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Multicystic dysplastic kidney disease at Chris Hani Baragwanath Academic Hospital ovevr a thirty year period

Lala, Nilesh

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MULTICYSTIC DYSPLASTIC KIDNEY DISEASE AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL OVER A THIRTY YEAR PERIOD

Nilesh Lala

Student Number: 8600833D

A research report submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in Paediatrics

Johannesburg 2017

DECLARATION

I, Nilesh Lala, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in Paediatrics at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

…..……

30th day of November 2017

DEDICATION

I dedicate this to my wife Aarti,

Who has helped in much more ways than I can express,

My son Soham,

My mother Savita

And my spiritual Master.

ABSTRACT

Introduction:

Multicystic dysplastic kidney (MCDK) disease is a common non-inherited developmental anomaly, increasingly diagnosed antenatally. It is a single functional kidney associated with increased risk of anomaly of the opposite kidney.

Methods:

A retrospective descriptive study of paediatric patients with MCDK disease was undertaken at a secondary-tertiary level hospital from January 1986 to December 2015.

Results:

Over a 30 year period, 59 patients were identified; 36 (59%) were male and 31 (52.5%) were left sided. Overall, 20 (33.9%) of cases were diagnosed antenatally, with an increased frequency of cases diagnosed in the last decade (p=0.015). Eight (13.6%) had associated contralateral abnormalities; none had reflux into contralateral kidney.

Conclusion:

The number of MCDK diagnosed was low but increasing, due to increased antenatal sonars in the last decade. None of the patients had reflux into the contralateral kidney. The patients (only study from Africa) showed similar demographics to the rest of the studies on MCDK.

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Finally I'd like to acknowledge Mrs Sandra Benn, she motivated me more than she will know.

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ABBREVIATIONS

AKI	Acute Kidney Injury
BMI	Body mass index
BP	Blood Pressure
CAT	Computerised Axial Tomography
CHBAH	Chris Hani Baragwanath Academic Hospital
CKD	Chronic Kidney Disease
DMSA	Dimercaptosuccinic Acid
DTPA	Diethylenetriaminepentacetate
GFR	Glomerular Filtration Rate
eGFR	estimated Glomerular Filtration Rate
ESRD	End Stage Renal Disease
HAZ	Height/length for age z score
HIV	Human Immunodeficiency Virus
IQR	Interquartile Range
IVP	Intravenous pyelogram
Mag3	Mercaptoacetoacetyltriglycine scan
MCDK	Multicystic Dysplastic Kidney
MRU	Magnetic Resonance Urography
PUJ	Posterior Urethral Junction
PUV	Posterior Urethral Valves
UTI	Urinary Tract Infection
VCU	Voiding Cystourethrogram
VUJ	Vesicoureteral Junction

VUR	Vesicoureteral Reflux
WAZ	Weight for age z score

1.0 Introduction

1.1 Epidemiology

Multicystic dysplastic kidney disease (MCDK) is defined as a non-inherited developmental anomaly of the kidney. It is characterised by multiple non-communicating cysts of varying sizes and no identifiable renal parenchymal tissue (1, 2). See Figure 1.1. It was first described by Cruveilhier in 1836 (3). MCDK is a common congenital anomaly with incidences ranging from 1 in 1000 to 1 in 4300 live births in developed countries (1, 4).

The aetiology is unknown, but is generally attributed to one of two embryological theories. The first theory postulates that there is atresia of the pelvic ureter, at the pelvic-ureteric junction, which results in severe urinary obstruction, hydronephrosis and development of MCDK (5). The second theory postulates an abnormal interaction between the ureteric bud and metanephric blastema resulting in failure of differentiation of the normal anatomical structures (6). Other theories include intra-uterine infection and drug exposures (7).

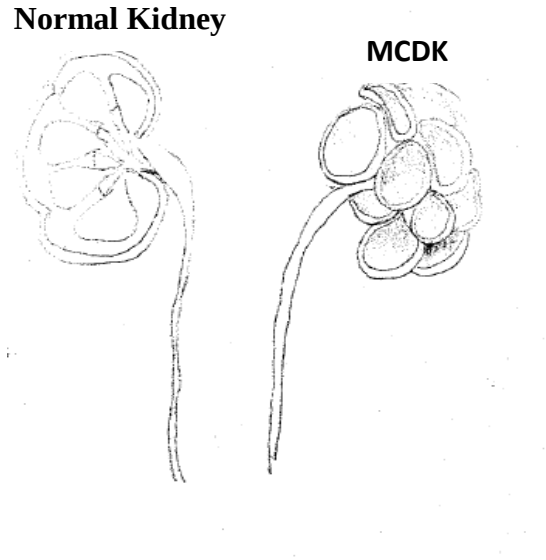


Figure 1.1: Schematic representation of a normal (left) and a multicystic dysplastic kidney (MCDK).Sketch drawn by Aarti Lala

1.2 Diagnosis and clinical presentation of MCDK

In developed countries the diagnosis is made on antenatal ultrasound screening (60-80%) in the majority of the patients (1, 5). Fewer cases are diagnosed antenatally in developing countries due to limited resources (8). MCDK patients are usually asymptomatic in childhood and therefore the diagnosis may be missed. Some cases are detected due to the presence of an abdominal mass, investigation of urinary tract infections (UTI) or an incidental finding on renal imaging (4).

Patients with MCDK will generally have a single functional kidney. The functional kidney can be associated with an increased risk of anomalies namely vesicoureteral reflux (VUR) obstruction in 7-26%, posterior urethral valves (PUV) in 1.5-5% and vesicoureteral junction (VUJ) obstruction in 2% (9).

Ureterocoeles, horseshoe kidney and undescended testis have also been occasionally described (9). Patients' with anomalies of the functional kidney have been found to have poorer outcomes. Thus numbers of authors have classified it into simple and complex MCDK (2, 10, 11). Therefore early diagnosis, further laboratory and radiological investigation of the single kidney are necessary. Bilateral MCDK have been described and present as Potter's sequence but do not survive in the absence of renal replacement therapy; kidney transplant or dialysis (12).

The natural history of MCDK is generally benign unless the single kidney is functionally abnormal. The MCDK either involutes in 35-63% or decreases in size in 30-44% (1). Generally, by the age of 15 years, the contralateral kidney hypertrophies in 95% of cases (5). There is debate as to whether MCDK increases or decreases the risk of hypertension (13). Nevertheless, BP (Blood Pressure) monitoring is essential in these cases. Although MCDK was thought to increase the risk of malignant transformation, this has not been proven (14). Thus the surgical removal of the kidney is not warranted unless other indications, such as recurrent UTI's and/or uncontrolled hypertension are present(7). Mortality is attributed to bilateral MCDK and the morbidity is due to long-term nephrological sequelae (9). Minimal data has been reported from developing countries and currently no data is available from Africa. Complications associated with MCDK with or without an evidence base include Wilms Tumour, hypertension, CKD (Chronic Kidney Disease) / ESRD (End Stage Renal Disease), UTI and VUR (10), as well as chronic hyperfiltration injury (15).

