Pediatr Radiol (1993) 23: 131–133

Pediatric Radiology

Association of congenital hepatic fibrosis with autosomal dominant polycystic kidney disease

Report of a family with review of literature

B. Lipschitz[1], W. E. Berdon[2], A. R. Defelice[1], J. Levy[3]

[1] Department of Pediatric Gastrointestinal Diseases, Babies Hospital, Columbia Presbyterian Medical Center, 3959 Broadway, New York, NY 10032, USA
[2] Department of Pediatric Radiology, Babies Hospital, Columbia Presbyterian Medical Center, 3959 Broadway, New York, NY 10032, USA
[3] Department of Gastrointestinal Diseases, New York Hospital, Cornell University, New York, NY 10021, USA

Received: 30 September 1992/Accepted: 16 December 1992

Abstract. The association of autosomal recessive polycystic kidney disease (ARPKD) with congential hepatic fibrosis (CHF) is well known; a rare occurrence is that of congenital hepatic fibrosis with autosomal dominant polycystic kidney disease (ADPKD). We report a family with ADPKD in which congenital hepatic fibrosis with severe portal hypertension (PHT) presented in a 4-year-old girl; the kidneys were initially normal. Typical changes of autosomal dominant polycystic kidney disease developed in the next decade and were also found in the mother and sister (neither of whom had any evidence of portal hypertension). Severe variceal bleeding was treated by sclerotherapy and beta receptor blocade.

Congenital hepatic fibrosis is an important cause of portal hypertension in the pediatric age group [1, 2]. It has also been recognized that in approximately half the cases of congenital hepatic fibrosis renal cystic disease occurs with varying degrees of severity [1–4]. This associated polycystic kidney disease is commonly of the autosomal recessive type [1–3, 5]. In the past two decades there are reports in which congenital hepatic fibrosis is associated with autosomal dominant polycystic kidney disease (ADPKD) [6–14]. Only one reference has been in the radiology literature [12].

We present a pediatric case of congenital hepatic fibrosis and severe portal hypertension in which the kidneys were initially normal; typical changes of ADPKD developed in the next decade. As noted in sonography of the patient and family, only the patient had hepatic fibrosis and portal hypertension.

Case report

A 19-year-old Hispanic female presented with a single episode of massive hematemesis. Endoscopy demonstrated esophageal varices. She complained of chronic epistaxis, easy bruisability and left upper quadrant fullness and discomfort.

Correspondence to: Dr. W. E. Berdon

Past history revealed that at age 4 years splenomegaly had been noted. Liver-spleen scan at that time demonstrated splenomegaly with uniformly increased tracer uptake. An IVP showed normal kidneys without evidence of polycystic disease. Routine biochemical and hematologic tests were normal.

At age 7 years hypersplenism was noted. The platelet count was 106,000, the white cell count was 4,600. At 8 years of age angiography revealed massive splenomegaly with a patent splenic vein and hepatofugal flow. Gastric fundal varices and umbilical vein varices were noted indicating significant portal hypertension. The kidneys were still normal.

At age 14 years a repeat liver-spleen scan showed uniform hepatic radiotracer uptake in a normal size liver with markedly enlarged spleen. The platelet count had dropped to 62,000 and the white cell count to 2,800. Liver transaminases, alkaline phosphatase, albumin and coagulation studies were normal at this time. Tests for Wilson's disease, alpha-1-antitrypsin deficiency, cystic fibrosis, hemochromatosis, and viral hepatitis were negative. UGI again demonstrated esophageal and fundal varices plus massive splenomegaly with displacement of the stomach and small bowel by the giant spleen (Fig. 1 a). The liver was not significantly enlarged. A percutaneous needle liver biopsy was diagnostic for congenital hepatic fibrosis.

