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Dominantly-Inherited Polycystic Kidneys in Infants: Association with Hypertrophic Pyloric Stenosis

J. P. Loh[1], J. O. Haller[1], E. G. Kassner[1], A. Aloni[3], and K. Glassberg[2]

[1] Departments of Radiology and [2] Urology of the State University of New York, Downstate Medical Center, Brooklyn, New York, and [3] Selden Medical Center, Selden, New York, New York, USA

Abstract. Newborn male fraternal twins presented at 10 days of age with bilateral flank masses; intravenous urograms showed polycystic kidney disease. Both babies also had hypertrophic pyloric stenosis (HPS). Their father has radiographic and sonographic findings of previously unsuspected polycystic kidneys and has a history of HPS in infancy. The association of dominantly-inherited polycystic kidneys (DPK) and HPS in this family is probably due to chance. However the authors speculate that the autosomal gene for DPK may occur at one of several loci that carry the genetic liability for HPS, a disorder transmitted by polygenic inheritance.

Key words: Cystic disease, kidneys - Polycystic kidneys, infants - Polycystic kidneys, adult type - Hypertrophic pyloric stenosis, inheritance

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We wish to report a family with both dominantly-inherited polycystic kidneys (DPK) and hypertrophic pyloric stenosis (HPS). The two affected infants are fraternal twins who were evaluated at 2 and 3 weeks of age for bilateral flank masses discovered at 10 days of age. Neither infant has had clinical or laboratory evidence of renal or hepatic impairment and both are thriving at 6 months of age. Their parents were evaluated and their father was found to have radiographic and sonographic features typical of the adult type of polycystic kidneys and a history of HPS in infancy. We have been unable to find any previous reports of DPK and HPS occurring together.

Case Reports

Case 1: R. R., is one of fraternal twin brothers who were born after 36 weeks gestation; the pregnancy was normal. His birth weight was 3,150 grams. He was seen by his pediatrician for a feeding problem at 10 days of age. Examination revealed large masses in both flanks and an inguinal hernia. At 18 days of age an intravenous urogram showed symmetrical enlargement of the kidneys. There was prompt excretion of contrast material and the calyces were splayed and distorted (Fig. 1). The nephrogram persisted and puddling of contrast material in numerous small structures was evident on the 24-hour

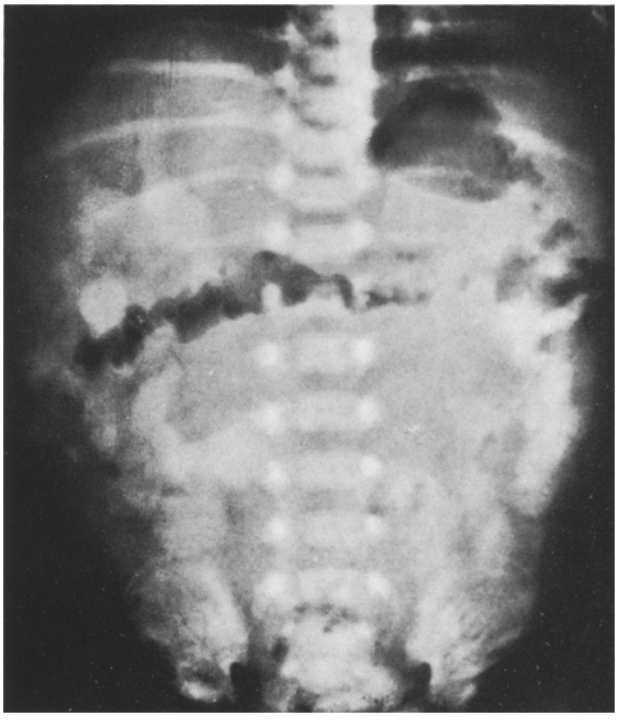

Fig. 1. *Case 1.* Intravenous urogram at 2 weeks of age (15-minute film), showing massive enlargement of the kidneys and distortion of the collecting systems

radiograph. Serum creatinine, BUN, urinalysis and hemogram were normal. While he was in the hospital projectile vomiting began; HPS was diagnosed and a Ramstedt pyloromyotomy was performed at 25 days of age. He made an uneventful recovery. At 3 months of age an ultrasonogram revealed large, strongly-echogenic kidneys with dilated calyses. There were interspersed foci in which the acoustical features resembled normal renal parenchyma. At 6 months of age he is thriving, although weight (3rd percentile) and height (10th percentile) remain in the low-normal range. His blood pressure, urinalysis, hemogram, BUN and serum creatinine are normal.