1.3 Management of MCDK

The standard of care for investigating MCDK includes an ultrasound examination of the kidneys and radionuclear scan to confirm the non-functionality of the kidney. See Figure 1.2 below which shows a Mag3 scan with no uptake in anatomical area of right kidney. The scan is taken posteriorly. In the past voiding cystourethrogram (VCU) was routinely used to exclude VUR. Recent data suggest that VCU offers little benefit (16). These imaging modalities are also used to confirm contralateral anomalies which may be correctable surgically. These recommendations might not be appropriate within a limited resource setting where the availability and quality of radiological imaging, including ultrasound, is limited. Whether this finding in our setting is consistent with that of other studies is not known. Most studies have thus far shown reasonable consistency in the natural progression and findings of MCDK patients.

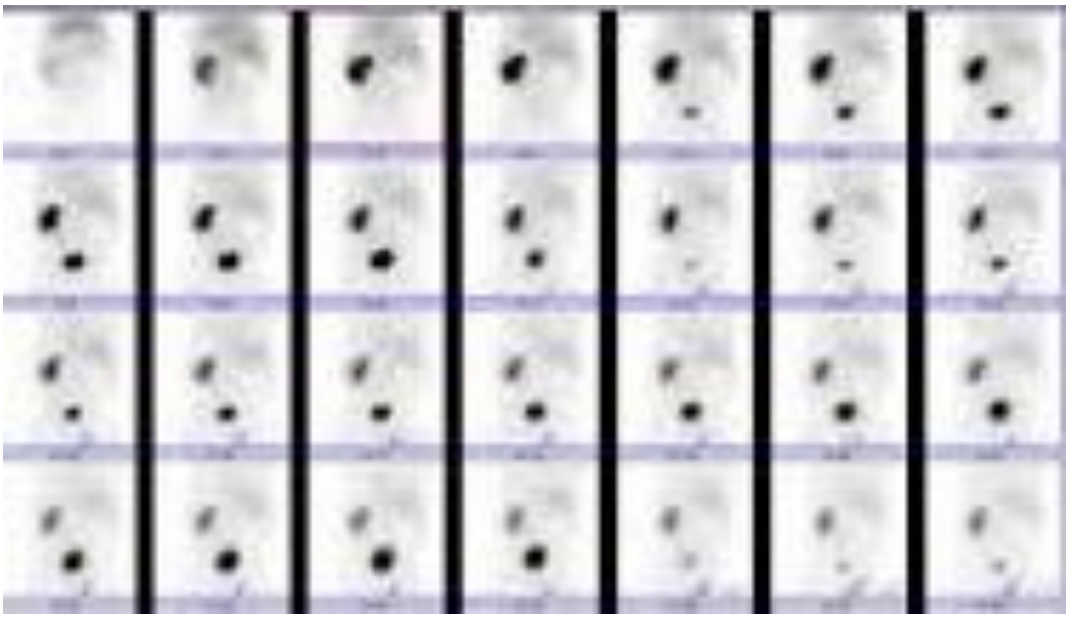


Figure 1.2: Mercaptoacetoacetyltriglycine (Mag3) scan of one of our patients. Showing lack of tracer uptake in area of right kidney

1.4 Prognosis of MCDK

The risk for chronic kidney disease (CKD) is negligent in MCDK but increases if the contralateral kidney has an abnormality (15). Generally MCDK has a favourable outcome.

1.5 Our experience at CHBAH (Chris Hani Baragwanath Academic Hospital)

Children presenting with kidney disease are referred to paediatric nephrology for investigation and management. The department of nephrology at the CHBAH was established in the late 1970's. To our knowledge, there is no data on the burden, clinical, laboratory or radiological presentation of MCKD in Africa. The aim of this long-term retrospective review is to describe the epidemiology of MCKD in a resource limited setting where antenatal diagnostic ultrasounds are limited. The data was obtained from the paediatric renal clinic at CHBAH to complete the study.

2.0 Objectives

2.1 To describe the clinical, laboratory and radiological characteristics of MCDK in children less than 15 years of age at the CHBAH.

2.2 To determine the outcomes of children with MCDK.

2.3 To determine the rate of lost to follow-up in children with MCDK

3.0 Methods

3.1 Study Design

This was a retrospective descriptive study. Case records of children less than 15 years of age with MCDK disease who were seen at CHBAH from January 1986 to December 2015 were reviewed.

3.2 Study population

CHBAH is the only government funded tertiary paediatric hospital to the residents of Soweto and surrounding areas. In addition, the hospital's catchment area for complicated renal pathology extends into other provinces, especially North West Province, and part of the neighbouring countries. Soweto is a peri-urban black-African community, situated south of Johannesburg, and has a large number of migrants living in informal settlements. Most residents are from lower socio-economic backgrounds and approximately 45% are unemployed (17). Most residents of Soweto are thus forced to utilise free government health care services.

3.3 Study Method

Children diagnosed with MCKD at CHBAH over the last 30 years have clinical and laboratory/radiological records stored in the department of paediatric nephrology. These files are clearly labelled and easily accessible to retrieve patient records. All files marked with a diagnosis of MCKD were retrieved. Clinical, laboratory and radiological information was collected and entered onto a specifically designed data collection sheet, documenting demographic information, the clinical presentation and patient outcomes, at baseline and at subsequent visits. The sex, age of presentation, presenting complaints, side of the MCDK, referral hospital, opposite kidney

abnormality and surgical interventions were recorded. MCDK were separated into two groups, simple and complex MCDK. Simple MCDK was defined as a unilateral dysplasia and normal contralateral kidney and complex MCDK was defined as bilateral dysplasia or abnormality of contralateral kidney (2, 10). A urine-dipsticks result from each visit was documented. Blood markers such were obtained from patient records and GFR (Glomerular Filtration Rate) calculated. Available ultrasound, voiding cysto-urethrogram and radio-nucleotide scan findings were recorded.

3.4 Sample Size Calculation

As this is a long-term descriptive retrospective study, no sample calculation was done.

3.5 Data Analysis

Data from study-specific data collection forms were entered into a specially designed database. Demographic and clinical findings which include laboratory and radiological characteristics was reported. Continuous variables were reported using means or medians depending on the distribution of the data. Categorical variables were reported as proportions. Clinical, laboratory and radiological data was compared at baseline to subsequent visits using the Student t-test, Pearson chi-squared or Fischer's exact test. 95% confidence intervals and $p<0.05$ was considered to be statistically significant. Data has been analysed using STATA version 13.1 (College Station, Texas, USA).

This study has been approved by the Human Research Ethics Committee of the University of Witwatersrand (M161027).

