Hepatic Cysts in Autosomal Dominant Polycystic Kidney Disease

In this issue of the Proceedings (pages 933 to 942), Telenti and associates describe the clinical manifestations and treatment of infected hepatic cysts in patients with autosomal dominant polycystic kidney disease (ADPKD). This article emphasizes the multisystem nature of ADPKD and demonstrates that complications arising in extrarenal sites may lead to substantial morbidity and even mortality. The goals of this editorial are twofold: to familiarize the reader with new information about risk factors and function of hepatic cysts and to evaluate the clinical approach to hepatic cyst infection.

The primary extrarenal manifestations of ADPKD are hepatic cysts, mitral valve prolapse, cerebral aneurysms, and, possibly, diverticular disease of the colon. Although two genetic variants of ADPKD exist, the frequency of each extrarenal manifestation, except perhaps intracranial aneurysm, is similar within all affected kindreds. Hepatic cysts, the most common extrarenal manifestation of ADPKD, are similar to renal cysts in that they are probably derived from epithelia engaged in transport of solutes. For these reasons, the study of hepatic cysts in ADPKD may yield insight about the pathogenesis of not only hepatic cysts but also ADPKD in general.

Risk Factors for Hepatic Cystic Disease.

Age.—The prevalence of hepatic cysts in patients with ADPKD increases with advancing age. Unlike renal cysts, hepatic cysts are not detected in utero and rarely are detected before puberty. In the most extensive autopsy study of ADPKD to date, 17% of patients 29 to 39 years old (N = 18) and 75% of those older than age 70 years (N = 8) had hepatic cysts. Hepatic imaging studies of patients with ADPKD have confirmed this initial impression. With use of radioisotope scintigraphy, Milutinovic and colleagues found that 10% of patients 20 to 29 years of age and 75% of patients older than 60 years had hepatic cysts. Grünfeld and co-workers, using the more sensitive technique of ultrasonography (mainly B-mode), found a higher prevalence of hepatic cysts with a linear increase in prevalence from the third (25%) to sixth (80%) decades of life. Thomsen and Thaysen used computed tomography and obtained age-related prevalence figures almost identical to those of Grünfeld and associates. Although all studies demonstrated that the prevalence of hepatic cystic disease increased with advancing age, none compared the age-related prevalence of hepatic and renal cysts, and no study was designed to determine whether age was an independent predictor of hepatic cyst formation.

My colleagues and I recently conducted a prospective study of risk factors for hepatic cysts in a large number of subjects enrolled in an investigation of the natural history of ADPKD. Overall, 239 patients with ADPKD and 189 unaffected family members underwent a formal history and physical examination, routine blood chemistry testing, and real-time ultrasonography of the liver and kidneys. The age-related prevalence of hepatic and renal cysts differed considerably (Fig. 1). Forty-six percent of patients younger than age 30 years who were at risk for ADPKD had renal cysts, but only 18% of the same patients had hepatic cysts. Renal cysts were commonly detected in childhood, but no patient younger than age 16 years had detectable hepatic cysts. By logistic regression analysis, age was an independent predictor of both prevalence and number of hepatic cysts. The increase in hepatic cystic disease with advancing age suggests that genetic or environmental factors may somehow exert a cumulative effect over time on the growth of hepatic cysts.

Address reprint requests to Dr. G. T. Everson, Gastroenterology Division, Box B-158, University of Colorado Health Sciences Center, 4200 East Ninth Avenue, Denver, CO 80262.
Gender, Pregnancy, and Female Steroid Hormones.—Several authors have suggested that massive hepatic cysts are more likely to develop in women than in men. Grünfeld and colleagues found that the prevalence of hepatic cysts in women was almost twice that in men in relatively young, nondialyzed patients. In contrast, they found no difference in prevalence of hepatic cysts between men and women among older patients on long-term hemodialysis. A recent study also found that women were more likely than men to have massive hepatic cystic disease. In our study of risk factors, we found that the overall prevalence of hepatic cysts in nonazotemic patients was similar between men (46%) and women (50%). Women, however, were more likely to have more and larger hepatic cysts. Women with hepatic cysts had more pregnancies than did those without hepatic cysts (2.9 ± 0.3 versus 1.6 ± 0.2; \( P < 0.0009 \)). The number of hepatic cysts correlated with the frequency of pregnancy (\( P < 0.004 \)), and the maximal size of hepatic cysts was larger in women who had been pregnant in comparison with women who had not (4.5 ± 0.4 versus 1.7 ± 0.5 cm; \( P < 0.001 \)). By logistic regression analysis, both female gender and pregnancy were independent predictors of extensive hepatic cystic disease, as defined by more than 15 hepatic cysts and maximal size of hepatic cysts.

