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Unilateral multicystic dysplastic kidney: a meta-analysis of observational studies on the incidence, associated urinary tract malformations and the contralateral kidney

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Abstract

Background. Many papers are published on cohorts with unilateral multicystic dysplastic kidney (MCDK) patients, but show variable results as to the incidence of associated urinary tract abnormalities. The objective of this study was to describe the status of the urinary tract, including contralateral hypertrophy and malformations, in patients with unilateral MCDK based on a meta-analysis of the literature, taking into account the timing of diagnosis (pre- versus postnatal) as a possible source of bias.

Methods. A systematic review of the scientific literature in English was conducted using PubMed and Embase. A meta-analysis was performed with the studies that were identified using our reproducible search.

Results. Based on analysis of the data in 19 populations, the overall incidence of unilateral MCDK is 1 in 4300 with an increasing trend over the years. A total of 67 cohorts with over 3500 patients with unilateral MCDK were included in the meta-analysis. Fifty-nine percent of patients were male and the MCDKs were significantly more often found on the left side (53.1%). Associated anomalies in the solitary functioning kidney were found in 1 in 3 patients, mainly vesicoureteric reflux (VUR, in 19.7%). In patients with VUR, 40% have severe contralateral VUR, defined as grade III–V. Contralateral hypertrophy, present in 77% of patients after a follow-up of at least 10 years, showed a trend to be less pronounced in patients with VUR. Timing of the diagnosis of MCDK did not essentially influence the results.

Conclusions. These aggregate results provide insight into the incidence, demographic data and associated anomalies in patients with unilateral MCDK. One in three patients with unilateral MCDK show anomalies in the contralateral, solitary functioning kidney. However, studies into the long-term consequences of these anomalies are scarce.

Keywords: meta-analysis; multicystic dysplastic kidney; urinary tract abnormalities; vesicoureteric reflux

Introduction

A multicystic dysplastic kidney (MCDK) is a form of renal dysplasia that leads to a non-functioning organ due to abnormal and incomplete kidney development. The first description of an MCDK at autopsy was in 1836, and the first description of an MCDK removed at surgery was reported a century later [1]. In 1955, MCDK was identified as a separate entity, distinct from polycystic kidneys, which it was generally clustered with until that time [2]. Edith Potter, in her book *Normal and Abnormal Development of the Kidney* [3], suggested that primary failure of nephron induction was the underlying mechanism leading to MCDKs, resulting in incompletely branched ducts surrounded by connective tissue, which contains undifferentiated and metaplastic cells such as cartilage- and smooth muscle-like cells. Even though no nephrogenic zone at any stage of nephrogenesis, and hence the complete absence of nephrons, was described by Potter, MCDKs sometimes do contain some functional renal tissue [4] with recognizable glomeruli and proximal tubules [5–10]. Alternatively, the disruption of normal nephrogenesis could, at least in part, be explained by an impaired fetal urine flow early in development, which is consistent with the general finding of non-patent or atretic ureters attached to MCDKs (for a review [11,12]).

Bilateral MCDK leads to absent fetal and neonatal renal function with associated pulmonary hypoplasia and is therefore generally considered incompatible with extra-uterine life [13]. However, unilateral MCDK is a condition that does not lead to any complaints *per se*, except for potential mechanical problems due to a large abdominal mass in rare cases [14]. Before the era of prenatal ultrasound screening, this condition was mainly diagnosed in patients that underwent ultrasound assessment of the renal tract for another reason like a urinary tract infection or a palpable abdominal mass. As many MCDKs are known to show spontaneous involution, even before birth, a significant proportion of

