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ARTICLE

Predictors of poor neonatal outcomes in prenatally diagnosed multicystic dysplastic kidney disease

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Abstract

Objective Multicystic dysplastic kidney (MCDK) is one of the most common anomalies detected by prenatal ultrasound. Our objective was to identify factors associated with severe adverse neonatal outcomes of prenatally diagnosed MCDK

Study design A retrospective review of prenatally diagnosed MCDK (1 January 2009 to 30 December 2014) from a single academic center was conducted. The primary outcome was death or need for dialysis among live-born infants. Associations between prenatal characteristics and outcome were analyzed by Fisher's exact test and Mann–Whitney test.

Results A total of 53 cases of prenatally suspected MCDK were included, of which 46 cases were live-born and confirmed postnatally (38 survivors, 8 non-survivors). Prenatally diagnosed extrarenal anomalies, bilateral MCDK, contralateral renal anomalies, and anhydramnios were significantly associated with death or need for dialysis (all $p < 0.0001$).

Conclusions Prenatally identified findings are associated with adverse neonatal outcome, and can guide counseling and management planning. In the absence of significant associated findings, prenatally diagnosed unilateral MCDK has a benign neonatal course.

Introduction

Multicystic dysplastic kidney (MCDK) is a congenital anomaly of the kidney and urinary tract (CAKUT), seen in 1 in 1000 to 1 in 4300 live births, most commonly affecting the left side, and with a male predominance [1, 2]. It consists of non-communicating multiple cysts which vary in size and shape, an atretic proximal ureter, and lack of identifiable renal parenchyma which contributes to the abnormal shape and function of the kidney [1, 3]. Because cysts are often evident between 15 and 20 weeks of gestation, and with the advent of routine second-trimester fetal ultrasound (US), MCDK is frequently diagnosed prenatally [1]. In a study of 3640 births, unilateral MCDK was the second most common CAKUT diagnosed antenatally [4, 5].

Previous studies have explored the incidence of MCDK, associated malformations, and natural history of MCDK in childhood [6–9], but questions remain about prenatally identified factors associated with adverse perinatal–neonatal outcomes. In the setting of prenatally suspected or known associated anomalies, prognosis has generally been expected to be driven by the severity of the other findings [8, 10] Furthermore, in studies focused on apparently isolated unilateral MCDK by prenatal imaging, excluding cases of known concurrent renal malformations or genetic conditions, postnatal findings have underscored the importance of detailed fetal evaluation and follow-up imaging since contralateral and non-renal findings could be missed [1].

For this relatively common renal finding, much is assumed although relatively little is published in the current era to guide antenatal counseling with respect to severity of neonatal and childhood challenges and outcome. The objectives of this study were to characterize clinical outcomes of prenatally diagnosed MCDK and to assess

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prenatal variables associated with the adverse outcomes of neonatal death or need for dialysis.

Methods

A retrospective review and analysis was conducted of all cases of prenatally diagnosed MCDK referred to the Fetal and Pregnancy Health Program at Lucile Packard Children's Hospital Stanford from 1 January 2009 to 30 December 2014, and entered into the Stanford University Institutional Review Board (IRB)-approved mother–fetus–baby-linked database. We reviewed (i) prenatal characteristics including amniotic fluid volume, associated fetal renal pathology, non-renal pathology; (ii) neonatal outcome data; and (iii) a minimum of 6 months of postnatal renal follow-up information including ultrasound and voiding cystourethrogram (VCUG) from medical records.

