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BRIEF REPORT

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Urinary tract infections, VUR, and autosomal dominant polycystic kidney disease

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Abstract This case series of 16 patients with autosomal dominant polycystic kidney disease (ADPKD) describes 4 girls who presented with a urinary tract infection (UTI). Radiological evaluation revealed that each of these patients had vesicoureteral reflux (VUR). The frequency of VUR was significantly higher in the patients with ADPKD compared with otherwise healthy age-matched children who underwent testing after a UTI (100% versus 15%, $P<0.002$). These findings suggest VUR is an associated somatic anomaly in children with ADPKD that may contribute to the occurrence of UTI in this patient population.

Keywords Autosomal dominant polycystic kidney disease · Urinary tract infection · Vesicoureteral reflux

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is a relatively frequent hereditary condition, affecting 1 in every 400–1000 live births [1]. Patients with ADPKD are usually asymptomatic until the 4th or 5th decade, when they begin to show signs of kidney disease and renal insufficiency [2]. Occasionally, signs and symptoms, such as hematuria, back pain, and hypertension, appear during childhood [3].

Urinary tract infections (UTI) are estimated to occur in 30%–50% of individuals with ADPKD [2, 3]. The infections are more prevalent in females and are usually caused by gram-negative enteric bacteria [2, 3]. However, there has been no prior documentation of an association of vesicoureteral reflux (VUR) with ADPKD. In this report, we present 4 children with ADPKD and UTI who were shown to have VUR.

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Case reports

Patient 1

A 2-year-old Caucasian girl presented with an *Escherichia coli* UTI. Renal ultrasonography revealed multiple small cysts in both kidneys consistent with ADPKD, but no hydronephrosis. The family history included ADPKD in the father, the paternal grandfather, and a paternal great uncle. A voiding cystourethrogram (VCUG) showed grade III/II VUR on the right and left sides, respectively. The patient was started on trimethoprim/sulfamethoxazole prophylaxis. The VUR resolved within a year and antibacterial prophylaxis was discontinued.

Patient 2

A 2.5-year-old Caucasian girl initially presented with a febrile UTI. Renal ultrasonography revealed two cysts in the right kidney but none in the left. There was no hydronephrosis. The VCUG revealed left grade II VUR. The mother and her maternal grandfather were known to have ADPKD. There have been no subsequent infections on nitrofurantoin prophylaxis.

Patient 3

A 6-week-old Caucasian girl, the sibling of patient 2, who was already known to have ADPKD, presented with a febrile UTI. Abdominal computed tomographic (CT) scan showed normal-sized kidneys with multiple cysts bilaterally. A VCUG revealed left grade I VUR and no hydronephrosis. On amoxicillin prophylaxis, there were no subsequent UTIs.

Patient 4

A 6-year-old Caucasian girl presented with gross hematuria, low back pain, and dysuria. A urine culture was positive for *E. coli*. Renal ultrasonography and an abdominal CT scan both showed

enlarged kidneys (right 9.0–9.5 cm, left 11.0–12.0 cm) with multiple cysts bilaterally consistent with ADPKD but no hydronephrosis. There was no family history of ADPKD. CT scans of the kidneys of the parents, both of whom were over 30 years of age, and renal ultrasonography of the brother and sister were normal except for the presence of a single small cyst in the brother's right kidney. A VCUG of the patient showed left grade II VUR. There have been no UTIs since the first episode while on nitrofurantoin prophylaxis.

Methods

A chart review was performed to identify all children seen at Schneider Children's Hospital (SCH) between 1985 and 2001 in whom the diagnosis of ADPKD was made. A child was considered positive for ADPKD if the family history indicated the presence of other affected individuals and by renal sonography if more than one cyst was present in a single kidney, or if one or more cysts were present in both kidneys [4, 5]. Autosomal recessive polycystic kidney disease was excluded based on serial radiological studies, the absence of bilateral renal enlargement with diffuse small cysts, and the absence of evidence of hepatic fibrosis [6]. The following information was recorded: demographic data including age at presentation, gender, and ethnicity, the mode of presentation, method of diagnosis, disease management, and clinical status at most recent visit.

The results of all VCUGs that were performed on children between 0 and 6 years old who did not have ADPKD and who were referred to SCH for evaluation of UTI during the 2-year period from 2000 to 20001 were compiled. The indications for a VCUG in these children were (1) any UTI in a child less than 3 years of age; (2) two or more UTI; or (3) unusual clinical features, such as an abdominal mass, or hypertension. The VCUGs were performed, according to standard techniques, within 2–4 weeks of the UTI after confirmation that the urine was sterile.

The difference in proportions between specific groups was evaluated with the Fisher exact test and the results were considered significant if the P value was less than 0.05.