At this time the family's involvement with autosomal dominant polycystic kidney disease was first noted. The patient's mother was diagnosed with 'renal disease' at 18 years; she proved to have PKD by ultrasound at age 35 (see below) during the diagnostic work-up of our patient and has been treated for systemic hypertension for 15 years; the mother's blood urea nitrogen and creatinine have remained normal. The maternal grandfather died for renal disease of unknown etiology at 46 years of age. Two maternal aunts, age 43 and 54 years, a 47-year-old uncle and a 31-year-old sister are known to have polycystic kidneys.

Serial abdominal sonograms were done on the patient from age 15 to 20 years; the spleen was persistently massively enlarged with large hilar veins (Fig. 1 b). Doppler studies showed flow to the liver and the main portal vein was patent. Both kidneys were normal in echo appearance except for multiple simple appearing cysts, typical of ADPKD (Fig. 1 c, d). A head CT scan was normal without evidence of cerebral aneurysms.

The patient's mother had several sonograms. These showed large kidneys filled with multiple cysts typical of ADPKD (Fig. 2 a), a normal size spleen, and several hepatic cysts (Fig. 2 b). An adult sister had a sonogram showing kidneys with cysts typical of ADPKD (Fig. 3), a normal size liver and spleen; her hepatic and renal function were normal.

Esophago-gastro-duodenoscopy revealed multiple distal esophageal varices and a single gastric varix. The patient was treated with sclerotherapy of esophageal varices using sodium tetradecyl sul-

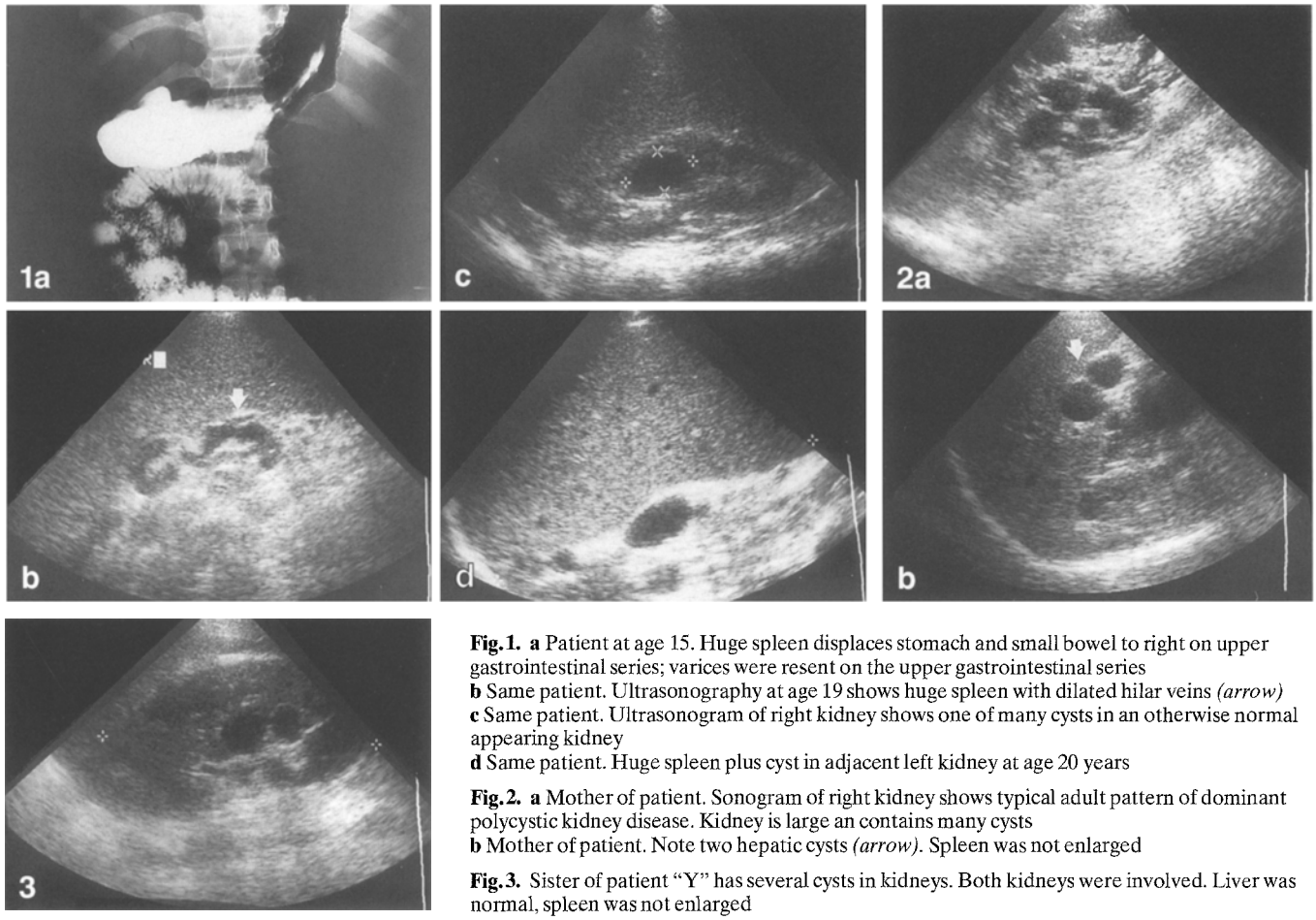
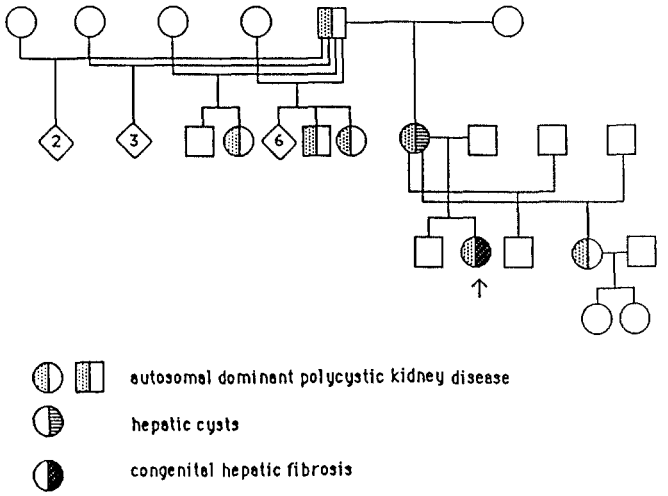


