Complications and Quality of Life in Long-Term Survivors of Biliary Atresia with Their Native Livers

Kazuhiko Bessho, MD, PhD

Biliary atresia is a rare neonatal disease of unknown etiology that results from a fibroinflammatory obstruction of extrahepatic bile ducts in the first few weeks of life. It is one of the most common causes of neonatal cholestasis, and if untreated, it rapidly proceeds to biliary cirrhosis, which could be fatal within the first few years. About 50 years ago, Japanese surgeons Morio Kasai and Sozo Suzuki introduced a surgical intervention with hepatoportoenterostomy to restore biliary flow to the intestine and prevent further liver damage.[1] This intervention, which has been subsequently modified,[2-4] is still called the "Kasai procedure." The worldwide dissemination of the Kasai procedure dramatically changed the outcome of biliary atresia. This procedure is not a cure, however, and even with prompt surgical intervention, ongoing injury to the intrahepatic bile ducts and progressive cholangiopathy leads to end-stage cirrhosis and the need for liver transplantation by 2 years of age in approximately 50% of affected children.[5,6] In contrast, those who can clear jaundice after surgery have been expected to survive long term to adulthood with good health status and quality of life.[7] Recent multicenter studies, however, have found that the majority of those who escaped the need for early transplantation showed some evidence of chronic liver disease.[8,9]

In this review we provide comprehensive and up-to-date information on the clinical status and late-onset complications of biliary atresia in patients who did not need early liver transplantation and survived long term with their native liver. It is anticipated that this will facilitate meticulous, longitudinal follow-up by caregivers and promote clinical studies that will develop understanding of factors affecting the progression of these problems.

Methods

We accessed the PubMed database in September 2014 by using the search terms "biliary atresia" and ("adulthood" or "long-term") and ("health status" or "complication"). We excluded articles on liver transplantation, and additional literature was cited second hand from the first-tier literatures. The data from large cohorts are summarized in the **Table**,[8-15] whereas specific case reports are cited.

Growth Failure

Failure to thrive is one of the main indications for liver transplantation in early infancy; however, it has been reported that somatic growth is not compromised in long-term survivors with native livers.[8,13,14,16,17] For example, Ng et al[8] found that in 219 patients with biliary atresia (ages 5.1-17.9 years) who survived more than 5 years after the Kasai procedure, median weight and height z-scores were 0.49 and 0 and mean z-scores for anthropometric markers such as mid-arm circumference, triceps skinfold, and subscapular skinfold were within the normal range for healthy children.[8] In contrast, neurologic development was reported as normal to subnormal for this population. In a study, among 26 patients whose serum bilirubin levels were less than 2.1 mg/dL, age-relevant school performance was normal for 8 patients, 1 year below normal for 11 patients, and 2 or 3 years below normal for 7 patients.[16] Another study reported that of 30 adult survivors, 26 were engaged in regular or part-time employment.[13] It is notable, however, that normal growth cannot always be considered a predictor of good prognosis.[18]

Cholangitis

The pathogenesis of cholangitis after the Kasai procedure is debatable but is widely thought to be a common complication. Cholangitis has been reported to occur in 30%-60% of children with biliary atresia, most commonly in the first few years after the Kasai procedure[19]; however, a considerable number of adult survivors of biliary atresia with native livers have been diagnosed with cholangitis.[8,9,12] Cholangitis impairs the quality of life of patients and their families, particularly because the treatment requires admission to the hospital for intravenous antibiotics. Prophylactic regimens with antibiotics[20,21] and probiotics[22] have been shown to decrease the incidence of cholangitis shortly after the Kasai procedure, with one study revealing that prevention of cholangitis also promoted patient growth.[22] Recurrent cholangitis as an independent risk factor for transplant-free survival remains controversial,[10,23,24] and studies on prophylactic measures for long-term survivors with late-onset cholangitis are limited and remain controversial.

Late-Onset Cholestasis (Jaundice and Pruritus)

Some long-term survivors redevelop significant cholestasis with jaundice and pruritus later in life despite achieving good bile drainage after the Kasai procedure in their early course. This cholestasis may be associated with symptoms of cholangitis, such as fever and leukocytosis, and is sometimes triggered by gastrointestinal bleeding. When an older patient presents with recurrent cholestasis without these prodromal episodes, however, it may be predictive of

From the Department of Pediatrics, Graduate School of Medicine, Osaka University, Suita-shi, Osaka, Japan

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Table. Summary of case series that report medical status of patients with biliary atresia with native livers more than 5 years

