Unilateral multicystic dysplastic kidney

AS Woolf[1]

[1]Nephro-Urology Unit, Institute of Child Health, University College London, London, UK

CASE PRESENTATION

A 4-year-old girl was referred to Great Ormond Street Hospital for Children NHS Trust, London, UK, for evaluation of solitary kidney. She had no symptoms. There were no dysmorphic features; a surgical scar was noted in the left flank. Her blood pressure was 97/65 mmHg. Hemoglobin was 12.6 g/dl, white blood cell count 8.2×10^9/l and platelet count 334×10^9/l. Plasma sodium was 144 mmol/l, potassium 3.6 mmol/l, creatinine 42 μmol/l (0.47 mg/dl), total calcium 2.35 mmol/l, magnesium 0.75 mmol/l, albumin 4.3 g/dl and parathyroid hormone 4.8 pmol/l (all normal). Plasma phosphate was raised at 2.28 mmol/l, but subsequent values were normal. Dipstick urinalysis revealed no blood, protein or glucose. Urinary microscopy revealed no red or white cells, and sparse coliforms (10^3–10^4/ml) on culture were interpreted as contaminants. Urinary albumin/creatinine ratio was 0.7 mg/mmol (normal range 0.5–3.3), but N-acetyl-β-D-glucosaminidase/creatinine was elevated at 75 U/ml (normal 2–22). Ultrasonography (US) showed no renal tissue on the left, with a right kidney of normal shape and echogenicity: its length was 8.2 cm (50th centile for age, 7.1 cm); there was no renal tract dilation, and the bladder was normal with minimal postmicturition residual.

The patient had been born in Sri Lanka at 39 weeks gestation. In the second trimester of the pregnancy, her mother had 'gestational glucose intolerance' with an elevated fasting blood glucose and a raised blood glucose at 1 h (but not at 2 h) during an oral glucose tolerance test. Diabetes mellitus had been diagnosed in the mother's father and aunt when they were adults. Fetal US at 18 and 34 weeks gestation showed normal overall growth but the internal organs were not specifically imaged. In the second week of life, she had diarrhea, prompting her father, a physician, to palpate her abdomen; he found a tender lump. A renal scan with ^{99m}technetium-diethylenetriaminepentaacetic acid (DTPA; an isotope undergoing glomerular filtration and tubular secretion) showed no functional tissue on the left. US showed a left kidney replaced by a large mass containing cysts, 1–3 cm across. A diagnosis of multicystic dysplastic kidney (MCDK) was considered and, at 3 months, she underwent left nephrectomy. The resected kidney was $4 \times 2 \times 2$ cm and histology confirmed renal dysplasia, with malformed tubules surrounded by stroma containing metaplastic cartilage; there was no tumor.

Both parents' renal ultrasonography (US) were normal. The patient's older sister had a history of urinary tract infection but a renal US scan had been normal. The father's uncle had undergone kidney transplantation at the age of 59 years (further details are unavailable) and this uncle's brother had a horseshoe kidney. In the present case, the parents consented an analysis of the *hepatocyte nuclear factor-1β (HNF1β)* gene, mutations of which cause renal malformations and diabetes mellitus; no mutation was found in the promoter and coding region.

Over the next year, the child had an episode of dysuria and high fever, with pyuria and $>10^5$/ml *Escherichia coli* on urine culture. The infection was treated with cephalosporin, and she was maintained on a prophylactic dose of nitrofurantoin, the organism being resistant to trimethoprim and amoxycillin. After 2 months, she was well; blood pressure was 94/72 mmHg, plasma creatinine was 42 μmol/l (0.47 mg/dl) and urine was sterile. US revealed that the solitary kidney had grown 0.4 cm since the examination 6 months previously. An indirect cystogram using ^{99m}technetium-mercaptoacetyltriglycine, an isotope handled like DTPA, showed normal uptake by the solitary kidney, with no vesicoureteric reflux; antibiotics were stopped. The ^{51}chromium-ethylenediaminetetraacetic acid glomerular filtration rate (GFR) was 89 ml/min/1.73 m^2. It was recommended that she receive no active treatment but that she should have her blood pressure measured and urinalysis for proteinuria performed every year or two throughout life; if either was abnormal, further investigations including plasma creatinine and renal imaging might be required.