The prenatal diagnosis of suspected MCDK was confirmed by a maternal–fetal medicine specialist (YJB) reviewing stored ultrasound images and cine-clips of second-trimester fetal anatomy and third-trimester ultrasound exams. Fetal renal images were obtained in coronal, sagittal, and cross-sectional views with documentation of the renal artery Doppler flow. MCDK was characterized by replacement of normal renal parenchyma by multiple non-communicating cysts in fetal kidneys that could be normal in size, hypoplastic, or enlarged (as determined by two-dimensional renal length compared to established nomograms) [11]. Cysts in MCDK may vary from only a few millimeters to several centimeters in diameter, giving the kidney a distinct hypo-echoic appearance with loss of normal corticomedullary differentiation [12, 13]. Ultrasound exams included a detailed anatomic survey of the entire fetus based on the American Institute of Ultrasound in Medicine guidelines [14]. Oligohydramnios and polyhydramnios were defined based on gestational age-appropriate nomograms. Anhydramnios was defined as absence of detectable amniotic fluid.

The primary outcome was prospectively defined as death or need for dialysis among live-born infants. Associations between prenatal characteristics and adverse neonatal outcome were analyzed using Fisher's exact test (SAS 9.3, Cary, NC) and continuous data using Mann–Whitney test. This study was approved by the Stanford University IRB.

Results

There were 76 pregnancies with prenatally suspected MCDK identified in the database. Of those cases, 23 patients gave birth at referring institutions due to lack of severe findings and uncomplicated nature of the antenatal course including absence of other fetal anomalies, normal fetal growth, normal amniotic fluid, absence of maternal complications, etc. Therefore, 53 (70%) gave birth at our institution and had prenatal and neonatal outcome data available. Of these, two patients elected to terminate the pregnancy; one had bilateral severe MCDK, and one had suspected Meckel Gruber syndrome with an encephalocele but diagnosis was not confirmed as autopsy was declined. There were two cases of stillbirth in the third trimester: one patient presented late to care, with suspected fetal MCDK and dilated ureter at 35 weeks of gestation, complicated by oligohydramnios. A second patient underwent iatrogenic preterm delivery due to fetal bilateral MCDK, long-standing anhydramnios, and an absent limb. The parents were counseled about the poor prognosis and decided prenatally on palliative care, but the infant was born without heart rate, respiratory effort, or movement. Among the remaining 49 live-born infants, 8 died, 3 did not have MCDK confirmed on postnatal ultrasound (one had severe hydronephrosis, one had posterior urethral valves with urinoma, one had an adrenal cyst without renal or urinary tract abnormalities), and 38 had postnatally confirmed MCDK (Fig. 1). We further explored antenatal and postnatal findings of

