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Arteriohepatic Dysplasia (Alagille's Syndrome): A Common Cause of Conjugated Hyperbilirubinemia

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ABSTRACT

Syndromatic paucity of interlobular bile ducts is a common cause of conjugated hyperbilirubinemia in children. The clinical presentation is not always obvious. Therefore, the liver biopsy may be a useful diagnostic tool in the definition of this entity.

The hepatic and biliary morphology of five children with arteriohepatic dysplasia (Alagille's syndrome) is described. Prior to diagnosis, four underwent Kasai procedures after intraoperative cholangiograms failed to demonstrate patency of the extrahepatic bile ducts. In three patients, a focal proximal hypoplasia of the common hepatic duct was demonstrated. Hypoplasia of the gallbladder occurred in two patients.

Hepatic features of sequential liver biopsies obtained in the five patients were divided into early and late changes. From birth to four months of age, the pathology consisted of cholestasis and bile duct destruction. After four months of age, there was persistent cholestasis, paucity of interlobular bile ducts and portal fibrosis.

The etiology of arteriohepatic dysplasia is unclear. The main pathogenic mechanisms are discussed. It is felt that the syndromatic duct paucity represents an acquired primary ductal defect resulting from a genetically determined immune response to as yet undefined agent or agents.

Introduction

Paucity of interlobular bile ducts is the most common cause of conjugated hyperbilirubinemia.[3,6,8] It may present as an isolated defect (nonsyndromatic paucity of interlobular bile ducts) or may be associated with other extrahepatic anomalies (structural syndromatic, Alagille's syndrome, arteriohepatic dysplasia).[3] These anomalies are variable and may not be obvious in the newborn. The liver biopsy has provided the clinician with perhaps a more objective means of characterizing this group of syndromatic children.[9,14]

In this report, the hepatic morphology of five patients with arteriohepatic dysplasia is described.

The clinical data are summarized in tables I and II. Prior to the diagnosis of arteriohepatic dysplasia, four of five pa-

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TABLE I

Clinical Data

Patient		Conjugated Hyperbilirubinemia	Hepatic Excretion of Radionuclide	Visualization of Intrahepatic B.T. by Cholangiogram	Portoenterostomy
#1	3d	+	-	-	+
#2	3d	+	-	-	+
#3	2m	+	-	-	+
#4	1m	+	-	-	+
#5	2m	+	*	-	-

B.T. = Biliary tree
d = Days
* = Not performed
m = Months

tients had undergone Kasai procedures after intraoperative cholangiograms had failed to demonstrate patency of the extrahepatic biliary tree.

Pathology

Microscopic examination of the extrahepatic biliary tree in three patients revealed a common bile duct of normal calibre and hypoplasia of the proximal hepatic duct (150 to 308 microns; normal = 900 microns (figure 1). The gallbladder was also hypoplastic in two patients (table III), hypoplasia being defined as a narrow but patent lumen.[1,12,20] Atresia denotes complete obliteration of the structure.[10,19]

Two to five sequential liver biopsies were obtained between 19 days and 27 months of age (table IV). Detailed microscopic findings have been recently reported.[9] The features of these biopsies can be divided into early (birth to four months) and later stages (older than four months).

Early hepatic morphology consists primarily of cholestasis associated with giant cell transformation. A decrease in the number of interlobular bile ducts is not apparent at this stage, although there is early duct destruction. This is reflected by pyknosis of the ductal epithelium, focal destruction of the basement membrane, luminal collapse, asymmetrical cellular infiltration of the portal spaces contiguous to interlobular bile ducts, periductal fibrosis, and focal ductal obliteration by cellular fibrous connective tissue (figure 2). Large bile ducts are either hypoplastic or completely obliterated by cellular fibrous connective tissue (figure 3). Portal spaces are of normal size and there is no ductular proliferation.

The late changes consist of persistent cholestasis, a decreased number of interlobular bile ducts, and a lack of ductular proliferation. Portal fibrosis is present. Hepatocellular and canalicular cholestasis is moderate to severe and centrilobular or diffuse. A paucity of interlobular bile ducts is apparent after four months. Most portal spaces do not contain bile ducts (figure 4).

Discussion

Arteriohepatic dysplasia is an autosomal dominant[16] or recessive[2] disease. It is characterized by a distinctive facies and specific extrahepatic anomalies, including cardiovascular (peripheral pulmonic stenosis, coarction of the aorta), ocular (prominent Schwalbe's line, retinal pigmentary changes), and vertebral (butterfly vertebrae) changes.[3,7,16,17] Delayed mental and sexual development as well as growth retardation have also been described. The disease is nonprogressive in the majority of the patients and its etiology remains unclear.