Fig. 1. **a** Patient at age 15. Huge spleen displaces stomach and small bowel to right on upper gastrointestinal series; varices were resent on the upper gastrointestinal series
b Same patient. Ultrasonography at age 19 shows huge spleen with dilated hilar veins *(arrow)*
c Same patient. Ultrasonogram of right kidney shows one of many cysts in an otherwise normal appearing kidney
d Same patient. Huge spleen plus cyst in adjacent left kidney at age 20 years

Fig. 2. **a** Mother of patient. Sonogram of right kidney shows typical adult pattern of dominant polycystic kidney disease. Kidney is large an contains many cysts
b Mother of patient. Note two hepatic cysts *(arrow)*. Spleen was not enlarged

Fig. 3. Sister of patient "Y" has several cysts in kidneys. Both kidneys were involved. Liver was normal, spleen was not enlarged



phate; beta-receptor blockade therapy (propranolol) was simultaneously started. No further bleeding of esophageal varices occurred over a one year course on this regimen.

Discussion

Kerr et al. [1] introduced the term congenital hepatic fibrosis in 1961 and noted that in some of their cases the disease appeared to be inherited in an autosomal recessive manner. (Earlier, Mac Mahon in 1929 [15] had described liver fibrosis distinct from cirrhosis.) Characteristic histological features of congenital hepatic fibrosis are broad bands of fibrous tissue predominating in periportal areas containing irregularly shaped interlobular bile ducts with portal vein hypoplasia. Islands of hepatic parenchyma are apparently normal with preserved architecture.