Results

The diagnosis of ADPKD was made during the study period in 16 children, including two pairs of siblings. The group comprised 8 females and 8 males, all Caucasian, who initially presented between the ages of 6 weeks and 18 years (mean 9 years). Of the 16 children, 4, including one pair of siblings, were diagnosed following a presentation with a UTI. A complete review of the medical records indicated that none of the other 12 children developed a UTI during follow-up.

All 4 children who presented with a UTI were Caucasian and female. They were initially evaluated between the ages of 6 weeks and 6 years, with a mean age of 2.5 years. Each of the 4 girls with a UTI had a VCUG and all had VUR ranging from grade I to III and affecting at least one kidney. A VCUG was not performed in the other 12 children with ADPKD who did not have a UTI.

All 4 of the girls with ADPKD and VUR were maintained on antibacterial prophylaxis and remained infection free. Bacterial prophylaxis was discontinued in 1 child following resolution of the VUR. At their most-recent visit, all 16 children, including the 4 with a UTI, were doing well clinically. In the latter group of children with ADPKD and VUR, the length of follow-up ranged from 1 to 7 years (mean 2.8 years). All patients were growing normally and had normal blood pressure levels without medication. None of the patients had impaired renal function, regardless of whether or not they had a UTI.

A chart review of children 6 years and younger referred for evaluation of UTI in 2000–2001 indicated that a total of 34 VCUGs were performed. Five of the tests were positive for VUR in this unselected group of patients. The yield of positive VCUGs was significantly higher in the children with ADPKD and UTI, 4 of 4, compared with 5 of 34 in the otherwise healthy children with UTI ($P<0.002$).

Discussion

We reviewed 16 children with ADPKD and specifically focused on the 4 cases where the child experienced at least one UTI. The percentage of children with a UTI (25%) is similar to previous reports in adults and children [2, 3]. Earlier studies of children with ADPKD suggested that VUR was the cause of UTI in this population, rather than cyst rupture or other parenchymal problems based on the etiological role of enteric Gram-negative bacteria and the predominance of infections in young females. Our results, in which 4 girls with ADPKD and UTI had radiographic evidence of VUR, are the first confirmation of the role of VUR in the pathogenesis of UTI in this specific group of children.

The percentage of children with UTI and ADPKD who had a positive VCUG (100%) was significantly higher than in children with UTI who did not have ADPKD (15%). It is interesting to note that the positive yield of screening VCUG in the children with a UTI but who did not have ADPKD was somewhat lower than the 25%–40% rate observed in previous clinical studies [7]. Given the presence of two potential causes for renal scarring in the growing kidney in children with ADPKD and UTI and the ease of preventing UTI with antibiotics, it would seem advisable for clinicians to perform a VCUG in any child with ADPKD who has a UTI.

It is tempting to speculate why children with ADPKD have VUR and an increased risk of UTI. One explanation may be the structure and function of polycystin, the protein product of the *PKD1* gene. While the function of polycystin remains unknown, it is widely distributed in the body and is present to varying degrees in arterial smooth muscle [8]. Its deposition in smooth muscle may contribute to the vascular lesions seen in patients with ADPKD [8, 9, 10]. In small studies of patients with ADPKD and intracranial aneurysms or aortic dissections, polycystin was demonstrated in the disrupted muscle tissue of the weakened vessel walls [8]. Polycystin is also present in large quantities in the fetal kidney and ureteric bud. In normal adults, the protein is downregulated, but this does not occur in patients with ADPKD [9]. Given the range of distribution of polycystin, it is

conceivable that it is present at the vesicoureteral junction, and that dysfunction in the protein contributes to the development of VUR and the subsequent risk of UTI. Immunohistochemical studies of the bladder and ureteral tissue from patients with ADPKD are needed to clarify this issue.

We acknowledge that our case series is too small to make a definitive statement about the prevalence of VUR in children with ADPKD. There was no clinical indication to perform a VCUG in the children with ADPKD who did not have a UTI. Therefore, we are unable to comment on the incidence or role of VUR in all patients with this hereditary kidney disease. Moreover, based on the findings in the 4 children who had a UTI, it is premature to make a broad recommendation to perform VCUG in children with ADPKD because the standard of care during radiological assessment after a UTI in childhood varies from center to center and is an area of much controversy. However, the high frequency of VUR in this discrete group of patients who had a UTI is striking and warrants further investigation to determine the incidence of this urological abnormality in children with ADPKD.

In summary, this case series presents 4 children with ADPKD out of a cohort of 16 patients who presented with a UTI and who had concomitant VUR. The frequency of VUR in the girls with ADPKD was significantly higher than in otherwise healthy children who suffered a UTI. Polycystin, the protein encoded by *PKD1* and expressed in smooth muscle, may play a role in the development of VUR in ADPKD. We recommend that pediatric nephrologists consider an evaluation for VUR in all children with ADPKD who experience a UTI. Continued investigation in this area will help determine the frequency and scope of any association between ADPKD and VUR in children with and without UTI and the clinical relevance of this urinary tract anomaly under these specific circumstances.

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