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ORIGINAL ARTICLE

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A familial case of multicystic dysplastic kidney

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Abstract A familial case of multicystic dysplastic kidney (MCDK) is described. The proband is a one-year-old boy with left MCDK, and his father was also revealed to have unilateral MCDK. The mother had two abortions; the second pregnancy was terminated because of bilateral MCDK of the fetus (Potter anomaly). The two patients and the aborted male fetus did not have any malformations except for MCDK. Thus in this family MCDK occurs as an isolated phenomenon in three individuals within two generations, presumably as a result of autosomal dominant inheritance.

Keywords Multicystic dysplastic kidney · MCDK · Hereditary renal dysplasia · Familial

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Introduction

Multicystic dysplastic kidney (MCDK) is a congenital renal disorder morphologically characterized by the presence of multicysts in the dysplastic kidney(s). Bilateral MCDK causes fatal Potter anomaly. The incidence of unilateral MCDK is reported to be approximately 1 in 4,000 live births [1]. Almost all cases of MCDK are sporadic. No patient with a family history of multicystic kidney disease was reported to the National Multicystic Kidney Registry until 1999 [2].

The primary etiology of MCDK has been believed to be the result of urinary tract obstruction. An early obstruction of the fetal urinary tract (during the first trimester) causes dysplastic evolution of renal tissue as in MCDK whereas later in pregnancy the same obstruction could induce a hydronephrosis with corticomedullary dysplasia [3, 4]. There is, however, another possible means of development of MCDK. A high incidence of genitourinary abnormalities has been reported in patients with MCDK [5]. This suggests disturbance of developmental programs common among the kidneys and other tissues in patients with MCDK.

The occurrence of MCDK in several members of a family has recently been reported [2, 6]. This would support the possibility that the development of MCDK is, at least in part, regulated by genetic factors. In this report we describe a familial case of MCDK in which three individuals within two generations have MCDK.

Case report

The proband is a one-year-old boy who was referred to our department for examination of the kidneys, because antenatal renal ultrasonography indicated multicysts in the left kidney. His prenatal and neonatal history was unremarkable. The ultrasonography revealed several cysts in the left kidney (Fig. 1A) with very mild hydronephrosis of the right kidney (SFU grade I), which improved subsequently. DTPA renography revealed no function in the left kidney. No other anomalies were detected in the genitourinary system. Results from blood examination at 2 months of age were: serum Na, 138 mEq L^{-1}; K, 5.2 mEq L^{-1}; Cl, 103 mEq L^{-1}; BUN, 9.7 mg dL^{-1}; Cr, 0.1 mg dL^{-1}; Alb, 4.1 g dL^{-1}; WBC 7,500 μL^{-1};

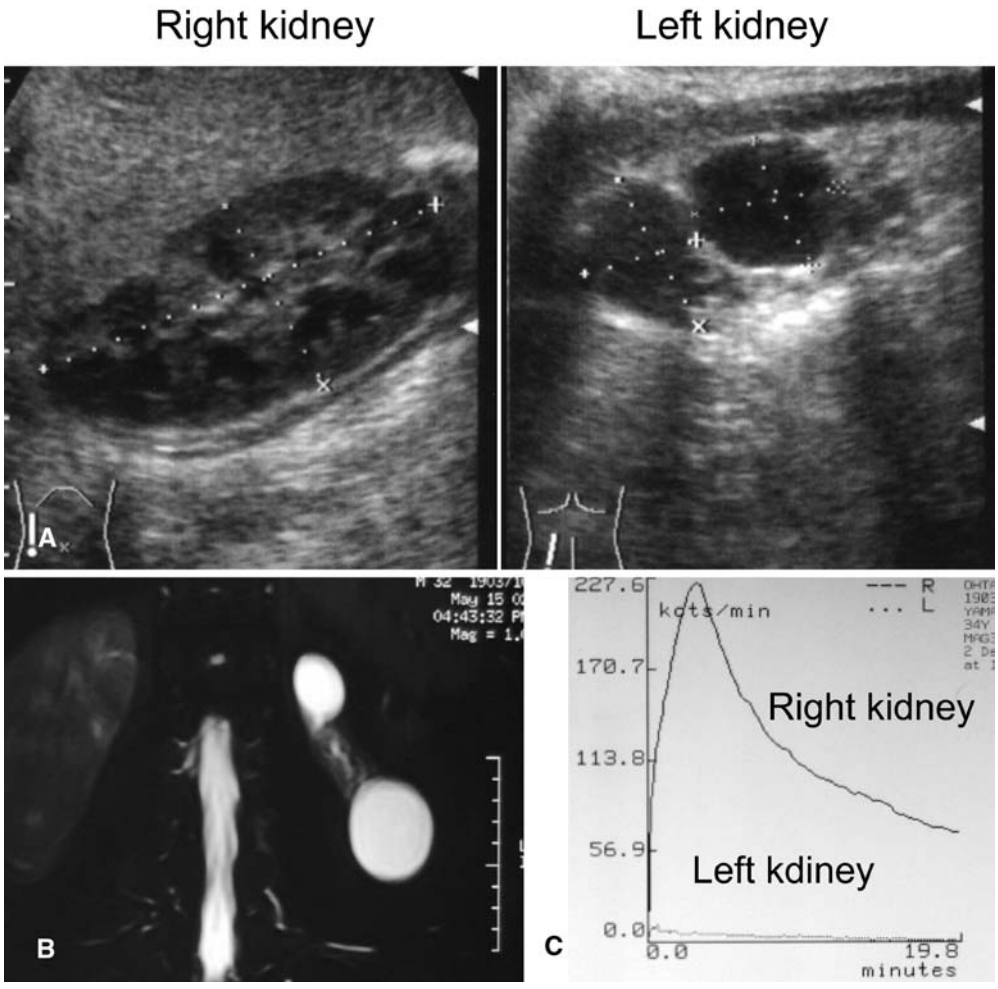

Fig. 1 Renal images and a functional evaluation of the proband and the father. (**A**) Ultrasonography of the proband at the age of 18 months revealed several cysts in the left kidney (*upper right panel*) and normal morphological appearance of the right kidney (*upper left panel*). (**B**) Magnetic resonance imaging of the father revealed dysplastic left kidney with two large cysts. (**C**) DTPA renography of the father showed no function of the left kidney with normal function of the right kidney

Hb 11.4 g dL^{-1}; Plt, 51.8×10^4 μL^{-1}. Urinalysis showed no proteinuria or hematuria, and urine sedimentation was normal. From these observations the diagnosis of left unilateral multicystic dysplastic kidney (MCDK) was made. Any anomalies including those of the eyes, ears, extremities, and visceral organs were not noted. His body weight and height at 8 months were 8.980 g and 73.3 cm, respectively, showing development was normal.

Before the delivery of the proband the mother had two abortions. The first and second pregnancies were terminated at 3 and 5 months, respectively. The cause of the first abortion was unknown. The second pregnancy was accompanied by oligohydramnios and intrauterine growth retardation. Antenatal ultrasonography suggested Potter anomaly of the fetus, and pregnancy was terminated. An autopsy of this fetus revealed bilateral MCDK (Fig. 2): both kidneys were enlarged (left, 3.5 g; right 3.4 g) (Fig. 2A), and light microscopy revealed multicysts in both kidneys (Fig. 2B). The atretic feature of both ureters and bladder in conjunction with oligohydramnios indicated no urine production by the kidneys. This fetus was a male, and no anomalies were noted except for bilateral MCDK.

The family history revealed the presence of MCDK in the father. The existence of multicysts in the unilateral kidney was indicated in his childhood. This time, a magnetic resonance image revealed a dysplastic left kidney with two cysts (Fig. 1B), and DTPA renography revealed no function of the left kidney (Fig. 1C). The right kidney of the father was unremarkable. The mother has no dysmorphism of the kidneys. She manifested proteinurina and hematuria when she was 29 years old; a histological examination revealed IgA nephropathy. The farther and mother are not consanguineous.

The pedigree of this family is depicted in Fig. 3.

Discussion

In this paper we report a familial occurrence of MCDK. In this family two patients and one aborted fetus were revealed to have MCDK. No anomalies indicative of syndromes with renal dysplasia were observed for any of these individuals. Because of the low incidence of sporadic MCDK (1/4,000 births), the occurrence of three MCDK cases in one family strongly suggests the presence of hereditary factor(s). To date, reports of familial cases of MCDK are extremely rare. Through Medline search we identified only two familial case reports of MCDK [2, 6].

In this family, autosomal dominant inheritance is suggested. Although affected members are all male, the disease is transmitted from the father to the offspring and the possibility of X-linked inheritance is denied. A possibility that the Y chromosome contains the gene(s) responsible for the development of MCDK could not be excluded, although candidate genes on the Y chromosome closely related to the development of the kidneys and urinary tract system have not been reported.

Hereditary renal adysplasia (HRA) is a clinical entity, described for the first time by Buchta [7], in which the agenesis and/or dysplasia of the kidneys with variable expressions is identified in the members of family. HRA

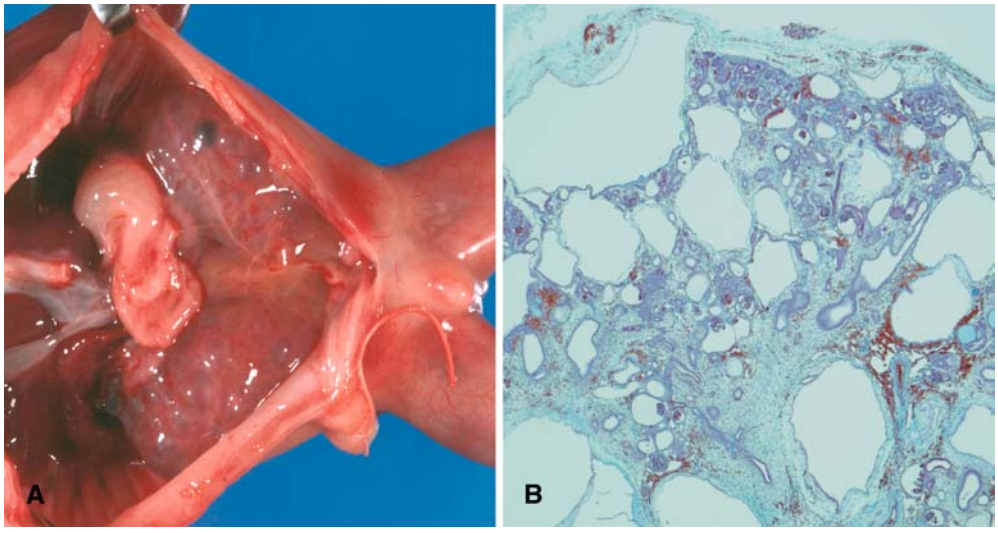

Fig. 2 Macroscopic and microscopic observations of aborted fetus with MCDK. (**A**) Both kidneys were enlarged and numerous cysts can be observed from the surface of the kidneys. The external genitalia have normal male appearance. No abnormalities were detected in the other organs. (**B**) Light microscopy revealed numerous cysts in the cortex and medulla. Note nephrogenic parenchyma is reduced

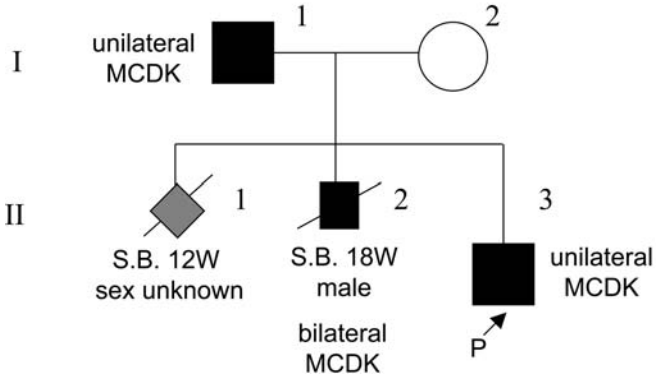

Fig. 3 Pedigree of the family. The father (I-1) and his son (II-3) have left unilateral MCDK. The first and second pregnancies of the mother were terminated at gestational ages of 12 and 18 weeks, respectively. The second aborted fetus (II-2) was diagnosed as having bilateral MCDK by autopsy

has an autosomal dominant trait of inheritance with incomplete penetrance and variable expressions [8]. Penetrance has been reported to be between 50% and 90%. To date many cases of HRA have been reported, and even occur in three generations [9]. From an autopsy of a case of HRA in which a balanced 6p/19q translocation was noted, Moerman and colleagues proposed that one of the loci responsible for HRA occurs in chromosome 6p [10]. Squiers et al. reported a case of unilateral multicystic dysplasia in an infant whose mother and maternal aunt had unilateral renal agenesis [11]. This report suggests that multicystic renal dysplasia can occur as a rare type of HRA. The occurrence of only MCDK in three members of this family suggests a distinct clinical entity. If this family is a specific case of HRA, it should comprise a subgroup in heterogeneous HRA. The conclusion should await further studies.

There have been several reports of genes related to the development of cystic lesions in the kidneys. PAX2 is one of the candidates responsible for cyst formation. In a unilateral ureteric obstruction model in fetal sheep, cystic epithelial cells express PAX2 [12]. Dysplastic tubules maintain a high rate of proliferation postnatally and PAX2 is expressed in these epithelia [13]. Thus the persistent expression of PAX2 occurs in a variety of renal cystic and dysplastic diseases, and correlates with continued proliferation of renal epithelial cells. The unregulated expression of PAX2 should be a key determinant in renal cystic diseases [14]. PAX2 mutations lead to urological abnormalities and renal failure whereas the overexpression of PAX2 in the kidneys of mice causes multifocal microcystic tubular dilatation [15]. BCL2, a protein preventing apoptosis, has been shown to be expressed ectopically in dysplastic kidney epithelial cells [13], and BCL2-knockout mice revealed renal hypoplasia due to mesenchymal apoptosis [16]. IGF-II and IGFBP-2 were overexpressed in abnormal tissue in the kidneys, and IGF-II gene expression was localized to mesenchyme. IGFBP-2 mRNA was found to be expressed exclusively in the cyst epithelia of all cysts whereas IGFBP-3 mRNA was absent from these epithelia [17]. Because genetic disorders of these genes should cause clinical manifestations other than MCDK, it is unlikely that one of these genes is the cause of the familial MCDK described in this study. Genetic misregulatory mechanisms specific to the kidneys might underlie familial MCDK.

To establish a distinct clinical entity, i.e. familial MCDK, in which only MCDK occurs as the renal manifestation, accumulation of information on cases similar to this case is essential. Because most cases of MCDK are sporadic and do not usually have apparent clinical manifestations, it is difficult to identify other affected members in the family. Because screening for MCDK is easily performed using ultrasonography, renal evaluation of relatives, at least parents and siblings, is encouraged. Accumulated knowledge would identify the clinical entity, and collaboratory studies would eventually lead to understanding of the genetic basis of MCDK.

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