Table 1. Reported incidences of unilateral multicystic dysplastic kidney

Source	Year	Country	Age at diagnosis	Number of patients with unilateral MCDK	Size of population screened	Incidence
Helin [18]	1986	Sweden	Prenatal with postnatal confirmation	7	11 986	1/1712
Gordon [19]	1988	UK	Prenatal with postnatal confirmation	10	43 175	1/4318
Evans [20]	1989	Canada	NR	14	83 893	1/5992
Sheih [21]	1989	China	6–12 years	21	132 686	1/6318
Al-Khaldi [22]	1994	UK	Prenatal with postnatal confirmation	14	43 419	1/3101
Gloor [23]	1995	USA	Prenatal with postnatal confirmation	11	26 770	1/2434
Gunn [24]	1995	New Zealand	Prenatal with postnatal confirmation	8	3856	1/482
Kim [25]	1996	Korea	Prenatal	5	5442	1/1088
Liebeschuetz [26]	1997	UK	Prenatal with postnatal confirmation	14	33 537	1/2395
Dillon [27]	1998	UK	Prenatal with postnatal confirmation	10	25 382	1/2538
James [28]	1998	UK	Prenatal with postnatal confirmation	22	105 542	1/4797
Kessler [29]	1998	Israel	Various ages	23	NR	1/3310
Harmat [30]	2001	Hungary	Postnatal	13	46 858	1/3604
Vial [31]	2001	Switzerland	Prenatal with postnatal confirmation	23	38 110	1/1657
Hiraoka [17]	2002	Japan	Neonatal	1	4000	1/4000
Raboei [32]	2002	Saudi Arabia	Prenatal	21	19 400	1/924
Ylinen [33]	2002	Finland	Prenatal with postnatal confirmation	51	209 125	1/4100
Wiesel [34]	2005	Europe-wide	Prenatal with postnatal confirmation	105	709 030	1/6753
Mallik [35]	2008	UK	Prenatal with postnatal confirmation	21	46 060	1/2193
Overall[a]				371	1 588 271	1/4281
All cohorts with postnatal ultrasound confirmation of prenatal diagnosis of MCDK				296	1 295 992	1/4378

MCDK, multicystic dysplastic kidney. NR, not reported.
[a]Excluding the article by Kessler *et al*. [29] as the size of the screened population was not provided.

patients diagnosed in the era before antenatal ultrasound screening with unilateral renal agenesis (based on the absence of a single kidney) may actually have had a completely regressed MCDK [15–17]. This may explain part of the differences in the incidence of unilateral MCDK that have been reported (Table 1) [17–35]. Based on the available ultrasound data, the general incidence can be estimated to be around 1 in 4300.

MCDK has been described to be associated with general dysmorphologies and contralateral urinary tract abnormalities, like vesicoureteric reflux (VUR) and pelviureteric junction obstruction (PUJO). However, these associated anomalies have been reported in highly variable frequencies. A likely factor in this variation may be the timing of diagnosis of the MCDK (i.e. pre- versus postnatally). It may be anticipated that before the introduction of prenatal ultrasound screening, patients presenting with MCDK were the ones that had clinically relevant associated anomalies. This makes it important to differentiate between cohorts that are defined by prenatal screening and cohorts that are based on patients with MCDK that presented with clinical symptoms.

In this paper, we set out to describe the status of the urinary tract, including contralateral hypertrophy and malformations, in patients with unilateral MCDK based on a meta-analysis of the literature, taking into account the timing of diagnosis.

Materials and methods

Search strategy

A PubMed search was conducted for articles published from January 1966 onwards that contained the keywords ‘multicystic dysplastic kidney’ or ‘multicystic kidney dysplasia’ and/or were labelled with the Medical Subject Heading (MeSH) ‘multicystic dysplastic kidney’ (total hits 373, 2 June 2008). An Embase search was conducted with the search strategy ‘multicystic’ and (‘dysplastic’ or ‘dysplasia’/exp or ‘dysplasia’) and (‘kidney’/exp or ‘kidney’), resulting in 714 hits (2 June 2008). In addition, the ‘related articles’ function in PubMed was used from articles that were considered for inclusion. Also, reference lists from included publications were searched manually.