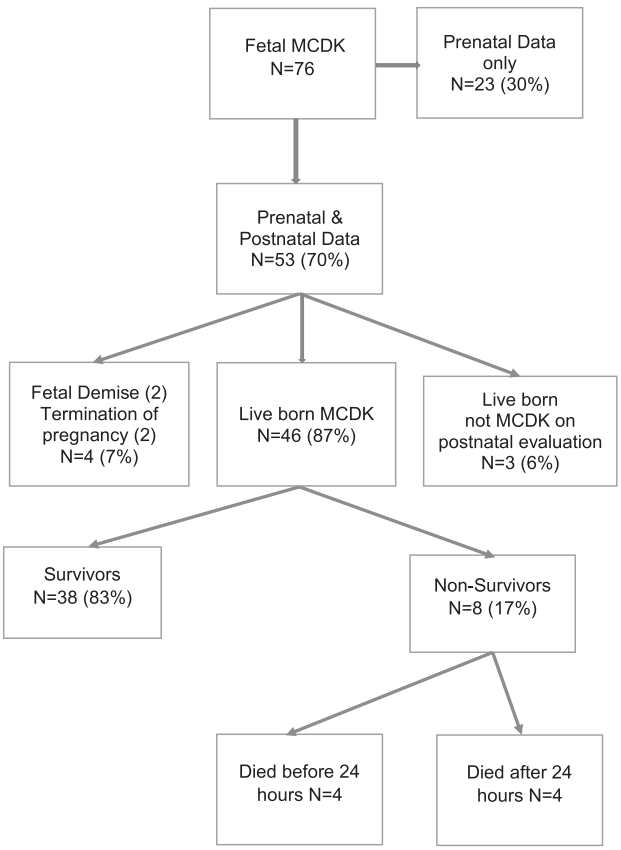

Fig. 1 Flow diagram

Table 1 Fetal characteristics of live-born

Fetal characteristics of live-born	Survivors,$N = 38$	Non-survivors,$N = 8$	*P* value
Initial presentation GA in weeks, median (range)	25 (18–37)	26 (20–32)	0.42
Anhydramnios	0 (0%)	4 (50%)	<0.001
Normal amniotic fluid volume	36 (95%)	3 (38%)	<0.001
Bilateral MCDK	1 (3%)	4 (50%)	<0.001
Prenatal contralateral renal anomalies	7 (18%)	8[a] (100%)	<0.001
Prenatal extrarenal anomalies	0 (0%)	5[b] (63%)	<0.001

[a] Hydronephrosis 2, ectopic fused kidney 1, echogenic kidney with ureterocele 1, bilateral echogenic kidney 1, renal agenesis 1, bilateral MCDK 2

[b] Tetralogy of Fallot, truncus arteriosus, double outlet right ventricle, Dandy–Walker, vertebral anomaly

survivors ($n = 38$, 83%) and non-survivors ($n = 8$, 17%) of live-born infants.

Fetal characteristics of live-born infants with confirmed MCDK

Table 1 presents fetal characteristics of the 46 live-born patients with confirmed MCDK. Anhydramnios, bilateral MCDK, and extrarenal anomalies were significantly more common among non-survivors compared to survivors. There was no difference in median gestational age between survivors and non-survivors (25 weeks vs. 26 weeks, $p = 0.42$) at initial presentation. Amniotic fluid volume was normal in 36/39 (95%) survivors, as compared to only 3/8 (38%) among those who died. Prenatal contralateral renal anomalies were diagnosed in 7 survivors (18%), including 5 cases with hydronephrosis (some with ureteral dilatation), 1 case with increased echogenicity, and 1 case of renal simple cysts. In comparison, all 8 (100%) non-survivors had contralateral renal anomalies, which included 2 with bilateral MCDK, 1 with bilateral echogenic kidneys, 1 with ectopic fused kidney, 1 with echogenic kidney with ureterocele, 1 with renal agenesis, and 2 with hydronephrosis. No prenatal extrarenal pathology was identified in live-born survivors compared to 5 of 8 non-survivors, and abnormal findings are listed in Table 1 footnote.

In our fetal program, prenatal pediatric urology, nephrology, genetics, and neonatology consultations are offered to all patients carrying fetuses with MCDK; among live-born patients in this analysis, 45/46 (98%) had prenatal consultations. One patient born preterm did not have specialist consultations. In addition to a detailed fetal anatomy survey conducted by maternal–fetal medicine specialists, 13/38 survivors had a fetal echocardiogram (ECHO) performed by a pediatric cardiologist, with all demonstrating normal cardiac structure. For non-survivors, 5/8 had a fetal ECHO but only two showed normal cardiac structure. A fetal echocardiogram was not a routine part of the prenatal paradigm during the study period, and the decision to obtain a fetal echocardiogram was at the discretion of the maternal–fetal medicine specialist and multidisciplinary prenatal care team reviewing the images. After prenatal genetics consultation, 4 (4/46, 9%) patients elected to undergo prenatal diagnostic testing; karyotype of 2 cases with bilateral MCDK and 1 with MCDK with contralateral severe hydronephrosis demonstrated normal karyotypes, while 1 with the presence of an associated cardiac anomaly showed 11q deletion (Jacobsen syndrome). Routine prenatal microarray testing was not instituted during the early part of the study period.

