

## IDIOPATHIC BILIARY DUCTOPENIA IN ADULTS WITHOUT SYMPTOMS OF LIVER DISEASE

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## ABSTRACT

**Background** Idiopathic adulthood ductopenia is a severe cholestatic liver disease of unknown cause characterized by loss of the interlobular bile ducts in more than 50 percent of the portal tracts. In most reported cases, cirrhosis and liver failure develop.

**Methods** We studied 24 adults with abnormal results on liver-function tests but no symptoms of liver disease. All had liver biopsies that showed a lack of bile ducts in many of the portal tracts.

**Results** The 17 women and 7 men had a mean age of 41 years (range, 27 to 57). All were asymptomatic and had high serum  $\gamma$ -glutamyltransferase concentrations (mean [ $\pm$ SD],  $179 \pm 84$  U per liter); 75 percent also had abnormal serum alanine aminotransferase concentrations. The proportion of portal tracts that had bile ducts was  $62 \pm 7$  percent (range, 55 to 78 percent). Three patients had a second liver biopsy three to nine years after the first; there were no changes over time. In four of the five patients treated with 600 to 900 mg of ursodiol two to three times daily, results of liver-function tests returned to normal.

**Conclusions** Idiopathic biliary ductopenia, with an apparently nonprogressive clinical course, can occur in adults who have no symptoms of biliary disease. (N Engl J Med 1997;336:835-8.)

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INTRALHEPATIC cholestasis with a paucity of interlobular bile ducts, or ductopenia, has been described as a common pathologic feature of many heterogeneous conditions, either inherited or acquired in childhood or adulthood.<sup>1</sup> In children, ductopenia has been associated with various congenital malformations constituting Alagille's syndrome.<sup>2,3</sup> A paucity of biliary ducts has also been described as idiopathic adulthood ductopenia after other known causes associated with a reduction in the number of bile ducts have been excluded. Diagnosis is based on the absence of bile ducts in at least 50 percent of the portal tracts.<sup>4</sup>

Idiopathic adulthood ductopenia is thought to produce severe liver disease associated with chronic cholestasis that generally progresses to cirrhosis and may be an indication for liver transplantation.

In this study, we describe a mild form of idiopathic biliary ductopenia in 24 adults with abnormal results of liver-function tests but no symptoms of liver disease.

## METHODS

From 1990 to 1995, we studied 24 patients with liver-biopsy specimens showing ductopenia. The biopsies had been performed to investigate the reason for the persistence, for at least one year, of abnormal results on liver-function tests. All the known causes of liver disease were ruled out by clinical, biologic, or histologic methods. The possibility of liver injury due to drugs or toxic agents was excluded after comprehensive and careful patient-by-patient interviews.

Hematologic and liver-function tests, including assessment of iron metabolism and measurements of urinary porphyrin and serum concentrations of alpha<sub>1</sub>-antitrypsin, ceruloplasmin, and copper, were carried out by standard methods. Non-organ-specific autoantibodies (antimitochondrial, antinuclear, anti-smooth-muscle, anti-liver-kidney microsome, and antimicrosomal antibodies) were assayed by indirect immunofluorescence on cryostat sections (Bio-System, Barcelona, Spain). Antibodies against hepatitis C virus (anti-HCV) were assayed by using a second-generation enzyme immunoassay (Ortho Diagnostic Systems, Raritan, N.J.). Hepatitis B surface antigen (HBsAg) was assayed by a commercially available radioimmunoassay (Abbott Laboratories, North Chicago, Ill.). Antibodies against human immunodeficiency virus (anti-HIV) were tested by enzyme immunoassay (Abbott). RNA of hepatitis GB virus type C (GBV-C RNA) was assayed in serum samples (stored at  $-20^{\circ}\text{C}$ ) from eight patients. Serum total RNA was isolated and amplified by reverse transcription-polymerase chain reaction with the use of specific primers of the putative *GBV-C helicase/NS3* gene, as described elsewhere.<sup>5,6</sup> Endoscopic retrograde cholangiopancreatography and abdominal ultrasonography were performed in all patients.

A total of 27 liver-biopsy specimens from the 24 patients were available for evaluation. Twenty-four were obtained at the time of entrance into the study. In one patient, a second biopsy was performed three years after the first. Two patients had liver biopsies six and nine years before entering the study. Twelve liver-biopsy specimens from patients with normal biochemical hepatic profiles were used as controls. Eight of those specimens were taken from organ donors before allograft implantation, and four were taken from patients with fever of unknown origin not related to any liver disease. A minimal length of 12 mm for each biopsy specimen was established as one of the criteria for inclusion in the study. All subjects gave their written informed consent for liver biopsy.