In another study, total hepatic cyst and parenchymal volume was measured from computed tomographic images in 25 patients with hepatic cystic disease. These study subjects were chosen on the basis of having more than five hepatic cysts. All patients with a total hepatic cyst volume greater than parenchymal volume were women (Fig. 2). Finally, in a retrospective mail survey, my co-workers and I found that the exogenous use of female steroid hormones was an additional risk factor for the development of massive hepatic cystic disease.
Liver Cyst Volumes

Fig. 2. Volume of hepatic cysts and parenchyma, as measured from computed tomographic images in subgroup of patients with autosomal dominant polycystic kidney disease who had more than five hepatic cysts. Cyst volume increased with advancing age in both sexes. Nine women had severe hepatic cystic disease (A). The other nine women had hepatic cyst volumes similar to those of seven men (B). (From Everson GT, Scherzinger A, Berger-Leff N, Reichen J, Lexotte D, Manco-Johnson M, Gabow P: Polycystic liver disease: quantitation of parenchymal and cyst volumes from computed tomography images and clinical correlates of hepatic cysts. Hepatology 8:1627-1634, 1988. By permission of the American Association for the Study of Liver Diseases.)

(unpublished data). Hepatic cysts did not develop in women with ADPKD who had neither used exogenous hormones nor been pregnant. Of those women who had used exogenous hormones but never been pregnant, 26% had hepatic cysts. Forty-six percent of women who had been pregnant but never used exogenous hormones and 65% of women who had both been pregnant and used exogenous hormones had hepatic cysts. The data suggest that female steroid hormones modulate hepatic cystogenesis and the severity of hepatic cystic disease.

Renal Cystic Disease and Renal Function.—Investigators have suggested that hepatic cysts are more prominent in patients with extensive renal cystic disease and severe renal functional impairment than in other patients.²³¹⁰ My colleagues and I found that patients with ADPKD and hepatic cysts had greater mean renal volumes, more renal cysts, larger renal cysts, less normal renal parenchyma, and greater reduction in creatinine clearances than such patients without hepatic cysts.⁹ By logistic regression analysis, both the degree of renal cystic disease and the severity of renal functional impairment were independent predictors of the degree of hepatic cystic disease. Patients with the most severe renal cystic disease and the greatest reduction in creatinine clearance had the most extensive hepatic cysts. These observations suggest not only that the expression of the ADPKD gene is parallel between the liver and
the kidney but also that factors released or not cleared by the diseased kidney may, in some unknown way, regulate the expression of hepatic cystic disease.

Functional Nature of Hepatic Cystic Epithelium.—The epithelium of hepatic cysts may be derived from biliary epithelium or a cell that is a precursor of biliary epithelium. Hepatic cystic epithelium does not transport organic anions that are commonly transported by hepatocytes such as cholylglycine, sulfobromophthalein, and \(^{99m}\text{Tc-diisopropyl-iminodiacetic acid.}\) Analysis of the composition of cyst fluid has suggested that cystic epithelium is probably derived from biliary epithelium.\(^{11}\) The solute content of the cyst fluid is similar to plasma, but glucose concentrations are uniformly low. In a recent study, my colleagues and I found that the epithelia of hepatic cysts secreted fluid in response to intravenous administration of secretin.\(^{12}\) After percutaneous puncture of hepatic cysts and mixing of nonabsorbable marker with cyst fluid, secretin was administered intravenously. Within 10 to 15 minutes after the administration of secretin, secretion by the cysts increased (Fig. 3). This result suggests that hepatic cystic epithelium has retained the hormone responsiveness characteristic of biliary epithelium. Both secretory component and immunoglobulin A (IgA) have been measured in cyst fluids. By Sephadex G200 chromatography, the form of IgA found in cyst fluids was determined to be secretory IgA.\(^{13}\) In humans, the transport of secretory component and secretory IgA into bile is performed by biliary epithelium.\(^{13}\) Thus, in the composite, the data strongly suggest that hepatic cystic epithelium is closely related to biliary epithelium.

Hepatic Cyst Infection.—The most severe complications associated with hepatic cysts tend to occur in patients with massive hepatic cystic disease.\(^{2,3,14}\) Because the prevalence, number, and size of hepatic cysts increase with advancing age, the frequency of patients who have a complication relative to a hepatic cyst is likely to increase as patients with ADPKD are maintained into later life by advances in medical management, dialysis, and renal transplantation. Recent studies suggest that complications of hepatic cysts, such as infections and malignant lesions, may be relatively common—in one study,\(^{2}\) 10.5\% of the overall mortality among patients with ADPKD on long-term hemodialysis was due to one of these two factors. In this issue of the Proceedings, Telenti and associates report their experience with infection of hepatic cysts in ADPKD. During the 10-year period from 1978 to 1988, the authors noted five cases of hepatic cyst infection. In a search of the medical literature for the same period, the authors discovered an additional nine cases that were sufficiently well defined to warrant review in conjunction with their own experience.

Clinical Manifestations and Imaging Studies.—Hepatic cyst infection is a well-recognized complication of hepatic cystic disease; nevertheless, the manifestations, diagnosis, and treatment of hepatic cyst infection have not been previously analyzed. Telenti and colleagues found that patients with infected hepatic cysts had fever, pain in the right upper quadrant of the abdomen, and leukocytosis. These findings, however, are nonspecific because they are also common in patients with infected renal cysts. Most patients with infected hepatic cysts had increased serum levels of alkaline phosphatase, bilirubin, or aspartate aminotransferase, particularly noteworthy findings because patients with uncomplicated hepatic cysts rarely have abnormalities of serum liver enzymes or bilirubin. Although these clinical observations and laboratory data provide clues to the diagnosis of hepatic cyst infection, radiologic imaging studies are necessary for localization of the infected cyst and planning of therapy.

