Clinical Profile of Autosomal Dominant Polycystic Liver Disease

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Most reports on the natural history, manifestations, and treatment of polycystic liver disease are based on the disease as it manifests in patients with autosomal dominant polycystic kidney disease (ADPKD). The purpose of this study was to develop a clinical profile of isolated autosomal dominant polycystic liver disease (ADPLD) using nonaffected family members as controls. The study included 146 probands, known affected relatives, and first-degree relatives of affected individuals. Participants underwent a formalized medical history interview and physical examination, ultrasonographic examination of the liver and kidneys, magnetic resonance angiography of the brain, and echocardiography. Thirty-eight of the 49 individuals diagnosed with polycystic liver disease before participation in the study were or had been symptomatic. Of 97 previously undiagnosed at-risk individuals, 23 were affected, 39 were unaffected, and 35 were indeterminate. Compared with patients with a negative or indeterminate diagnosis, those with polycystic liver disease had slightly higher levels of serum alkaline phosphatase and total bilirubin and lower levels of total cholesterol and triglycerides. Female patients had a significantly higher mean cyst score than male patients. The cysts were found to arise from the dilatation of biliary microhamartomas and from peribiliary glands. Structural mitral leaflet abnormalities were detected more frequently in affected than in indeterminate or nonaffected individuals. A vascular phenotype was detected in 5.6% of the patients with isolated ADPLD diagnosed clinically and/or by linkage analysis but in none of the unaffected patients. In conclusion, isolated ADPLD is underdiagnosed and genetically distinct from polycystic liver disease associated with ADPKD but with similar pathogenesis, manifestations, and management. (HEPATOLOGY **2003;37:164-171.**)

Autosomal dominant polycystic liver disease (ADPLD) is an inherited condition characterized by the presence of multiple scattered cysts of biliary origin in the liver parenchyma.[1-3] Polycystic liver disease often occurs in association with autosomal dominant polycystic kidney disease (ADPKD) but also exists as a distinct genetic entity. The occurrence of polycystic liver disease independently from polycystic kidney disease has been known for a long time.[4-6] In old autopsy or surgical series of polycystic liver disease, the frequency of polycystic kidneys was in the order of 50% to 60%. It is possible that underdiagnosis of ADPKD in an era without sophisticated imaging techniques and the inclusion of patients with simple hepatic cysts might have contributed to the high frequencies of isolated polycystic liver disease. More recently, a number of families with ADPLD without or with only a few renal cysts have been reported. A large study of 33,700 medicolegal autopsies from Finland identified 22 cases with either polycystic liver or polycystic kidney disease, most in the early stages of the disease.[7] Macroscopic cysts in both organs were present in only one of these cases, leading the investigators to conclude that polycystic liver disease and polycystic kidney disease are separate entities. Further support for the existence of ADPLD as a distinct genetic entity came from 3 studies in which isolated familial polycystic liver disease was shown to be unlinked to the PKD1

Abbreviations: ADPLD, autosomal dominant polycystic liver disease; ADPKD, autosomal dominant polycystic kidney disease.

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Received July 31, 2002; accepted October 5, 2002.

Supported by National Institutes of Health grant DK51041 (to S.S. and V.E.T.), Mayo Clinic General Clinical Research Center grant M01-RR00585, and Yale Liver Center Training grant T32 DK07356 (to A.L.). A.L. and S.S. are members of the Yale Center for the Study of Polycystic Kidney Disease (grant P50 DK57328).

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0270-9139/03/3701-0024$35.00/0

doi:10.1053/jhep.2003.50006

or PKD2 loci.[8-10] Finally, a locus for ADPLD was identified on chromosome 19p13.2-13.1.[11]

Most of the studies on the natural history, manifestations, and treatment of polycystic liver disease are based on the disease as it manifests in patients with ADPKD.[3] The purpose of this study was to develop a clinical profile of isolated ADPLD and to define the symptoms, signs, and laboratory findings in individuals affected by the disease using nonaffected family members as controls.

