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Natural History of Contralateral Hypertrophy in Patients with Multicystic Dysplastic Kidneys

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Natural history of contralateral hypertrophy in patients with multicystic dysplastic kidneys

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Abstract

Purpose

To evaluate predictive factors for compensatory hypertrophy and renal outcomes in a large cohort of patients with multicystic dysplastic kidneys (MCDK).

Materials and Methods

We conducted a retrospective review from 1997 to 2016. Contralateral kidney and MCDK length were recorded from all ultrasounds as well as creatinine when available. We used generalized estimating equations to determine predictors of contralateral kidney length.

Results

443 children with MCDK were identified based on sonographic finding and lack of function on nuclear scan. The average follow-up was 3.2 years, interquartile range (1.5-5.7). The median time to involution of patients diagnosed before the age of 2 was 5.5 years (95% CI 3.8-7.0). In all patients, the median time to contralateral hypertrophy was 2.7 years (95% CI 2.2-3.3), and 90% of patients had undergone contralateral hypertrophy by 10 years. After adjusting for age, sex, MCDK side, and cohort status, for each year a patient had undergone involution after the age of 2, the contralateral kidney grows 0.35 centimeter longer (95% CI 0.01-0.68, p=0.04) compared to patients who had not involuted. Patients with contralateral hypertrophy had higher creatinine clearance at follow-up (83 v. 61, p=0.07), although this finding was not statistically significant due to limited data.

Conclusions

The majority of children with MCDK will have contralateral hypertrophy by the age of 3. MCDK involution predicts contralateral kidney growth rate after 2 years of age. **A small cohort of patients' with MCDK will not undergo contralateral hypertrophy and may be at risk for renal insufficiency.**

Introduction

Multicystic dysplastic kidney (MCDK) disease is a form of renal cystic dysplasia that is commonly detected on prenatal ultrasound.[1] Conservative management of children with MCDK is recommended as the natural history of the disease has been shown to be benign.[2] Recent systematic reviews demonstrated MCDK is not associated with hypertension or Wilms' tumor.[3, 4] Despite these findings, patients are often followed long-term and associated yearly costs for serial ultrasound are estimated to be around $8-10 million USD for every 1000 children with MCDK.[5]

Which MCDK patients require long-term follow-up is currently debated, **as a small cohort of patient's** may develop renal impairment or insufficiency.[6, 7] Contralateral kidney hypertrophy has been thought to be an indication of renal health and has been found to occur in about one-fourth of patients at birth.[8] A previous MCDK patient analysis revealed that when evaluating the contralateral kidney, compensatory hypertrophy was observed in 77% of patients at follow-up and was directly correlated with involution of the MCDK.[9] This review surmised that follow-up ultrasounds provide little information, urologic follow-up is unnecessary, and is based on a sample of 61 patients. To overcome these limitations, we retrospectively analyzed a large cohort of patients with MCDK with long-term follow-up to evaluate predictive factors (including MCDK involution) for compensatory hypertrophy. The results of this study may provide more focused knowledge of subgroups at risk for renal insufficiency.

Patients and Methods

Study sample

We retrospectively reviewed medical charts of patients diagnosed with "dysplastic kidney" from a radiographic research database at two large pediatric, tertiary care centers in the San Francisco Bay Area (n=451). We searched the database for all years data was available (1997-2016). All cases of MCDK were confirmed via sonographic findings. Patients with segmental dysplasia, bilateral cystic disease, and cystic dysplasia associated with ureteroceles or duplicated systems were removed from the analysis (n=8). **Patients entered the study at the time of their first postnatal ultrasound. Follow-up was defined as the latest ultrasound date in our database.**

We collected demographic and clinical characteristics listed in Table 1. All patients who had a renal nuclear scan showed less than 10% function on the affected kidney. We recorded all MCDK and contralateral kidney lengths from ultrasounds available in the database. Involution status was defined as undetectable evidence of the MCDK on ultrasound. The first **ultrasound date that showed** involution was used to determine the time to involution. Finally, we collected height, weight, and creatinine when available from clinic and laboratory notes. Creatinine clearance was calculated in all patients with a follow-up creatinine.[10] The majority of patients were diagnosed before the age of 2 (74%), and the rest of patients entered our study after the age of 2. Because records of these patients from earlier years were unobtainable, we performed sensitivity analyses to ensure data quality.