4.0 Results

4.1 Demographic data

Characteristics of the patients over the thirty year period were noted. The median age of presentation was 19 days with an IQR (Interquartile Range) of six to 121 days. The patients were divided in two groups. The first group were patients that had simple MCDK and the second group had complex MCDK. The median age of presentation was 19 days (IQR six to 191 days) in the simple MCDK and 17 days in complex MCDK (IQR nine to 34 days).

The total numbers of patients were 59. Of these only eight (13.6%) patients were complex MCDK. Seven (11.9%) patients had PUJ (Posterior Urethral Junction) obstruction on the opposite side. Three of these patients needed pyeloplasty. One (1.7%) patient had a ureteric stricture and was treated conservatively.

There were an increased number of males compared to females. In total there were 36 (61.0%) males and 23 (49.0%) females. The simple MCDK had 30 (55.8%) males whereas the complex MCDK had six (75.0%) males. These values were not found to be statistically significantly different in the two groups.

Table 4.1: Demographic characteristics of patients stratified by simple and complex Multicystic Dysplastic Kidney (MCDK) disease

Characteristics	Overall n=59 (%)	Simple n=51 (%)	Complex n=8 (%)	p-value[1]
Gender				
Male	36 (61.0)	30 (55.8)	6 (75.0)	0.464
Age (days) at presentation				
Median (IQR)	19 (6-121)	19 (6-191)	17 (9-34)	0.698
Side of MCDK				
Right	28 (47.5)	23 (45.1)	5 (62.5)	0.458
Left	31 (52.5)	28 (54.9)	3 (37.5)	
Presenting complaint[2]				
Antenatal ultrasound	11	10	1	0.564
Abdominal mass	29	23	6	
Antenatal ultrasound and mass	9	9	0	
Urinary tract infection	7	6	1	
Acute kidney injury	2	2	0	
Incidental cardiac catheterization finding	1	1	0	
Incidental ultrasound finding	6	6	0	
Referral Other hospital	20 (33.9)	15 (29.4)	5 (62.5)	0.106

[1]p-value - using the chi-squared, Fishers exact or Mann Whitney test, [2]Patients may have had more than one presenting complaint

Table 4.2: Age stratification at diagnosis

Age	**Number (n=59)**	**Percentage**
Prenatal	20	33.9
<1 month	15	25.4
1 month to 1 year	18	30.5
>1 year	6	10.2

Table 4.3: Opposite kidney abnormality of patients stratified by simple and complex Multicystic Dysplastic Kidney (MCDK) disease

Opposite Kidney Abnormality	**Overall n=59 (%)**	**Simple n=51 (%)**	**Complex n=8 (%)**	**p-value[1]**
PUJ[3] obstruction	7 (11.9)	0	7 (87.5)	-
Ureteric stricture	1 (1.7)	0	1 (12.5)	
VCU[4]	*n=43*	*n=35*	*n=8*	
Reflux into MCDK	1 (2.3)	0	1 (12.5)	0.186
Normal	42 (97.7)	35 (100)	7 (87.5)	

[3]PUJ- Posterior Urethral Junction, [4]VCU- Voiding Cystourethrogram

The weight, height/length and BMI (Body Mass Index) at presentation and at the last visit are shown in the Figure 4.1 below. No significant differences in weight for age, length/height for age and BMI for age were observed in children with MCDK when comparing these parameters between presentation and at the last visit.

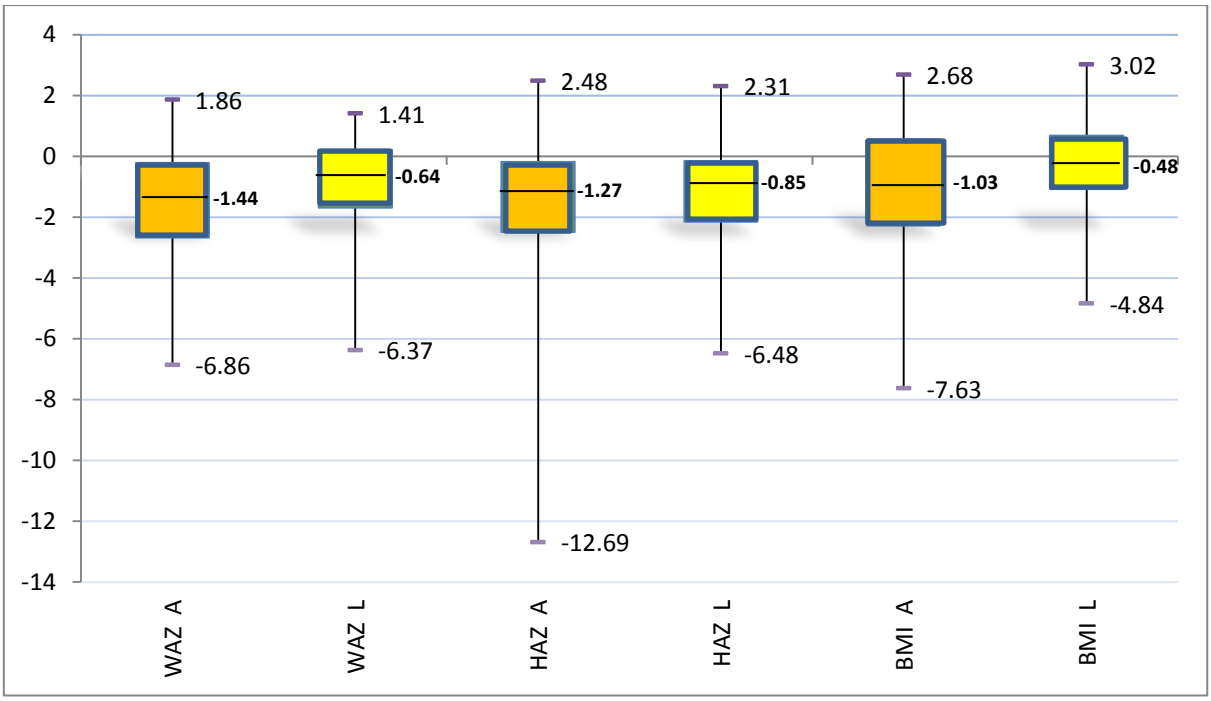


Figure 4.1: Box and whisker plot for weight, height and BMI at admission and last visit

Footnote: WAZ A/L-Weight for age z score at admission/last visit, HAZ A/L - Height/length for age z score at admission/last visit, BMI A/L - Body mass index for age z score at admission/last visit

4.2 Clinical Parameters

The presenting complaints varied. The majority of the patients presented with an abdominal mass (49%) 29 of total patients (Table 4.1). Antenatal ultrasound diagnosis of MCKD was made in 11 (18.6%) patients; a further nine patients were, in addition to presenting with a mass, also found to have been diagnosed on antenatal ultrasound making it a total of 33.9%. UTI was found in seven patients at presentation. However 11 patients grew organisms on urine culture. Two patients presented with AKI (Acute Kidney Injury). One patient was referred from cardiology after a cardiac catheterisation study showing lack of uptake of contrast during the study. Six patients were found to have MCDK incidentally during an ultrasound study. These characteristics were not compared between the two groups because some had multiple presentations. Some patients presented with more than one complaint and hence a statistical analysis was not done between the simple and complex MCDK groups.