Perinatal characteristics of live-born infants with confirmed MCDK

Table 2 presents perinatal characteristics of live-born patients with confirmed MCDK. Non-survivors were more likely to be born by cesarean section (88% vs., 31%, $p = 0.005$), and have lower estimated gestational age (37 weeks vs. 39 weeks, $p = 0.003$) at delivery. Of the live-born

Table 2 Perinatal and postnatal findings of live-born patients

Characteristics	Survivors,$N = 38$	Non-survivors, $N = 8$	*P* value
GA at delivery, median (range)	39 (34–40)	37 (27–38)	0.003
C-section[a]	12 (31%)	7 (88%)	0.005
Male	22 (58%)	5 (62%)	0.67
Contralateral kidney anomalies	13 (34%)	7/7[b] (100%)	0.02
Extrarenal anomalies	2[c] (5%)	5/5[d] (100%)	<0.001
Vesicoureteral reflux	2/35 (6%)	1/2 (50%)	0.15
Nephrectomy/dialysis	1 (3%)	0 (0%)	1

[a] Prolonged labor, fetal distress, or malpresentation

[b] Due to death in delivery room, only 7 patients (all in Table 3 except no. 4 patient) had postnatal renal imaging

[c] Imperforate anus, atrial septal defect

[d] Due to rapid nature of death, only 5 patients (nos. 3, 5, 6, 7, and 8 in Table 3) had complete postnatal evaluation for extrarenal anomalies (i.e., including cardiac, brain imaging). Findings are described in Table 3 column 5

Table 3 Renal and extrarenal anomalies and time of death among live-born non-survivors

Non-survivors	Right kidney	Left kidney	Amniotic fluid	Postnatal evaluation	Time of death
1	Absent	MCDK	Anhydramnios	No extrarenal studies done[a]	<24 h
2	MCDK	MCDK	Anhydramnios	No extrarenal studies done[a]	<24 h
3	MCDK	Hydronephrosis	Normal	Truncus arteriosus, Jacobsen Syndrome	1 Month
4	MCDK	MCDK	Anhydramnios	No renal or extrarenal studies done[b]	DR
5	MCDK	Hydronephrosis	Normal	TOF, PS, ectopia cordis,	1 Month
6	MCDK	Ectopic fused	Normal	[c]Trisomy 18, VSD, Grade 4 reflux	2 Months
7	MCDK	MCDK	Oligohydramnios	DORV, imperforate anus	9 Days
8	MCDK	MCDK	Anhydramnios	Vertebral anomaly, imperforate anus (VACTERAL)	8 h

DORV double outlet right ventricle, *TOF* tetralogy of Fallot, *PS* pulmonic stenosis, *DR*delivery room, *VSD* ventricular septal defect

[a] Fetuses had normal cardiac anatomy

[b] Patient had antenatal diagnosis of Dandy–Walker malformation, microcephaly; fetal echo was not done due to preterm delivery

[c] Normal antenatal extrarenal work up but postnatal diagnosis of extrarenal anomalies

survivors, 97% had unilateral MCDK (20/38), and 53% had left-sided MCDK. Among 8 live-born non-survivors, 4 had unilateral MCDK, with 3 being right-sided MCDK. No gender differences were noted between groups. All non-survivors were admitted to the neonatal intensive care unit (NICU) for respiratory, renal, or cardiac management. Among survivors, 25 (66%) were admitted to the well-baby nursery and were subsequently discharged home, 7 (18%) were initially admitted to the NICU due to prematurity, respiratory distress, and imperforate anus, and the remainder were admitted to a level 2 nursery.

Postnatal characteristics of live-born infants with confirmed MCDK

Table 2 also shows postnatal imaging findings. Among survivors, all infants had postnatal ultrasounds at birth and at 4–6 weeks of life and follow-up renal ultrasounds every 6 months until involution of MCDK. Nine of 38 infants (24%) had ultrasound confirmed involution of MCDK in the time period of 1 to 28 months of life. Thirty-five survivors (92%) in our study had a VCUG by 6–8 weeks of life and 2 (6%) were found to have vesicoureteral reflux (VUR) (grade 1 and grade 3). Two non-survivors had VCUG work up and one had grade 4 reflux. Six infants in the survivor group had postnatal contralateral kidney anomalies that were not diagnosed prenatally. In total, 34% of infants in the survivor group had postnatal contralateral kidney anomalies compared to 18% by prenatal imaging.