Selection of articles

All cohort studies describing the pre- and/or postnatal characteristics of patients with unilateral MCDK were of interest. Title and/or abstract of

all articles identified were screened by one of the authors (MFS), and relevant original studies were read in full. Case reports were specifically excluded from the meta-analysis, as were abstracts only and articles in non-English languages, as this prevented us from accurate analysis of the cohort description. When several articles described (part of) the same cohort, only the study with the most accurate description of the largest cohort was included. In total, 72 articles were considered for the meta-analysis. Papers excluding part of the cohort on the basis of concomitant anomalies were excluded from our analysis.

Data abstraction

Data on timing of diagnosis (prenatal or postnatal) and the reason for the postnatal investigation were extracted, together with, when specified, the number of patients with complete prenatal ultrasonic involution of the MCDK, and the number of patients with any activity on postnatal renography at the site of the MCDK. Also, the patients' gender and side of the MCDK were obtained. From the retrieved cohorts, we intended to only analyse the children who were diagnosed with unilateral MCDK. However, as some papers reported genders for the unilateral and bilateral MCDK patients combined, data are presented for all studies together and for studies with only unilateral MCDK patients separately. Based on the classification of the original paper, the number and/or proportion of patients classified as having any urinary tract abnormality (either structural or functional), and the number and/or proportion of patients classified as having extra-urinary tract abnormalities were noted (labelled as associated abnormalities).

The number of patients evaluated with a micturating cystourethrogram (MCUG) was extracted from the papers, and the percentage of patients evaluated with an MCUG was calculated. In order to minimize the effect of possible selection of patients that showed clinical abnormalities, a separate analysis of the MCUG results was performed in cohorts where at least 95% of patients were evaluated with a MCUG. VUR was classified as present or absent, and, when present, as ipsilateral (i.e. at the side of the MCDK), contralateral or bilateral. When available, the grading of VUR according to the International Reflux Study Committee classification was noted [36]. As some papers showed the number of patients per cluster of VUR grades, the clustering as used by the International Reflux Study in Children was adapted, classifying grades III–V as 'severe' [37].

In each cohort, the number of patients with specific urinary tract abnormalities based on ultrasound and/or renography were noted, and classified as PUJO, ureterovesical junction obstruction, non-obstructive megaureter, ureterocele, posterior urethral valves (PUV), horseshoe kidney or miscellaneous. When noted, the number of patients with contralateral renal hypertrophy (renal length $\geq$95th percentile based on the centile chart used in the specific paper) was obtained, as well as differences in renal size between patients with and without contralateral VUR.

Analysis

With these data, a cumulative meta-analysis was performed. Since not all items were reported in all publications, each item is presented as the number of patients in which that item was present divided by the total number of patients in the cohorts that presented data on that specific item. For the associated urinary tract abnormalities, the denominator is based on the number of patients that were evaluated with ultrasound in the cohorts that presented data on this. As a consequence of the highly variable presentation of items amongst the cohorts, the total number presented as denominator in Tables 2–4 is different for nearly every item.

Comparison of two proportions of categorical data was done by the chi-square test. As some data indicate that the presence of VUR may influence the size of the solitary functioning kidney opposite the MCDK [38,39], data from studies comparing renal size between patients with and without VUR [38–40] were combined, and analysed using Review Manager (RevMan) version 4.2 for Windows (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2003). This enables the calculation of a pooled effect size of weighted mean differences for continuous data together with a 95% confidence interval (95% CI), based on a random-effects model. A random-effects model was chosen *a priori* as we had the impression that a variation in the study populations would result in between-study heterogeneity beyond that of sampling variability. The weight (%) is based on study size and variation of the data (standard deviation). Statistical differences were considered significant if $P < 0.05$ (two-tailed).