Patients and Methods

Study Population. This study included 146 persons from 35 families in which at least one individual was known to have isolated polycystic liver disease. The study subjects included probands, known affected relatives, and first-degree relatives of affected individuals (at-risk individuals). Forty-nine individuals had a diagnosis of polycystic liver disease before participation in the study. Twenty-one of the 49 known affected and 97 at-risk individuals were studied at the General Clinical Research Center of the Mayo Clinic. Clinical and imaging information on the additional 28 affected individuals was obtained whenever possible. These studies were approved by the Mayo Clinic Institutional Review Board, and the patients gave informed written consent.

General Clinical Research Center Study Visit. Participants were admitted to the General Clinical Research Center for a 1-day visit on the evening before the day of the study. They underwent a formalized medical history interview and physical examination, ultrasonographic examination of the liver and kidneys, magnetic resonance angiography of the brain using a 1.5-T superconducting imaging system, high-resolution 3-dimensional time-of-flight technique, and combined 2-dimensional echocardiography, 2-dimensional–guided M-mode echocardiography, and Doppler ultrasonography, including color flow imaging. Blood samples were obtained for levels of serum electrolytes, calcium, phosphorus, bilirubin, liver enzymes, uric acid, creatinine, albumin, total and high-density lipoprotein cholesterol, and triglycerides as well as a complete blood count and DNA studies.

Definitions. Probands had more than 20 liver cysts and did not fulfill the criteria for ADPKD as described by Ravine et al.[12] Other persons clinically affected with ADPLD were at-risk individuals aged 40 years or younger with any liver cysts and individuals older than 40 years with 4 or more liver cysts. Persons with an indeterminate clinical status for ADPLD were those aged 40 years or younger with no liver cysts or older than 40 years with 1 to 3 liver cysts. Unaffected persons were those older than 40 years with no liver cysts. The criteria used to classify the affection status of the participants in the 2 largest families were supported by the results of the gene linkage analysis.[11] The severity of the polycystic liver disease was graded from 0 to 4 depending on the number of cysts detected by ultrasonography and the presence of symptomatic hepatomegaly: 0, 0 cysts; 1, 1-10 cysts; 2, 11-20 cysts; 3, more than 20 cysts; 4, more than 20 cysts and symptomatic hepatomegaly. The 2-dimensional echo criteria reported by Marks et al.[13] and the M-mode criteria by Nishimura et al.[14] were used for the diagnosis of mitral valve prolapse. The magnetic resonance angiography and echocardiography studies were read blinded to the clinical phenotypes.

Histology. Paraffin-embedded tissue sections were stained for hematoxylin-eosin, cytokeratin 7, and mucicarmine. Cytokeratin 7 is expressed by the intrahepatic bile duct cells.[15] Neutral mucin, sialomucin, and sulfomucin are strongly expressed at the apical borders of the cells lining the peribiliary glands.[16] The sections for cytokeratin 7 (DAKO, Carpinteria, CA; 1:100) were steam pretreated in ethylenediaminetetraacetic acid buffer, rinsed, and stained using the labeled streptavidin biotin detection chemistry system on the Ventana (Tucson, AZ) ES autostainer. Sections stained with mucicarmine were deparaffinized and rehydrated to water. The slides were stained with Weigert's hematoxylin, rinsed, stained with mucicarmine working solution, rinsed, and stained with metanil yellow solution. Sections were then rinsed, dehydrated, cleared in xylene, and cover slipped.

Data Management and Statistical Analysis. All data were recorded into computer-compatible data forms for data entry. Data were entered into SAS (SAS Institute Inc., Cary, NC) data sets using the SAS/assist program on the GNS computer in the Mayo Research Computing Facility. Comparisons between groups were made using the χ^2 test of association and the 2-sample t test or the rank sum test as appropriate.