Two infants in the survivor group had extrarenal anomalies identified postnatally; one had an atrial septal defect (ASD) and another had imperforate anus. The imperforate anus patient had bilateral MCDK and underwent a diverting colostomy and peritoneal dialysis, as well as nephrectomy due to mass effect. Two non-survivors also had imperforate anus. Table 3 describes the individual non-survivor amniotic fluid status, renal and extrarenal anomalies, and time of death. Among non-survivors, 7 of 8 had postnatal renal imaging which demonstrated contralateral kidney anomalies. Five non-survivors had extrarenal imaging evaluation (including echocardiogram and cranial US), which revealed anomalies in all. Of non-survivors, 4 died within 24 h of life due to complications of pulmonary hypoplasia, pneumothorax, and hypoxia. Four died after 24 h of life: 3 due to cardiac failure and post-surgical cardiac complications and 1 had Trisomy 18 and died at 2 months of life due to aspiration pneumonia.

Three patients among survivors were offered postnatal microarray by genetic specialists and had significant postnatal genetic findings, including duplication of 22q12.3 (patient had ear pit and ASD), chromosome gain 7q21, 22q11 (patient had bilateral MCDK, imperforate anus, diverting colostomy, nephrectomy, peritoneal dialysis), and chromosome 17q12 deletion (patient had family history of renal disease). Two chromosomal anomalies (prenatal diagnosis of Jacobsen syndrome with 11q deletion and postnatal diagnosis of Trisomy 18) were identified out of the four non-survivors who had a karyotype.

Discussion

In this single-center study of prenatally diagnosed MCDK, we found that death or need for dialysis was significantly

associated with prenatally diagnosed extrarenal anomalies, bilateral MCDK, and anhydraminos. Even during this recent period, when detailed prenatal US were routine, we found that unanticipated new renal (5/46; 11%) and extrarenal findings (4/46; 9%) were identified postnatally in all live-born infants. These data contribute to the existing literature, particularly given the link between prenatal findings and neonatal outcome data.

In previous studies, MCDK-associated renal anomalies ranged from 21 to 75% of cases [10]. The most commonly reported contralateral abnormality in MCDK is VUR [15]. In our study, associated contralateral renal anomalies included VUR, as well as hydronephrosis, simple cyst, ureterocele, renal agenesis, and bilateral MCDK. The VUR rate has been reported to range from 4.5 to 28% with a weighted mean of 16% for MCDK patients [16]. Given the high incidence of VUR with MCDK [17, 18], VCUG was previously typically performed as a standard diagnostic test in MCDK patients. Recent literature [19–21] highlights that the majority of VUR diagnosed on VCUG is low grade, most of which resolves spontaneously. In our study VUR rate was 6% (2/35) in live-born survivors and 8% (3/37) in all live-born births (both survivor and non-survivors). Our study was not designed to address the necessity of VCUG in all cases of MCDK, but these single-center findings suggest consistency with the low incidence of VUR in previous studies [19, 20, 22, 23].