In over 50% of congenital hepatic fibrosis cases there is associated autosomal recessive polycystic kidney disease of varying severity [3, 4, 6, 16]. This association has been shown in 33% of sporadic cases and in 70% of familial cases [2].

Blyth and Ockendon [4] had classified ARPKD, in terms of the renal and hepatic manifestations, by age. Though histologic evidence of congenital hepatic fibrosis occurs in patients with autosomal recessive PKD even in the neonatal/perinatal period, clinical manifestations of the associated infantile polycystic kidney disease predominate, with death due to renal failure and/or pulmonary insufficiency. During childhood, if the renal disease is less severe and the patient survives, the hepatic lesion becomes more prominent because of more extensive hepatic fibrosis [11]. Symptoms of portal hypertension then develop [5].

Though adult type ADPKD may be associated with the development of hepatic cysts, these cysts (apart from

occasional hemorrhage or infection in them) seldom give rise to symptoms [3, 11, 17]. Portal hypertension, reported only once [13] is *rare,* and splenomegaly is rarely noted. Rather, patients with ADPKD present typically with signs of renal/systemic hypertension and develop azotemia and progressive renal failure in later adulthood.

In the past two decades a small number of reports have noted aggregates of congenital hepatic fibrosis in families with APKD [6–13]; seven cases in four families with concurrence of congenital hepatic fibrosis and ADPKD have been reported [7]. In our case there is clear evidence of an association of congenital hepatic fibrosis and ADPKD bringing the number of reported cases in the literature to 18 in 13 families. Interestingly, as in our case, most of the reported cases presented *initially with portal hypertension* and were only later found to have incidental ADPKD. (In our case, as in those of Tazelaar et al. [6] and Bradford et al. [18], the patient presented with portal hypertension in early childhood, and was only later found to have renal cysts with family aggregation of ADPKD. In the more commonly encountered association of congenital hepatic fibrosis with "recessive PKD", renal disease frequently precedes the development of congenital hepatic fibrosis and complications of portal hypertension [4, 5, 11].)

Investigators have speculated on genetic aspects of the association of congenital hepatic fibrosis (previously assumed to be inherited in an autosomal recessive mode) with ADPKD. The distinction between autosomal dominant and recessive PKD has been investigated by linkage analysis with informative markers, e.g. a-hemoglobin [19, 20]. ADPKD is now known to be caused by mutations at more than one locus [19], the first being located on chromosome 16 and accounting for most families. Moreover, variability of phenotype is found in ADPKD including aneurysms of the circle of Willis and thoraco-abdominal aorta and cysts of the pancreas, spleen and subarachnoid space [21–24].

Of the cases reported with concomitant congenital hepatic fibrosis and ADPKD, those analyzed had acquired the morbid allele for ADPKD [7]. Speculatively, an independent allele may modify ADPKD and produce a phenocopy of the recessive form of PKD with congenital hepatic fibrosis and the noted difference in timing of presentation of congenital hepatic fibrosis and portal hypertension. It is not clear whether such an independent allele is inherited in an autosomal dominant or recessive mode.

In conclusion, portal hypertension with congenital hepatic fibrosis may be the initial manifestation of ADPKD. Current treatment modalities for portal hypertension and hypersplenism include sclerotherapy, beta blockers, and portal systemic shunting. Since the congenital hepatic fibrosis and portal hypertension usually precede the diagnosis of ADPKD, monitoring by ultrasound for ADPKD in these patients and their families is recommended.

