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ORIGINAL ARTICLE

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Clinical course and outcome for children with multicystic dysplastic kidneys

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Abstract The purpose of this study was to evaluate the clinical course and outcome for children with multicystic dysplastic kidney (MCDK) disease and to non-invasively predict which of these patients are at significant risk for developing urinary tract infection (UTI) and renal insufficiency. Patients were divided, on the basis of postnatal physical examination and renal ultrasonography, into simple or complex MCDK. Simple MCDK was defined as unilateral renal dysplasia without additional genitourinary (GU) abnormalities. Complex MCDK included patients with bilateral renal dysplasia or unilateral renal dysplasia with other GU abnormalities. The designation as simple or complex MCDK was independent of reflux, since routine voiding cystourethrography (VCUG) was not performed. The charts of all patients with the diagnosis of MCDK disease seen from August 1995 to March 1999 at Yale University School of Medicine were examined to determine: (1) if UTI had occurred and (2) the level of renal function at last follow-up. Thirty-five patients were evaluated: 28 (80%) patients had unilateral MCDK, 7 (20%) were bilateral, and 14 (40%) had associated GU anomalies. Overall, 21 patients had unilateral MCDK without GU abnormalities (simple MCDK), while 14 had complex MCDK. The final outcome for patients with simple MCDK was quite good, with normal renal function and compensatory hypertrophy of the contralateral kidney in all patients. Although the patients with simple MCDK did not have routine VCUG or prophylactic antibiotics, the development of UTI was infrequent, damage to the contralateral kidney did not occur, and renal function was well preserved. In contrast, patients with bilateral disease or associated GU anomalies had a higher incidence of UTI and progression to renal failure. Complex MCDK was associated with a worse outcome (50% chronic renal insufficiency or failure).

Key words Multicystic dysplastic kidney · Urinary tract infection · Vesicoureteral reflux · Voiding cystourethrogram

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Introduction

A multicystic dysplastic kidney (MCDK) is a relatively common entity, estimated to occur in 1 in 4,300 live births [1]. The pathogenesis of this disorder is still poorly understood, but may involve failure of the ureteric bud to integrate and branch appropriately into the metanephros during development [2]. The result is a kidney that appears as a grape-like cluster of cysts absent of normal renal architecture and function [3]. The widespread use of prenatal ultrasonography identifies many cases in utero, but MCDK disease is still the most-common etiology for an abdominal mass found in the neonate [4]. In the majority of cases, a unilateral MCDK will completely involute over time [5], and will no longer be visible by ultrasonography. Some patients, particularly those with bilateral disease, may have a more-complex clinical course, which includes urinary tract infection (UTI), hypertension, or malignancy. Due to the poorly understood nature of these complications, management of this disorder has historically been varied and controversial, ranging from simple observation to nephrectomy [3, 6].

It has long been recognized that associated anomalies of both the upper and lower genitourinary (GU) tract often occur in patients with MCDK [1, 3, 7, 8] and that the incidence of vesicoureteral reflux (VUR) in patients with MCDK is higher than in the general population. In fact, VUR is the most-common abnormality associated with MCDK [8]. Since it is thought that VUR in the ipsilateral kidney may cause additional damage, or VUR in a normal contralateral kidney may be associated with renal

scaring, especially if UTI occurs, many centers advocate obtaining voiding cystourethrograms (VCUG) on all patients with MCDK at the time of diagnosis. It is not clear from the existing data, however, whether undetected VUR leads to a higher frequency of UTI or places the contralateral kidney at risk for injury in children with isolated unilateral MCDK. Consequently, patients in this study were divided into simple or complex MCDK based on ultrasound evaluation and physical examination, independent of findings on VCUG. Simple MCDK was defined as unilateral renal dysplasia without additional GU abnormalities, and complex MCDK included patients with bilateral renal dysplasia with or without GU abnormalities and unilateral renal dysplasia with GU abnormalities.