Because the diagnosis of arteriohepatic dysplasia may not be obvious, patients

TABLE II

Clinical Features of Arteriohepatic Dysplasia

Patient	Typical Facies	Peripheral Pulmonic Stenosis	Butterfly Vertebrae	Abnormal Ophthalmologic Findings
#1	+	+		+
#2	+	+	+	
#3	+	+	+	+
#4	+	+		
#5	+	+		

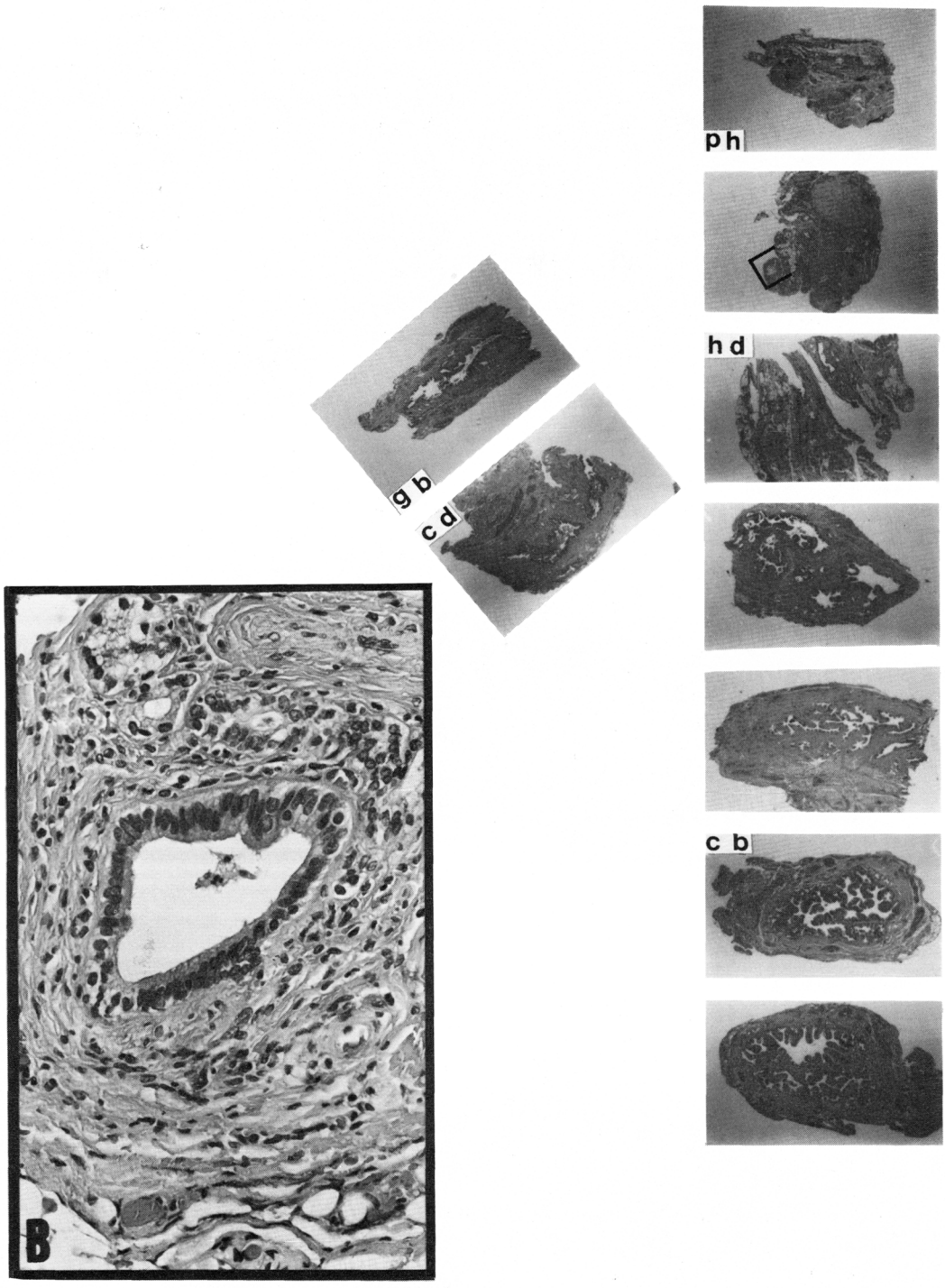

FIGURE 1. A. Serial sections of the extrahepatic biliary system. Patent common bile duct (c.b.) and cystic duct (c.d.) Hypoplasia of the gallbladder (g.b.) and of the common hepatic duct (h.d.) is apparent. (p.h.) porta hepatis. B. Higher magnification of the bracketed area depicting a hypoplastic 150 micron hepatic duct. Hematoxylin-eosin ×50.

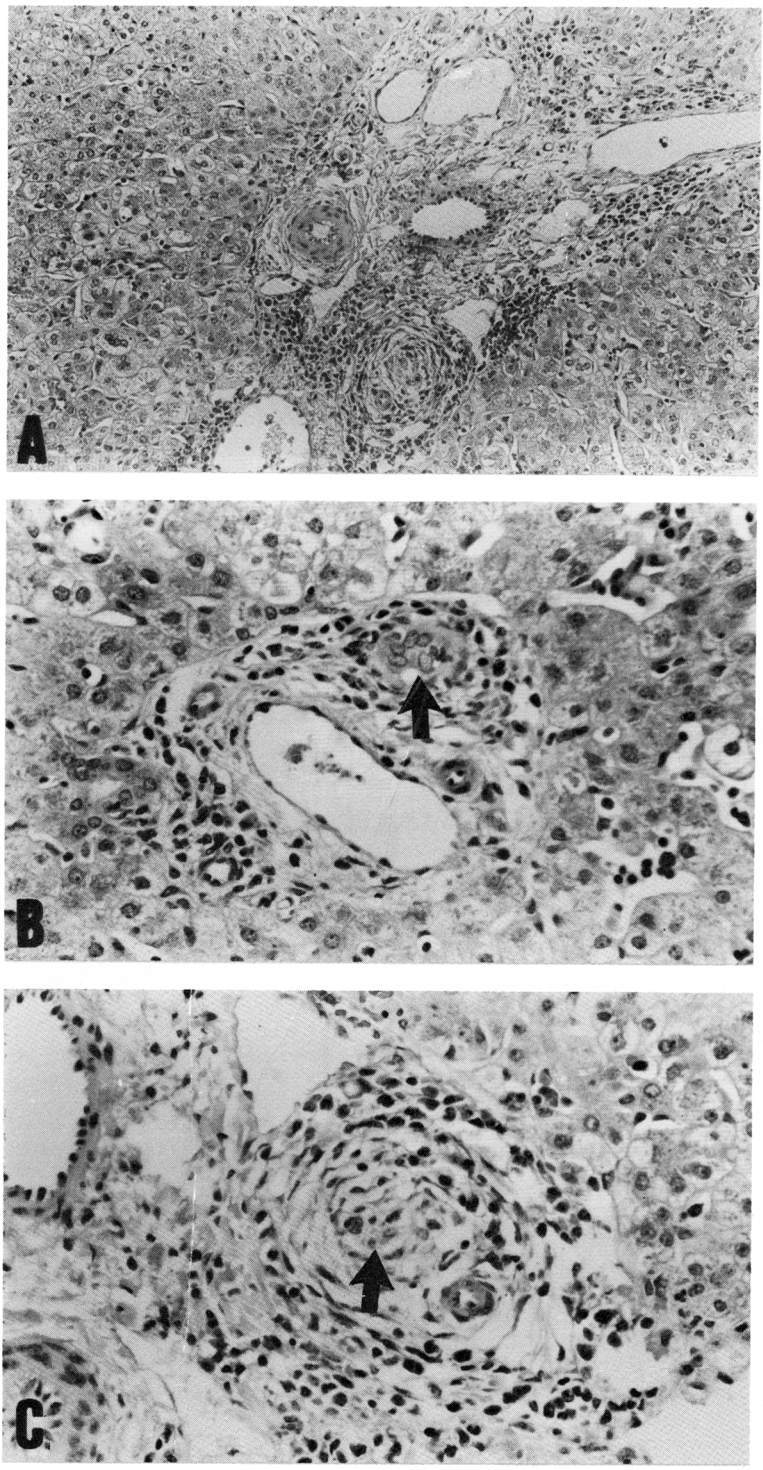

FIGURE 2. Composite of progressive destruction of interlobular bile ducts. A. Portal space with asymmetrical mononuclear infiltration adjacent to an interlobular bile duct. Hematoxylin-eosin ×120. B. Bile duct seen as solid cluster of epithelial cells (arrows). Hematoxylin-eosin ×300. C. Higher magnification of figure 2a; obliterated interlobular bile duct (arrow). Hematoxylin-eosin ×300.