Twenty of the patients were referred to our hospital from outside of Soweto. Although not statistically significant a higher percentage of the complex MCDK (62.5%) were referred compared to the simple MCDK (29.4%). None of our patients tested for HIV (Human Immunodeficiency Virus) were found to be positive. However 29 patients (49.2%) were not tested.

The left sided MCDK was found be more common in both groups. Left sided simple MCDK was observed in 52.5% of the patients and left sided complex MCDK was observed in 54.9% of the patients. In our patients over the 30 years only four patients had nephrectomies done. One had the nephrectomy together with a pyeloplasty.

4.3 Urinary tract infection

At presentation 11 patients were shown to have proven urinary tract infections. Eight patients had *Escherichia coli*, two of which had complex MCDK. Two patients had *Klebsiella* species and one had a *Candida* species.

Besides the children with UTI none of the urine dipsticks showed significant proteinuria or haematuria.

Table 4.4: Cultured organisms in children with a urinary tract infection (UTI) stratified by simple and complex Multicystic Dysplastic Kidney (MCDK) disease

Organism	**Overall n=59 (%)**	**Simple n=51 (%)**	**Complex n=8 (%)**
Escherichia coli	8 (13.6)	6 (11.8)	2 (25.0)
Klebsiella species	2 (3.4)	2 (3.9)	0
Candida species	1 (1.7)	1 (2.0)	0

4.4 Radiological investigations

A number of imaging modalities were used to investigate MCDK patients (Table 4.5).
All patients had abdominal ultrasounds done. Ultrasounds were repeated in some patients up to six times. In our 59 patients 58 patients had at least one nuclear scan done. Patients without proven non-functional kidney were excluded from our study. A further 20 patients had a second scan and four patients had three scans.

VCU is one of the routine investigations done to rule out VUR. In our study, 43 patients had VCUs including all eight with complex MCDK patients. None of the patients in our study had reflux into the contralateral kidney (see Table.4.3 above). One patient had reflux into the MCDK. The radiological investigations done are shown in Table 4.5.

Table 4.5: Frequency of radiological investigations of patients stratified by simple and complex Multicystic Dysplastic Kidney (MCDK) disease

Imaging Type	Overall n=59	Simple n=51	Complex n=8
1st Nuclear Scan	58	50	8
Mag 3[1]	42	36	6
DTPA[2]	4	4	0
DMSA[3]	12	10	2
2nd Nuclear Scan	20	15	5
Mag 3	9	6	3
DTPA	4	3	1
DMSA	7	6	1
3rd Nuclear Scan	4	1	3
Mag 3	3	0	3
DMSA	1	1	0
1st VCU[4]	43	35	8
2nd VCU	3	1	2
1st Ultrasound	58	50	8
2nd Ultrasound	31	24	7
3rd Ultrasound	20	13	7
4th Ultrasound	6	4	2
5th Ultrasound	3	3	0
6th Ultrasound	1	1	0
CAT[5] Scan Abdomen	6	5	1
MRU[6]	3	2	1
IVP[7]	6	3	2
Angiogram	1	1	0

[1]Mag3-Mercaptoacetoacetyltriglycine scan, [2]DTPA-Diethylenetriaminepentacetate scan, [3]DMSA-Dimercaptosuccinic Acid scan, [4]VCU-Voiding Cystourethrogram, [5]CAT-Computerised Axial Tomography, [6]MRU- Magnetic Resonance Urography, [7]IVP-Intravenous pyelogram

4.5 Renal surgical interventions

Seven of the patients needed renal surgical intervention. Table 4.6 below shows the procedures done and stratifies it according to simple and complex MCDK. The statistical significance was not calculated since all correctable surgery was done on complex MCDK and preventative surgery on simple MCDK.

Table 4.6: Renal surgery of patients stratified by simple and complex Multicystic Dysplastic Kidney (MCDK) disease

Surgical procedure	Overall n=59 (%)	Simple n=51 (%)	Complex n=8 (%)
Nephrectomy	3 (5.1)	3 (5.9)	0
PUJ pyeloplasty	2 (3.4)	0	2 (25.0)
Nephrectomy & pyeloplasty	1 (1.7)	0	1 (12.5)
Orchidopexy	1 (1.7)	0	1 (12.5)

4.6 Glomerular filtration rate

The GFR was calculated using the Schwartz formula (18). The results are shown in Table 4.7 below. The creatinine is calculated using the modified Jaffe method in our laboratory which uses the Roche Cobas® 8000 machine. At the first visit we calculated 41 of the 59 patients GFR. Those patients whose creatinine or height/length were not available could not be calculated. Most of the patients were very young. At the last visit many patients did not have their bloods done and only ten patients could have their GFR calculated. Patients older than two years and those that had bloods done before their last visit or before being loss to follow up had their GFR calculated. Of our 59 patients 31 were older than two years old and 25 had bloods done to calculate GFR.

Table 4.7: Glomerular filtration rate (GFR) at admission, last visit and last calculable value

	Number	Median GFR (ml/min/1.73m^2)	Interquartile Range (ml/min/1.73m^2)
Admission	41	45.4	25.5 to 71.8
Last visit	10	130.4	108.2 to 164.5
Last calculable value[1]	25	157.0	129.7 to 174.6

[1]Last calculable value- GFR of patients older than 2 years with last available creatinine and height

4.7 Outcomes

The outcomes of patients are outlined in Table 4.8 and in Figure 4.2. Of the patients that presented to us three were palliated. They were all young patients, two with CKD and one with Trisomy 13. Two were complex with a hypoplastic contralateral kidney and had a Potter's like sequence presenting with respiratory distress and both needing ventilation. The simple MCDK patient had trisomy 13. Only three (5.1%) over the 30 year period were transferred to adult clinic. The majority of patients twenty nine (49.2%) were lost to follow up and twenty four (40.7%) are currently being followed up at our follow up clinic.

Duration of follow up days was not significantly different between the simple and complex MCDK patients. In fact it was almost identical. The age at last visit was also not statistically significant. Simple MCDK 631 days (IQR 218-3555 days) versus complex MCDK 635 days (IQR 200 – 3747 days) with a p-value of 0.808.

Table 4.8: Outcomes of patients with simple and complex Multicystic Dysplastic Kidney (MCDK) disease

	Overall n=59 (%)	**Simple n=51 (%)**	**Complex n=8 (%)**	**p-value[1]**
Outcome				
Demised	3 (5.1)	1 (2.0)	2 (25.0)	[2]
Lost to follow-up	29 (49.2)	26 (51.0)	3 (37.5)	
Currently follow-up	24 (40.7)	21 (41.2)	3 (37.5)	
Transferred to adult services	3 (5.1)	3 (5.8)	0	
Duration of follow-up (days)				
Median (IQR[3])	631 (147-3037)	631 (147-3073)	582 (185-3736)	0.938
Age at last visit (days)				
Median (IQR)	870 (218-3555)	870 (218-3855)	635 (200-3747)	0.808

[1]p-value - using the chi-squared, Fishers exact or Mann Whitney test, [2] the statistical calculation was not done due to the extremely small numbers, [3]IQR-interquartile range

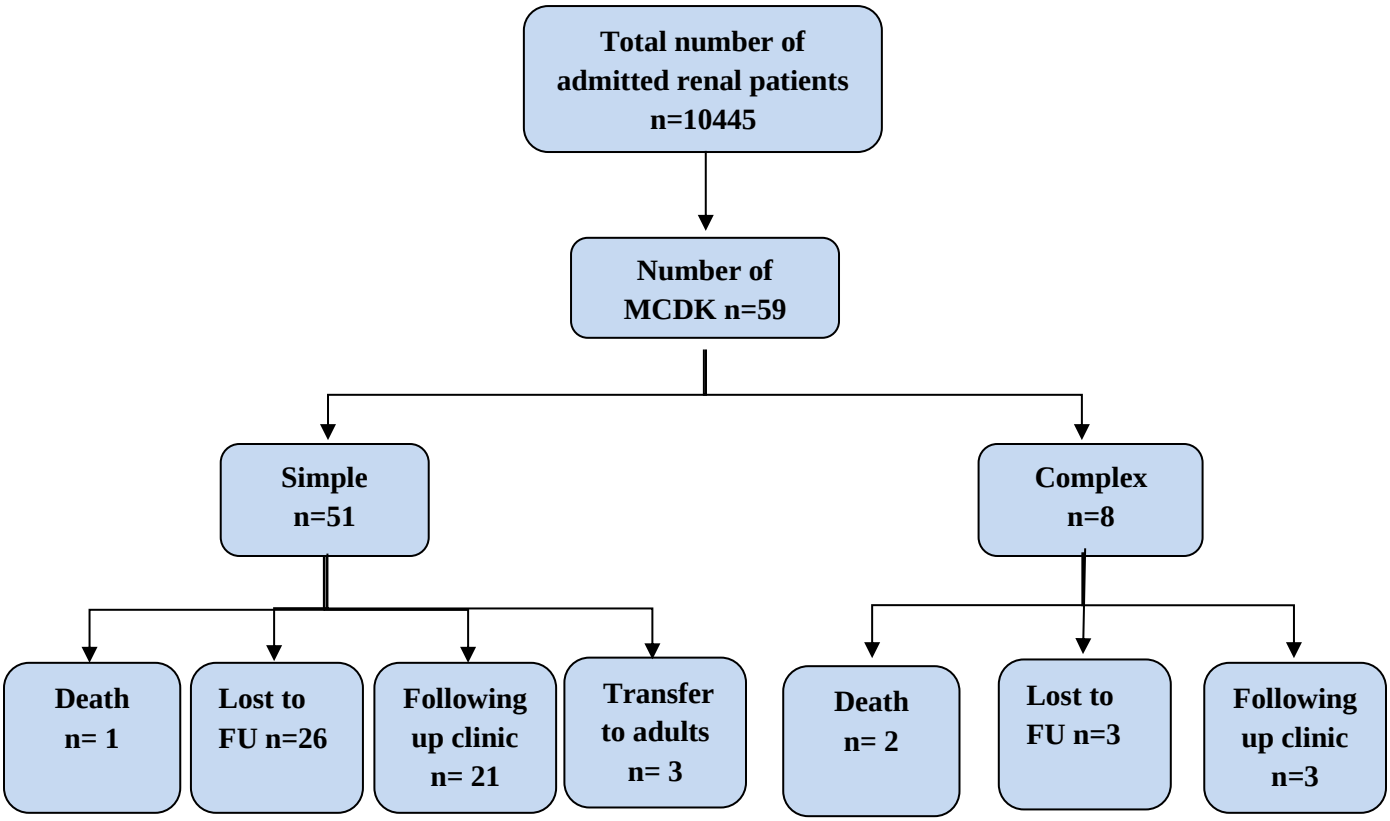


Figure 4.2: Flow diagram showing the outcome of patients with MCDK stratified by simple and complex MCDK

4.8 Changes in antenatal presentation over study period

An analysis of the patients was done over the three decades, 1986 to 1995, 1996 to 2005 and 2006 to 2015.See Table 4.9. In terms of the number of patients, of the 59 in this study nine (15.25%) were in the first decade, 22 (37.29%) were in the second decade and 28 (47.5%) were in the third decade. In the first decade no patients were diagnosed with antenatal ultrasound, seven in the second decade and 13 in the third decade. Comparing the first decade and the third decade in terms of the number of patients diagnosed with ultrasound there is significant statistical difference with a p-value of 0.015.

Table 4.9: Proportion of patients diagnosed on antenatal ultrasound over three decades

	1986 to 1995	**1996 to 2005**	**2006 to 2015**	**p-value[1]**
Number of patients with MCDK disease	n=9	n=22	n=28	
Proportion of patients diagnosed by antenatal ultrasound	0	7 (31.2)	13 (46.4)	0.015

[1]p-value -comparing the 1st and 3rd decade using a Fishers exact test

5.0 Discussion

The number of patients in our series over 30 years was only 59. Separating the patients into three separate epochs, of ten years each, demonstrated a progressive increase in our numbers with each successive decade (Table 4.9). This was most likely due to the increased use of antenatal ultrasound. The most common abnormalities detected by antenatal screening are those of the urinary tract (19). The incidence of MCDK is quoted as 1 in 1000 to 1 in 4300 births (1, 4). However this figure has never been evaluated in Africa. It is possible that there is a genetic variance, and hence a different incidence, in Africa but the statistical difference between the first and third decade ($p=0.015$) indicates that we can expect an increase in the detection number of cases of MCDK over the coming years. This follows international trends where more patients are being diagnosed on antenatal ultrasound as it became more freely available (6). In fact MCDK has been described as a diagnosis that is increasingly rare in the postnatal period (9). Only 33.89% of the patients were diagnosed antenatally in our series of patients. The numbers have almost doubled in the third decade from the first decade. If this trend continues, even at a conservative figure, we should be seeing one MCDK in 4300 live births. Soweto has approximately 25 000 births per annum (20) which would translate into 5.8 cases per year i.e. 58 per decade or 174 in three decades. Of our patients in the clinic 33.9% were referred from outside of Soweto, which means we should have at least 263 patients in this series. This demonstrates that if we are not prepared for this load of patients in the nephrology department we will be swamped with MCDK disease. Internationally there seems to be an increase in MCDK as well as other urinary tract abnormalities. This could be attributed to better trained radiologists with more sensitive equipment (19). Ylinen and Wikstrom also suggest that diabetic mothers have an increased risk of MCDK in their children leading to the increasing incidence of MCDK (21).

The differentiation of patients into simple and complex is important as many authors have shown the differences in outcome between the two groups (2, 10, 11). We have also analyzed our data showing our patients in these two categories. But the number of patients in the complex MCDK was only eight (13.6%) and too small a number to show statistical significance as shown in many of the tables in the Results section above. In the study by Hayes et al, they had 14% of their patients with contralateral abnormality of the kidney (22). This is similar to our results but our numbers are small. In the paper by Psooy it is recommended that patients with simple MCDK should be followed by primary health care workers as opposed to those with complex MCDK

who should be followed up by specialist clinics (23). In a resource limited setting it is essential to rationalize these resources. Feldenberg and Siegel found 40% of their patients to have complex MCDK with 50% of the complex MCDK in CRF or ESRD requiring RRT (2). They concluded that the prognosis is poorer in complex MCDK. They had only 35 patients of whom 14 were complex MCDK, thus the numbers were small making it difficult to interpret or draw definitive conclusions.

On literature review the meta-analysis by Schreuder et al best demonstrated the increased number of males (59.2%) and left sided MCDK (53.1%) in which 67 cohorts were reviewed (6). Our set of patients showed more males (61%) and more left sided kidneys (52.5%) involved. This is in keeping with the international trends. Why this is more than the 51% expected in males is not clear but consistent in both MCDK and in other renal malformations (6).

The median age of presentation was 19 days which was no different from the literature review. Figure 4.1 show that the children born with MCDK grew well. A lot more children caught up their growth at their last visit. A possible reason for the increased number of children below the -2 SD at first presentation could be due to the fact that majority of the children presented in the neonatal period. This study is a retrospective study and it was not possible to determine if the patients were premature, small for gestation or both. The patients seem to have caught up growth by the time they came to their last visit as seen in Figure 4.1. This shows normal growth of children born with MCDK.

The presenting complaints varied. Initial literature showed similar results, however many of these centres now have very high percentage of antenatal ultrasound diagnosed MCDK. Unless we have a significantly different predisposition in our population we should see an increase in the number of patients diagnosed with MCDK.

UTI as a presenting complaint was found in seven patients but confirmed UTI with an organism was found in 11 patients at presentation. This difference can be explained by the fact that the majority of the patients were neonates (median age of 17 days) and neonates have non-specific symptoms and signs because they are immuno-compromised. The organisms grown were typically as expected as shown in Table 4.4 (24).

Twenty of our patients were referred from hospitals outside of the Soweto region. Since we are a tertiary centre this is expected. This does highlight the fact that over a 30 year period we have only seen thirty nine patients from Soweto. We saw 29.4% simple MCDK and 62.5% complex MCDK patients referred from these hospitals. This was as expected as complex MCDK is more complicated (2), however the actual number of complex MCDK were too few to make any statistical significance.

In the era when HIV prevalence was very high it is surprising that none of the patients that were tested was positive. A large percentage (49.2%) was not tested. 87.5% of the complex MCDK tested negative for HIV. Again due to the small numbers it is difficult to evaluate statistically.

The contralateral kidney abnormality was predominantly PUJ obstruction in seven (87.5%) patients of which 42.9% needed pyeloplasty. See Table 4.6. One patient had ureteric stricture which did not need intervention. Ureteric stricture associated with MCDK has been reported as a case study (25). Other studies showed a variety of abnormalities and the most common being VUR (6). None of our patients had VUR in the contralateral kidney.

Only four (6.7%) patients had nephrectomies done. There were no patients with malignancies. All the nephrectomies were done to avoid any malignancies from developing. Some studies have shown that the risk of malignancies is at most equivalent to that of the normal paediatric population (23, 26). These studies have concluded there is no real risk for malignant transformation. Homsy et al showed two cases of early transformation of MCDK remnant tissue to become Wilms Tumour (27). Five other cases have been documented but with questionable certainty (10). These two cases are not sufficient to conclude the need for nephrectomy. However the review by Truong et al suggest that there is insufficient evidence to link malignancy to MCDK (28). Thus there is a need for good transition of patients from paediatric to adult services so that this population can be monitored carefully for malignancies in the adult services.

One of the associations with MCDK is undescended testes and it is only beginning to be described as an association (5). In our series it is difficult to comment due to our study being a retrospective; however we did have one patient who had orchidopexy done. Feldenberg and

Siegel also found one patient with undescended testes (2). Carazo-Palacios et al found 10.7% of their patients with cryptorchidism (3). Specifically checking for undescended testes should be done routinely in all males with MCDK. The Canadian Urology Society now advocates to routinely look for anomalies of internal genitalia associated with MCDK (10).

First radiological study on our patients was abdominal sonography. All our patients had at least one ultrasound scan and one as many as 6 ultrasound scans. It is an excellent mode to detect MCDK, but it is operator and apparatus dependant. In our setting we have a variety of people ranging from training radiographers, radiology registrars, fellows in paediatric radiology to experienced paediatric radiologists doing ultrasonography. We also have a high turnover of staff in our radiology department. Due to these factors the actual diagnosis of MCDK could be missed and a confirmatory functional nuclear scan is generally required. Only one patient did not have a nuclear scan to confirm a non-functional kidney. This patient had a CAT (Computerised Axial Tomography) scan of the abdomen which confirmed a non-functional kidney. A few patients were not included in the study because they had nuclear scans that showed function in the kidney and hence excluded as MCDK. This is in contrast to the experience of Carazo-Palacios et al which showed a 100% positive predictive value of renal ultrasound to diagnose MCDK and question the need of a radio nuclear scan (3).

Routine VCU in MCDK were encouraged by the study done by Zerin and Leiser (29). A number of studies have questioned the routine use of VCU in MCDK patients (16, 30). These are in centres that have high rates of VUR. VUR is also described as the most common abnormality associated with the contralateral kidney in patients with MCDK (31). This is confirmed by the meta-analysis done by Schreuder et al showing VUR to be the most common abnormality in MCDK at 19.7% (6). The majority of our patients, 43 (72.9%) had a VCU done. In our setting not a single patient had reflux into the opposite kidney and only one patient had mild reflux in the MCDK. This finding of low rate of reflux is shown to be true in our population in the study by Kala and Jacobs (24) in which they looked at reflux in malnourished children at the same hospital. Selzman and Elder showed 4% of black patients as opposed to 22% of white patients with MCDK had contralateral VUR (32). These studies imply that there might be a genetic predisposition in African children to be less likely to have VUR. Hence routine VCU in our patients should not be done. The cost effectiveness of this is huge in terms of discomfort,

irradiation and finance. This is more so in our resource limited environment. This is in contrast to recommendation by Kaneko et al who found VUR the most common contralateral abnormality (33) and a VCU was recommended. Kanyema et al did a study in solitary kidneys and came to the same conclusion (34). However in the commentary by Friedman, the recommendation is not to do routine VCU even in patients that commonly have VUR (35).