Case 2: J. R., his fraternal twin brother, was found to have bilateral flank masses at 10 days of age. At 3 weeks intravenous urography revealed massive enlargement of both kidneys. The contrast material was excreted promptly. Early films showed a mottled nephrogram and distortion of the calyces (Fig. 2 A). At 16 hours there was puddling of contrast material in numerous small structures, which were interspersed with lucent images of approximately the same size (Fig. 2 B). By 24 hours the nephrogram had almost completely faded. An ultrasonogram showed renal abnormalities that closely resembled those of his brother. BUN, serum creatinine, urinalysis and hemogram were normal. Blood pressure was 100 mg Hg by the palpation method.

On the 4th hospital day postprandial vomiting began; on the 6th day a barium meal showed typical HPS and a Ramstedt pyloromyotomy was done. Liver biopsy showed mild acute inflammation of the portal triads, extramedullary hematopoesis and focal infiltrates of eosinophils. Biliary ductal proliferation and ectasia and periportal fibrosis were not present. Renal biopsy was not performed. He made an uneventful recovery. At 6 months of age he is thriving, although his weight (3rd percentile) and height (10th percentile) remain in the low-normal range. Blood pressure, urinalysis, hemogram, BUN and serum creatinine are normal.

Case 3: G. R., The 32-year-old father of the twins, is in good health. Annual physical examinations have revealed no evidence of hypertension or renal disease. He passed a kidney stone at 20 years of age. He is quite certain that he was treated surgically for HPS at 4 weeks of age and there is a typical Ramstedt pyloromyotomy scar on his abdomen. Because of the findings in his sons, he agreed to undergo intravenous urography and ultrasonography. Both examinations revealed polycystic kidneys (Fig. 3).

Family History

The pedigree is shown in Figure 4. The twin's mother and 2 1/2-year-old sister are in good health and have no history of renal disease or hypertension; intravenous urography and ultrasonography were normal in both. Polycystic kidneys have not been diagnosed in any relative of the twins' father; one of his third cousins had pyloric stenosis. The twins' 55-year-old paternal grandmother has recently been told that she is hypertensive, but she has not had an intravenous

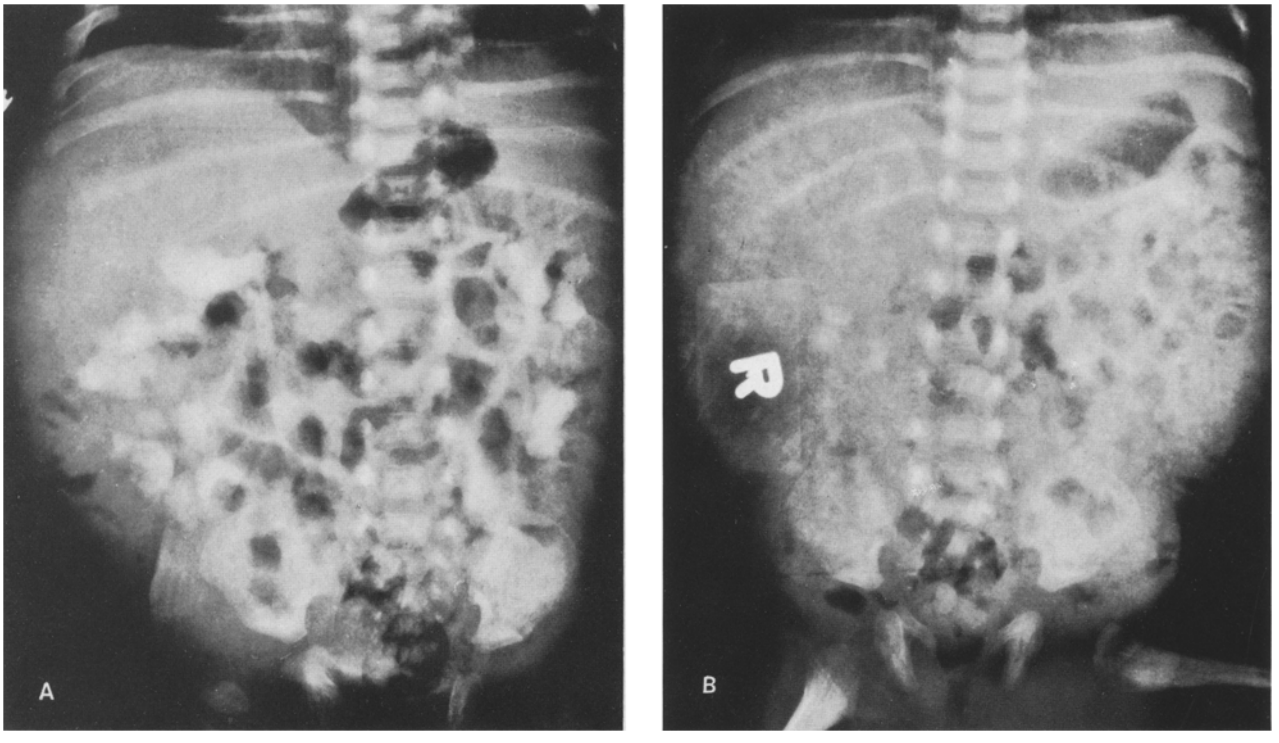

Fig. 2. *Case 2.* A–B, intravenous urogram at 3 weeks of age. **A** 15 minutes. The kidneys are massively enlarged and there is excellent opacification of the distorted collecting systems. **B** 16 hours. Both kidneys show puddling of contrast material with interspersed lucent foci