Results

Characteristics of the cohorts included, including a meta-analysis, are presented in Table 2. Four articles excluded part of the cohort based on contralateral urinary tract anomalies, like hydronephrosis or abnormal renal position [41] or the complexity of cases [42–44], and for another paper, data of patients with MCDK could not be separated from other diagnoses [45]. These cohorts were therefore excluded from our analysis. Other cohorts excluded patients in which not all diagnostic scans were performed [46–48] or that underwent nephrectomy [49]; the demographic data of these cohorts were included in the analysis. Three papers reported results from autopsies, and did not provide any data on the function of the urinary system like VUR [50–52]. Nevertheless, the characteristics were included in Table 2. Presentation of the data from 11 cohorts included patients with bilateral MCDK [7,22,50,53–60]. In order to analyse the demographic data of subjects with unilateral MCDK separately, Table 2 also shows obtained data from all patients with unilateral MCDK only.

Overall, the majority of subjects with a unilateral MCDK were male (59.2%, $P < 0.0001$ compared with the expected 51% [61]), and MCDKs were found on the left side in just over half (53.1%, $P < 0.02$ when compared with the expected 50%). Based on the papers that reported the timing of diagnosis, 19.2% of patients were diagnosed with MCDK postnatally. Indications for ultrasound evaluation of the abdomen and/or urinary tract were an abdominal mass in 64.2%, a urinary tract infection in 7.1%, and various in the rest.

Five studies reported the number of patients that had shown a (sign of) MCDK on prenatal screening but showed no visible renal tissue on the first postnatal ultrasound, thereby showing complete prenatal involution of MCDK [58,62–65]. Combining the data from these five studies, 21 out of 389 (5.4%) individuals showed complete prenatal involution of the MCDK. MCDKs are occasionally reported to show activity on postnatal renography even though histology is consistent with MCDK [4]; seven of the included cohorts reported that some patients (in total 27) showed activity on a postnatal renogram at the site of the MCDK (range of activity 1–18%) [4,46,66–70].

Data on contralateral renal hypertrophy at the first ultrasound soon after birth were reported by two papers, and showed that hypertrophy was present in 12 out of 26 (46.2%) [42] and 8 out of 33 (24.2%) [71] patients. Four papers presented data on compensatory renal hypertrophy after a follow-up of at least 10 years, which showed hypertrophy in 1/3 (33%) [72], 2/2 (100%) [71], 3/5 (60%) [62] and 35/43 (81%) [65] patients (overall 41/53, 77%).

Table 3 shows the data on associated abnormalities. Overall, 14.9% of patients showed malformations outside the urinary tract, which was similar in the selected cohorts with 100% prenatal diagnosis. Urinary tract malformations were described in 31.3% of patients with unilateral MCDK, which was significantly higher (35.9%, $P < 0.02$) in the

