be effective in these patients. This article reports our experience with TBD and describes that the procedure was both safe and efficacious in reducing symptoms in four PFIC patients and one patient with Alagille syndrome.

1. Patients and methods

1.1. Patients

Five patients, four with PFIC and one with Alagille syndrome, underwent TBD in our hospital during the 1999–2010 period. Medical charts were reviewed for patient characteristics (Table 1) and most recent growth and laboratory parameters (Table 2). Four patients, originating from the same village, were diagnosed with familial intrahepatic cholestasis type 1, all having a homozygous c.2932-3 C > A mutation in *ATP8B1*. The first three patients presented with jaundice and pruritus complicated by coagulopathy and malnutrition during infancy. They initially suffered from recurrent episodes of cholestasis which became permanent during adolescence [9]. They then had severe pruritus refractory to medical therapy and nasobiliary drainage. PFIC patient no. 4 presented with a subdural hemorrhage due to vitamin K deficiency caused by cholestasis at the age of 5 months. The final patient (no. 5) presented with neonatal cholestasis, pulmonary artery branch stenosis and posterior embryotoxon and was diagnosed with the

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Table 1
Patient characteristics and surgical procedures.

Patient	Diagnosis	Sex	Age at TBD (years)	PEBD procedure	TBD procedure	Bile acids pre-TBD (μmol/l)	Follow-up (years)
1	PFIC1	Female	10	Cholecystoappendicostomy	Hepaticojejunostomy	370	15
2	PFIC1	Male	18	Cholecystoappendicostomy	Hepaticojejunostomy	265	8
3	PFIC1	Female	14	–	Hepaticojejunostomy	260	8
4	PFIC1	Male	2	Cholecystojejunostomy	Choledochal duct ligation	366	5
5	Alagille	Male	1	Cholecystojejunostomy	Choledochal duct ligation	23	5

PFIC1, progressive familial intrahepatic cholestasis type 1; PEBD, partial external biliary diversion; TBD, total biliary diversion.

autosomal dominant Alagille syndrome due to a heterozygous c.2209delGGAA mutation in the *Jagged 1* gene (*JAG1*). Patient nos. 4 and 5 suffered from permanent cholestasis and unmanageable pruritus immediately after diagnosis.

1.2. Surgical procedures

Two patients underwent PEBD by a cholecystoappendicostomy without improvement of symptoms (nos. 1 and 2). Therefore TBD by hepaticojejunostomy was performed respectively one and three months later by end-to side anastomosis of the non-dilated choledochal duct to a jejunal segment terminating as an end stoma resulting in total drainage of bile through the stoma. The gallbladder and appendix were removed. Patient no. 3, sister of patient no. 2, directly underwent TBD by hepaticojejunostomy due to the good results of this procedure in her brother. Patient nos. 4 and 5 underwent PEBD by cholecystojejunocutaneostomy respectively at the age of 14 and 11 months. Patient no. 4 was symptom-free for more than a year before a new cholestatic episode developed, persisting for several months. To abort this episode, TBD was performed by disconnecting the choledochal duct, completely preventing bile flow to the gastrointestinal tract. In patient no. 5 PEBD was unsuccessful with insufficient bile drainage and persistence of pruritus despite low levels of bile acids. TBD by choledochal duct disconnection was therefore performed one month later. A pre-operative liver biopsy was only performed in patient no. 2 showing pericentral canalicular cholestasis and mild fibrosis.