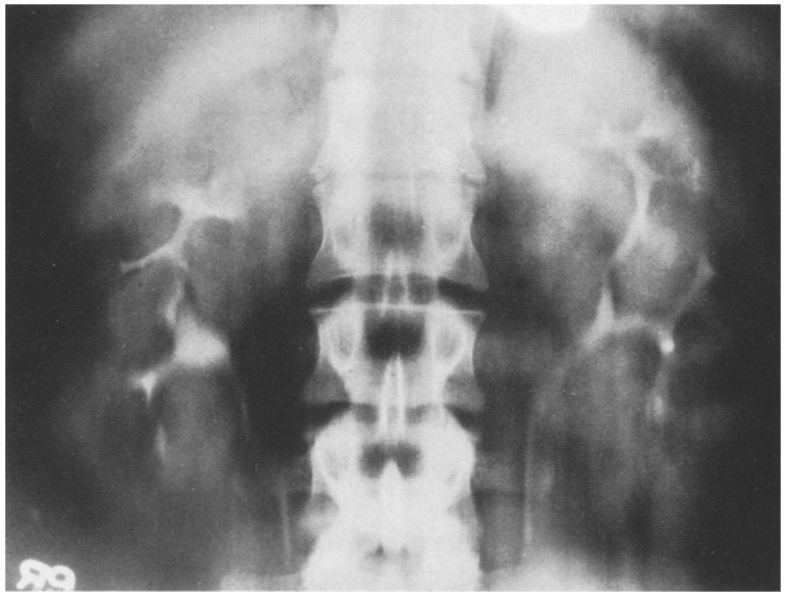

Fig. 3. *Case 3.* Intravenous urogram (tomographic cut), showing bilateral renal enlargement, splaying of calyces and numerous cysts

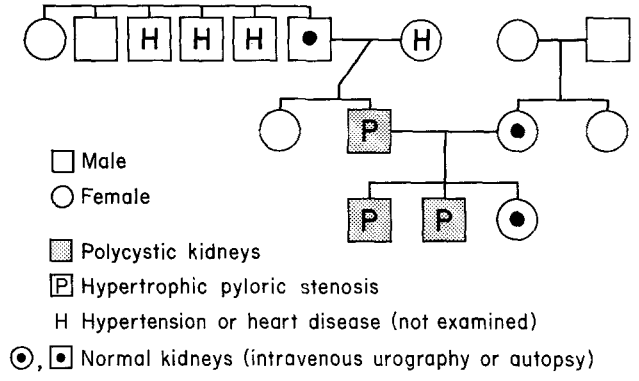

Fig. 4. Pedigree of R. family

urogram. The twins' paternal grandfather died in an accident at age 36; his kidneys were apparently normal at autopsy. He had 5 siblings, none of whom were examined radiographically: 3 brothers died of hypertension or heart disease, and a brother and sister are living and well.

Discussion

The most common type of polycystic kidneys in neonates and young infants is inherited as an *autosomal recessive* disorder. Blyth and Ockenden [2] defined 4 distinct types of recessively-inherited childhood polycystic kidney disease which differed in time of onset, clinical course, proportion of affected nephrons and severity of associated liver disease (widespread proliferation and ectasia of biliary ducts and ductules, with periportal fibrosis). Infants who present at birth (perinatal type) rarely survive more than a few months; those presenting during the first month of life (neonatal type) generally succumb to progressive renal failure before their first birthday [2, 6]. There was no variation in the clinical course within a family; e. g., if a child presented at birth with massively enlarged kidneys and died shortly afterward, all affected children in the family did the same. More than 90% of the tubules were dilated in the perinatal type; about 60% were dilated in the neonatal type; and proportionately fewer tubules were affected in the infantile type (onset under 6 months) and juvenile type. Six et al. [12] have proposed a radiographic classification of renal cystic disease based on the Blyth and Ockenden classification.