Table 2. Characteristics of included studies

Source	Year	No. of subjects	MCDK side (right:left)	Gender distribution (male:female)	Diagnosis (prenatal: postnatal)	Percentage of unilateral cases evaluated with MCUG	No. (n/N) of nephrectomies
Pathak [50]	1964	21[a]	9:11	15:6	0:21	NR	9/12
Greene [53]	1971	38[a]	NR	23:15	NR	NR	15/30
Risdon [51]	1971	14	5:9	7:7	NR	NR	14/14
Gipson [91]	1976	22	9:13	11:11	0:22	NR	22/22
De Klerk [54]	1977	29[a]	9:17	19:10	0:29	24%	26/26
Walker [92]	1978	11	6:5	7:4	0:11	NR	8/11
Stuck [66]	1982	15	7:8	NR	1:14	NR	9/15
Kleiner [93]	1986	22	7:15	NR	22:0[b]	NR	0/18
Pedicelli [94]	1986	9	5:4	5:4	3:6	NR	1/9
Avni [55]	1987	13[a]	NR	NR	13:0[b]	NR	NR
Bachmann [95]	1988	11	NR	6:5	4:7	82%	3/11
Gordon [19]	1988	23	7:16	13:10	18:5	NR	7/21
Vinocur [5]	1988	30	12:18	17:13	5:25	50%	9/30
Kullendorff [96]	1990	29	13:16	21:8	17:12	59%	26/29
Atiyeh [97]	1992	56	28:28	25:31	22:34	88%	NR
Orejas [56]	1992	24[a]	11:12	18:6	16:8	50%	11/23
Rickwood [57]	1992	44[a]	22:21	32:12	44:0[b]	NR	5/43
Akl [98]	1993	24	6:18	11:13	17:7	42%	NR
Chang [99]	1993	12	2:10	7:5	5:7	8%	10/12
Flack [100]	1993	29	15:14	1910	22:7	97%	NR
Strife [46]	1993	48	21:27	26:22	28:20	92%	5/48
Wacksman [101]	1993	441	198:233[c]	250:191	288:153	15%	181/441
Al-Khaldi [22]	1994	44[a]	15:15	27:17	30:0[b]	100%	2/44
Mandell [67]	1994	30	14:16	20:10	30:0[b]	87%	NR
Sapin [7]	1994	60[a]	26:33	40:20	54:6	Few	35/59
Gloor [23]	1995	11	4:7	9:2	11:0[b]	64%	1/11
Gough [68]	1995	62	23:39	41:21	62:0[b]	100%	37/62
Han [102]	1995	11	4:7	8:3	7:4	18%	9/11
Kaneko [103]	1995	7	4:3	2:5	5:2	100%	6/7
Selzman [104]	1995	65	28:37	37:28	57:8	100%	NR
Karmazyn [48]	1997	68[c]	NR	35:24	NR	87%	NR
Rottenberg [47]	1997	66	39:28	NR	60:6	100%	14/55
John [71]	1998	35	14:21	20:15	35:0[b]	100%	6/33
Kessler [29]	1998	23	8:15	16:7	18:5	87%	4/23
Perez [105]	1998	49	NR	32:17	48:1	90%	12/49
Rudnik-Schoneborn [72]	1998	204	111:93	108:96	134:70	42%	40/204
White [106]	1998	33	NR	NR	NR	100%	10/33
Lazebnik [58]	1999	102[a]	39:39	72:30	102:0[b]	24%	NR
Feldenberg [59]	2000	35[a]	9:19	28:7	NR	23%	NR
Sukthankar [62]	2000	70	28:42	31:39	70:0[b]	90%	4/70
Fanos [38]	2001	27	14:13	17:10	27:0[b]	100%	6/27
Oliveira [107]	2001	20	6:14	10:10	20:0[b]	100%	0/20
Ranke [60]	2001	138[a]	50:75	83:52[d]	138:0[b]	99%	85/108
Seeman [108]	2001	25	12:13	9:16	19:6	92%	11/25
Abidari [109]	2002	48	22:26	30:18	NR	100%	NR
Aubertin [63]	2002	73	35:38	33:32[d]	73:0[b]	NR	9/26
Van Eijk [69]	2002	38	18:20	24:14	38:0[b]	97%	33/35
Metcalfe [4]	2002	54	24:30	32:22	52:2	NR	NR
Eckoldt [110]	2003	93	NR	NR	93:0[b]	95%	51/93
Okada [111]	2003	10	3:7	3:7	10:0[b]	100%	0/10
Tilemis [112]	2003	41	19:22	28:13	25:16	78%	21/41
Kaneyama [113]	2004	30	NR	NR	22:8	100%	NR
Kuwertz-Broeking [114]	2004	97	55:42	60:37	82:15	92%	17/97
Miller [39]	2004	75	48:27	44:31	52:23	100%	25/75
Ylinen [115]	2004	48	20:28	26:22	37:11	NR	32/48
Alconcher [64]	2005	31	9:22	17:14	31:0[b]	42%	4/31
Al Ghwery [116]	2005	35	18:17	18:17	35:0[b]	100%	0/35
Damen-Elias [70]	2005	100	53:47	58:41[d]	100:0[b]	83%	79/87
Guarino [117]	2005	62	31:31	40:22	NR	100%	NR
Ismaili [40]	2005	76	35:41	44:32	76:0[b]	100%	NR
Rahman [118]	2005	69	30:39	39:30	46:23	100%	8/69

