Biliary Atresia and Its Complications*

A. S. Knisely, M.D.

Departments of Hematology and Pathology,
University of Utah School of Medicine,
Salt Lake City, UT 84132

ABSTRACT

Infants with idiopathic perinatal fibroinflammatory obliteration of the lumen of the extrahepatic biliary tree ("biliary atresia") invariably died of biliary cirrhosis before surgical techniques were devised to permit drainage of bile into the duodenum. Survival rates in operated patients now approach 75 percent at 10 years. While definitive diagnosis of biliary atresia without the use of cholangiography at laparotomy is difficult, because other disorders have similar clinical features, early diagnosis is important. The earlier surgery is undertaken, the more successful it is. With delay, irreversible changes occur in the liver that produce portal hypertension. This and liver failure eventually make liver transplantation necessary even in some operated patients. Hepatic disease associated with biliary atresia is in part due to delay in diagnosis, but complications of surgical therapy, such as ascending cholangitis, also play a role. With prolonged survival and as numbers of liver transplant recipients rise, new therapy-related complications, such as those associated with immunosuppression, will become more important in surgically treated biliary atresia.

Introduction

Extrahepatic biliary atresia (biliary atresia) occurs in one of approximately 14,000 to 15,000 infants.8,44 The primary anatomic lesion consists of inflammatory and fibrous obliteration of the lumen of part or all of the extrahepatic biliary tree.14,15 If bile drainage is not reestablished by surgery, the child with biliary atresia succumbs to cirrhosis and the sequelae of portal hypertension at an average age of 19 months.16

Infants with biliary atresia present as well-appearing infants with "physiologic" jaundice that has failed to clear within several weeks after birth.8 They are generally well-nourished and well-developed otherwise,8 although associated errors in morphogenesis and organogenesis—cardiac defects, situs inversus, abnormal topography of the spleen, portal venous system, and gut—are present in as many as 25 percent.10,27,30 Biliary atresia is almost never seen in premature or stillborn infants.8 Bile pigment may be present in the stools early in postnatal life, only to disappear after several weeks.8 Clusters of affected infants seem to occur,8,44 but sets of twins have been reported in which only one had biliary atresia,40 and recurrence of the disorder

* Supported in part by NIH Grant 5T32 DK07115.
within a sibship is rare. These observations have led to the hypothesis that in most infants, particularly those without associated cardiovascular lesions, biliary atresia is not a heritable disorder, but instead is related to an exogenous perinatal insult.

A murine model exists of reovirus-associated hepatobiliary disease. Elevated serum titers of anti-reovirus antibodies have been observed in a higher proportion of infants with biliary atresia than of comparison infants, but others have not been able to reproduce this finding. IgM-class antibodies have been demonstrated at biliary-epithelium basement membranes in 44 of 128 excised specimens of the extrahepatic biliary tract, but without apparent correlation to the presence of inflammation. Characterization of the specificity of eluted antibodies has not been undertaken. Prospective studies of biliary atresia in large populations, attempting to identify common agents in samples of blood or serum obtained from newborn infants among whom some later manifest the disorder, have not been performed. The polymerase chain reaction may offer a sensitive approach to screening body fluids or surgically obtained tissues for particular infective candidates. At present, biliary atresia remains an idiopathic disorder.

Diagnosis

Evaluation of abnormally persistent conjugated hyperbilirubinemia in the newborn infant requires assessment for infections and various metabolic and anatomic disorders. The list of etiologies other than biliary atresia that require consideration is long, and can be found elsewhere. Very rarely, biliary atresia and other metabolic disorders with similar clinical manifestations may coexist, but an exclusionary approach to the diagnosis is generally appropriate. After testing has ruled out infective or metabolic diseases, three principal entities remain. These are biliary atresia, paucity of intrahepatic bile ducts, and idiopathic neonatal hepatitis. In all three, cholestasis and conjugated hyperbilirubinemia may be present, and the duodenal contents or stool may be acholic.

While laparotomy with cholangiography can definitively distinguish among these three disorders, much effort has been directed toward establishing diagnostic criteria using less invasive techniques. Sonographic assessment of decreases in gallbladder size with feeding, measurement of serum concentrations of various bile acids and hepatocellular enzymatic activities, imaging for radioactive tracer substances excreted with bile, examination of duodenal contents for bile, and endoscopic retrograde choledochopancreatography have been evaluated. Portal tract histology can be examined in percutaneous needle biopsy specimens of the liver. Expansion of portal tracts by fibrous tissue, with proliferation of bile ducts, is characteristic of biliary atresia, and its identification permits highly accurate diagnosis in some hands. This combination of studies will spare some infants from laparotomy.