Patients and methods

The records of all patients with the diagnosis of MCDK disease seen either for the first time or as follow-up at Yale University School of Medicine from August 1995 to March 1999 were reviewed. Any patient with the diagnosis of hereditary cystic kidney disease was excluded from the study. The diagnosis of MCDK was made using standard renal ultrasonography and was confirmed by a pediatric radiologist. The diagnosis was based on established ultrasound criteria: (1) multiple non-communicating cysts, (2) absence of renal sinus, (3) absence of parenchymal tissue.

A total of 35 patients were entered into the study, of which 80% were males and 20% were females. The mean patient age at the time of last follow-up was 6.5 years, with a range from 1 month to 23 years. Patients were considered to have simple MCDK if: (1) the dysplasia was unilateral, (2) the contralateral kidney appeared normal, and (3) there were no associated GU anomalies detected by renal ultrasonography or physical examination.

Patients with complex MCDK had bilateral cystic dysplasia or unilateral renal dysplasia with one or more of the following structural GU anomalies: duplication of the collecting system, dilation of the ureter or renal pelvis, posterior urethral valves, neurogenic bladder, uretocele, or cryptorchism. VUR was not included in the definition of additional GU anomalies. Only 8 patients had a VCUG at any time during their clinical course. Thus, in this study the risk of UTI, status of the contralateral kidney, and renal failure was assessed independent of knowledge of the presence of VUR.

All patients had serial renal ultrasonography performed as a component of follow-up, as well as serum creatinine measurements, to evaluate renal function. The Schwartz equation was used to estimate glomerular filtration rate (GFR). In both groups, the data were then analyzed to determine the incidence of UTI, clinical outcome based on GFR and, in simple MCDK, status of the contralateral kidney. Permission was obtained from the Human Investigation Committee at Yale University School of Medicine prior to initiating the study.

Results

Of the 35 patients in the study, 28 (80%) had unilateral MCDK with 65% involving the left and 35% the right kidney. The remaining 7 patients had bilateral renal involvement. As shown in Table 1, patients were divided into simple MCDK (21 patients, mean follow-up 5.4 years, range 1 month to 22 years) and complex MCDK (14 patients, mean follow-up 8.4 years, range 1.9–23 years), including 6 patients with bilateral cystic dysplasia alone, 1 with bilateral MCDK and GU anomalies, and 7 with unilateral MCDK and GU anomalies.

Table 1 Characteristics of groups (*VCUG* voiding cystourethrogram, *VUR* vesicoureteral reflux)

	Simple	Complex
Total patients	21	14
Follow-up		
Mean (years)	5.4	8.4
Range (years)	0.1–22	1.9–23
VCUG at diagnosis	5	3
VUR	4	2
Prophylactic antibiotics	2 (10%)	7 (50%)

Table 2 Outcome of patients with multicystic dysplastic kidney (MCDK) disease (*UTI* urinary tract infection *ESRD* end-stage renal disease)[a]

	Simple MCDK	Complex MCDK
Total patients	21	14
UTI	1	4
Chronic renal insufficiency	0	4
ESRD	0	3

[a] The number of patients are listed for each category

In the simple MCDK group, 5 patients had a VCUG at diagnosis, of which 4 were positive for some degree of reflux (3 into the contralateral ureter and 1 into the ipsilateral ureter). Two of these patients with grade III–IV reflux were begun on prophylactic antibiotics at birth. Only 3 of the patients with complex MCDK had a VCUG performed at initial presentation, 2 of which were positive for VUR. Seven (50%) of the complex MCDK patients were placed on prophylactic antibiotics at the time of diagnosis.

As shown in Table 2, in the simple MCDK group, only 1 patient had UTI. In fact, this was one of the patients with VUR on prophylactic antibiotics. The contralateral kidney was normal and demonstrated compensatory growth in all patients, including the 3 patients known to have reflux into this kidney. At the end of the follow-up period, there were no instances of renal insufficiency or failure in the simple MCDK groups: mean serum creatinine was 0.6 mg/dl (range 0.3–0.7 mg/dl) with mean estimated GFR 90 ml/min per 1.73 m^2. All patients in the simple MCDK group had a blood pressure less than the 95th percentile for age throughout their clinical course.