Continued

Table 2. *Continued*

Source	Year	No. of subjects	MCDK side (right:left)	Gender distribution (male:female)	Diagnosis (prenatal: postnatal)	Percentage of unilateral cases evaluated with MCUG	No. (n/N) of nephrectomies
Aslam [65]	2006	202	99:103	NR	202:0[b]	71%	11/202
Kakkar [52]	2006	27	NR	NR	NR	NR	NR
Krzemien [119]	2006	17	8:9	NR	10:7	100%	6/17
Merrot [120]	2006	93	49:44	52:41	93:0[b]	100%	NR
Onal [49]	2006	61	33:28	43:18	49:12	100%	4/72
Vu [121]	2008	36	18:18	23:13	NR	NR	4/36
Overall		3,557[a]	1467:1663 46.9%:53.1%	1791:1236 59.2%:40.8%	2581:613 80.8%:19.2%		947/2630 36.0%
Overall, excluding all bilateral cases		3.009		1434:1061 57.5%:42.5%			

MCDK, multicystic dysplastic kidney; MCUG, micturating cystourethrogram.
[a]Some patients were diagnosed with bilateral MCDK.
[b]Included in sub-group analysis of cohorts with 100% prenatal diagnosis. NR, not reported.
[c]Data of some patients were not available.
[d]The gender of some patients was unknown, for instance due to a termination of the pregnancy.

Table 3. Demographic details of subjects with multicystic dysplastic kidneys

	All cohorts	Cohorts with 100% prenatal diagnosis only	*P*-value
No. of articles	67	23	
No. of subjects	3557	1369	
Male[a]	1791/3027 (59.2%)	611/1027 (59.5%)	NS
left-sided MCDK[a]	1663/3,130 (53.1%)	656/1211 (54.2%)	NS
Associated anomalies[a]	199/1340 (14.9%)	136/915 (14.9%)	NS
Associated urinary tract abnormalities[a]	757/2415 (31.3%)	299/834 (35.9%)	<0.02
VUR present[a]	415/2104 (19.7%)	196/962 (20.4%)	NS
PUJO[a]	103/2159 (4.8%)	34/934 (3.6%)	NS
Ureterocele[a]	29/2159 (1.3%)	12/934 (1.3%)	NS
Horseshoe kidney[a]	13/2159 (0.60%)	4/934 (0.43%)	NS
PUV[a]	9/2159 (0.42%)	5/934 (0.54%)	NS

[a]Data presented as n/N (%).
NS, not significant; VUR, vesicoureteric reflux; PUJO, pelviureteric junction obstruction; PUV, posterior urethral valves.

prenatally diagnosed cohorts; the majority of these abnormalities consisted of VUR.

In cohorts that described results from MCUGs ($n = 51$), on average 70% of the subjects within the cohort had at least one MCUG performed (Table 2). Overall, 19.7% of patients with a unilateral MCDK had VUR (Table 4); the mean of the reported incidences was 19.3% (95% CI 15.3–23.3%). This could be classified as severe in 40.5% (i.e. 8.0% of patients with unilateral MCDK show severe VUR). Excluding studies that could potentially have caused bias did not influence these results significantly (17.8% VUR, of which 40.0% graded severe, i.e. 7.1% of patients with unilateral MCDK show severe VUR). Other malformations included PUJO in 4.8% of patients, ureteroceles in 1.3% of patients, horseshoe kidney in 0.60% of patients and PUV in 0.42% of patients (Table 3).

A few cohorts reported data on renal size differences between patients with and without VUR [38–40]. One paper showed significantly smaller kidneys at birth and at 2 years of age in patients with VUR compared with patients without VUR [38], whereas the other two reported no significant difference between the groups [39,40]. Combining the data at the age of ∼2 years, available from two papers [38,39], the solitary functioning kidney with VUR showed a trend to be smaller than the one without VUR [mean difference −0.88 cm (95% CI −1.82–0.07 cm, $P = 0.07$)].