A number of patients had a variety of imaging done besides ultrasound (as shown in Table 4.5) including CT abdomen, retrograde pyelogram, MRU, IVP and angiogram. Follow up ultrasound is important to look for involution and compensatory hypertrophy in the opposite kidney. Our study could not define these due to the fact that ultrasound was not repeated at fixed intervals and hence difficult to compare. MCDK can involute prenatally in 5% of patients and then at any time after birth to many years later (9). It has been shown that the smaller the MCDK (<5 to 6 cm) the more likely it will involute (5, 36). Compensatory hypertrophy of the contralateral kidney has been surprisingly shown to occur intrauterine and at one, five, ten and fifteen years in 49, 78, 89 and 95% of patients respectively (5). Cardona-Grau and Kogan came to a conclusion in their study that limited radiological evaluation is preferable and further evaluation should be guided on clinical findings of hypertension, UTI and palpable mass or on the findings of an abdominal sonar (9). The study by Kalisvaart et al shows that even in a well-resourced setting ultrasonography is still preferred over MRU (37).

Three patients demised in the early period. One child was diagnosed with trisomy 13 and was palliated and demised but the renal function was normal. The other two children had CKD at diagnosis in the neonatal period and were palliated because we could not offer renal replacement therapy in this early age and both had severe respiratory distress requiring ventilation. One went home on oxygen for several months before demising, the other demised at an earlier age. The patients had hypoplastic kidneys and demonstrated a Potter's like sequence in their presentation. The lack of resources and poor prognosis in these children precluded them from renal replacement therapy. We also struggled to get post mortem due to cultural and religious believes. There is very little in the literature on CKD with unilateral MCDK.

At the other extreme we have managed to graduate three patients to adult services. At 5.1% it really requires a lot of work to improve. All three patients were from the simple MCDK group,

we would have expected that more would have been from the complex MCDK since they have poorer outcomes (2). Again, with the small numbers that we have, it is difficult to express the statistical significance and analyse it statistically. The largest group of patients were lost to follow up (49.2%). In the context of the good outcome of MCDK Mashat et al attributes the lost to follow up to the fact that the family are relieved at the good prognosis (38). However this trend of high percentage of patients lost to follow up seems to be constant in our population. A research project on MCNS showed a rate of 62% (39) and a research on prune belly syndrome showed a lost to follow up of 57% (40). Unpublished research by B Sangweni RN showed in the renal unit at Charlotte Maxeke Johannesburg Academic Hospital, one of the three hospitals attached to the University of the Witwatersrand, the average spend on transport to health care facilities ranged from 4.9 to 27.1% of the families total income depending on whether they did peritoneal or haemo-dialysis (41). This also partially explains the poor follow up. It also highlights the importance of social services in a setting were the government spends huge amounts on management of medical conditions but patients are lost to follow up due to lack of a small fraction of the actual spend for transport and social services to follow up and retrieve these patients. This emphasises the importance of a multidisciplinary and multi-departmental approach to get good outcomes and the prudent use of our limited resources. In the study by Mallik et al they had 3.4% of their patients lost to follow up (19). This demonstrates how much can be achieved in improving our follow up rate. We had 49.2% of our patients lost to follow up clinic. Possibly new strategies to include in their management: increased counselling of patients and parents, decreased number of follow up visits per year, and an increased use of social services would improve the number of patients being followed up and decrease the number lost to follow up clinic.

The median age at last visit is 2.4 years and the median duration of follow up is 1.7 years. This is in contrast to the study by the Trent and Anglia MCDK study group where median follow up was 10.1 years (22).

The figure 4.2 summarises the outcome of our patients. Of note is the fact that the prevalence of MCDK of all our renal patients at our clinic over the 30 years is 5.7 per 1000 renal patients admitted in CHBAH. This seems to imply that many of our MCDK are missed due to the fact that very few patients have antenatal ultrasound. There is a current drive in the National

Department of Health to increase the number of ANC (antenatal) visits among pregnant women. This will also translate to increased number of pregnant women getting antenatal ultrasounds in a country where antenatal ultrasound are done in few patients as highlighted by Stewart (8). As the number of ultrasounds done antenatally increase there will be more patients with MCDK diagnosed. Statistical significance of this is shown in our study as seen in Table 4.9. With this increase, our renal services are going to be put under pressure in terms of resources. Rationalisation and protocol driven services will help streamline this process. The European renal anomaly detection program in which more than 700 000 foetal examinations were done showed MCDK in 0.014% of the patients (42). This clearly shows that the number of patients with MCDK can be overwhelming.

The eGFR (estimated Glomerular Filtration Rate) using the modified Schwartz formula (18) on presentation was low, median of 45.4 ml/min/1.73m^2 (IQ 25.3 – 71.83 ml/min/1.73m^2). This was due to the fact that most of the children were neonates. There were a total of 41 patients on whom we could calculate eGFR at the first visit. The others did not have eGFR calculated due to missing length/height or creatinine at presentation. At the last visit the eGFR was much higher, median of 130.4 ml/min/1.73m^2 (IQR 108.2–164.5 ml/min/1.73m^2). In this group only ten patients' eGFR could be calculated primarily due to the fact that they were the only patients on whom bloods were taken at the last visit. Two children were less than two years, and the other eight were above two years old. The eGFR in these patients showed that three of the ten patients have hyperfiltration but all without proteinuria. We further analysed the eGFR of 25 patients. They were all above the age of two years and had bloods done. This was out of a group of 31 patients. The results clearly showed hyperfiltration with a median of 157.0 ml/min/1.73m^2 (IQR129.7 to 174.6 ml/min/1.73m^2) all without proteinuria. In the study by Sharada et al they showed 29% of their patients had sub-nephrotic proteinuria and all had complete involution of the MCDK, proposing that it was all due to hyperfiltration (43). None of our patients had CKD. Hayes et al in their study found a median eGFR of 93 ml/min/1.73m^2 (range 47 – 181 ml/min/1.73 m^2) (22). In the same study they found 40 patients with normal eGFR, 33 patients were classified as CKD 2 and two patients with eGFR > 160 ml/min/1.73m^2 without proteinuria. This concern is due to Brenner's hypothesis of hyperfiltration. This is possibly compounded by the fact that we also have increasing number of premature births who also have a predisposition to decrease in number of glomeruli according to Barker's hypothesis (44). Mansoor et al also

found patients with CKD and proteinuria (45). Hence we need to monitor the eGFR in these patients for life. None of our patients had CKD outside of the neonatal period. However our eGFR was much higher than other studies (22, 38, 46) and this could point towards a genetic predisposition as well as a possible increase risk of CKD/ESRD. This needs more research and investigation, but black African paediatric patients in our cohort seem not to have proteinuria.