Statistical Analysis

All analyses were performed in Stata v.13 (College Station, TX, USA). We used Student's t-tests and chi-squared tests to compare continuous and categorical variables, respectively. Continuous variables that were not normally distributed (i.e. creatinine clearance at follow-up) were compared using the Mann-Whitney U test. Kaplan-Meier curves were constructed for two separate outcomes, involution of the MCDK and contralateral hypertrophy. Contralateral hypertrophy was defined as 2 standard deviations above the mean kidney length by age.[11, 12] Patients entered the analysis at the time of diagnosis and contributed time until an event occurred or we no longer had sonographic data for them at which time they were censored. We constructed separate and combined Kaplan-Meier curve to visually inspect differences between those who entered the study before and after the age of 2. We randomly selected approximately 10% of our sample to assess whether or not contralateral hypertrophy was a consistent finding.

Predictors of Involution and Hypertrophy

We used Cox proportional hazard models to determine the rate of involution and contralateral hypertrophy. We tested MCDK length at diagnosis, contralateral kidney length at diagnosis, sex, and side. These predictors were selected *a priori* based off previous research.[13, 14] For all time to event analysis, patients were excluded who had the event during study entry (i.e. involution or contralateral hypertrophy). We then used generalized estimating equations (GEE) to model contralateral kidney length due to the

longitudinal aspect of the data.[15] Here, we aimed to determine if MCDK involution is associated with contralateral kidney growth after controlling for factors listed above. Because kidney growth is rapid within the first few years of life, we used linear splines to determine the natural cut-off age within the dataset of which we developed separate models to test for interactions (age= 1.9). Robust confidence intervals were obtained within the GEE model.[16] Any *p* values less than 0.05 were considered statistically significant, and all statistical tests were two-sided.

Results

443 children with MCDK were identified based on sonographic finding and lack of function on nuclear scan. The average follow-up was 3.2 years, interquartile range (1.5-5.7). 327 children were diagnosed with MCDK before the age of 2, and 116 children were diagnosed after the age of 2. Baseline demographic and medical characteristics between the two cohorts can be seen in Table 1. Of note, a greater proportion of patients in the older cohort had MCDK involution at diagnosis, 42 (36%) compared to patients presenting before the age of 2, 36 (11%), $p<0.001$. A list of associated congenital anomalies can be found in Supplemental Table 1. No patients in our study were diagnosed with any renal tumors. None of the 23 female patients greater than 10 years of age had Mullerian abnormalities.

Time to Involution

The median time to involution of patients diagnosed before the age of 2 was 5.5 years (95% CI 3.8-7.0). Similarly, the median time to involution for patients diagnosed after the age of 2 was 2.7 years (95% CI 2.0-5.6) (graphs shown in Supplemental Figure 1). Thus, the median time to involution from diagnosis in the entire sample was 4.9 years (95% CI 3.6-6.4) (Figure 1). **The cumulative probability of involution at one year of age was approximately 14%, 28% at 2 years, 50% at 5 years, and 75% at 10 years.** We observed no patients who had undergone involution if they had not undergone involution by around 10 years.

Regardless of cohort status, the **smaller** the length of the MCDK kidney at diagnosis, the **faster** the rates of involution. In patients **at** diagnos**is** less than 2 years of age, the rate of involution was **1.29** times as fast (95% CI 1.17-1.41) for patients with one-centimeter smaller MCDK length at diagnosis. Contralateral kidney length, sex, and side were not associated with time to involution (Table 2).

Time to Contralateral Hypertrophy

The median time to contralateral hypertrophy for patients diagnosed before the age of 2 was 2.7 years (95% CI 2.2-3.3). Similarly, the median time to contralateral hypertrophy for patients diagnosed after the age of 2 was 2.7 years (CI not determined due to small sample size) (graphs not shown). In all patients, the median time to contralateral hypertrophy was 2.7 years (95% CI 2.2-3.3), and 90% of patients had undergone contralateral hypertrophy by 10 years (Figure 2). **Thus, the cumulative probability of contralateral hypertrophy at one year of age was approximately 19%,**

38% at 2 years, 70% at 5 years, and 90% at 10 years. MCDK and contralateral kidney length, sex, and side were not associated with time to contralateral hypertrophy (Table 2). In the 10% random sample of our cohort, contralateral hypertrophy was a consistent finding **throughout follow-up** after it was first documented.