Results

General. A total of 146 persons from 35 families participated in the study. The age distribution of the participants according to their status (affected, unaffected, and indeterminate) is shown in Fig. 1. Fifteen families each supplied one person, and 13 families provided 4 or more persons. The 2 better-studied families provided 35 and 27 persons, respectively. A genome-wide scan for linkage analysis on families 1 and 2 had identified the causative gene, *PCLD*, in chromosome 19p13.2-13.1.[11] The other families in the study are thus far too small to allow inclusion or exclusion of linkage to this locus (data not shown). However, the genetic linkage-based diagnosis in the 2 largest kindreds allowed ascertainment of the sensitivity

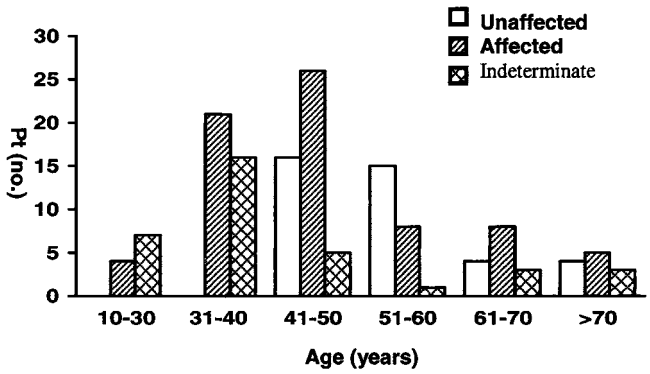

Fig. 1. Distribution of study participants by age and status.

and specificity of the imaging criteria for diagnosis in these 2 families (Table 1).

Prevalence of ADPLD in Previously Undiagnosed At-Risk Individuals. Of 97 previously undiagnosed at-risk individuals, 23 were affected, 39 were unaffected, and 35 were indeterminate (23 without cysts with ages 40 years or younger and 12 with 1-3 liver cysts and ages older than 40 years). All patients with ADPLD diagnosed at the General Clinical Research Center were asymptomatic.

Symptoms and Signs. Thirty-eight of the 49 individuals (77.6%) diagnosed with polycystic liver disease before participation in the study were or had been symptomatic, mainly with abdominal distention, fullness, and discomfort and, in some cases, early satiety, dyspnea, and back pain associated with massive polycystic liver disease. Two of 49 patients (4%) had episodes of fever and chills and a diagnosis of cyst infection/hemorrhage. Twenty-one of the 49 patients (42.8%) had required cyst fenestration, partial hepatectomy, or liver transplantation. Seventeen of these 21 patients had a liver resection performed (13 at the Mayo Clinic and 4 at other centers). No mortality was associated with this surgery in patients with isolated polycystic liver disease, and all but one of the patients had sustained relief of their symptoms. Forty-one of the 139 patients (29.4%) in whom the information was available had a diagnosis of hypertension (Table 2), but there was no difference in the prevalence of hypertension between those with and without polycystic liver disease.

Laboratory Parameters. The results of the laboratory parameters of the patients with a clinical diagnosis of polycystic liver disease as well as those of the participants with a positive, negative, or indeterminate diagnosis made at the General Clinical Research Center are shown in Table 3. Compared to the patients with a negative or indeterminate diagnosis, those with polycystic liver disease had slightly higher levels of serum alkaline phosphatase and total bilirubin and lower levels of total cholesterol and triglycerides.

Abdominal Ultrasonography and Other Imaging Data. Female patients had a significantly higher mean cyst score than male patients (3.5 ± 0.9 compared with 2.1 ± 1.2, respectively; $P = .001$). The age of the female and male patients was similar (48 ± 14 vs. 45 ± 9 years). In the female patients, there was a weak positive correlation between the number of pregnancies and the severity of the polycystic liver disease reflected by the cyst scores ($r = 0.21$, $P = .09$). The cyst scores were 3.7 ± 0.8 at 53.8 years of age in women with more than 3 pregnancies, 3.5 ± 0.9 at 48.7 years of age in those with 1 to 3 pregnancies, and 3.1 ± 1.7 at 47.9 years of age in those with no pregnancies. Nevertheless, 2 patients in this study who had never been pregnant or taken birth control pills were found to have severe polycystic liver disease. Abdominal computed tomographic scans obtained in clinically diagnosed patients were reviewed when available. These examinations showed the presence of both peripheral and peribiliary cysts (Fig. 2). Despite severe polycystic liver disease in some cases, relative sparing of part of the liver was usually observed.