Extrarenal anomalies associated with MCDK have been reported to occur in 5–35% of cases [1, 10] and contralateral renal anomalies in 21–75% [24, 25]. Previous studies have reported the incidence of extrarenal and contralateral renal anomalies, but did not necessarily report findings among both survivors and non-survivors from the fetal through postnatal period. By contrast, we focused on a prenatally diagnosed group in a single center, evaluated a composite outcome including death and need for dialysis, and explored both fetal and perinatal–neonatal findings related to adverse outcome. This broader view adds to our collective knowledge of key prognostic factors and may enhance prenatal counseling and perinatal management. For example, among our (5/8) non-survivors who had comprehensive evaluation, all had extrarenal anomalies compared to only 5% of survivors. Although extrarenal anomalies are often diagnosed prenatally, that is not always the case. In our study, all cardiac anomalies were diagnosed prenatally and confirmed postnatally, but imperforate anus was diagnosed in one survivor and two non-survivors only postnatally. These results emphasize that prenatal information related to extrarenal anomalies is very important, but careful postnatal exam is critical. Similarly, determination of contralateral renal findings during the prenatal period may direct enhanced surveillance and counseling. In our study, 47% (7/15) of all live-born MCDK patients with prenatal contralateral renal findings had evidence of fetal renal failure such as oligohydramnios or anhydramnios, and half of live-born patients who later died had evidence of fetal renal failure. Our findings are conforming with commonly held assumptions that contralateral renal findings in MCDK are at higher risk for adverse fetal and neonatal outcomes, whereas those with isolated unilateral MCDK are more likely to have a benign course, at least in the short term.

Consistent with the concept that prenatal information may help to direct appropriate care, counseling, and options for further evaluation, 98% of the patients in our analysis had prenatal consultation with at least one specialist. In our center, we provide genetic counseling and offer amniocentesis and karyotype and microarray-based comparative genomic hybridization (CGH) for single or multiple fetal abnormalities, but it is the expectant mother's decision whether she chooses to pursue this test. In our study, 9% of live-born had prenatal chromosomal analysis. Postnatally, an additional three more live-born survivors had chromosomal analysis, and were noted to have variants at 17q12 and duplication of 22q11.2 locus, which are among the most frequently detected copy number variants in isolated MCDK [27]. Implications of these and other genetic diagnoses are not confined to renal findings, but may be associated with a range of other organ system anomalies and complex outcomes, with the potential for learning disabilities or severe malformations with profound mental retardation [28–30]. Prenatal CGH may therefore be helpful in informing family counseling for a fetus with MCDK, as well as potentially for future pregnancies [29, 31, 32]. However, expectant mothers may decide that any information gained from genetic screening or testing will not influence decisions in the current pregnancy, and may decline to pursue such investigations. Nonetheless, knowledge of extrarenal and contralateral renal abnormalities associated with MCDK, serial fetal imaging and amniotic fluid assessment, and consideration of genetic testing will better inform antenatal counseling and direct delivery location and postnatal management planning.

Our data may be limited by several factors. First, we excluded patients with lack of neonatal outcome data who were born at outside institutions. While this has limited the size of our cohort, most of these cases were simple unilateral MCDK without additional anomalies, permitting delivery at a local hospital, and we suspect neonatal outcomes were reassuring. Second, although our data are retrospective, the size of our cohort is consistent with previously published single-center studies and we were able to obtain granular prenatal imaging and neonatal outcome data. Unfortunately, we had few patients undergo prenatal genetic testing. We were also not able to assess long-term pediatric outcomes such as rate of kidney involution, kidney function (creatinine level, cystatin C level), and

hypertension, which is one of the limitations of our study and we plan to include this information in subsequent studies. However, the rate of long-term hypertension in MCDK patients may not be higher than the general population [33].

In conclusion, unilateral MCDK may be benign in the absence of significant associated findings. Infants with a prenatal diagnosis of extrarenal anomalies, bilateral MCDK, presence of contralateral renal anomalies, or anhydramnios may be at higher risk for death or need for dialysis. Improved counseling and postnatal guidance may occur after identification of these findings on US. Delineation of optimal pre- and post-natal imaging is essential for the MCDK population. Prospective multi-center collaborative studies are needed to develop guidelines for serial US, to provide an evidence-based framework for family counseling, and to clarify expectations for prenatal and postnatal subspecialty involvement.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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