Hepatocellular Carcinoma in Biliary Atresia: King's College Hospital Experience

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Objectives To establish risks for development of hepatocellular carcinoma (HCC) in children with biliary atresia (BA), the most common chronic liver disease of childhood.

Study design In our tertiary referral center database we have identified children with BA who had development of or have been incidentally found to have HCC. Their demographic, clinical, radiologic, and histologic features were analyzed.

Results Between 1990 and 2008, 387 infants were diagnosed with BA at our center. Of these, three (0.8 %) who underwent operation at a median age of 68 (range 66 to 71) days had development of a histologically proven HCC detected at a median age of 2.1 (range 1.8 to 4.9) years. Another two, referred later, were diagnosed with HCC on their liver explants at ages 1.1 and 17.75 years, respectively. Overall, two had elevated serum levels of alpha-fetoprotein. All five children underwent successful liver transplantation at a median age of 2.1 years (range 1.1 to 17.75) and remain well after a median of 2.5 (range 2 to 5.7) years.

Conclusion HCC develops in a small percentage of children with BA. Serum alpha-fetoprotein levels and ultrasound screening are helpful but not absolute markers of the malignant change. In the absence of the extrahepatic involvement, liver transplantation represents an effective treatment. *(J Pediatr 2011;159:617-22)*.

Biliary atresia (BA) is an obstructive cholangiopathy of the newborn that, if untreated, leads to biliary cirrhosis and end-stage liver disease.[1] Treatment is largely surgical, with an initial attempt to restore bile flow by excision of usually solid extrahepatic biliary remnants and biliary reconstruction (Kasai portoenterostomy [KPE]). In large centers, more than half of infants will clear their jaundice but still have a degree of chronic liver disease (CLD).[2] BA remains the most common pediatric indication for liver transplantation (LT), but approximately one-third of children will reach adulthood without undergoing transplantation.[3]

Malignant change is a well-recognized complication of CLD from whatever cause.[4-6] This is usually hepatocellular carcinoma (HCC). In children, HCC is the second-most common liver tumor, after hepatoblastoma.[6,7] Between 1979 and 1996 the reported incidence of HCC in the United States has been declining from 0.45 to 0.29 per million children.[7] Approximately 65% of all HCCs occur in children older than 10 years, and they are of sporadic nature.[6] Some genetic conditions, such as tyrosinemia type I[8] and bile salt export pump (BSEP) deficiency[9] represent examples where HCC develops on a strikingly short timescale, often within the first few years of life. A number of other hepatic disorders have been described with HCC in childhood, although much less frequently.[6] Apart from increased cellular turnover, pathophysiological mechanisms of the neoplastic transformation in CLD remain poorly understood.

Occasional case reports have described HCC in BA,[10-16] but there have been no studies on its relative incidence in a large cohort. The aim of this study was to estimate the risk of malignant transformation in BA and define optimal management.

Methods

King's College Hospital is the largest tertiary referral center for infants and children with liver diseases in the United Kingdom. Annually, between 25 and 30 infants are diagnosed with BA and treated with corrective biliary surgery, typically KPE. If this fails then they are considered for LT.[17]

AFP	Alpha-fetoprotein
BA	Biliary atresia
BSEP	Bile salt export pump
CLD	Chronic liver disease
CT	Computed tomography
HCC	Hepatocellular carcinoma
KPE	Kasai portoenterostomy
LT	Liver transplantation
MDR	Multi-drug resistance

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Our prospectively acquired database of children with BA (from January 1990 to December 2008) was examined to identify those who were subsequently diagnosed with HCC. Archived histologic material was retrospectively reexamined by two histopathologists, unaware of the clinical details. In addition to standard histologic techniques, the following antibodies were used: monoclonal Ki-67 (Mib-1) (1/200), CD34 (QBEnd 10) (1/100) (both Dako, Ely, United Kingdom), beta-catenin (1/50) (Novocastra, Newcastle, United Kingdom), glypican 3 (1G12) (1/100) (Menarini Winnersh, Berkshire, United Kingdom), and polyclonal rabbit alpha-fetoprotein (1/400) (Dako). Data are quoted as median (range) unless otherwise indicated.