Biopsy specimens were routinely processed in paraffin. Liver sections were stained with hematoxylin and eosin, Masson's trichrome, periodic acid-Schiff (PAS) after diastase digestion, and Shikata's orcein. Two of us assessed the sections histologically under code. We excluded large trabecular portal tracts and their bile ducts from this evaluation. The numbers of small portal tracts and interlobular bile ducts were counted.

We calculated the proportion of bile ducts by dividing the number of portal tracts with bile ducts by the total number of portal tracts in each liver-biopsy specimen. In all the specimens

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we studied, bile ducts were present in at least 55 percent of the portal tracts as an isolated finding; there were no other cholestatic or inflammatory abnormalities. Therefore, we used histologic evidence of inflammatory infiltration, cholangitis, biliary piecemeal necrosis, fibrosis, or granuloma as a criterion for exclusion from the study. We recorded any additional findings, such as lipofuscin deposits, ground-glass hepatocytes, PAS-positive macrophages, sinusoidal dilatation, and arteriole-wall thickness, and graded them semiquantitatively as absent, mild, moderate, or severe.

Five patients were treated with ursodiol (Ursochol, Zambon, Barcelona, Spain) at a dose of 600 to 900 mg two to three times daily.

We performed statistical analysis using Student's t-test. Results are reported as means  $\pm$ SD.

**RESULTS**

The characteristics of the 24 patients (17 women and 7 men) are shown in Table 1. All were asymptomatic and had no relevant clinical history. None reported exposure to drugs or toxic agents. Three had familial histories of liver disease. None had had any biliary tract disease or undergone cholecystectomy. All had had abnormal results on routine liver tests for at least 1 year (range, 1 to 12) since their first hospital visit as well as increases in  $\gamma$ -glutamyltransferase to more than the upper limit of normal. Eighteen (75 percent) and 13 (54 percent) also had increased se-

rum concentrations of alanine aminotransferase and alkaline phosphatase, respectively. Serum albumin, gamma globulin, copper, ceruloplasmin, and alpha<sub>1</sub>-antitrypsin concentrations were normal in all the patients, as were urinary porphyrin excretion and the results of iron studies (data not shown). None of the patients were positive for HB-sAg, anti-HCV, or anti-HIV, and all but two (one with a 1:1600 titer of antimicrobial antibodies and the other with a 1:160 titer of anti-smooth-muscle antibodies) were negative for non-organ-specific autoantibodies, including antimitochondrial autoantibodies. All eight patients with available samples were negative for hepatitis GBV-C RNA. Ultrasonography showed normal biliary tracts in all the patients and moderate enlargement of the liver in 3 of 24. Endoscopic retrograde cholangiopancreatography also showed normal biliary tracts in all the patients.

The mean length of the control biopsy specimens (1.4 $\pm$ 0.3 cm) was significantly less (P=0.05) than that of the specimens obtained from the patients (1.9 $\pm$ 0.7 cm). However, the number of portal tracts was significantly lower (P=0.008) in the specimens from the patients than in those from the controls (10.8 $\pm$ 4.2 vs. 14.7 $\pm$ 3.4). The proportion of portal tracts with bile ducts was significantly lower in the patients (62 $\pm$ 7; range, 55 to 78) than in the controls (96 $\pm$ 5; range, 83 to 100) (P<0.001). Other histologic findings are shown in Table 2.

Hepatic arterioles with thickened walls were found in 17 biopsy specimens from the patients (Fig. 1A). All the biopsies showed pericanalicular lipofuscin deposits in centrozonal hepatocytes, associated with various degrees of a ground-glass appearance in the cytoplasm of these cells in 18 specimens (Fig. 1B). Periportal sinusoidal dilatation was present in 17 specimens (Fig. 1C). A few scattered lobular and PAS-positive portal macrophages were identified in all but one specimen. Four had mild steatosis and periportal vacuolated nuclei. No histologic differences were noted between the patients who had only an elevated serum  $\gamma$ -glutamyltransferase concentration and those who also had an elevated serum alkaline phosphatase concentration.

Two sequential liver-biopsy specimens were available from three patients each. One patient had identical histologic findings in the two specimens, obtained three years apart. In the two other patients, who had second biopsies six and nine years after the first, a slight decrease in the proportion of bile ducts was seen (base-line proportions of 63 and 60 percent vs. final proportions of 55 and 55 percent, respectively). The number of ground-glass hepatocytes increased from a mild to a moderate grade in both. No other significant histologic changes were observed.