DISCUSSION

Incidence of MCDK and complications in childhood

Some modes of presentation of unilateral MCDK, and associated features, are shown in Tables 1 and 2. The girl currently under consideration had a 'classical' postnatal presentation of MCDK, that is, an organ lacking excretory function, presenting as an abdominal mass in infancy. US

Correspondence: *AS Woolf, Nephro-Urology Unit, Institute of Child Health, University College London, 30 Guilford Street, London WC1N 1EH, UK. E-mail: a.woolf@ich.ucl.ac.uk*

Kidney International (2006) **69,** 190–193. doi:10.1038/sj.ki.5000015

Received 12 September 2005; accepted 19 September 2005

Table 1 | Presentations of unilateral MCDK

Renal mass detected by routine prenatal US screening
Painful abdominal mass (in first months of life)
Renal mass detected during postnatal screening (e.g. in an individual with a multiorgan malformation syndrome)
Renal mass detected in a child investigated for renal impairment or hypertension
Solitary functioning kidney in an older child or adult (i.e. apparent 'unilateral renal agenesis' after spontaneous involution of MCDK)

Table 2 | Associated features of unilateral MCDK

In childhood
Systemic hypertension (contested in childhood in the absence of contralateral disease – see text)
Renal malignancy (contested – see text)
Renal impairment (if present, suspect contralateral renal disease)
In adulthood
Systemic hypertension, proteinuria and progressive renal impairment (can occur but exact risk unknown)

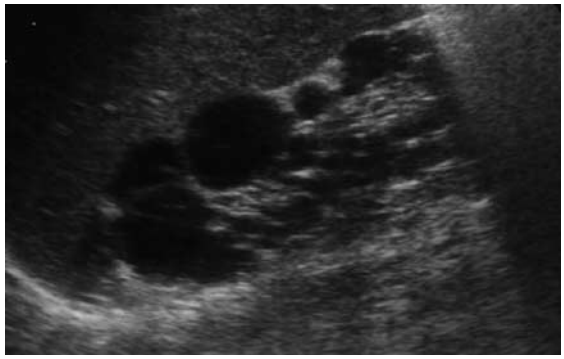

Figure 1 | Ultrasound scan of MCDK. The image was taken from a young child with MCDK. Note the collection of non-communicating cysts (akin to 'a bunch of grapes') separated by dysplastic tissue.

visualizes the organ as a collection of non-communicating cysts each surrounded by denser material (Figure 1). As in this case, the condition is usually unilateral, with a quoted incidence of 1:1–4000;[1–3] bilateral cases are rarer.[4] MCDK is somewhat commoner in male subjects.[5]

The decision to perform nephrectomy was probably driven by the symptomatic presentation and by considerations that MCDK may cause systemic hypertension or become malignant. The associations of both 'complications' with MCDK have been contended.

Reports of hypertension with MCDK certainly exist;[6–8] plasma renin activity and angiotensin can be raised in hypertensive patients[7] and renin immunolocalizes to stromal macrophages in MCDK, versus the normal vascular localization.[8] Others have noted transient hypertension, with reversion to normotension, sometimes correlating with involution of MCDK.[7,9] In other cases, contralateral kidney disease probably causes hypertension.[9] Narchi[10] reviewed 29 studies of unilateral MCDK in children, and noted that just six cases of hypertension developed in 1115. Although this is a low incidence, the mean follow-up time of each study was usually less than 5 years and the long-term risk remains to be defined (see below).

Reports exist of malignancies, both Wilms' tumor and renal carcinoma, arising in MCDK[6,11] but when Narchi[12] reviewed prospective and retrospective cohort studies of unilateral, uncomplicated MCDK, no Wilms' tumors were noted in 1041 children. Hence, malignancy risk appears very low. An additional consideration is that MDCK can occur in defined overgrowth (e.g. Beckwith–Wiedemann, Perlman and Simpson–Golabi–Behmel) syndromes, themselves predisposing to tumorigenesis. Of note, our patient lacked defining features of any multiorgan syndrome associated with renal dysplasia.[13]

Disappearing kidneys

An extraordinary feature of MCDK has come to light through US screening for fetal kidney anomalies. These often massive structures usually involute over weeks to months, prenatally or postnatally, becoming undetectable by US.[14] The MCDK in our case probably partially regressed between diagnosis and nephrectomy. The fact that MCKD can regress prenatally may in part explain variations in reported incidence; for example, unilateral MCDK has been found to be 1:1–2000 on fetal screening[1,2] versus 1:4000 on neonatal screening.[3] Hiraoka *et al.*[3] reported that non-cystic dysplastic kidneys can also involute, and suggested that many patients diagnosed in later childhood or adulthood as having 'unilateral renal agenesis' actually have regressed dysplastic kidneys, rather than having kidneys that never formed. Winyard *et al.*[15] examined histology from human dysplastic kidneys, including MCDK, reporting increased apoptosis versus age-matched controls; so involution may be driven by accelerated programmed cell death. The observation that MCDK generally spontaneously regresses, and the low risk of hypertension and malignancy, has led many to avoid nephrectomy for uncomplicated MCDK. Such surgery, however, may be indicated when a massive organ fails to regress.

