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Surgical outcomes in Alagille syndrome and PFIC: A single institution's 20-year experience☆

Celia D. Flores [a,b], Yangyang R. Yu [a,b], Tamir A. Miloh [c], John Goss [b], Mary L. Brandt [a,b,*]

[a] Division of Pediatric Surgery, Department of Surgery, Texas Children's Hospital, Houston, TX, United States
[b] Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, TX, United States
[c] Section of Hepatology and Liver Transplant Medicine, Department of Pediatrics, Texas Children's Hospital, , Houston, TX, United States

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ABSTRACT

Background: Alagille Syndrome (AGS) and Progressive Familial Intrahepatic Cholestasis (PFIC) are rare pediatric biliary disorders that lead to progressive liver disease. This study reviews our experience with the surgical management of these disorders over the last 20 years.
Methods: We retrospectively reviewed the records of children diagnosed with AGS or PFIC from January 1996 to December 2016. Data collected included demographics, surgical intervention (liver transplant or biliary diversion), and complications.
Results: Of 37 patients identified with these disorders, 17 patients (8 AGS,9 PFIC) underwent surgical intervention. Mean postsurgical follow-up was 6.9 ± 4.7 years. Liver transplantation was the most common procedure (n = 14). Two patients who were initially thought to have biliary atresia underwent hepatoportoenterostomy, but were subsequently shown to have Alagille syndrome. Biliary diversion procedures were performed in 3 patients (external n = 1, internal n = 2). PFIC patients tended to be older at the time of liver transplant compared to AGS (4.3 ± 3.9 years vs. 2.4 ± 1.1 years, p = 0.25). The AGS patient with external diversion had resolution of symptoms and no complications (follow-up: 12.5 years). Both PFIC patients with internal diversion (conduit between gallbladder and transverse colon) had resolution of pruritus and no progression of liver disease (follow-up: 3.8 and 4.5 years).
Conclusions: AGS and PFIC are rare biliary disorders in children which result in pruritus and progressive liver failure. Three patients in this series (8%) benefited from biliary diversion for control of pruritus and have not to date required transplantation for progressive liver disease. 38% underwent transplantation owing to pruritus and severe liver dysfunction.
Level of Evidence: 2b

Alagille Syndrome (AGS) and Progressive Familial Intrahepatic Cholestasis (PFIC) are rare pediatric biliary disorders that can cause life-limiting pruritus and lead to progressive liver disease. AGS is an autosomal dominant disorder characterized by paucity of intrahepatic bile ducts, typical facies, congenital cardiac defects, posterior embryotoxon of the eye, and butterfly vertebrae. Renal disease, growth retardation, and neurovascular accidents may also be associated with this syndrome. Ineffective bile excretion from the liver leads to intrahepatic cholestasis, hyperbilirubinemia, and hypercholesterolemia in patients with AGS [1]. Most patients with AGS respond to nutritional optimization, fat-soluble vitamin supplementation and medications to help relieve pruritus [1] including urodeoxycholic acid, cholestyramine, phenobarbital and rifampin [2]. For patients who do not respond to these medications, biliary diversion can be considered to treat severe pruritus with severe skin excoriation, excessive irritability, sleep disturbance, anorexia, and marked failure to thrive [3]. In contrast, PFIC is an autosomal recessive disorder characterized by defective genes responsible for bile transportation, limiting the ability of the hepatocyte to transport bile salts into the biliary tree. Progressive hepatocellular cholestasis along with the subsequent retention and accumulation of bile salts within the hepatocyte leads to progressive liver damage and pruritus [2]. PFIC1 and PFIC2 usually appear in the first months of life, whereas PFIC3 typically surfaces later in infancy, in childhood or even during young adulthood [4].

The goal of biliary diversion in the treatment of AGS and PFIC is to disrupt the enterohepatic circulation and decrease the accumulation of excess bile salts in serum. These procedures affect biliary acid composition, improving cholestasis and may also delay progression to cirrhosis

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* Corresponding author at: Texas Children's Hospital / Baylor College of Medicine, 6701 Fannin Drive, Suite 1210, Houston, TX 77030. Tel.: +1 832 822 3135; fax: +1 832 825 3141.
E-mail address: mlbrandt@texaschildrens.org (M.L. Brandt).

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Table 1
Biliary diversion patient profiles.