References

1. Kerr DNS, Harrison CV, Sherlock S, Walker RM (1961) Congenital hepatic fibrosis. Q J Med 30: 91–117
2. Sommerschild HC, Langmark F, Maurseth K (1973) Congenital hepatic fibrosis: report of two new cases and review of the literature. Surgery 73: 53–58
3. Kerr DNS, Warrick CK, Hart-Mercer J (1962) A lesion resembling medullary sponge kidney in patients with congenital hepatic fibrosis. Clin Radiol 13: 85–91
4. Blyth H, Ockenden BG (1971) Polycystic disease of kidneys and liver presenting in childhood. J Med Genet 8: 257–284
5. Premkumar A, Berdon WE, Levy J, Amodio J, Abramson SJ, Newhouse JH (1988) The emergence of hepatic fibrosis and portal hypertension in infants and children with autosomal recessive polycystic kidney disease. Pediatr Radiol 18: 123–129
6. Tazelaar HD, Payne JA, Patel NS (1984) Congenital hepatic fibrosis and asymptomatic familial adult-type polycystic kidney disease in a 19-year-old woman. Gastroenterology 86: 757–760
7. Cobben JM, Breuning MH, Schoots C, Ten Kate LP, Zerres K (1990) Congenital hepatic fibrosis in autosomal-dominant polycystic kidney disease. Kidney Int 38: 880–885
8. Matsuda O, Ideura T, Shinoda T et al (1990) Polycystic kidney of autosomal dominant inheritance, polycystic liver and congenital hepatic fibrosis in a single kindred. Am J Nephrol 10: 237–241
9. De Vos M, Barbier F, Cuvelier C (1988) Congenital hepatic fibrosis. J Hepatol 6: 222–228
10. Lee FI, Paes AR (1985) Congenital hepatic fibrosis and adult-type autosomal dominant polycystic kidney disease in a child. Postgrad Med J 61: 641–642
11. Murray-Lyon IM, Ockenden BG, Williams R (1973) Congenital hepatic fibrosis – is it a single clinical entity? Gastroenterology 64: 653–656
12. Hoeffel J-C, Jacottin G, Bourgeois J-M (1971) A propos d'une famille associant des cas de polykystose rénale de type juvénile et de type adulte. Ann Radiol 14: 205–209
13. Gaisford W, Bloor K (1968) Congenital polycystic disease of kidneys and liver. Portal hypertension – portocaval anastomosis. Proc R Soc Med 61: 305
14. Lieberman E, Salinas-Madrigal L, Gwinn JL, Brennan LP, Fine RN, Landing BH (1971) Infantile polycystic disease of the kidneys and liver. Medicine 50: 277–318
15. MacMahon, HE (1929) Congenital anomalies of the liver. Am J Pathol 5: 499–507
16. Alvarez F, Bernard O, Brunelle F et al (1981) Congenital hepatic fibrosis in children. J Pediatr 99: 370–375
17. Mulutinovac J, Fialkow PJ, Rudd TG, Agada LY, Phillips LA, Brant JI (1980) Liver cysts in patients with autosomal dominant polycystic kidney disease. Am J Med 68: 741–744
18. Bradford WD, Bradford JW, Porter FS, Sidbury JB (1968) Cystic disease of the liver and kidney with portal hypertension: a cause of sudden unexpected hematemesis. Clin Pediatr 7: 299–306
19. Reeders ST, Breuning MH, Davies KE et al (1988) A highly polymorphic DNA marker linked to adult polycystic kidney disease on chromosome 16. Nature 317: 542–544
20. Romeo G, Devoto M, Costa G (1988) A second genetic locus for autosomal dominant polycystic kidney disease. Lancet I: 8–10
21. Kimberling WJ, Fain PR, Kenyon JB, Goldgar D, Sujansky E, Gabow PA (1988) Linkage heterogeneity of autosomal dominant polycystic kidney disease. N Engl J Med 319: 913–918
22. Grantham JJ (1988) Polycystic kidney disease – a old problem in a context. N Engl J Med 319: 944–946
23. Nathan M, Batsakis JG (1969) Congenital hepatic fibrosis. Surgery 128: 1033–1041
24. Wakabayashi T, Fugita S, Ohbara Y et al (1983) Polycystic kidney disease and intracranial aneurysms. Early angiographic diagnosis and early operation for the unruptured aneurysms. J Neurosurg 58: 488–491