Discussion

With this meta-analysis on demographic data and analysis of the contralateral urinary tract in patients with unilateral MCDK, we have provided an overview of the available cohorts that were published in English. Based on the data in Table 1, the overall incidence of unilateral MCDK can be estimated to be around 1 in 4300. The data on complete prenatal involution of MCDKs indicate that a difference can be expected in the incidence between pre- and postnatal diagnosed cohorts. Including only the papers that based the diagnosis of MCDK on combined prenatal and postnatal

Table 4. Data on vesicoureteric reflux in subjects with a unilateral multicystic dysplastic kidney

	All cohorts	Cohorts with MCUG in at least 95% of subjects	Cohorts with MCUG in at least 95% of subjects and 100% prenatal diagnosis of MCDK
No. of papers	67	24	12
No. of subjects	3557	1233	671
VUR[a]	415/2104 (19.7%)	212/1164 (18.2%)	109/614 (17.8%)
Contralateral[a]	267/1783 (15.0%)	154/1032 (14.9%)	78/577 (13.5%)
Ipsilateral[a]	59/1766 (3.3%)	29/1032 (2.8%)	25/577 (4.3%)
Bilateral[a]	42/1766 (2.4%)	24/1032 (2.3%)	17/577 (2.9%)
VUR contralateral			
Mild (I-II)[a]	100/168 (59.5%)	60/107 (56.1%)	27/45 (60.0%)
Severe (III-V)[a]	68/168 (40.5%)	47/107 (43.9%)	18/45 (40.0%)
Grade I[a]	21/135 (15.6%)	15/101 (14.9%)	10/45 (22.2%)
Grade II[a]	54/135 (40.0%)	40/101 (39.6%)	17/45 (37.8%)
Grade III[a]	32/135 (23.7%)	22/101 (21.8%)	7/45 (15.6%)
Grade IV[a]	21/135 (15.6%)	17/101 (16.8%)	9/45 (20.0%)
Grade V[a]	7/135 (5.2%)	7/101 (6.9%)	2/45 (4.4%)

[a]Data presented as n/N (%).
MCUG, micturating cystourethrogram; MCDK, multicystic dysplastic kidney; VUR, vesicoureteric reflux.

ultrasound evaluation, the incidence is ∼1 in 4400, which is slightly lower than all incidence data together. The fact that the incidence of MCDK may be increasing is also important in the interpretation of our results. Data from consecutive large cohorts in a specific region in the UK showed an incidence of 1 in ∼4800 births in 1984–88 [28], whereas in the recent cohort (1999–2003) MCDK was present in 1 in ∼2200 births [35]. The overall incidence of urinary tract abnormalities has increased as well in this region, which, according to the authors, is most likely to be secondary to the increasing sensitivity and accuracy of ultrasound screening [35]. Even though the reported sensitivity for the prenatal diagnosis of MCDK is only 53.3% during the period from 1985 to 1996 [73], the doubling in incidence of a gross malformation as MCDK is less likely to be explained by an increase in diagnostic sensitivity alone. Another explanation for the increasing incidence may be found in the increasing incidence of pre-existing diabetes during pregnancy [74,75], which has been associated with a higher incidence of MCDK [33]. On the other hand, an alternative explanation for the association between diabetes and MCDK can be found in the renal cysts and diabetes syndrome (RCAD syndrome, OMIM 137920), a syndrome based on mutations of the hepatocyte nuclear factor-1beta (HNF-1β) [76]. This may explain some of the familial associations that have been described to occur for MCDK [77–81]. Environmental influences, such as maternal antiepileptic drugs [82], on the occurrence of MCDK have been identified, as well as chromosomal defects [83] and other syndromes than RCAD that are associated with MCDK [84].