Authors	Ng et al,[8] 2014	Lee et al,[10] 2013	Nio et al,[11] 2012	Kumagi et al,[12] 2012	Shinkai et al,[13] 2009	Lykavieris et al,[14] 2005	Nio et al,[15] 1996	Bijl et al,[9] 2013
Country of study	US, Canada	Korea	Japan	Canada	Japan	France	Japan	Article review
Age	5.1-17.9 y	7∼191 mo	>20 y	18∼46 y	20∼31 y	20∼35 y	20∼39 y	>20 y
No. subjects	<219*	24	92	22	35	63	22	162
Overall complications	215 (98.2%)	14 (58.3%)	20 (%)	22 (100%)				98 (60.5%)
Cholangitis	136 (62.1%)			11 (50.0%)	13 (37%)	19 (30.1%)	6 (27.3%)	98 (60.5%)
Gastrointestinal varices/bleeding	20 (9%)	7 (29.2%)		11 (63.3%)	6 (17%)	37 (58.7%)	9 (40.9%)	35 (21.6%)
Hepatopulmonary syndrome/ portal hypertension	3 (1.5%)			21 (99.5%)		44 (69.8%)	8 (36.4%)	78 (48.1%)
Ascites	37 (17%)	2 (8.3%)		3 (13.6%)				
Bone fracture	33 (15%)							
Malignancies						0 (0%)		1 (0.62%)
Biochemical abnormalities	170 (92.7%)			17 (77.3%)		42 (66.7%)	10 (45.5%)	
Impaired quality of life	44 (27.3%)					14 (26.9%)	6 (27.3%)	

*A total of 219 patients were enrolled in the study, but there were some missing data for each item.

a rapid deterioration of liver function in the near future, and this complication can be an indication for liver transplantation in adolescence or adulthood.[18]

Varices and Gastrointestinal Bleeding

Variceal bleeding is a potentially life-threatening complication that develops in a significant number of patients with biliary atresia.[9,10,12] It can develop even in patients with intact hepatic synthetic function. Thrombocytopenia has been known as a symptom of hypersplenism along with gastrointestinal varices and is also a known risk factor for bleeding.[25,26] Splenectomy and partial splenic embolization can be performed to correct thrombocytopenia and decrease the frequency of bleeding episodes[27,28]; however, given the nature of portal hypertension associated with this disease, clinical decision-making should take into consideration a need for liver transplantation in the near future for individual patients. In cases of bleeding, absence of bile flow is a predictor of a high risk of near-term mortality.[29] The need for regular endoscopy for primary prophylaxis in pediatric populations is controversial.

Hepatopulmonary Syndrome and Portopulmonary Hypertension

Hepatopulmonary syndrome is a complication typically encountered in the long-term follow-up of patients with biliary atresia. The prevalence of this complication varies, possibly as the result of differences in screening modalities.[8,9,12] In a study that used contrast echocardiography, the authors found that more than 50% of children with biliary atresia had a sign of this complication.[30] This complication may be an indication for early transplantation even when liver function is retained[31] and is reversible after transplantation.[30]

Portopulmonary hypertension is a rare but potentially life-threatening complication of biliary atresia.[32] Patients with mild and moderate cases should be prioritized for liver transplantation with Model for End-Stage Liver Disease/ Pediatric End-Stage Liver Disease Model exception, whereas liver transplantation is a contraindication for advanced cases because of increased perioperative morbidity and mortality.[33,34] Therefore, it is important to screen long-term survivors for this complication in its earliest stages after the Kasai procedure.[5] Chest radiography and electrocardiography are screening tools that are insensitive to this complication.[35] Screening with Doppler echocardiography with subsequent right-heart cardiac catheterization to confirm the diagnosis is recommended for any patient with end-stage liver disease or portal hypertension.[36] Liver transplantation can reverse this complication, but it can develop even after successful transplantation.[37]

Ascites

Ascites develops in a significant number of children with biliary atresia.[8,10,12,38] Even though it is rarely the primary indication for transplantation when presented alone, when it presents with other major complications of end-stage liver disease and is refractory to medical therapies, including salt restriction and diuretic regimens, it supports the indication of liver transplantation.[38]

Bone Fracture

Patients with biliary atresia are at risk for bone fracture as the result of vitamin D deficiency, which is attributed to malabsorption of fat-soluble vitamins and poor hepatic 25-hydroxylation.[39] The reported prevalence of bone fracture before liver transplantation in patients with biliary atresia varies from 8% to 35%,[8,40,41] with the most common fracture site the upper extremity (ie, forearm, arm, buckle wrist, hand, radial bone, arm, or thumb).[8] It may be beneficial to check serum vitamin D, calcium, and parathyroid hormone levels regularly and perform early bone mineral density measurements. Preventive vitamin D supplements such as ergocalciferol (vitamin D2) or cholecalciferol (vitamin D3), with a target 25-hydroxyvitamin D level of >20 ng/mL (50 nmol/L), should be administered orally or intramuscularly.[41]