TABLE III

Hypoplasia of the Extrahepatic Biliary Tree

	Patients				
	#1	#2	#3	#4	#5
Gallbladder	NL	NL	+	+	*
Common Hepatic Duct	+	*	+	+	*
Common Bile Duct	NL	NL	NL	NL	NL

The common hepatic ducts in patients 3 and 4 were serially sectioned. Patency persists throughout.
*Not examined
NL = Normal
+Hypoplasia present

may be subjected to laparotomy and intraoperative cholangiography. Intraoperative cholangiograms may be indistinguishable from those seen in children with extrahepatic biliary atresia. Hypoplasia of the common hepatic duct, observed in three of the infants, most likely accounted for the nonvisualization of the intrahepatic radicles. Indeed, hypoplasia of the extrahepatic biliary tree may be common in patients with arteriohepatic dysplasia. The hepatic morphology of the portal spaces seems to be quite characteristic. Before four months of age, the portal spaces are not increased in size and contain a normal number of interlobular bile ducts with the ratio of interlobular bile ducts to portal spaces being 0.9 to 1.8.[3] Bile duct destruction is associated with a mononuclear cell infiltration.

Three main theories have been proposed to explain paucity of interlobular bile ducts: failure of development, atrophy, and ductal destruction. The consensus is that arteriohepatic dysplasia is not a developmental anomaly but rather an acquired disease.[4,9,18] The actual destruction of interlobular bile ducts in the early stage with eventual disappearance of these structures mitigates against a developmental anomaly. Some[15] have proposed a primary hepatocellular defect resulting in atrophy and subsequent ductal paucity. This is based on ultrastructural signs of hepatocellular bile retention not associated with biliary canalicular changes seen with cholestasis of other etiologies. Electron microscopic examination was not performed in our patients prior to portoenterostomy.

The autosomal dominant or recessive inheritance of arteriohepatic dysplasia implies a possible genetic predisposition among certain individuals.[16] What triggers the destruction of the interlobular bile ducts and whether this process begins distally or proximally in the biliary system is unclear. Toxins and infectious agents have been implicated.[3,6,11] Our observations seem to suggest that ductal destruction begins in the larger and intermediate size bile ducts, while small interlobular bile ducts are affected later in the course of the disease. On purely morphologic criteria, the ductal destruction seen in our patients, including the basement membrane destruction and disappearance of ducts without scarring, bears strong resemblance to that seen in primary biliary cirrhosis, an autoimmune process observed in adults. In primary biliary cirrhosis, there is also a periductal mononuclear response followed by disappearance of intermediate bile ducts without subsequent ductal fibrosis.[13] Paucity of interlobular bile ducts has also been described in graft versus host disease and in liver transplant,[5,18] further supporting an immune etiology for the duct destruction. Hypoplasia of the extrahepatic biliary tree might be interpreted either as a manifestation of "disuse" or perhaps, inasmuch as it was present early in the course, a less severe involvement by the same basic pathogenic process.

TABLE IV

Nature of Material and Time of Liver Biopsies

	Pt. 1 5W 14M 27M	Pt. 2 19D 7W 3M 8M 17M	Pt.3 3M 7M	Pt. 4 6W 3M 5M	Pt. 1 11W 7M 27M
WB	+ +	+ +	+	+ +	+
NB	+	+ + +		+	+ +
Autopsy			+		