Rapid and accurate diagnosis is urgent in this setting because the prognoses in idiopathic neonatal hepatitis, paucity of intrahepatic bile ducts, and biliary atresia differ so markedly. In idiopathic neonatal hepatitis, although progression to cirrhosis may occur, spontaneous resolution is the rule. In syndromic paucity of intrahepatic bile ducts, the extrahepatic biliary tree may be patent but hypoplastic; cholestasis in these children tends to resolve, although abnormalities on liver function testing may persist into adulthood. The prognosis in nonsyndromic paucity, the product of a nonspecific response of the intrahepatic biliary ducts to a variety of injurious agents,
depends on the extent of damage done, but is much more favorable than that in untreated biliary atresia.

Biliary atresia is surgically treated by any of several variants of hepatic portoenterostomy, a procedure in which the lumen of a segment of jejunum is sutured into apposition to the porta hepatis at the site from which the atretic extrahepatic biliary tree has been resected. This therapy is inappropriate in idiopathic neonatal hepatitis or paucity of intrahepatic bile ducts. Its efficacy in biliary atresia decreases precipitously over both the short and long term with advancing postnatal age. In one series, resolution of jaundice occurred in 86 percent of infants who were operated on before eight weeks of age but in only 36 percent of infants who were operated on after eight weeks of age. Over the long term, survival after 10 years was 75 percent for those under 60 days old at surgery, and was 10 percent for those over 90 days old. Accordingly, if biliary atresia cannot quickly be excluded from the differential diagnosis of neonatal conjugated hyperbilirubinemia, laparotomy, cholangiography, and, if indicated, hepatic portoenterostomy should be performed without delay.

Management Following Hepatic Portoenterostomy

While early hepatic portoenterostomy is likely to establish bile drainage, it is not invariably successful. Granulation tissue at the porta hepatis or growth of bowel epithelium onto the site of biliary tract resection may block bile outflow. Revision of the bowel loop with removal of obstructive material under direct vision can let bile drainage resume, as can endoscopic curettage.

With free passage out from the liver, however, comes free passage up into the liver. Ascending cholangitis causes substantial morbidity among patients who have undergone hepatic portoenterostomy and worsens their long-term prognosis by nearly 50 percent. Efforts to promote bile flow with choluretics and orally administered bile-binding resins have not decreased the incidence of cholangitis, nor has administration of antibiotics. Increased susceptibility to ascending cholangitis is perhaps the most serious adverse effect of hepatic portoenterostomy.

It is difficult to separate the histologic sequelae of ascending cholangitis from the changes that are due to obstructive cholestasis, but varying degrees of portal scarring, loss of interlobular bile ducts, and biliary cirrhosis are commonly seen in patients who have undergone hepatic portoenterostomy. While these findings are not associated with impaired absorption of fat-soluble vitamins or abnormalities in vitamin K-dependent clotting in nonjaundiced patients, growth retardation is usual. Portal hypertension, accompanied by hypertrophy of smooth muscle in intrahepatic portal venules, is frequent even in patients without jaundice, and may already be present at two months of age. The most severe complication of portal hypertension is hemorrhage from esophagogastric varices; this can be effectively treated by endoscopic sclerotherapy. Hypersplenism and thrombocytopenia can be expected to assume greater significance with increased long-term survival. Hepatocellular carcinoma is a known complication of secondary biliary cirrhosis that may be expected in some survivors of biliary atresia.

Deteriorating liver function and portal hypertension may eventually make it necessary to consider liver transplantation in either long-term survivors or infants in whom hepatic portoenterostomy has failed to establish bile drainage. Three-year survival was calculated as 73 percent in one series of 80 children who underwent liver transplantation at
an average age of five years; 44 percent had biliary atresia, and previous surgery in these children did not complicate transplantation. In another series of 36 children with biliary atresia who underwent liver transplantation at an average age of 30 months, calculated three-year survival was 75 percent. The rates of survival were 82 percent and 63 percent for patients who respectively had and had not previously undergone hepatic portoenterostomy; those who had were older (32 vs. 20 months) and larger (12.5 vs. 8 kg), and may have been better able to withstand surgery.

Morbidity after liver transplantation is not specific to biliary atresia, and can be expected to be high; as defined by days hospitalized as a percentage of total number of days under consideration, it was 50 percent in one small series of six children with biliary atresia. Of interest is that in another series of more than 50 children who underwent liver transplantation, two died of lymphoma.

Conclusions

With aggressive efforts at early diagnosis and surgical therapy, hepatic portoenterostomy may be expected to yield very good results in most cases of biliary atresia. The majority of complications can be ascribed to some combination of ascending cholangitis and of obstructive hepatic disease, worsened with delayed diagnosis. Orthotopic liver transplantation may offer prolonged survival to those patients in whom the results of hepatic portoenterostomy were compromised. This procedure carries with it its own set of complications.

Acknowledgments

This review could not have been written without the friendship and generosity of Mrs. Junko Nakamura, Professor Ryoji Ohi, and Dr. Ted Pysher.

References

117


44. STRICKLAND, A. D., and SHANNON, K.: Studies in the etiology of extrahepatic biliary atresia:


