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Urological anomalies in children with renal agenesis or multicystic dysplastic kidney

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Abstract. This study aimed to determine the frequency of associated urological abnormalities in children with unilateral renal agenesis (RA) or multicystic dysplastic kidney (MCDK). In total, 38 children (10 girls, 28 boys) were studied: 21 with RA and 17 with MCDK. In 14 children (37%) anomalies of the urinary tract were suspected prenatally in ultrasound studies. In the remaining 24 children the diagnosis of RA/MCDK was made postnatally: in 13 (34%) in the first 7 days of life, in 11 (29%) at the age of 8 days to 34 months, mean 10.6 ± 8.05 months. Voiding cystourethrography was done in 36 (95%) children, the isotopic ^{99m}Tc-EC/DMSA scan of the kidney in 29 (67%), and urography in 8. Urological anomalies were present in 11 (29%) children: in 7 (33%) with RA and in 4 (24%) with MCDK. Vesicoureteral reflux was diagnosed in 8 children: grade II in 4, III in 3, and IV in 1 (in 1 child to duplicated, in 1 to ectopic kidney); ureterovesical junction obstruction in 2 (9.5%); and ureteropelvic junction obstruction in 1 (4.8%). Among them, 2 children demanded surgery on the contralateral urinary tract: pyeloplasty in 1, antireflux procedure in 1; while 9 children were treated conservatively. Compensatory hypertrophy of the contralateral kidney was found in 90% of children. Thus due to an increased risk of pathological changes in the single functioning kidney, lifelong nephrological care is recommended in patients with unilateral RA/MCDK.

Key words: multicystic dysplastic kidney, renal agenesis, urological anomalies.

Introduction

Kidney malformations develop during organogenesis, between 4 and 12 weeks of fetal life. Renal agenesis (RA) is a usually unilateral congenital complete lack of kidney tissue. This anomaly results from abnormal mesonephros differentiation, or rarely from abnormal development of metanephros. Unilateral RA occurs with a prevalence of 1:500 to 1:3200 live births and is one of the most commonly diagnosed congenital defects of the urinary tract (Parikh et al. 2002).

Multicystic dysplastic kidney (MCDK) is characterized by replacement of normal kidney tissue with numerous cysts, with lack of normal renal cortex and pyelocalyceal system, and hypoplastic or completely obstructed ureter. This malformation results from abnormal metanephros differentiation, probably due to disturbed connection of ureteric bud with renal blastema and abnormal division at the stage of metanephros (Abidari et al. 2002). Unilateral MCDK occurs in 1:2400 to 1:4300 live births (Belk et al. 2002; Feldenberg and Siegiel 2000) and is one of the most common causes of congenital abdominal tumors in children (Miller et al. 2004; Ylinen et al. 2004).

Prenatal ultrasound scans detect 77–88% cases of MCDK (Ylinen et al. 2004; Selzman and Elder 1995), while RA is rarely revealed prenatally (Kaneyama et al. 2004). Both malformations are more commonly diagnosed in boys (Cascio et al. 1999; John et al. 1998) and usually found on

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the left side (Kaneyama et al. 2004; Ranke et al. 2001), but they may also be bilateral (Feldenberg and Siegiel 2000; Parikh et al. 2002). Cases of familial occurrence of MCDK and RA suggest that both anomalies are genetically conditioned (Belk et al. 2002; Doray et al. 1999; Morse et al. 1987). Unilateral RA/MCDK occurs as an isolated defect or is accompanied by other urological anomalies. Most commonly found additional abnormalities in patients with RA/MCDK include vesicoureteral reflux (VUR), ureteropelvic junction (UPJ) obstruction, and ureterovesical junction (UVJ) obstruction (Abidari et al. 2002; Kaneyama et al. 2004; Ylinen et al. 2004). The aim of the present study was to assess the frequency of urological anomalies in children with unilateral RA/MCDK.

Material and methods

We retrospectively assessed 38 children (10 girls and 28 boys), including 21 patients with unilateral RA and 17 patients with unilateral MCDK, diagnosed in the Department of Pediatrics and Nephrology at the Medical University of Warsaw between January 1997 and December 2004. The age of children admitted to our center ranged from 1 day to 34 months (mean 3.7 ± 1.7 months). Data from long-term follow-up were available for 29 patients, including 16 patients with RA and 13 patients with MCDK. Mean duration of follow-up was 27±21.7 months (range 1–85 months).

Urinary tract malformation was suspected in prenatal ultrasound tests in 14 (37%) children, including 7 children with MCDK, 6 children with dilated pyelocalyceal system (PCS), and 1 child with a fluid-containing space in the small pelvis. Ultrasounds performed soon after birth revealed RA in 4 children and MCDK in 10 children. In 13 (34%) children, RA/MCDK was diagnosed (in 9 and 4 children, respectively) by ultrasound tests performed in the neonatal ward within the first 7 days of life. Indications for ultrasounds included prematurity in 4 cases, intrauterine infection in 4 cases, abdominal tumor in 1 case, routine ultrasound in 3 cases, and a congenital heart defect in 1 case. In the remaining 11 (29%) children, RA/MCDK was diagnosed (in 8 and 3 children, respectively) at the age ranging from 8 days to 34 months (mean 10.6 ± 8.05 months). Indications for ultrasound included urinary tract infection (UTI) in 5 cases, cryptorchidism in 1 case, and incidental study in 5 cases. Evaluation of family history revealed unilateral lack of kidneys in 2 fathers of patients with RA, but not all parents were subjected to ultrasound tests.

Abdominal ultrasounds were performed in all children by using a Philips HDI 3000 scanner with 4–7 MHz bandwidth transducer (Convex). The tests were repeated every 3–6 months. Kidney size was evaluated by using body-length-based nomograms according to Dinkiel et al. (1985). In addition, 95% of patients underwent voiding cystourethrography (VCUG): at the age of 4–6 weeks in the children with RA/MCDK diagnosed at birth or soon after birth, and soon after the diagnosis in the remaining children. VUR was graded according to an international classification. Follow-up VCUG was performed after 12–18 months.

Renal scintigraphy was performed with 2 tracers labeled with technetium-99m, dimercaptosuccinic acid (^{99m}Tc-DMSA) and L,-L-ethyleno-1-dicysteine (^{99m}Tc-EC). ^{99m}Tc-DMSA renal scanning was performed to confirm RA/MCDK and evaluate renal scarring in the contralateral kidney. ^{99m}Tc-EC renal scanning was indicated when anteroposterior renal pelvis diameter assessed by ultrasound was > 10 mm and a urodynamically significant ureter obstruction was suspected. Before the year 2000, only ^{99m}Tc-EC renal scanning was performed due to the unavailability of ^{99m}Tc-DMSA. Abnormal tracer uptake was evaluated by using the classification suggested by Goldraich and Goldraich (1984).

Intravenous urography was indicated when ureterocele and/or duplex kidney and/or a urodynamically significant ureter obstruction was suspected in ultrasound tests or ^{99m}Tc-EC renal scintigraphy. Blood pressure was measured in all children; additionally serum urea and creatinine measurements, as well as urinalysis and urine culture were performed at baseline and periodically repeated thereafter. The presence of urological anomalies in children with RA/MCDK was an indication for antimicrobial prophylaxis (with nitrofurantoin or trimethoprim).

Results

Left-sided RA/MCDK was diagnosed in 22 children (13 and 9 patients, respectively), and right-sided RA/MCDK was diagnosed in 16 children (in 8 patients each). Abdominal ultrasound scans performed on admission to our center revealed abnormalities contralateral to RA/MCDK in 9 children (24%): dilated PCS in 8 children

(with ureter dilatation in 3 children, duplicated collecting system in 1 child, megaureter with MCDK in 1 child), and renal ectopia in 1 child. In 2 children the dilated PCS contralateral to RA/MCDK was found during the follow-up. VCUG was performed in 36 (95%) children aged 0.1–35 months (mean 4.9 ± 7.4 months), and the remaining 2 children did not show up for the study. Renal scintigraphy was performed in 29 (76%) children (^{99m}Tc-DMSA in 20 children, ^{99m}Tc-EC in 4 children, ^{99m}Tc-DMSA and ^{99m}Tc-EC in 5 children), and intravenous urography in 8 children. Urological anomalies were present in 11 children (29% of the total), including 7 (33%) of the patients with RA and 4 (24%) of those with MCDK (Table 1).

Table 1. Urological anomalies in 38 children (10 girls and 28 boys) with unilateral renal agenesis (RA) or multicystic dysplastic kidney (MCDK) diagnosed in the Department of Pediatrics and Nephrology at the Medical University of Warsaw in 1997–2004

Type of anomaly	RA n = 21 (19)[1]	MCDK n = 17 (17)[1]	Overall n = 38 (36)[1]
Vesicoureteral reflux	4 (19%)	4 (23.5%)	8 (21%)
– grade II	2	2[2]	4
– grade III	1	2	3
– grade IV	1	–	1
– to an ectopic kidney	–	1	1
– to a duplex kidney	–	1	1
Ureterovesical junction obstruction	2 (9.5%)	–	2 (5.3%)
Ureteropelvic junction obstruction	1 (4.8%)	–	1 (2.6%)

[1]Number of children who underwent VCUG is given in brackets; [2]One child with bilateral VUR

Other non-urological malformations were found in 16 (42%) children with RA/MCDK, including congenital heart disease in 8 children (persistent foramen ovale in 4 patients, atrial septal defect in 2 patients, persistent ductus arteriosus in 1 patient, and tetralogy of Fallot in 1 patient), syndactyly in 2 children, and single cases of ovarian cyst, cryptorchidism, fistula of the auricular concha, large hemangioma within the chest wall, and umbilical hernia.

Antimicrobial prophylaxis was applied in 12 (32%) children. Indications for antimicrobial prophylaxis included VUR in 8 children, UVJ obstruction in 2 children, UPJ obstruction in 1 child, and dilated PCS without urodynamically significant ureter obstruction in 1 child. UTI was diagnosed in 12 (32%) children with RA/MCDK, including 4 children with coexisting urological anomalies (VUR in 3 children and UPJ obstruction in 1 child).

Among the 11 children with urological anomalies accompanying RA/MCDK, 2 children underwent invasive therapeutic procedures: ureteropyeloplasty was performed in a 3-month- old child with RA and UPJ obstruction, whereas a 36-month-old child with MCDK, bilateral grade II VUR and recurrent UTIs, was treated with subureteral polytetrafluoroethylene (Teflon) injections at the UVJ contralaterally to MCDK. The remaining 9 children with coexisting urological anomalies were treated conservatively. Duration of their follow-up ranged from 2 to 18 months (mean 8.9 ± 6.8 months). Among the 7 children with VUR who were treated medically, follow-up VCUG was performed in 2 children after 12 months, showing resolution of grade II VUR in a child, and regression from grade III to grade II VUR in another child. No follow-up VCUG was performed prior to study termination in the remaining 5 children with VUR who were treated medically. Renal scarring (grade 2) in ^{99m}Tc-DMSA/EC was found in 7 (24%) children aged 3 weeks to 36 months (mean 8.7±12.9 months), including 5 children with urological anomalies (grade II–IV VUR in 4 children, UPJ obstruction in 1 child). UTI occurred in 3 of these children.

Among 17 children with MCDK, 6 underwent nephrectomy at the age of 4–55 months (mean 28.4 ± 18.9 months). The indication for nephrectomy in 5 children was no decrease in the dysplastic kidney size in serial ultrasound studies. In 1 child, the indication for nephrectomy at the age of 4 months was MCDK coexisting with megaureter occupying most of the abdominal cavity. The diagnosis of MCDK was confirmed by histopathology in all patients who underwent nephrectomy. Four children with MCDK did not show up for the follow-up visits, and the remaining 7 children were followed-up for 1–55 months (mean 19.9 ± 19.6). Atrophy of the dysplastic kidney was found in 1 child at the age of 6 months, and the dysplastic kidney size decreased in 6 children.

Among 29 children with long-term follow-up, compensatory hypertrophy of the contralateral kidney was found in 26 (90%) children. No evi-

dence of hypertrophy was found in only 1 patient with RA and 2 patients with MCDK, and no coexisting anomalies in the urinary tract. In 12 children compensatory hypertrophy was noted in an ultrasound scan after birth. Blood pressure values, serum urea, creatinine and urinalysis were within the normal range in all children.

Discussion

Urological anomalies have been estimated to occur in 48–65% of subjects with RA (Cascio et al. 1999; Kaneyama et al. 2004) and in 17–43% of subjects with MCDK (Kaneyama et al. 2004; Kuwertz-Broeking et al. 2004; Miller et al. 2004; Ranke et al. 2001). In the present study, urological anomalies were also more frequent in children with RA (33%) than in children with MCDK (24%).

In our study population, non-urological malformations were diagnosed in 42% children; cardiac and skeletal anomalies predominated. The association of RA/MCDK with other non-urological malformations, such as cardiac, gastrointestinal, genital, skeletal, has been well described (Cascio et al. 1999; Ranke et al. 2000). According to Kaneyama et al. (2004), the frequency of these anomalies is significantly higher in children with RA (53%) than with MCDK (13%). RA may be part of a syndrome of multiple abnormalities and chromosome aberrations can be present (Moerman et al. 1994).

The most commonly found developmental abnormality in children with RA/MCDK is VUR. The frequency of VUR is 28–41% in patients with RA (Cascio et al. 1999; Kaneyama et al. 2004) and 5–25% in patients with MCDK (Kuwertz-Broeking et al. 2004; Miller et al. 2004). Both contralateral and ipsilateral VUR may occur in patients with MCDK (Feldenberg and Siegiel 2000). The majority of children with RA had severe (grade IV-V) VUR (Cascio et al. 1999), while mild (grade I–II) or moderate (grade III) VUR was found in most patients with MCDK, with a tendency to resolve spontaneously (John et al. 1998; Kuwertz- Broeking et al. 2004; Miller et al. 2004; Selzman and Elder 1995). VUR in children with MCDK rarely requires surgical correction. Subureteral injections of teflon or other agents at the UVJ or ureter transplantation may be necessary in children with recurrent UTIs (Miller et al. 2004). Among our patients, grade II–IV VUR was diagnosed in 21% children, including 19% of children with RA and 23.5% of children with MCDK. Invasive therapeutic procedures were necessary in a child with bilateral grade II VUR and recurrent UTIs.

Long-term sequelae of VUR are a subject of debate. Miller et al. (2004) believe that VUR does not pose any significant threat to the solitary kidney growth in the first years of life. Those authors did not show any significant difference in the annual kidney growth in relation to the grade of VUR in patients followed up for more than 5 years. Similarly, John et al. (1998) found no difference in the extent of compensatory kidney hypertrophy in patients with or without urological anomalies, suggesting good growth potential of kidneys with developmental abnormalities. In contrast, Abidari et al. (2002) found disturbed growth of a single functioning kidney in 18.7% of patients with MCDK, including 33.3% of patients with and 13% of patients without contralateral kidney anomalies. In our study, compensatory hypertrophy of the contralateral kidney was found in 90% children with RA/MCDK in a long-term follow-up.

Most authors believe that VCUG is indicated in all patients with a single functioning kidney due to the risk of renal scarring resulting from acute pyelonephritis and/or reflux nephropathy (Kaneyama et al. 2004; Ranke et al. 2001; Selzman and Elder 1995). In patients with renal developmental abnormalities diagnosed prenatally or shortly after birth, VCUG is usually performed at the age of 4–6 weeks (John et al. 1998; Ylinen et al. 2004). As most cases of VUR resolve spontaneously by 12–33 months of follow-up, additional VCUG is suggested at the age of 2–3 years (Miller et al. 2004; John et al. 1998). Some authors question the need for routine VCUG in all children with RA/MCDK due to the mostly mild grade of VUR and low risk of scarring in the contralateral kidney (Feldenberg and Siegiel 2000). Kuwertz-Broeking et al. (2004) suggested that indications for VCUG include PCS and/or ureter dilatation found by ultrasounds, sings of dysplasia in the contralateral kidney, and symptomatic UTI.

Other urological anomalies in patients with RA/MCDK are much less common than VUR. UPJ obstruction is diagnosed in 6–7% of children with RA (Cascio et al. 1999; Kaneyama et al. 2004) and 6.7–15% children with MCDK (John et al. 1998; Miller et al. 2004), and UVJ obstruction in 11–18% (Casio et al. 1999, Kaneyama et al. 2004) and 0–9% of children (John et al. 1998, Kaneyama et al. 2004), respectively. Some children with UPJ or UVJ obstruction require surgical

intervention (Cascio et al. 1999; Kuwertz-Broeking et al. 2004). In our study group, UPJ or UVJ obstruction was diagnosed only in 3 patients with MCDK. One patient required surgical correction at the age of 3 months.

According to the literature, the rate of UTIs in patients with RA/MCDK is 5–28% (Belk et al. 2002; Cascio et al. 1999; Feldenberg and Siegiel 2000; Miller et al. 2004). UTIs are more common in children with RA/MCDK and other coexisting anomalies in the urinary system. Feldenberg and Siegiel (2000) reported a low (only 5%) risk of UTI in patients with MCDK and no other coexisting anomalies in the urinary system. The risk is increased to 28% in children with bilateral MCDK, duplex or dilated PCS, or neurogenic bladder. Among our patients, UTI was diagnosed in 32% of children, including only 4 patients with coexisting urological anomalies.

Diagnosis and treatment of MCDK changed significantly in the last 2 decades. In the past, MCDK was diagnosed after birth when an abdominal tumor was palpated, and nephrectomy was the common therapeutic option (Farnham et al. 2005; John et al. 1998; Ylinen et al. 2004). This approach to management has been affected by the reports on numerous cases of spontaneous regression of MCDK. Elective nephrectomies in patients with MCDK were discontinued in the late 1980s (Kuwertz-Broeking et al. 2004). Recent studies suggest that 20–52% of dysplastic kidneys undergo atrophy within 3–144 months (Belk et al. 2002; Miller et al. 2004; Rabelo et al. 2005; Ylinen et al. 2004), and compensatory hypertrophy develops in 43–100% of normal contralateral kidneys (Abidari et al. 2002; Feldenberg and Siegiel 2000; Kuwertz-Broeking et al. 2004). Until recently it has been thought that the compensatory hypertrophy does not occur during fetal life due to the presence of functioning placenta. However, autopsy and ultrasound studies suggest that the compensatory hypertrophy already occurs in the prenatal period and continues later in childhood (John et al. 1998; Miller et al. 2004). In our study group, atrophy of the dysplastic kidney was found in 1 child after 6 months of follow-up. Compensatory hypertrophy of the contralateral kidney was found during long-term follow-up in 90% of patients with RA/MCDK.

Outcomes in patients with bilateral MCDK or other coexisting anomalies in the urinary system may be more adverse and include recurrent UTIs and development of hypertension or chronic renal failure (Feldenberg and Siegiel 2000; Kuwertz-Broeking et al. 2004). Late sequelae of MCDK, i.e. malignancies (Wilms tumor in children and renal cell carcinoma in adults), hypertension of renal parenchymal disease, and chronic renal failure occur rarely and should not influence the decision to proceed with nephrectomy (Ylinen et al. 2004). Data from the United States show that the risk of Wilms tumor is 1:10 000 in the general pediatric population, compared with 1:1000 to 1:3300 in children with MCDK (Beckwith 1992). Beckwith (1997) reported that the risk of Wilms tumor developing in a dysplastic kidney was 1:2000, with the rate among children with MCDK estimated at 1:4300. The risk of hypertension and/or chronic renal failure in patients with MCDK is believed to be related to the development of scarring in the contralateral kidney and not to the presence of the dysplastic kidney itself. Renal scarring in patients with MCDK may result from hypoplasia or dysplasia of the contralateral kidney, reflux nephropathy, obstructive uropathy or late postinflammatory lesions complicating acute pyelonephritis (Farnham et al. 2005; Kuwertz-Broeking et al. 2004). In the present study, evidence of renal scarring was found in radionuclide imaging in 24% of children with RA/MCDK, including 5 children with coexisting urological anomalies. Blood pressure values and serum urea and creatinine were normal in all these children.

It is currently believed that patients with prenatal or postnatal diagnosis of MCDK should be initially managed medically. Indications for nephrectomy may include a very large dysplastic kidney resulting in disturbed breathing or intestinal function in the neonatal period, or a dysplastic kidney containing areas of solid tissue with a tendency to increase in size in serial ultrasound evaluations during long-term follow-up (Kuweretz-Broeking et al. 2004). There are no well- documented long-term studies of MCDK. Lack of a kidney in an adult may result from both congenital RA and atrophy of MCDK. Argueso et al. (1992) found renal dysfunction in 13% and hypertension in 47% of adult patients with unilateral RA.

Both RA and MCDK can be sporadic or familial (Doray et al. 1999; Belk et al. 2002). A review of the literature on familial RA suggests that hereditary renal adysplasia (severe renal dysplasia or agenesis) (OMIM 191830) is more common than previously supposed and may account for most recurrences of bilateral RA (McPherson et al. 1987). Non-syndromic RA and dysplasia are pathogenetically related and often inherited as an

autosomal dominant trait with incomplete penetrance and variable expression (Moerman et al. 1994; Doray et al. 1999; McPherson et al. 1987). Many authors recommend an ultrasound study of the kidney in all family members with a history of unilateral or bilateral RA in the family to detect the presence of asymptomatic anomalies of the genitourinary system. Morse et al. (1987) and McPherson et al. (1987) suggest that the risk of recurrence of severe renal adysplasia is very high. Multicystic dysplastic kidney can be familial but is most commonly a sporadic anomaly, so formal screening of relatives is not recommended (Belk et al. 2002). In our study 2 cases of unilateral RA in the fathers were detected among parents of children with RA, but not all parents had ultrasound examination.

Conclusions

Due to an increased risk of pathological changes in the single functioning kidney, lifelong nephrological care is recommended in patients with unilateral RA/MCDK. This knowledge is important not only for nephrologists but also for clinical geneticists counseling the families.

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