Pt. = Patient
D = Days
W = Week
WB = Wedge biopsy
M = Months
NB = Needle biopsy

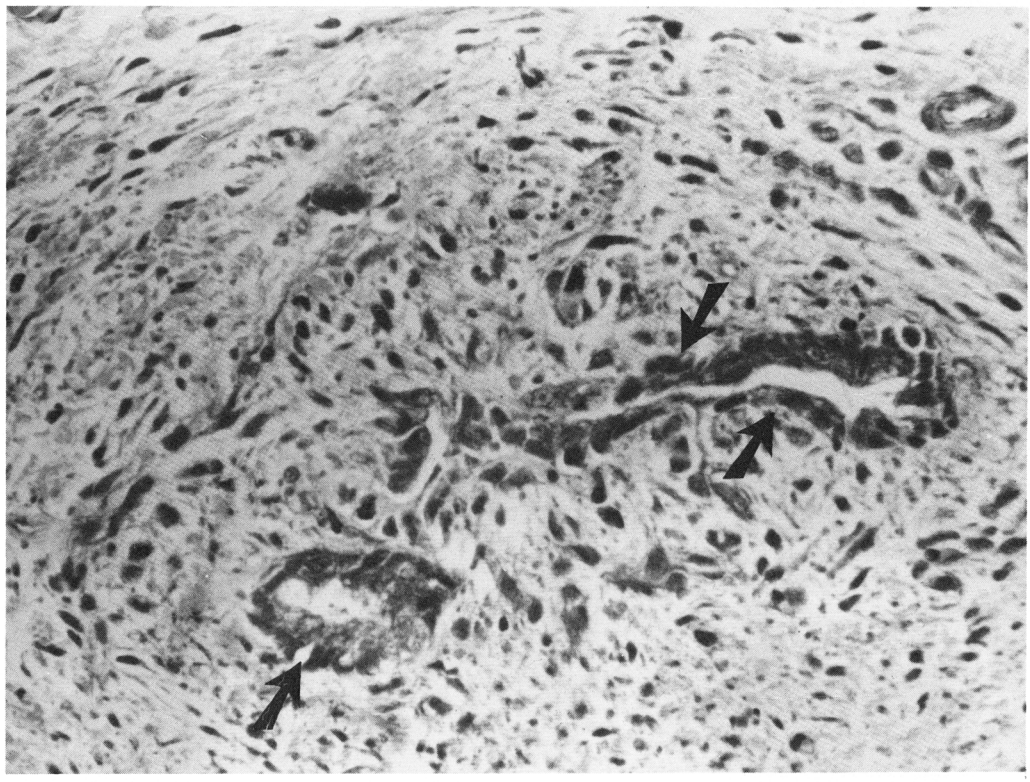

FIGURE 3. Large bile duct obliterated by fibrous connective tissue. Remnants of cuboidal epithelium are indicated by arrows. Hematoxylin-eosin ×500.

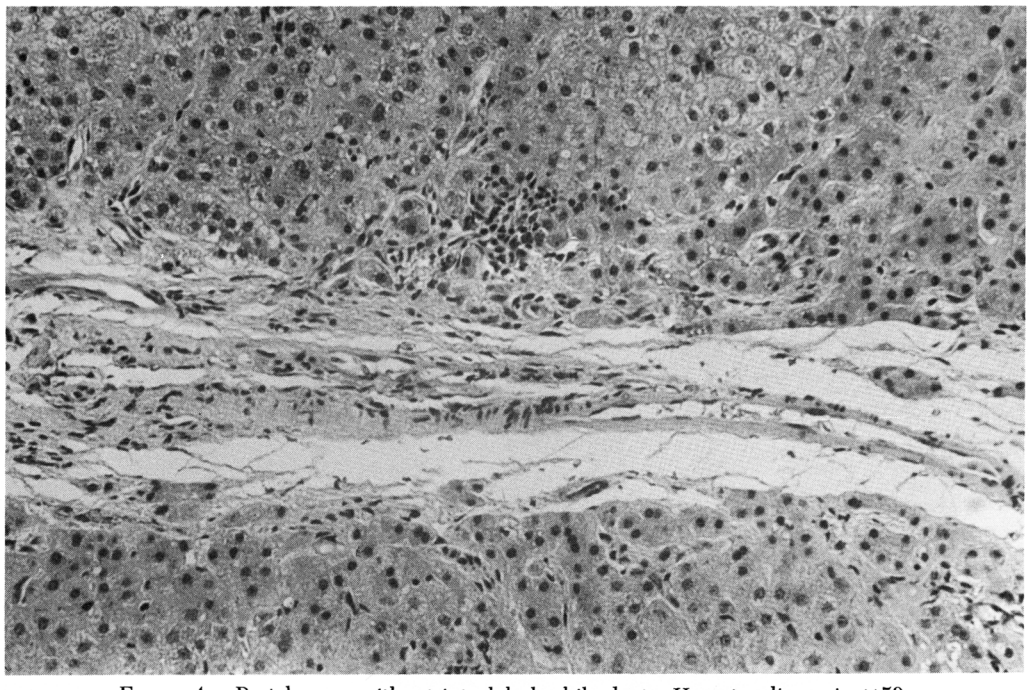

FIGURE 4. Portal space without interlobular bile ducts. Hematoxylin-eosin ×50.

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