Based on data from the 67 included studies, MCDK is significantly more frequently found on the left side (53.1%). Also, there is a male predominance (59.2% male), which is commonly found with renal tract malformations [13]. In total, seven cohorts reported on activity on renography at the side of the MCDK in a total of 27 patients. No overall percentage is presented for this number, as most cohorts did not report the number of positive or negative cases on renography; most likely as it was found to be 0. In our opinion, estimation of the overall percentage of MCDKs that show activity on renography is less important than to recognize the fact that some activity on renography does not exclude the diagnosis of MCDK.

Prenatal hypertrophy of the contralateral kidney was found in 24–46% of patients with unilateral MCDK in 2 cohorts included in our analysis. Glazebrook *et al*. [85] described prenatal hypertrophy in 17 out of 27 (63.0%) patients with congenital solitary functioning kidneys and Hill *et al*. [86] in 16 out of 36 (44.4%). However, both papers did not report the data for patients with unilateral renal agenesis and unilateral MCDK separately. Whether this hypertrophy is associated with an increase in nephron number remains to be determined. However, this was only to ∼70% of total numbers in two kidney controls, which would still leave these patients with a low nephron endowment.

Overall, ∼1 in 3 patients with unilateral MCDK has an associated urinary tract malformation, mostly being VUR in ∼1 in 5. Of the patients with VUR, ∼40% will have severe (grade III–V) VUR. As low-grade VUR is more and more recognized to be relatively self-limiting and not harmful, the discussion about the need to perform MCUG in children with urinary tract infections with 'normal' renal tracts is ongoing. As 1 in 12–14 children with unilateral MCDK will have severe VUR (Table 4), we feel that it is important to be informed about the presence of VUR in children with unilateral MCDK. Whether normal ultrasounds of the solitary kidney can be used to rule out non-low-grade VUR, and therefore the need for MCUG as suggested by Ismaili *et al*. [40], remains to be determined in larger cohorts.

Another contralateral urinary tract malformation is PUJO, which occurs in ∼4–5% and may be severe enough to cause acute renal failure [65,87]. Ureteroceles have been described frequently as well in patients with MCDK, but usually show a benign course [88]. A horseshoe kidney was described in 0.6%, which is higher than the estimated incidence of 0.15% in the general population [89]; indeed, several reports on MCDK in horseshoe kidneys have been published, which may show an association between the two conditions (for an overview, see [90]).

Our meta-analysis has several limitations. Most importantly, there was a high variability in the reported incidences of MCDK and the various associated (urinary tract and general) malformations. The high variability in the reported incidences may be explained by the era in which the diagnosis was made (i.e. before introduction of prenatal ultrasound screening vs. after introduction of standard prenatal ultrasound screening). Other possible explanations may be found in the size of the reported cohorts, the introduction of prenatal screening and adherence to a standardized schema of postnatal investigations once the diagnosis was made. Excluding cohorts that included patients in whom the diagnosis of MCDK was made postnatally did not basically influence the results. Only a difference in the proportion of associated urinary tract malformations was found, which was higher when the postnatally diagnosed patients were excluded. This was surprising, as we expected that patients diagnosed postnatally would have had a clinical reason to suspect a urinary tract malformation, thereby focussing on a group with a higher incidence of associated anomalies. A possible explanation may be that the reason for the postnatal investigation was a palpable abdominal mass in two-thirds, which is not expected to be influenced by any associated malformations like VUR.

In conclusion, our meta-analysis of 67 cohorts with over 3500 patients with unilateral MCDK has shown the demographics of this patient cohorts, male and the majority of MCKDs on the left side. Analysis of the data in 19 populations showed an overall incidence of unilateral MCDK of 1 in 4300 with an increasing trend over the years. Associated anomalies in the solitary functioning kidney were found in 1 in 3 patients, mainly VUR and PUJO. Severe contralateral VUR, defined as grade III–V, was found in 1 in every 12–14 patients with unilateral MCDK.

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