Cr Clearance and Kidney Length

Creatinine clearance was calculated in 43 patients. The median age at follow-up for these patients was 6, range (3-12). Patients who developed contralateral hypertrophy over the study period had higher creatinine clearance, mL/min (median= 83, IQR 68-138) than those who did not develop contralateral hypertrophy (median= 61, IQR 57-76), although this finding did not reach statistical significance (p=0.07).

In total, 1238 ultrasounds of contralateral kidney lengths were analyzed. Figure 3 shows contralateral kidney length plotted by age in years for both cohorts. After adjusting for age, sex, MCDK side, and cohort status, for each year a patient had undergone involution after the age of 2, the contralateral kidney **grew** 0.35 centimeter longer (95% CI 0.01-0.68, p=0.04) compared to patients who had not involuted (Figure 3). Involution status before the age of two did not predict contralateral growth, 0.14 cm (95% CI -0.13-0.40).

Discussion

Most patients **with MCDK** developed contralateral hypertrophy by 3 years of age, and a small minority (~10%) did not develop any contralateral hypertrophy during the study period. Involution status predicts contralateral kidney growth after 2 years of age. The mechanism and temporal relationship behind this relationship is unclear and requires future research. Based on our data presented in Table 3, our findings are consistent with **the follow-up algorithm proposed by Eickmeyer et al.[17] If** compensatory hypertrophy has occurred by age three **with a stable MCDK** then further monitoring by sonography is not necessary. **This leaves a small cohort of patient's with MCDK by age three that have not undergone contralateral hypertrophy. In this minority cohort, a sonogram at age 3 or after could help stratify (based on the Table 3), which patients have not undergone contralateral hypertrophy and may be at future risk for renal insufficiency.**

This recommendation is consistent with findings found by Onal et al. Contralateral hypertrophy was observed in 77% of patients and was directly correlated with involution of the MCKD.[9] Compensatory hypertrophy is common in patients with MCDK, but it does not occur in all patients.[18-20] In a prospective cohort of patients with MCDK, 35/43 (81%) demonstrated compensatory hypertrophy at 10 year follow-up.[18] In our study, the time to event analysis showed that about 90% of patients have compensatory hypertrophy by 10 years after diagnosis. This leaves approximately 10% of patients without compensatory hypertrophy; whether this puts patients at risk for renal insufficiency is not well understood. However, renal length has been linked to glomerular filtration rate,[21, 22] and we provide inconclusive evidence that patients with compensatory

hypertrophy have higher creatinine clearance. Future studies are required to confirm this finding.

Once a patient has documented hypertrophy, the hypertrophy appears to be a consistent finding. **If a patient presents later in childhood with a history of MCDK and renal status is not documented, Table 3 provides comparison data based on sonographic renal lengths to determine if contralateral hypertrophy is present and hence low risk for future renal insufficiency. If the child continues without hypertrophy, and especially without involution, monitoring of blood pressure and proteinuria may be required with referral to nephrology.** Whether or not contralateral hypertrophy remains in adulthood is not known. **Additionally, hypertrophy could be a sign of glomerular hyperfiltration, which in the long-term could actually lead to renal insufficiency. We did not see evidence of glomerular hyperfiltration in our cohort. Longer follow-up in adults with MCDK would allow exploration of this possibility.**

No baseline factors in our study predicted the rate of contralateral hypertrophy. However, patients who had involuted had greater contralateral kidney growth after the age of 2 compared to patient who have not involuted. Reasons for this result may be that inherent renal growth factors in the beginning of life outweigh the influence of the MCDK kidney, as even in non-pathological kidneys much growth occurs in the first few years of life.[11, 23] **MCDK involution may invoke changes in a humoral substance that controls renal hypertrophy, or a persistent dysplastic kidney may act as a "vascular steal" that prevents contralateral growth.[24] As noted s**maller MCDK kidneys at

diagnosis involute faster. We replicate this finding from many studies showing that length of MCDK at diagnosis predicts involution status.[13, 14, 25, 26]