Five patients were treated with ursodiol. Four (including one who had a base-line anti-smooth-mus-

**TABLE 1. CLINICAL CHARACTERISTICS OF THE 24 PATIENTS.**

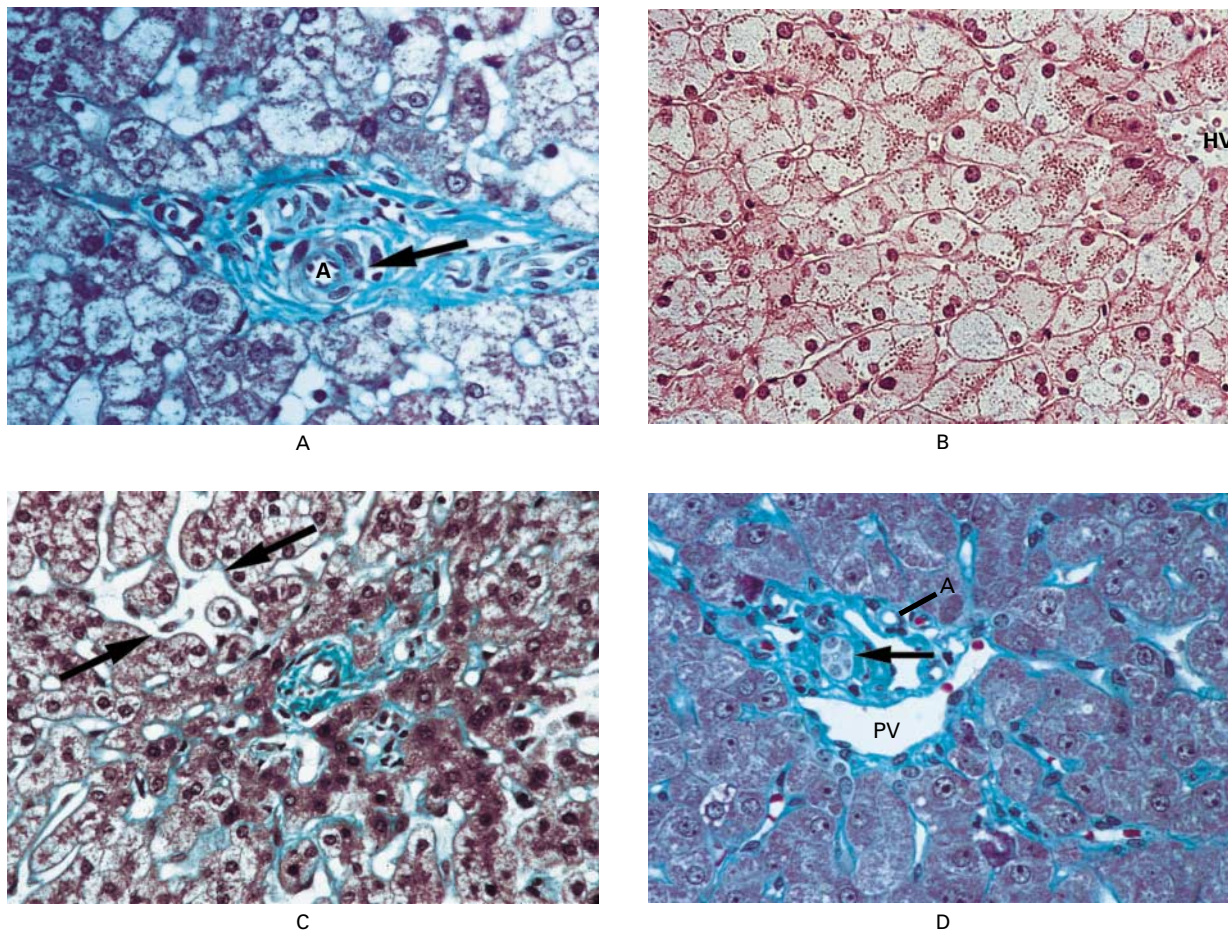
CHARACTERISTIC	MEAN $\pm$ SD VALUE (RANGE)	NORMAL RANGE
Age at diagnosis (yr)	41 $\pm$ 11 (27-57)	—
Known duration of liver-function abnormalities (yr)	4 $\pm$ 4 (1-12)	—
Serum total bilirubin (mg/dl)*	0.6 $\pm$ 0.2 (0.4-1.2)	0.1-1.3
Serum alkaline phosphatase (U/liter)	306 $\pm$ 107 (200-433)	41-280
Serum $\gamma$ -glutamyltransferase (U/liter)	179 $\pm$ 84 (85-224)	6-50
Serum alanine aminotransferase (U/liter)	76 $\pm$ 32 (37-115)	5-40

\*To convert the value for total bilirubin to micromoles per liter, multiply by 17.1.