Diagnosis	Surgical Procedure	Liver Biopsy	Symptoms	Labs Before Diversion	Recent Labs	Medications Trialed
AGS	External Biliary Diversion	Focal Bile duct proliferation. Mild bridging portal fibrosis, Stage 2, Moderate chronic inflammation with eosinophils in portal tracts	Pruritus	**07/26/2004** AST: 171 ALT: 209 AlkP: 835 GGT 676 Albumin: 4.4 Bili U: 0.2 Bili C: 0.0 PTT: 37.6 PROTIME: 12.9 INR: 1.0	**07/26/2017** AST: 98 ALT: 111 AlkP: 289 GGT: 233 Albumin: 4.4 Bili U: 0.7 Bili C: 0.6	Phenobarbital Rifampin Ursodiol
PFIC1	Internal Biliary Diversion	Interface hepatitis with moderate portal inflammation and focal zone 1 hepatocyte necrosis. Lobular chronic inflammation, mild. Ultrastructural granular bile in canaliculi with thickened canalicular walls and affected pseudopodia, consistent with Byler's bile. Fibrous expansion of portal tracts with occasional portal to portal bridging.	Pruritus	**7/30/2012** AST: 60 ALT: 111 AlkP: 264 GGT: 19 Albumin: 3.9 Bili U: 0.1 Bili C: 0.0	**7/28/17** AST: 51 ALT: 84 AlkP: 263 GGT: 13 Bili U: 0.2 Bili C: 0.1 PT: 11.2	AquaDEKs Ursodiol Rifampin
PFIC2	Internal Biliary Diversion	Intrahepatic cholestasis, moderate with rare hepatocellular giant cell transformation	Pruritus	**11/05/12** AST: 32 ALT: 51 Alkp: 284 GGT: 14 Albumin: 3.7 Bili U: 0.5 Bili C: 0.0	**11/10/16:** AST: 27 ALT: 12 AlkP: 392 GGT: 9 Albumin: 4.4 Bili U: 0.4 Bili C: 0.1	AquaDEKs Rifampin Atarax Ursodiol

AlkP: Alkaline phosphatase, Bili U: Unconjugated Bilirubin, Bili C: Conjugated Bilirubin.

[5]. Biliary diversion procedures that have been described include partial external biliary diversion, 1,2 ileoileal bypass procedure, and partial internal biliary diversion to the transverse colon [6].

This study reviews our experience with the surgical management of PFIC and AGS over the last 20 years.

1. Material and methods

1.1. Patient population

After approval for this study by the Institutional Review Board (H-38987), we performed a retrospective review of all children at Texas Children's Hospital with a diagnosis of AGS or PFIC from January 1996 to December 2016. Patients were identified using the ICD-9 diagnosis codes: 759.89, Q44.7, 573.8, 576.8, 277.4, 698.8 or CPT 51.37, 47.91 for diversion procedure. Patients were excluded from the study if they were not confirmed by either imaging, genetics or labs to have AGS or PFIC. Additionally, patients who did not undergo surgical intervention were also excluded from our analysis.

1.2. Study design and clinical variables

We performed a retrospective review of medical records. Patient demographic data collected included gender and age at the time of surgery. Preoperative diagnosis and indication for surgery were determined based on a multidisciplinary evaluation of clinical, laboratory findings and liver biopsies [Table 1]. Operative data, complications, symptoms, and follow-up were collected.

Table 2
Procedures undergone by patients.

Procedure	Total patients (n = 17)
Liver Transplant	14 (82%)
Internal Diversion	2 (12%)
External Diversion	1 (6%)

1.3. Surgical procedure

Two patients underwent an internal biliary diversion with a pedicle from the gallbladder to the transverse colon. The abdomen was entered through a right subcostal incision. The ligament of Treitz was identified and a loop approximately 40 cm distal was chosen for the pedicle graft. The arterial arcade was inspected and the pedicle was based on two arteries. This was done deliberately to ensure adequate vascularization if revision to an exteriorized loop was ever deemed necessary. The bowel was transected to create a 16–18 cm length of bowel based on this pedicle using GIA staplers. A single layer end to side anastomosis with 4-0 PDS was carried out between the proximal end of the bowel and the mid ventral portion of the gallbladder. The distal end was anastomosed end to side to the proximal transverse colon. Although using a jejunal pedicle, as described above, is by far the most common technique used for creating external biliary drainage, the patient in our series who underwent external drainage had a large and perfectly placed appendix, allowing a cholecystoappendicostomy to be performed.

1.4. Statistical analysis

Baseline patient demographics were analyzed using descriptive statistics. All continuous data were analyzed using Mann Whitney U test for nonparametric and Student's T test for parametric data. Categorical variables were compared using χ^2 test or Fisher's Exact test. All statistical analyses were performed using SPSS (version 24, IBM SPSS). A p-value <0.05 was considered significant.

Table 3
Patient age of intervention.

Diagnosis	Age (years)
AGS	4.3 ± 3.9
PFIC	2.4 ± 1.1
AGS	3.1
PFIC1	2.4
PFIC2	3.2