Associated urologic and other congenital anomalies are common in patients with MCDK. In a systematic review of patients with MCDK, associated anomalies occurred in 14% of patients, which is similar to our findings.[20, 27] Reflux has been reported in a large range from 4% to 28% of patients with MCDK.[20, 28] Very few patients had reflux in our cohort, which could be due to missing data. The influence of reflux on compensatory hypertrophy and MCDK involution is not completely known, although one report shows an association between reflux and smaller contralateral kidneys during the first year of life.[29] Embryologically, since the fetal kidneys and Mullerian structures form in close proximity in respect to time and space you might expect to see an increase in Mullerian abnormalities in post-pubertal females with MCDK. In our cohort of 23 female patients followed beyond 10 years of age we did not see any significant Mullerian abnormalities suggesting that sonographic evaluation of post pubertal girls with MCDK should be reserved for those with symptoms suggestive of abnormal menstruation and not routinely performed. Chromosomal analysis has been suggested for prenatally diagnosed MCDK.[30] The physical characteristics of our cohort of patients with MCDK do not support the routine use of prenatal chromosomal analysis. Expecting parents should be counseled in regards to the associated risk of non-specific anomalies.

Patients presenting to our tertiary care center after the age of 2 may be different than those referred at birth. Important differences between the two groups merit

discussion. First, fewer congenital anomalies were found in patients who presented after the age of 2. We believe this is due to poor data quality in the medical records, and perhaps other anomalies were more likely to be mentioned in those around birth. Three times as many patients had undergone involution at diagnosis in the older group of patients, which is consistent with the idea that involution occurs in the majority of patients by age 3. The trajectory of kidney lengths between the two cohorts did not significantly differ (Figure 3), which suggested their kidney lengths seemed to be on par with patients in the birth cohort. Because these cohorts could differ in unmeasured ways, we adjusted for cohort status in all the GEE models.

We use kidney length as a surrogate for kidney function. Creatinine clearance, although trending to significance, did not statistically differ between those with and without contralateral hypertrophy. This analysis was on a very small subset of patients and should be replicated. Patients who had a blood draw in our sample may have lower creatinine clearance than patients who were monitored clinically and may not represent the entire MCDK population. Not all patients had equal follow-up times and present opportunities for selection bias**, especially in regards to those with and without VCUG data.** Despite these limitations, we provide evidence that not all MCDK patients are the same, and these results have implications for differential follow-up in this population.

Conclusion

The majority of children with MCDK will have contralateral hypertrophy by the age of 3. MCDK involution predicts contralateral kidney growth rate after 2 years of age.

A small minority (~ 10%) of patients whose MCDK commonly does not involute early in life do not exhibit compensatory hypertrophy and are at risk for renal insufficiency. Patients without **contralateral** hypertrophy of the MCDK by age of 3 should have continued follow-up to assess for normal renal function. **Table 3 defines renal length percentiles by age in our large cohort of patients with MCDK.**

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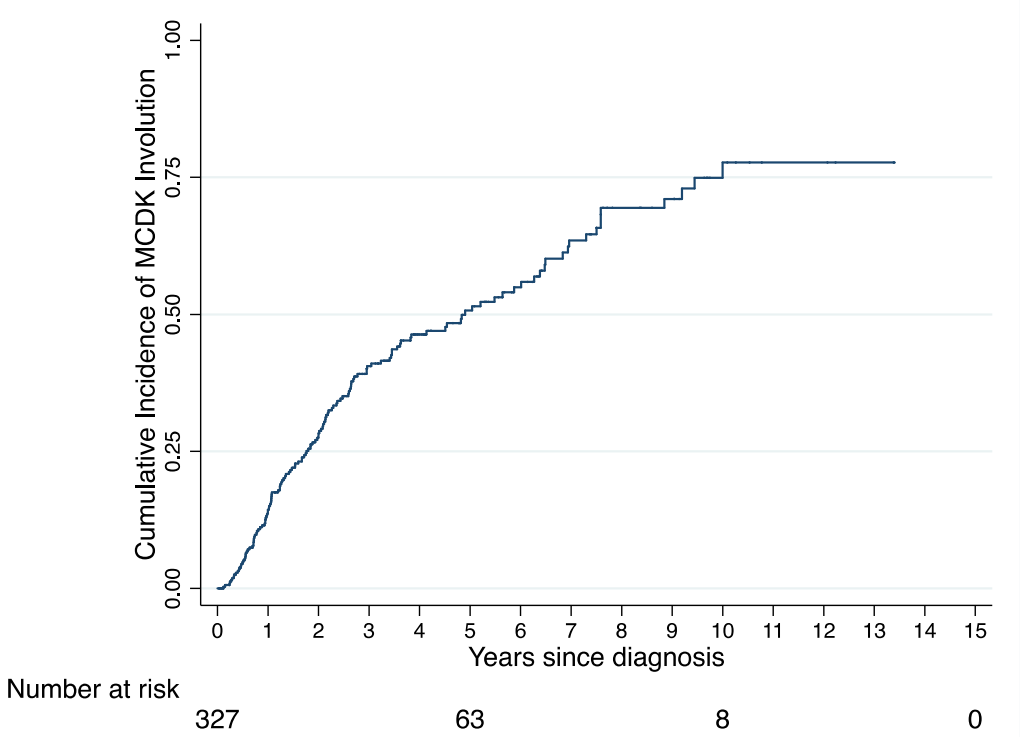
Figure 1 revised

Figure 1 Cumulative Incidence of involution of all patients diagnosed with MCDK*



*Patients whose MCDK had involuted at **diagnosis** were excluded from this analysis

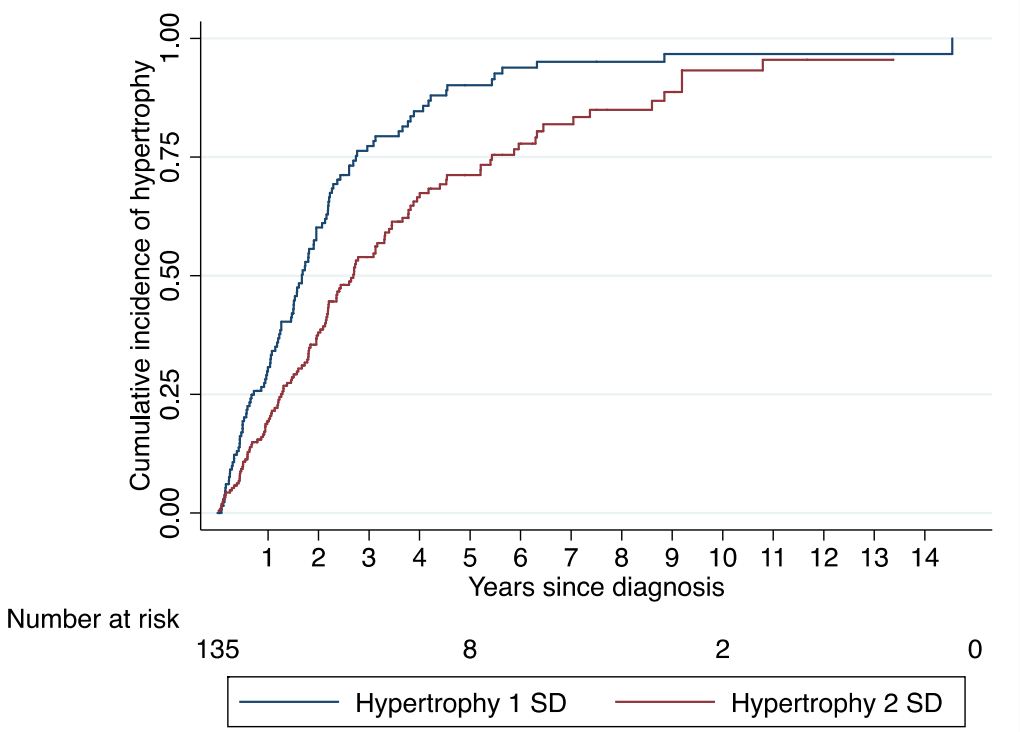
Table 2 Univariate and multivariate hazard ratios for time to involution and contralateral hypertrophy by cohort status

Involution		**Multivariate Hazard Ratio Diagnosis < 2 yo OR (95% CI)**	**p-value**	**Multivariate Hazard Ratio Diagnosis > 2 yo OR (95% CI)**	**p-value**
Smaller MCDK length (cm) at diagnosis		**1.29 (1.17-1.41)**	<0.001	**1.39 (1.17-1.66)**	<0.001
Contralateral kidney length (cm) at diagnosis		1.17 (0.96-1.42)	0.12	0.90 (0.03-27.1)	0.95
Sex					
	Female	0.97 (0.66-1.42)	0.87	1.07 (0.07-15.7)	0.96
	Male	1.00 (reference)		1.00 (reference)	
Side					
	Right	1.40 (0.94-2.08)	0.10	6.82 (0.10-444)	0.37
	Left	1.00 (reference)		1.00 (reference)	
Contralateral hypertrophy					
Smaller MCDK length (cm) at diagnosis		**0.94 (0.86-1.03)**	0.18	**1.08 (0.61-1.92)**	0.79
Contralateral kidney length (cm) at diagnosis		1.10 (0.92-1.32)	0.30	1.16 (0.95-1.40)	0.14
Sex					
	Female	1.00 (0.70-1.45)	0.96	1.00 (0.68-1.47)	0.99
	Male	1.00 (reference)		1.00 (reference)	
Side					
	Right	1.25 (0.87-1.80)	0.24	1.34 (0.90-2.00)	0.15
	Left	1.00 (reference)		1.00 (reference)	

Key of Definitions for Abbreviations (only include abbreviations used 3 times or more in manuscript)

Abbreviations: Multicystic Dysplastic Kidney (MCDK)

Figure 2 Time to contralateral kidney hypertrophy in all patients with MCDK*



* Patients with contralateral hypertrophy at diagnosis were excluded from this analysis

Figure 3 Actual and predicted contralateral kidney length by involution status in patients with MCDK

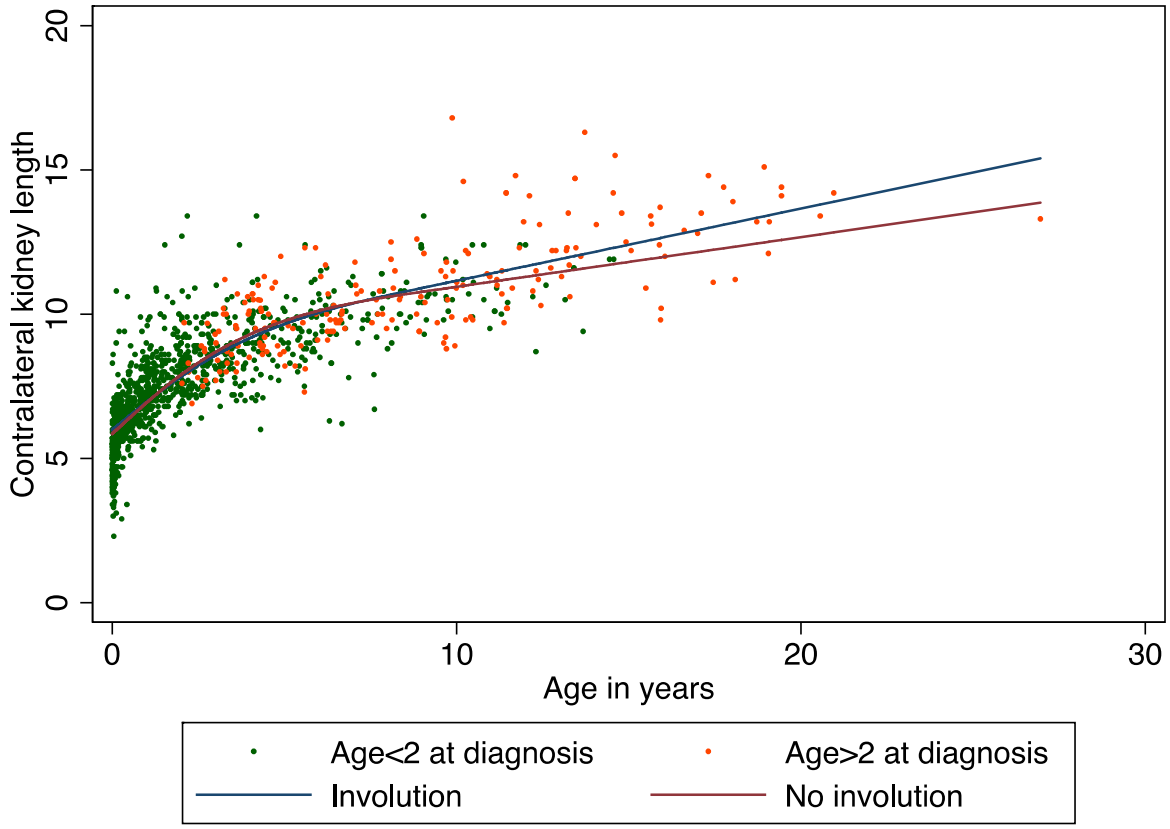


Table 1 Demographic and medical characteristics of patients with MCDK by cohort status

	Cohort Diagnosis <2 n = 327	Cohort Diagnosis >2 n = 116	p- value
Age at first recorded postnatal US, median years (range)	0.12 (0.04-0.45)	5.2 (2-19)	<0.001
Gestational age, median months (IQR)	38 (34-39)	33 (32-34)	0.11
Preterm, n (%)	26/105 (25)	3/5 (38)	0.44
Other congenital anomaly, n (%)[a]	38/313 (12)	4/110 (4)	0.01
Mortality at perinatal period, n (%)	1/327 (0.3)	1/116 (1)	0.44
Sex, n (%)			
Male	169 (52)	66 (58)	0.23
Female	159 (48)	48 (42)	
MCDK side, n (%)			
Left	170 (52)	68 (59)	0.20
Right	157 (48)	47 (41)	
Median age at last follow-up (years)	3.4 (1.7-5.9)	10 (6-13)	<0.001
Involution of MCDK, n (%)			
Yes	125 (38)	57 (49)	0.04
Involution at diagnosis, n (%)			
Yes	36 (11)	42 (36)	<0.001
VCUG completed, n (%)			
Yes	167/ 274 (61)	16/54 (30)	<0.001
Reflux, n (%)			

	MCDK Side	8/167 (5)	0/54 (0)	0.09
	Contralateral Side	12/167 (7)	0/54 (0)	0.05
Nuclear Scan Completed, n (%)				
	Yes	152/279 (54)	16/62 (26)	<0.001
Nephrectomy at latest follow-up, n (%)				
	Yes	8 (2)	0 (0)	0.12

Table 3 Natural history of contralateral kidney length (cm) by age

Age	No. of observations	Mean (SD)	25th Percentile	50th percentile	75th percentile	Hypertrophy cut-off 1 SD*	Hypertrophy cut-off 2 SD*
1-3 months	235	5.6 (1.1)	5.0	5.5	6.1	5.6	6.1
4-6 months	88	6.4 (1.0)	5.9	6.4	6.8	6.2	6.7
7-9 months	73	6.7 (0.8)	6.3	6.6	7.1	6.6	7.0
1-2.5 years	267	7.9 (1.2)	7.2	7.9	8.5	7.1	7.7
3-4 years	172	9.1 (1.2)	8.3	9.0	9.9	7.6	8.0
5-6 years	98	9.6 (1.1)	9.0	9.6	10.1	8.5	9.1
7-8 years	52	10.4 (1.1)	9.8	10.3	10.9	9.1	9.7
9-10 years	47	10.9 (1.5)	9.9	10.7	11.5	9.1	9.9
11-12 years	33	11.5 (1.5)	10.3	11.0	12.3	9.9	10.8
13-14 years	22	12.6 (1.7)	11.6	12.3	13.5	10.5	11.4
15-16 years	10	12.1 (1.3)	10.9	12.3	13.1	10.7	11.4
17+ years	16	13.4 (1.2)	13.0	13.5	14.3	N/A	N/A

UCSF Cohort data: Note after 3 years of age the overwhelming majority of patients with contralateral compensatory hypertrophy are above the 1 and 2 SD cut-off value

Defined as one or two standard deviations from *normal* kidney means by age (Konus et al, 1998)