Of all our patients only three (5.1%) patients were diagnosed with hypertension and were put on treatment. Hypertension was found to be very low (5.4 per thousand) in patients with MCDK in the study done by Narchi et al as opposed to the normal population rate of 4-5% (13). This low to normal rate was supported by other subsequent studies (2, 5, 47).

No patient was diagnosed with any form of malignancy. This is in keeping with the systemic review done by Narchi et al in which none of the 1041 patients reported had Wilms tumour in all of the 26 studies that were reviewed (26). Eickmeyer et al also did not find any malignancy in 300 patients studied over 30 years (5). This has been the reason why paediatric nephrologists have opted for conservative treatment and stopped nephrectomies to prevent Wilms tumour or other malignancies from the remnants of MCDK. The review by Psooy indicates that there is a possibility of renal cell carcinoma in adulthood but further studies are required to prove this association (10).

Proteinuria, CKD, HPT and the possibility of malignancy are factors that may become a problem in adulthood. Hence MCKD patients need closer monitoring and better transition to adult services. There seem to be very few longitudinal follow up studies out of the paediatric age range since single kidney/MCKD patients form a very small percentage of CKD/ESRD in adults (48).

The main limitations of the study were that it was a retrospective review, with a lack of stringent protocol for investigations and a very high rate of loss to follow up.

6.0 Conclusion

The demographics of the patients in our study essentially are very similar to other studies done worldwide. It should be noted that this is the first description of MCDK from Africa. Over a period of 30 years we have had only 59 patients out of 10445 renal patients admitted in our nephrology services over this period. This is more likely due to the small percentage of pregnant women that are offered antenatal ultrasounds. Our study showed a statistical difference in the number of patients diagnosed with MCDK in the first and third decade of the patients reviewed in this series. It also showed that the number of children diagnosed increased from nine to 28 in this period. This seems to indicate that with increased antenatal diagnosis we should approximate the international incidence. However there is a possibility that our population might have a different predisposition to MCDK. All studies seem to indicate the incidence to be 1 in 1000 to 1 in 3700 live births**.**

Out of 43 children who had VCUs done only one child had reflux and that was into the MCDK. The recommendation of decreased number of VCU is in keeping with worldwide recommendations (6, 9, 30, 35) and due to our low rate of reflux we can stop routine VCU for MCDK.

Although there is a sentiment that it would be safe to diagnose MCDK in most cases without nuclear imaging, I strongly recommend that we continue to do nuclear imaging on every MCDK patient to confirm diagnosis due to the fact that we do not have a dedicated and experienced sonography services and the radio nucleotide demonstrated unequivocally non function in the kidney.

The two early deaths from CKD were patients with Potter's like sequence who had severe hypoplastic contralateral kidneys. Post mortem studies would have assisted in the diagnosis but that is difficult in our setting due to cultural, belief systems and socio-economic reasons.

An important differentiation to be made in MCDK is to separate them into simple MCDK and complex MCDK. In this study the patients were separated into the two groups but there were too few cases of complex MCDK and hence very difficult to show any statistical differences. More investigations in this area needs to done with larger numbers in a prospective study.

The small number of patients being transferred to adult services is worrying since the majority of the patients are lost to follow up clinic. This trend needs to be addressed and an attempt has to be made to reverse it. Firstly, by intensive counselling and education of the patients and their families on presentation by doctors, nursing staff and counsellors. Secondly, the utilisation of social workers to contact patients missing their appointments and providing transport to attend the clinic. Thirdly, the stream lining of services with an attempt to decrease the number of visits a patient has to attend.

7.0 Recommendations

The recommendations emerging from this study are as follows:

1. VCU should not be done routinely on patients with MCDK, more so in patients of Black African descent.
2. Patients with MCDK should be separated into simple and complex MCDK. The simple group does not need to be followed up as closely as the complex group.
3. All patients with MCDK need to be followed up to monitor for proteinuria, hypertension and CRF.
4. More research needs to be done to monitor patients beyond the paediatric age group to monitor if they have a genuine predisposition to malignancies and or CKD.
5. All our patients need more counselling and social services intervention. Recommendations and interventions at provincial and central government needs to be advocated for, so as to improve follow up of these and other chronically ill patients. In light of the fact that resources are being spent on investigations and management of these patients but are lost to follow up due to lack of transport money and poor social circumstances.
6. The utilisation of antenatal sonars should be encouraged to allow for early detection of patients with MCDK and other congenital abnormality allowing for early intervention and management to improve outcomes. In severe bilateral involvement of the kidneys termination of pregnancy can be offered.
7. The follow up of MCDK should be protocol driven especially as the number being diagnosed increases.
8. Undescended testis need to be checked for in every boy with MCDK.
9. Utilisation of telephonic reminders for the clinic dates using short message services (SMS) to improve attendance at follow up clinic.

8.0 References

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9.0 Appendices

Appendix A: Ethics clearance certificate

R14/49 Dr Nilesh Lala

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M161027

NAME: (Principal Investigator)	Dr Nilesh Lala
DEPARTMENT:	School of Clinical Medicine Division of Paediatrics Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Multicystic Dysplastic Kidney Disease at Chris Hani Baragwanath Academic Hospital over a Thirty Year Period
DATE CONSIDERED:	28/10/2016
DECISION: CONDITIONS:	Approved unconditionally
SUPERVISOR:	Prof Udai Kala
APPROVED BY:	Prof C Feldman, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	20/12/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in October and will therefore be due in the month of October each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 22 · 12 2016

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix B: Data Collection Sheet

Participant number:

Gender:

Date of Birth:

Date of presentation: Referred from:

Weight: ____kg

Height/Length: ____cm

HIV Status (positive/negative/exposed/unknown):

Urine dipstick (leucocytes, nitrites, protein, blood):

UTI (yes/no):

Organism on UTI:

Abdominal mass presentation (yes/no):

Intrauterine ultrasound done (yes/no):

Systolic BP: _____mmHg Diastolic BP: _____mmHg

Associated abnormality:

Blood results (Full Blood Count / Urea, Creatinine and electrolytes /Calcium, Phosphate/ HIV):

Date:

Results:

Follow up: Date:

Weight: _____kg

Height/Length: _____cm

Blood results (Full Blood Count / Urea, Creatinine and electrolytes / Calcium & Phosphate):

Imaging:

Abdomen ultrasound: Date:

Findings:

VCU: Date:

Findings:

Nuclear Scan: Date:

Type of Scan:

Findings:

Outcomes:

Death (yes/no):
ESRD (yes/no):
Surgery (yes/no):
Details: Type ___ Date ____
Transfer to adults (yes/no):
Lost to follow-up (yes/no): Date _____

Appendix C: Turnitin Report

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by Null Null

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