Renal cysts were found in 39 of the 138 patients (28.3%) in which the information was available, but their frequency was not different between those with and without ADPLD (Table 2). Most patients had only one renal cyst, and none of the patients had more than 5 renal cysts. The renal cysts were associated with male sex (37% vs. 27%) and older age (7.5% in patients 30 years or older, 37.5% in those 31-50 years old, and 55% in those older than 50 years; $P < .001$).

Histology. Liver tissue for histologic review was available in the 13 patients who underwent a hepatic resection at the Mayo Clinic. The gross appearance of the resected livers was indistinguishable from that of those resected in patients with severe polycystic liver disease associated with ADPKD (Fig. 3A). All of the specimens contained variable numbers of biliary microhamartomas (von Meyenburg complexes) characterized by clusters of dilated bile ducts lined by a layer of cuboidal cells surrounded by a fibrous stroma (Fig. 3B). The epithelium lining of the biliary microhamartomas and most of the cysts was cytokeratin 7 positive (Fig. 3C and D), consistent with their

Table 1. Sensitivity and Specificity of Sonographic Imaging Criteria (Number of Liver Cysts) Used for Diagnosis in Families 1 and 2

Age (yr)	No. of Cysts	False Negatives	Sensitivity (%)	False Positives	Specificity (%)
≤40	1 or more	3/11	72.7	0/7	100
>40	4 or more	4/22	81.8	0/20	100
	3 or more	3/22	86.4	1/20	95
	2 or more	2/22	90.9	1/20	95

Table 2. Frequency of Hypertension and Imaging Findings in Study Participants According to Status

Phenotype	Female (%)	Kidney Cysts (%)	Hypertension (%)	Abnormal Mitral Leaflets (%)	Intracranial Aneurysms/Dissection (%)
Clinical PLD diagnosis	43/49 (88)	15/44 (34)	20/47 (43)	4/25 (16)	2/31 (6)
GCRC PLD+	14/23 (61)	6/23 (26)	4/24 (17)	6/24 (25)	0/24 (0)
GCRC PLD−	27/39 (69)	9/37 (24)	13/37 (35)	0/35 (0)	1/35 (3)
GCRC PLD?	23/35 (66)	9/34 (26)	4/31 (7)	2/30 (7)	1/29 (3)
ADPLD*	28/37 (76)	12/34 (35)	6/33 (18)	7/34 (21)	2/36 (5.6)

NOTE. Data indicate patients with positive finding/patients with study available (%). Ages at the time of the studies are shown in Table 3.
Abbreviations: PLD, polycystic liver disease; GCRC, General Clinical Research Center.
*Confirmed by linkage analysis.

origin from intrahepatic bile ducts. Small cysts often seem to arise from biliary microhamartomas (Fig. 3D). Intraluminal bile was present in a few lesions (Fig. 3E). Large cysts were lined by flattened biliary epithelium. The surrounding hepatic parenchyma in most cases appeared normal, with focal fibrosis near the larger cysts. Occasional dilated peribiliary glands surrounding larger intrahepatic bile ducts showed mucicarmine staining (Fig. 3F).

Echocardiography Data. Structural mitral leaflet abnormalities were detected more frequently in affected (10 of 49 [20.4%]) than in indeterminate (2 of 30 [6.7%]) or nonaffected (0 of 35) individuals ($P = .006$) (Table 2). Interestingly, the 2 indeterminate patients with structural mitral leaflet abnormalities were predicted to be affected by linkage analysis. These structural mitral leaflet abnormalities included mitral valve prolapse in 4 patients, bowing of mitral valve leaflets without frank prolapse in 7 patients, and a thickened mitral valve in 1 patient. No other significant differences in echocardiographic parameters between affected, indeterminate, and unaffected individuals were detected.

Data From Magnetic Resonance Angiography of the Brain. Data from magnetic resonance angiography of the brain are summarized in Table 2. A 50-year-old female patient with ADPLD was found to have an occlusion of the right internal carotid artery. Further evaluation with conventional angiography showed this to be secondary to a carotid artery dissection. Years before participation in the study, this patient had an episode of neck pain and headache consistent with a carotid artery dissection that was not diagnosed at the time. A 30-year-old female patient with ADPLD had an ectatic right cavernous carotid artery. A 75-year-old male patient had dolichoectatic left vertebral and proximal basilar arteries. This individual was affected by gene linkage analysis but was clinically normal by liver cyst criteria (nonpenetrance). A small 2 × 3–mm aneurysm at the bifurcation of the anterior cerebral and middle cerebral artery was detected in an individual with indeterminate status.

Table 3. Laboratory Parameters in Study Participants According to Status

	Clinical Diagnosis	CGRC Diagnosis			ADPLD*
	(n = 49)	Positive (n = 23)	Negative (n = 39)	Indeterminate (n = 35)	(n = 37)
Age (yr)	62 ± 15	44 ± 13	56 ± 12	44 ± 17	52 ± 15
Albumin	4.1 ± 1.5	4 ± 0.3	3.94 ± 0.28	4 ± 0.35	4.0 ± 0.26
Aspartate aminotransferase	31 ± 22	25 ± 12	24 ± 12	22 ± 10	22 ± 13
Alkaline phosphatase	200 ± 131	157 ± 57†	146 ± 35	140 ± 47	159 ± 68
Total bilirubin	0.62 ± 0.35	0.58 ± 0.34†	0.48 ± 0.21	0.47 ± 0.24	0.5 ± 0.37
Total cholesterol	190 ± 33	177 ± 32†	202 ± 34	193 ± 32	191 ± 36
High-density lipoprotein	54.5 ± 33	45 ± 13	49 ± 14	48 ± 13	45 ± 14
Low-density lipoprotein	114 ± 28	106 ± 27	118 ± 32	113 ± 31	113 ± 33
Triglycerides	115 ± 54	129 ± 56†	180 ± 137	157 ± 85	136 ± 51
Serum creatinine	0.95 ± 0.21	0.99 ± 0.13	0.99 ± 0.19	1 ± 0.23	0.99 ± 0.13
Hematocrit	38.6 ± 4.4	40 ± 5.3	40.2 ± 3.1	39 ± 3	38.8 ± 3.6
White blood count	6.8 ± 1.7	6.4 ± 2	6.3 ± 1.4	6 ± 1.4	6.4 ± 1.6
Platelets	215 ± 51	260 ± 86	240 ± 53	228 ± 71	239 ± 56

NOTE. Results are expressed as means ± SD.
Abbreviations: GCRC, General Clinical Research Center.
*Confirmed by linkage analysis ($P < .05$).
†Versus CGRC negative or indeterminate.

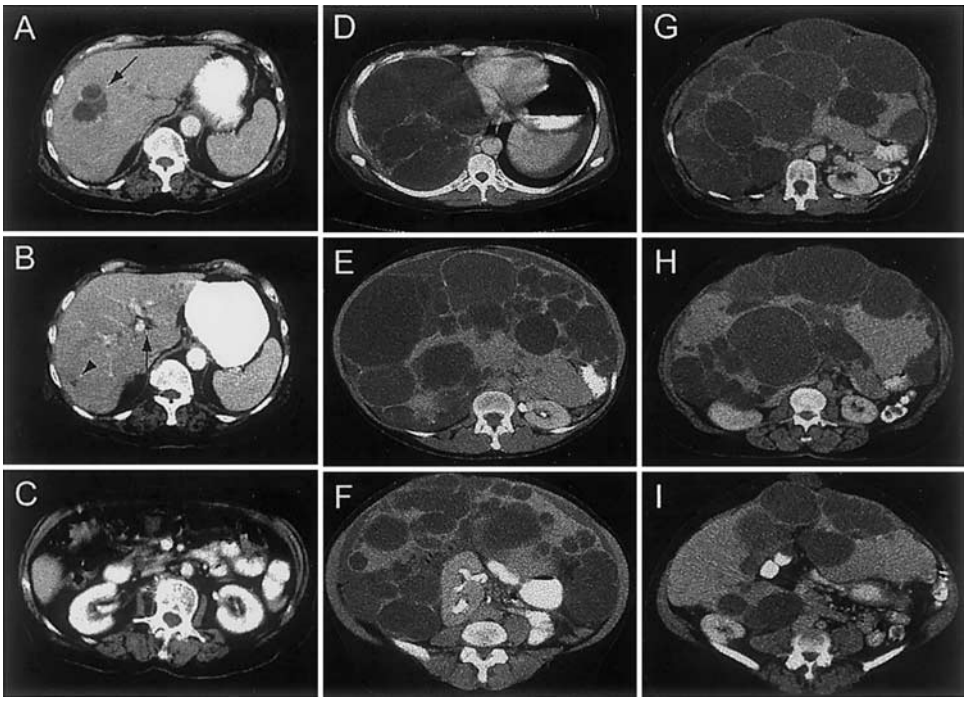

Fig. 2. Computed tomographic scans from 3 patients, showing various degrees of severity of the polycystic liver disease. Note the presence of peribiliary (**arrows**) and peripheral (**arrowhead**) cysts in the patient with milder polycystic liver disease (A-C). Note the displacement of the kidneys by a massively enlarged liver in the two patients with more severe disease (D-I). The kidneys are normal and contain no cysts.

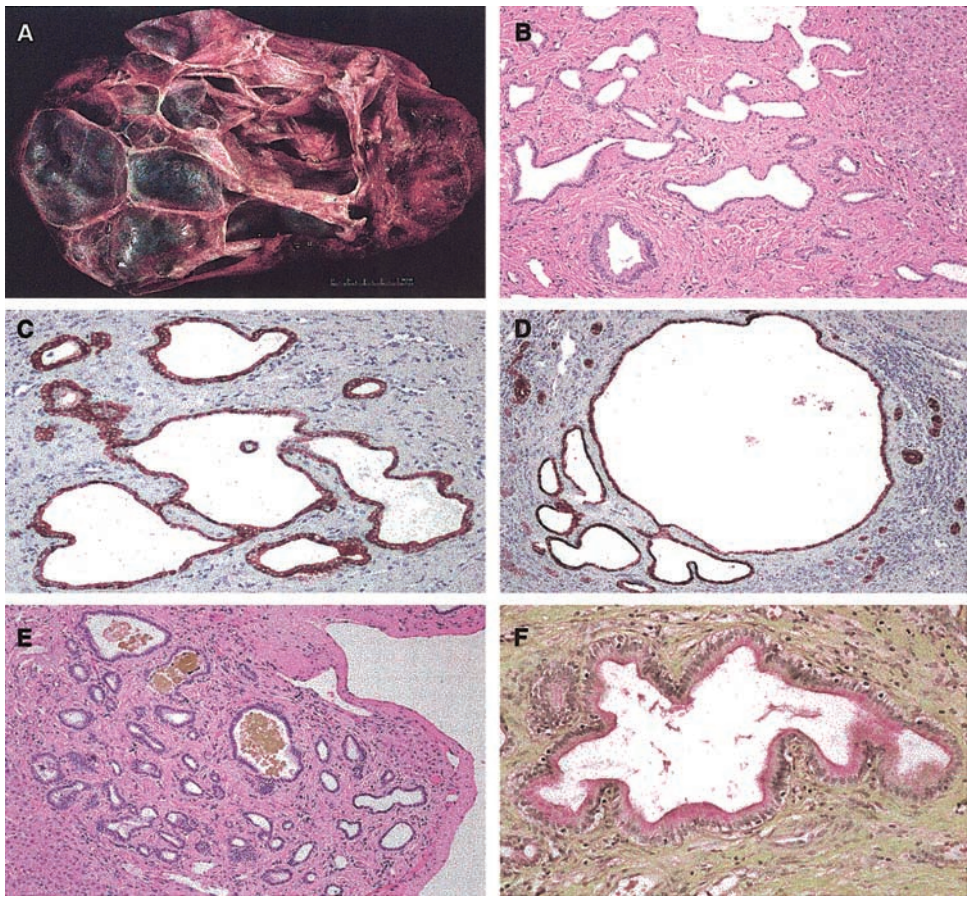

Fig. 3. (A) Surgical specimen obtained from a combined hepatic resection/cyst fenestration procedure for severe isolated polycystic liver disease. (B) Biliary microhamartoma (hematoxylin-eosin stain; original magnification ×100). (C) Biliary microhamartoma (cytokeratin 7 stain; original magnification ×100). (D) Cyst arising from a biliary microhamartoma (cytokeratin 7 stain; original magnification ×100). (E) Biliary microhamartoma containing bile (hematoxylin-eosin stain; original magnification ×100). (F) Dilated peribiliary gland (mucicarmine stain; original magnification ×200).