In contrast, 4 (28%) of the 14 patients in the complex MCDK group experienced at least one episode of documented UTI, and all 4 had been given prophylactic antibiotics. Seven (50%) patients developed chronic renal insufficiency or end-stage renal disease (ESRD). Of the 3 patients who developed ESRD, 2 are currently doing well after receiving a living related donor renal transplant, and the other patient is on chronic hemodialysis.

Table 3 Impact of bilateral MCDK and genitourinary (GU) anomalies on clinical course and outcome

	Total number of GU anomalies in the complex MCDK group	Number with UTIs	Number with ESRD
Bilateral dysplasia	7	1	6
Duplicated collecting system	2	2	1
Dilated collecting system	2	1	0
Posterior urethral valves	2	0	1
Neurogenic bladder	1	1	0
Uretocele	1	0	0
Cryptorchism	1	0	0

One patient had both a dilated and duplicated collecting system

The 4 patients with chronic renal insufficiency have a serum creatinine ranging from 1.7 to 4.0 mg/dl, with an estimated GFR of 20–40 ml/min per 1.73 m^2.

The impact of bilateral dysplasia and GU abnormalities on the development of UTI and final outcome is shown in Table 3. Of the 7 complex MCDK patients with bilateral dysplasia, 6 developed ESRD. The seventh patient died at birth. The only structural GU anomalies that were not associated with either ESRD or UTI were uretocele and cryptorchism.

Discussion

Due to improved imaging technology and the routine use of prenatal ultrasonography, MCDK is being diagnosed earlier and more often. The increasing number of patients identified early in life with this condition presents a new challenge to the clinician in how best to manage this disorder in a safe and effective way. Only recently has the natural history of unilateral MCDK disease been recognized to have a generally favorable prognosis. Recent studies have shown that 48% of affected kidneys involute, and there is compensatory hypertrophy of the contralateral kidney in 93% of patients when MCDK is unilateral [5]. Because of this compensatory hypertrophy, the contralateral kidney adapts, patients maintain normal kidney function, and additional risks to the patient are minimal.

VUR has been found in up to 30% of MCDK cases, and because of this association many centers routinely obtain a VCUG on patients with MCDK at the time of diagnosis. However, data to substantiate that this associated anomaly predisposes to the development of UTI or influences the clinical outcome, particularly in children with unilateral MCDK, are lacking. To address this issue, patients were divided into two groups based on ultrasound evaluation and physical diagnosis, independent of whether or not VUR was present at the time of diagnosis of MCDK.

Despite the small number of patients in this study, the contrast between patients with simple and complex MCDK is evident. Patients classified as simple MCDK had an incidence of UTI similar to that reported in children without MCDK (1/21, 5%) [9–12]. When complex MCDK disease is present the risk of infection increases significantly (approximately 28%). While 4 patients with simple MCDK were known to have VUR at diagnosis, only 1 developed a UTI, and of the patients in whom the presence of VUR was unknown at diagnosis, none developed UTI. Therefore, the presence or absences of VUR may not be a strong predictor of UTI in patients with simple MCDK disease. In fact, UTI was more closely associated with bilateral renal dysplasia, duplication of the collecting system, dilation of the ureter or renal pelvis, and neurogenic bladder.

Since the use of prophylactic antibiotics was not controlled in either group, it could be argued that the incidence of UTI in the two groups of patients has been influenced by this factor. Accordingly, since a larger proportion of patients with complex MCDK received prophylactic antibiotics, one might have anticipated that the incidence of UTI in that group would have been less than that in simple MCDK. However, the proportion of patients with complex MCDK who develop UTI is considerably greater than that in patients with isolated unilateral MCDK. Thus, these data suggest that bilateral MCDK or unilateral MCDK with associated GU abnormalities place the patient at increased risk of UTI independent of VUR.