2. Results

During the immediate postoperative period, re-operation was necessary in two patients. Patient no. 2 suffered from intra-abdominal bleeding four days postoperatively. Laparotomy showed intra-abdominal blood suggesting a mesenteric origin but there was no evidence of active bleeding. In patient no. 3, biliary leakage at the biliodigestive anastomosis necessitated multiple revisions. In all patients adequate bile drainage was achieved after TBD varying from 100 to 2000 ml per day (Table 2). Patient nos. 1–4 showed marked improvement of biochemical parameters and relief of their pruritus. Serum levels of bile acids, which were far above normal limits pre-operatively, decreased rapidly to normal values within three months (Fig. 1). During follow-up no serious surgical complications were encountered, although prolapse and stenosis of the stoma necessitated re-operation in patient nos. 2 and 4 respectively. Patient nos. 2–4 remained completely symptom-free with normal biochemical parameters during long-term follow-up (Table 2). Symptomatic cholestatic episodes recurred only in patient no. 1, who suffered from two short and two major episodes of pruritus and cholestasis in the subsequent 15 years. Patient no. 5 also reported improvement of clinical symptoms although moderate pruritus persisted. Hepatic function and serum levels of bile acids did not improve but remained stable over time. Since hepatic function improved or stabilized in all patients, no liver biopsies were obtained during follow-up. Repeated abdominal ultrasound showed no signs of liver cirrhosis or portal hypertension, no bile duct dilatation and normal spleen size in all patients. Platelet count was also stable and in the normal range for all patients. On four occasions during follow-up, patient no. 5 developed fever possibly due to cholangitis, confirmed by positive blood culture only once, which resolved quickly after antibiotic administration. Given the recurrent unexplained febrile episodes, antibiotic prophylaxis (sulfamethoxazole/trimethoprim) was started after the second hospital admission. In the other patients no episodes of cholangitis were encountered. Urine oxalate/creatinine ratios, measured to detect hyperoxaluria, were normal in all patients. Furthermore, no clinical signs of malabsorption were seen in any of the patients e.g. weight loss and diarrhea. All patients were on a normal diet without restrictions. Patient no. 5 received additional tube feeding due to resistance to oral feeding. Even when TBD was performed at a very young age, growth and defecation pattern were normal. Pubertal development was normal and both girls had a regular menstrual pattern without excessive bleeding. Yet, in patient nos. 1–3, it was difficult to maintain normal biochemical levels of fat-soluble vitamins and supplementation with large doses was necessary, especially for vitamin K (Table 3). Despite this supplementation, vitamin K plasma levels remained below the reference value. However, prothrombin time (PT), which usually is prolonged by vitamin K deficiency, was normal or almost normal and no clinical signs of coagulopathy were observed. In pre-adolescent patient no. 4, no deficiency of fat-soluble vitamins was detected during 5 years of follow-up with low dose supplementation. However, in pre-adolescent patient no. 5, a vitamin K dose of 10 mg/day was necessary to obtain a normal prothrombin time. Despite a permanent stoma, all adult patients reported a good quality of life, due to the remarkable and persistent relief of pruritus and cessation of disease progression.

3. Discussion

Patients with PFIC and Alagille syndrome, usually present during infancy or childhood with pruritus, cholestasis and frequently develop

Table 2
Most recent growth parameters and laboratory profiles.

Patient	Age (years)	Length (cm)	Weight (kg)	BMI (kg/m^2)	Bilirubin (μmol/l)	ALT (U/l)	AST (U/l)	Bile acids (μmol/l)	GGT (U/l)	Stomal bile (ml/day)
1	26	176 (+1 SDS)	78	25.2 (+1.1 SDS)	38 (↑)	171 (↑)	90 (↑)	12	40	800–1000
2	27	194 (+1.3 SDS)	94.2	25.0 (+1.1 SDS)	9	43	35	4	27	500
3	22	173 (+0.4 SDS)	70.1	23.4 (+0.9 SDS)	10	31	32	4	13	2000
4	7	128 (−0.5 SDS)	27.1	16.6 (+0.9 SDS)	11	20	33	7	8	300–400
5	6	121 (+0.2 SDS)	23	15.7 (+0.4 SDS)	20 (↑)	376 (↑)	260 (↑)	55 (↑)	497 (↑)	100

BMI, body mass index; SDS, standard deviation score; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma glutamyl transpeptidase.