Results

Over the period of the study, 387 infants were diagnosed with BA. Of these, three (0.8%) had development of histologically proven HCC, detected at a median age of 2.1 (1.8 to 4.9) years. They all had isolated type 3 BA, with initial biliary surgery performed at a median age of 68 (66 to 71) days. All three patients had undergone KPE. During the same time period, two additional children, originally not treated at our center, were diagnosed with BA and HCC: (1) a child who had undergone KPE overseas was referred for follow-up and eventually diagnosed with HCC (patient 4); and (2) a child referred to us for LT because of cryptogenic end-stage CLD, had features of BA and incidental HCC in his explanted liver (patient 5). Histologic diagnosis of BA was reconfirmed in patients 1 to 3 by reviewing the presentation liver biopsy specimens and bile duct remnants for this study. In patient 4, for whom the original biopsy specimen was not available, the operative notes and histologic study of the explanted liver were compatible with BA. There were no clinical features of Alagille syndrome and multi-drug resistance (MDR) polypeptide-3 was immunohistochemically well expressed in the liver tissue in all patients.

Case Reports

Case 1. A white boy underwent KPE at 66 days of age. He cleared his jaundice to a normal serum bilirubin level (<20 μmol/L) and remained well until 38 months of age when he became suddenly jaundiced (bilirubin 232 μmol/L). Radionucleotide scanning and percutaneous transhepatic cholangiography suggested a Roux loop obstruction that was corrected surgically, and the patient's bilirubin level fell to 31 μmol/L thereafter. During routine post-KPE ultrasound surveillance, a focal parenchymal lesion was noted at 28 months. Abdominal magnetic resonance imaging did not suggest malignant features, and serum levels of alpha-fetoprotein (AFP) remained normal (<2 kU/L [normal range <7 kU/L]) throughout. At 40 months of age, another nodule appeared, prompting biphasic computed tomography (CT) scanning, which showed arterialization of the original, but not of the new lesion. The child was listed for LT, and hepatectomy confirmed a 54-mm-diameter, well-differentiated HCC. The second lesion had features of adenomatous hyperplasia. The patient's post-transplantation recovery was uneventful, and he was discharged on tacrolimus and prednisolone. He remains well at 2.5 years after LT.

Case 2. A white girl underwent KPE at age 71 days. She never cleared the jaundice and had development of ascites and intractable pruritus during the second year of life. At age 26 months she received a cadaveric LT: two small HCCs were found incidentally in her explanted liver. Her stored preoperative blood sample showed serum AFP of 1259 kU/L. Five days after LT her serum AFP levels decreased to 97 kU/L. The postoperative course was complicated by one episode of cellular rejection that was treated with steroids. The patient remains well at 4.1 years after LT, on tacrolimus and mycophenolate mofetil.

Case 3. A girl of South-Asian origin, but born in the United Kingdom, underwent KPE at 68 days. She never cleared her jaundice and after one episode of gastrointestinal bleeding associated with the development of ascites was listed for LT at age 15 months. Four months later she was noted to have rising serum AFP (51 kU/L to 220 kU/L to 777 kU/L), but no focal lesions could be shown on ultrasonography. However, 3 months later the patient had development of a 27-mm arterialized nodule within the right lobe, evident on biphasic CT scanning, and retroperitoneal and mesenteric adenopathy with right portal vein branch thrombosis. By then her serum AFP was 22 687 kU/L. The patient was prioritized on the waiting list and underwent LT at age 2 years. The explanted liver confirmed the nodule as HCC, with another smaller HCC (19 mm) detected in the right lobe. Preoperative AFP peaked at 139 929 kU/L, but sharply declined (61 kU/L) 1 month after LT and became normal (<2 kU/L) 6 months later. The patient remains well on tacrolimus and mycophenolate at 2.5 years after LT.

Case 4. A white girl with severe visual impairment caused by macular degeneration had had successful KPE performed at 49 days in Cyprus. Because of mild chronic cholestasis (bilirubin 70 μmol/L), she was referred to our center at age 14 years for follow-up. Routine ultrasonography at 17 years identified a large focal lesion (approximate diameter 10 cm), suggestive of adenoma. The patient was clinically well, and her serum AFP level was <2 kU/L. She was listed for transplantation and 6 months later received a liver graft: the hepatectomy specimen showed a 105-mm–diameter HCC. She remains well on tacrolimus and sirolimus at 5.7 years after LT.

Case 5. A boy from a consanguineous Arab family, born in the United Kingdom, had development of progressive cholestatic liver disease. Liver biopsy performed at 21 days of age showed features of nonspecific giant cell hepatitis. The patient remained jaundiced, and at 6 months the liver biopsy was repeated and now showed features of "large bile duct obstruction" with bridging fibrosis. Progressive cholestasis with intractable pruritus and gastrointestinal bleeding prompted