Although numerous imaging modalities (including radionuclide imaging, ultrasonography, computed tomography, magnetic resonance imaging, cholangiography, and \(^{111}\text{In leukocyte scans}\)) have been used, the relative value of each modality has not been systematically evaluated. Nonetheless, the article by Telenti and associates sheds some light on the potential utility of certain techniques. An infected cyst was accurately identified by ultrasonography in four of eight patients and by computed tomography in
Fig. 3. Secretory response to intravenously administered bolus of secretin (1 U/kg) by hepatic cysts in two patients with autosomal dominant polycystic kidney disease. Cumulative volume secreted is plotted against time. After percutaneous puncture (t = -15 minutes), 15 minutes were allowed to elapse before starting the secretion study at t = 0. Secretin was administered as indicated, approximately 35 minutes after puncture of cysts and stimulated sustained secretion of fluid by cysts. (From Everson and associates.

Management.—Antibiotics alone have been ineffective in eradicating hepatic cyst infection. Most authors have advocated a combination of drainage and antibiotics for the treatment of hepatic cyst infection because of its proven efficacy in the treatment of pyogenic hepatic abscess. Because percutaneous drainage is readily accomplished under computed tomographic or ultrasound guidance, this approach seems the most effective and prudent. In most cases, percutaneous puncture of the cyst and aspiration of its contents with use of a fine-gauge needle should first be done to verify the site of the infection. Because several cysts may be traversed before the infected cyst is reached, the needle tract is a potential conduit for extension of infection into adjacent cysts. The limited reported data on puncture and drainage of hepatic cysts, however, have not substantiated contiguous extension of infection to adjacent cysts.

The choice of antibiotics for treatment of hepatic cyst infection remains controversial. If drainage is not performed, antibiotics that penetrate the cyst are necessary to eradicate cyst infection. The study by Telenti and co-workers has shed some light on this issue because the authors found that ciprofloxacin, but not chloramphenicol, is concentrated within hepatic cysts. Further studies are needed to determine what other antibiotics may penetrate well into hepatic cysts. If cyst drainage is used, the choice of antibiotic may not be so critical inasmuch as the drug may not have to enter the cyst but simply yield sufficient tissue concentrations to prevent spread of the infection from the cyst into the adjacent parenchyma or bloodstream. Thus, with use of drainage, many antibiotics other than ciprofloxacin may be effective. Indeed, Telenti and associates obtained a satisfactory therapeutic result by using drainage of the

six of nine. Magnetic resonance imaging and $^{111}$In leukocyte scans accurately detected an infected cyst in all patients (two and four, respectively) in whom these studies were used. $^{67}$Ga scans were positive in only one of three patients. Thus, a reasonable approach to the diagnosis of an infected hepatic cyst might include initial ultrasonography followed by either magnetic resonance imaging or $^{111}$In leukocyte scanning if ultrasonography is nondiagnostic.
cyst in combination with a wide variety of antibiotic agents.

**Prevention.**—In contrast to pyogenic hepatic abscesses, which are characterized microbiologically by multiple organisms, infected hepatic cysts are usually colonized by a single species of bacterium. This finding suggests that the types of infections originating within hepatic cysts are hematogenously borne, perhaps from concomitant or prior renal infection. Thus, prompt therapy for renal cyst infection may prevent the hematogenous dissemination of organisms to the liver and hepatic cyst infection. Despite the serious nature of hepatic cyst infection, as proved by its association with a relatively high mortality rate, the prophylactic use of antibiotics seems unreasonable. In contrast, early detection of renal infection and prompt initiation of antibiotic therapy may be the most practical approach to prophylaxis against hepatic cyst infection.

**Summary.**—Hepatic cysts are one of several extrarenal manifestations of the ADPKD gene. Several factors, including age, gender, pregnancy, the degree of renal cystic disease, and the extent of renal functional impairment, may modify the expression of hepatic cystic disease. With advances in medical care, such as improvement in the management of end-stage renal disease, hemodialysis, and renal transplantation, patients with ADPKD will experience an increased life expectancy. As a result, complications associated with hepatic cysts may become more common, and physicians may encounter an increasing number of patients with ADPKD who have infected hepatic cysts. Several issues in the management of this complication remain unresolved, but the article by Telenti and associates in this issue of the Proceedings addresses some of the critical issues that physicians who are responsible for the care of these patients will certainly confront in future years.

Gregory T. Everson, M.D.
Gastroenterology Division
University of Colorado Health Sciences Center
Denver, Colorado

**REFERENCES**


15. McDonald MI, Corey GR, Gallis HA, Durack DT: Single and multiple pyogenic liver abscesses: natural history, diagnosis and treatment, with emphasis on percutaneous drainage. Medicine 63:291-302, 1984