Discussion

Although recent studies have shown that isolated ADPLD exists as an entity genetically distinct from ADPKD, most of the reports on the pathogenesis and natural history of polycystic liver disease are based on the disease as it manifests in ADPKD.[1-3,17-19] In polycystic liver disease associated with ADPKD, liver cysts arise from the dilatation of biliary microhamartomas and from peribiliary glands.[16,20] The biliary microhamartomas result from an overgrowth of the biliary epithelium of the intralobular bile ductules. These 2 types of cysts can be identified by computed tomography.[21,22] The intrahepatic cysts are within the liver parenchyma but not in contact with the larger portal triads, whereas the peribiliary cysts are adjacent to the larger portal triads or in the hepatic hilum. In our study, both types of cysts were detected radiologically and histologically in patients with isolated ADPLD, suggesting that isolated ADPLD and polycystic liver disease associated with ADPKD have similar pathogenesis.

The natural history of polycystic liver disease associated with ADPKD has been well studied. Hepatic cysts are very rare in children, even microscopically.[23] There is an age-dependent increase in the frequency of hepatic cysts in patients with ADPKD, from 20% in the third decade to 75% by the seventh decade of life.[1-3,17-19] Hepatic cysts may not develop in certain families with ADPKD.[24] The present study suggests that isolated polycystic liver disease is less penetrant in the liver than polycystic kidney disease is in the kidney and that the development of liver cysts in isolated ADPLD may not occur until late in life. Women with ADPKD are more likely to have more and larger cysts than men. Nulliparous women who have never used estrogens are less likely to have cysts than those who have been pregnant and/or used hormones.[17,20] Postmenopausal estrogen replacement is also associated with selective liver enlargement in ADPKD.[25] Similarly, in the present study, we observed that isolated ADPLD is more severe in women than in men and that there is a positive correlation between the severity of the polycystic liver disease and the number of pregnancies in these patients. These observations are consistent with a role for estrogens in the development of polycystic liver disease and support the similarity in the mechanisms of liver cyst formation between ADPKD and isolated ADPLD.

The polycystic liver disease associated with ADPKD is most often asymptomatic and usually comes to medical attention during evaluations for renal disease. Isolated ADPLD is similarly most often asymptomatic, and the disease may go undetected and is likely to be underdiagnosed. The results of this study confirm this to be the case even in families of patients with highly symptomatic disease, in which relatives are more likely to be aware of the symptoms and to undergo diagnostic testing.

When symptoms develop in patients with polycystic liver disease associated with ADPKD, these are usually due to the mass effect of very large or a large number of cysts or from cyst complications such as hemorrhage, infection, or rupture.[3] Symptoms caused by the mass effect of the cysts include abdominal distention, early satiety, dyspnea, back pain, and, rarely, development of ascites because of hepatic venous outflow obstruction or of lower extremity edema due to inferior vena cava compression.[3,26] The results of the current study show a similar spectrum of clinical manifestations in patients with isolated symptomatic ADPLD. The high percentage of symptomatic patients in this study likely reflects selection bias. Most patients with polycystic liver disease require no treatment, but percutaneous cyst aspiration and sclerosis, cyst fenestration, partial hepatectomy, and liver transplantation, depending on the extent, distribution, and anatomy of the cysts, may be indicated in highly symptomatic patients.[27,28]