Patients with simple MCDK have an excellent outcome whether or not VUR is detected at diagnosis. Of particular note, the contralateral kidney demonstrated compensatory hypertrophy in all patients, including the patient with a documented UTI and VUR into the contralateral kidney. Thus, concern that damage to the intact contralateral kidney may occur after a UTI or in the presence of undetected VUR does not appear to be confirmed or documented in this small cohort of patients.

For children with complex MCDK, the outcome and prognosis is, as expected, more ominous. The presence of bilateral MCDK is the strongest predictor of renal insufficiency and ESRD, as anticipated. However, the severity and impact of associated GU anomalies has a more-profound effect on outcome than UTI or the presence or absence of VUR. Although the mean follow-up in the complex group was greater than in the simple group, it is unlikely that this influenced the final outcome, because of the profound effect of bilateral MCDK on the development of ESRD.

While the small number of patients in this study precludes establishing statistically valid predictors or risk factors, it is clear that the clinical course and final outcome for patients with MCDK can be anticipated without an initial VCUG, and independent of the presence of absence of VUR at the time of diagnosis.

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LITERATURE ABSTRACTS

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Hepatocyte growth factor in renal failure: promise and reality

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Can science discover some secrets of Greek mythology? In the case of Prometheus, we can now suppose that his amazing hepatic regeneration was caused by a peptide growth factor called hepatocyte growth factor (HGF). Increasing evidence indicates that HGF acts as a multifunctional cytokine on different cell types. This review addresses the molecular mechanisms that are responsible for the pleiotropic effects of HGF. HGF binds with high affinity to its specific tyrosine kinase receptor c-met, thereby stimulating not only cell proliferation and differentiation, but also cell migration and tumorigenesis. The three fundamental principles of medicine-prevention, diagnosis, and therapy-may be benefited by the rational use of HGF. In renal tubular cells, HGF induces mitogenic and morphogenetic responses. In animal models of toxic or ischemic acute renal failure, HGF acts in a renotropic and nephroprotective manner. HGF expression is rapidly up-regulated in the remnant kidney of nephrectomized rats, inducing compensatory growth. In a mouse model of chronic renal disease, HGF inhibits the progression of tubulointerstitial fibrosis and kidney dysfunction. Increased HGF mRNA transcripts were detected in mesenchymal and tubular epithelial cells of rejecting kidney. In transplanted patients, elevated HGF levels may indicate renal rejection. When HGF is considered as a therapeutic agent in human medicine, for example, to stimulate kidney regeneration after acute injury, strategies need to be developed to stimulate cell regeneration and differentiation without an induction of tumorigenesis.

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The role of vasoactive compounds, growth factors and cytokines in the progression of renal disease

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A number of kidney diseases, and their progression to end-stage renal disease, are driven, in part, by the effects of angiotensin II. Increasing levels of angiotensin II may in turn up-regulate the expression of growth factors and cytokines, such as transforming growth factor-beta1 (TGF-beta1), tumor necrosis factor-alpha (TNF-alpha), osteopontin, vascular cell adhesion molecule-1 (VCAM-1), nuclear factor-kappaB (NF-kappaB), platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF) and insulin-like growth factor. Most of these compounds promote cell growth and fibrosis. Angiotensin II also stimulates oxidative stress. This stress in turn may potentiate the vasoconstrictor effect of the peptide due, in part, to increased catabolism of nitric oxide (NO). Oxidative stress, fueled in part by angiotensin II, up-regulates the expression of adhesion molecules, chemoattractant compounds and cytokines. The angiotensinogen gene, which provides the precursor for angiotensin production, is stimulated by NF-kappaB activation. NF-kappaB is activated by angiotensin in the liver and in the kidney. This provides an autocrine reinforcing loop that up-regulates angiotensin production. Angiotensin II activates NF-kappaB through both AT1 and AT2 receptors. In addition, angiotensin-converting enzyme (ACE) inhibition markedly decreases NF-kappaB activation in the setting of renal disease.