**TABLE 2. HISTOLOGIC FINDINGS OTHER THAN DUCTOPENIA IN THE 24 PATIENTS.**

FINDING	ABSENT	MILD	MODERATE	SEVERE
	number (percent)			
Arteriole-wall thickening	7 (29)	5 (21)	9 (38)	3 (12)
Lipofuscin deposits	0	15 (62)	6 (25)	3 (12)
Ground-glass hepatocytes	6 (25)	3 (12)	12 (50)	3 (12)
Sinusoidal dilatation	7 (29)	16 (67)	1 (4)	0
PAS-positive macrophages*	1 (4)	20 (83)	3 (12)	0

\*PAS denotes periodic acid-Schiff.



**Figure 1.** Liver Histopathological Findings in a Study Patient (Panels A, B, and C) and in a Normal Control (Panel D). The patient was a 43-year-old woman with results of liver-function tests that were persistently abnormal for 40 months. The serum  $\gamma$ -glutamyltransferase and alanine aminotransferase concentrations were 163 U per liter and 63 U per liter, respectively. The patient had normal serum alkaline phosphatase and bilirubin concentrations. In Panel A, a portal tract without an interlobular bile duct shows a thickened arteriolar wall (arrow). There is no cellular infiltrate, fibrosis, or biliary piecemeal necrosis (A indicates a hepatic arteriole) (Masson stain,  $\times 400$ ). Panel B shows lipofuscin deposits and ground-glass hepatocytes. A hepatic vein (HV) is also seen at the upper right (hematoxylin and eosin,  $\times 300$ ). Panel C shows a small portal tract (center) without an interlobular bile duct. There is mild dilatation of adjacent periportal sinusoids (arrows) (Masson stain,  $\times 300$ ). Panel D shows a normal portal tract from a 23-year-old male organ donor (the arrow indicates a bile duct; A, a hepatic arteriole; and PV, a portal vein) (Masson stain,  $\times 400$ ).

cle antibody titer of 1:160 that subsequently became negative) had normal serum alanine aminotransferase,  $\gamma$ -glutamyltransferase, and alkaline phosphatase concentrations after two to five months of treatment. These four, who are still being treated at this writing, have received the drug for a mean of 20 months (range, 10 to 29). Liver function, tested every two months, has remained normal. The other patient has been treated for 48 months, with decreases in serum  $\gamma$ -glutamyltransferase and alanine aminotransferase of 63 percent and 47 percent, respectively, from base-line levels, although both values were still abnormal. There were no side effects during treatment.

## DISCUSSION

Adults with unexplained chronic cholestatic liver disease, a condition known as idiopathic adulthood ductopenia, have been described.<sup>7-10</sup> Clinically, this disease is characterized by pruritus or jaundice. Histologic study of the liver shows a decrease in intrahepatic bile ducts in at least 50 percent of the portal tracts, together with several cholestatic features and marked fibrosis or cirrhosis.

We have described 24 asymptomatic adults with moderate impairment of liver function of unknown cause, whose liver biopsies showed mild ductopenia. According to established criteria,<sup>4</sup> these patients could not be given a diagnosis of idiopathic adulthood

ductopenia, since their liver biopsies showed a loss of bile ducts in fewer than 50 percent of the portal tracts, with no other cholestatic or inflammatory findings.

Although abnormal results of liver-function tests were recorded for these patients for as long as 12 years, the histologic lesions of the liver were mild and nonprogressive, as seen in sequential liver biopsies performed in three patients. The disease course in our patients has seemed to be benign, although we cannot exclude eventual progression over a longer period.

Consideration was given to other liver diseases in which liver biopsies may show ductopenia.<sup>11-21</sup> The possibility of an adverse drug reaction was excluded through a detailed review of the patients' histories. Antimitochondrial-antibody-negative primary biliary cirrhosis and autoimmune cholangitis, well-known causes of ductopenia,<sup>22-24</sup> could also be excluded. The diagnosis of these entities is based on the presence of a florid ductal lesion (granulomatous destructive cholangitis) or other histologic features, such as biliary piecemeal necrosis, portal inflammation, a variable degree of fibrosis, and granuloma. In addition, most of the patients with these diseases have antinuclear antibodies and are clinically symptomatic. By contrast, none of our patients had any of the histologic, serologic, or clinical features described in these diseases. Other conditions, such as sclerosing cholangitis or sarcoidosis, were ruled out by the absence of clinical or histologic findings.

Although the hallmark of the mild idiopathic adulthood ductopenia we describe is a decrease in the number of bile ducts, other histologic features were frequently observed. Their importance is not known.

The results of liver-function tests became normal in four of five patients while they were being treated with ursodiol. Although the prognosis of the disease is apparently benign, further studies are needed to determine whether patients should be treated.

In summary, we have observed idiopathic biliary ductopenia in adults without symptoms of liver disease. The clinicopathologic characteristics — an apparently nonprogressive clinical course and a frequent response to therapy — differ from those of classic idiopathic adulthood ductopenia, which is a severe and progressive disease.

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