Including the present report, *autosomal dominant* inheritance, i. e., 2-5 consecutive generations affected with polycystic kidneys, has been documented in at least 13 infants who were under 3 months of age at the time of diagnosis [1, 2, 5-7, 9-11, 13]. Adult relatives of infants with DPK have had typical adult-type polycystic kidneys. Morphologic studies in 7 infants with DPK have shown that the cysts are rounded, vary in size and shape, and are unevenly distributed, with intervening foci of normal renal parenchyma [1, 2, 5, 9, 11]. Thus there is greater similarity to adult-type polycystic kidneys than to the recessively-inherited childhood type (Blyth and Ockenden classification), in which the cysts are radially-arranged,

elongated and uniform in size and distribution. Biliary duct and ductule ectasia and periportal fibrosis have been described in only 1 infant with DPK [2].

The course of neonates and young infants with DPK has been very variable, but the prognosis is clearly better than in recessively-inherited polycystic kidney disease in this age group. Only 5 of the 13 patients died during infancy [1, 2, 9, 11]; in 2 of these cases renal disease was probably not a major contributing cause of death [9, 11]. In the remaining cases the period of followup has been too short to establish the ultimate outcome. One patient was in renal failure and hypertensive at 8 months [5]. One patient had impaired creatinine clearance and severe hypertension at 14 weeks, but her renal function was stable and her hypertension controlled at 2 years [7]. Three other patients had apparently adequate renal function at 6–9 months [5; present report]. The only patient followed beyond 2 years had recurrent urinary tract infections, but his blood pressure, renal function and growth were normal at 9 years [10]. None of the patients had clinical or pathologic evidence of portal hypertension.

The existence of a group of neonates and young infants in whom polycystic kidneys were associated with dominant inheritance, adequate renal function, normal livers and relatively good prognosis led us to consider whether radiographic criteria could be used to distinguish dominantly inherited from recessively inherited polycystic kidney disease. The radiographic findings in the most severely affected patients with DPK are not known, since the 2 infants who died during the first 2 days of life did not undergo intravenous urography [1, 11]. A patient who died of renal failure (at 3 months) had the "characteristic bubble effect of polycystic kidneys" at 1 month, but her radiograph was not published [2]. Nine other infants with DPK underwent intravenous urography during the first 2 months of life. Seven had bilaterally symmetrical renal enlargement and involvement; one had non-visualization of the smaller kidney (which was found to be severely affected at operation) [5]; and one had apparent unilateral involvement [5]. In 7 cases the calyces were well opacified on early films; in one case opacification was delayed [9]; and in one case the timing of calyceal opacification was not stated [5]. Mild or moderate calyceal distortion was usually present. The early nephrogram was not described by most authors. However, delayed films (up to 24 hours) usually showed "puddling" or "pooling" of contrast material, i. e., a mottled pattern of opacification of small round and linear structures throughout the parenchyma. Only one long-term survivor has been followed with serial intravenous urograms [10]: at $2\,^1/_2$ months the urographic findings suggested "polycystic disease of the infantile type;" at 23 months bilateral renal enlargement, calyceal distortion, tubular ectasia extending to the margins of the kidneys and small round dots of diminished density (non-opacified cysts?) were noted; and at 7 years of age marked tubular ectasia and large zones of diminished density (which closely resembled the noncommunicating cysts of adult polycystic kidneys) were evident.

Although general conclusions cannot be drawn from the small number of intravenous urograms that have been performed in infants with DPK, the radiographic abnormalities observed cannot be distinguished from those observed in recessively inherited polycystic kidney disease. Clinical, genetic, radiologic and pathologic evidence must be used to determine the type and prognosis of polycystic kidney disease in an affected patient.

Each of our patients with DPK had HPS. The occurrence of HPS in multiple family members is not unusual. Carter and Evans' long-term study of the relatives of 1,239 English children with HPS showed that children of affected parents are at significantly greater risk: about 5% of the sons and 2.5% of the daughters of boy patients and about 20% of the sons and 7% of the daughters of girl patients developed HPS. (The estimated population incidence of HPS is 0.5% of liveborn boys and 0.1% of live-born girls; thus the incidence in the offspring of affected individuals relative to that in the general population of the same sex was 11, 24, 38 and 70 fold greater, respectively.) The incidence in sibs was less than that in offspring, but still many times greater than in the general population [3]. Studies of twins have yielded similar results. In one large study the incidence of HPS in partners of affected twins was 8.6%. The partners of monozygotic (identical) twins were at slightly greater risk than the partners of dizygotic (fraternal) twins [8].

Carter and Evans have concluded that the genetic component in liability for HPS is polygenic and that no single gene makes a major contribution [3]. Inheritance of DPK appears to be due to a single autosomal gene [4]. The association of DPK and HPS in our patients is probably due to chance. However it is possible that the gene that transmits DPK (or a nearby gene on the same chromosome) also carries a portion of the "genetic liability" for HPS.

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E. G. Kassner, M. D.
Professor of Clinical Radiology
Downstate Medical Center (Box 45)
450 Clarkson Avenue
Brooklyn, NY 11203
USA