ADPKD is more than a cystic disease affecting the kidneys and the liver. Extrarenal noncystic manifestations of ADPKD include vascular manifestations such as intracranial aneurysms and valvular heart disease.[29] Whether patients with isolated ADPLD are at an increased risk for intracranial aneurysms and valvular heart disease is not known. In the study by Karhunen and Tenhu proposing that polycystic liver disease and polycystic kidney disease are separate entities, these investigators indicated that cerebral hemorrhages were found only in the patients with ADPKD.[7] On the other hand, the association of an intracranial aneurysm in a patient with isolated ADPLD was recently described by Schievink and Spetzler.[30] In the present study, we found intracranial aneurysms or dissection in 3.6% of patients with isolated ADPLD and 2.9% of their clinically unaffected relatives. However, the apparently clinically unaffected individual with a dolichoectatic intracranial artery was in fact found to be affected using linkage analysis. A vascular phenotype was detected in 5.6% of the patients with isolated ADPLD confirmed by linkage analysis (Table 2) but in none of the unaffected patients. This difference is not statistically significant because of the relatively small number of patients and families in the study; future studies will be required to determine whether ADPLD is an independent risk factor for intracranial vascular abnormalities. In ADPKD, the overall prevalence of intracranial aneurysms is 8% but ranges from 6% of patients without a family history of intracranial aneurysms to 21% of patients with a family history of intracranial aneurysms.[31] Because most intra-

cranial aneurysms detected by presymptomatic screening of patients with ADPKD are small and have a very low risk of rupture, widespread screening of patients with ADPKD for intracranial aneurysms is not recommended.[32] Presymptomatic screening is considered for a selected subset of patients, such as those with a strong family history of intracranial aneurysms. Until more information becomes available, similar recommendations seem appropriate for patients with isolated ADPLD.

The higher prevalence of mitral valve abnormalities in patients with ADPLD compared with their unaffected relatives indicates that isolated ADPLD, like ADPKD, is a systemic disorder with noncystic as well as cystic manifestations.[29] As is often the case in ADPKD, none of the patients with ADPLD in this study had severe or symptomatic valvular heart disease.

In polycystic liver disease associated with ADPKD, the volume of noncystic hepatic parenchyma and the liver function remain normal.[33] In the present study, patients with isolated ADPLD had minimal, clinically insignificant elevations of serum alkaline phosphatase and total bilirubin levels. The other biochemical abnormalities detected in patients with isolated ADPLD were lower serum levels of total cholesterol and triglycerides compared with their unaffected or indeterminate relatives. Patients with massive polycystic liver disease associated with ADPKD have been reported to have low levels of total and HDL cholesterol and triglycerides.[28] These low levels have been believed to reflect poor nutritional status. This seems a less likely explanation in the present study, which included many patients without severe polycystic liver disease. In addition, Luoma et al. found that 4 affected individuals in a family with polycystic liver disease had low serum total cholesterol, high-density lipoprotein cholesterol, and apoprotein A-II levels and suggested that the hepatic lipid metabolism may be altered in patients with polycystic liver disease.[34]

In 2 families in which genetic linkage diagnosis was available, we established that the sensitivity and specificity of our clinical criteria were 70% and 100%, respectively, in individuals younger than 40 years. Therefore, the presence of any cysts in at-risk individuals younger than 40 years is diagnostic of the disease; however, negative findings on ultrasonography are insufficient to exclude the diagnosis in this age group. In those older than 40 years, using our published criteria,[11] specificity remained 100% but sensitivity was 78.3%. Although the numbers are too small to be conclusive, we propose modifying our clinical criteria in those older than 40 years as follows. Individuals at risk between the ages of 40 and 65 years with more than 1 cyst are affected, as are those older than 65 years with more than 3 cysts. Individuals aged 40 to 65 years with only 1 cyst will remain indeterminate, as will those older than 65 years with 1 to 3 cysts.

In summary, this study shows that isolated ADPLD is likely to be underdiagnosed and that it often goes undetected even in first-degree relatives of patients with highly symptomatic polycystic liver disease. As in the case of polycystic liver disease associated with ADPKD, isolated ADPLD is more severe in women than in men. Liver function tests remain normal and, when symptoms develop, these are related to mass effects or complications such as cyst hemorrhage or infection. Although a few patients with highly symptomatic ADPLD may require interventions ranging from cyst aspiration and sclerosis to hepatic resection or liver transplantation, most patients remain asymptomatic and require no treatment. Similar to ADPKD, isolated ADPLD is a systemic disorder with noncystic manifestations. Awareness of the possible extrarenal manifestations of this disease is helpful, but presymptomatic screening is usually not indicated.

Acknowledgment: The authors thank the family members for their generous participation in this study.

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