Long-term renal prognosis of MCDK

Considering that MCDK is a major malformation, it is intriguing that the contralateral renal tract is generally normal. In our patient, there was no impairment of urine flow or vesicoureteric reflux, and she had an 'appropriately' large contralateral kidney. This overgrowth initiates before birth[5] and continues postnatally:[14] although often envisaged as simply representing nephron enlargement, stereological analyses of solitary kidneys from uninephrectomized fetal sheep show that glomerular numbers significantly increase above normal.[16] Our patient's kidney maintained normal GFR at 3 years of age.

Some caveats about renal function are, however, in order. A minority of patients with unilateral MCDK have malformed contralateral renal tracts; for example, some have contralteral agenesis or dysplasia, and here renal failure may occur neonatally or later in childhood.[17,18] Argueso *et al.*[19]

reported on 157 patients with 'unilateral renal agenesis': mean age at diagnosis was 37 years and hence some might well have had regressed unilateral MCDK; proteinuria (>50 mg/day) was found in 19% of 37 patients tested and hypertension in 47% of 47 patients, renal function was impaired in 13% of 32 patients and, on follow-up, six deaths occurred with chronic renal failure. Another study of solitary kidney in the context of a multiorgan (Kallmann) syndrome also noted cases with hypertension, proteinuria and renal failure.[20] Recently, Gonzalez *et al.*[21] reported on a retrospective study of 33 adults with a diagnosis of 'unilateral renal agenesis'. In the subgroup with normal renal function and absence of proteinuria, about half developed proteinuria and/or abnormal renal function over 24–288 months: a high body mass index appeared to positively correlate with progression. In the subgroup with renal impairment and/or proteinuria at the start of the observation period, progression was again positively correlated with being overweight, while treatment with angiotenisin-converting enzyme inhibitor negatively correlated with risk of progression.

Given the lack of large prospective studies into adulthood, it is reasonable to suggest that individuals with a history of unilateral MCDK should have their blood pressure measured and urine tested for protein/albumin at regular intervals throughout life.

Causes of MDCK

MDCK is a prominent example of an accident of renal development and these organs contain bizarrely shaped tubules surrounded by a stroma, which contains undifferentiated and metaplastic (e.g. smooth muscle like and cartilage) cells.[4,13] The human metanephros arises at 5 weeks of gestation, when it consists of ureteric bud epithelium and renal mesenchymal cells, which will induce each other to form collecting ducts and nephrons (i.e. glomeruli and proximal tubules), respectively.[4] The classic view of MCDK pathogenesis, outlined by Potter[4] several decades ago, is that these organs represent a primary failure of renal mesenchyme induction. This view has been challenged because MCDKs do sometimes contain some recognizable glomeruli and proximal tubules,[22] and an alternative view would be that at least some of the perturbation of nephrogenesis arises from impairment of fetal urine flow very early in development: indeed, each MCDK is generally attached to an 'atretic', nonpatent ureter (reviewed by Woolf *et al.*[13]).

In our case, there was a maternal history of glucose intolerance, and it is known that offspring of mothers with diabetes mellitus are at increased risk of malformations, typically of the neural tube, but also of the renal tract;[23] furthermore, nephrogenesis in organ culture is disrupted by high concentrations of D-glucose, indicating a direct teratogenic action.[24] Our case may have been exposed to hyperglycemia *in utero* because the mother had 'gestational glucose intolerance'; however, the 'typical' renal tract anomaly induced by maternal diabetes mellitus is renal agenesis rather than MCDK. MCDK can occur in the context of many multiorgan malformation syndromes, several of which have defined genetic bases (reviewed by Woolf *et al.*[13]).

HNF1β is a transcription factor expressed in the human metanephros[25] and mutations can cause a spectrum of renal malformations (including dysplastic kidneys): the gene prevents already-formed kidney tubules from becoming cystic[26] and probably has yet-to-be defined early roles in nephrogenesis. *HNF1β* mutations are also associated with diabetes mellitus and, because there was a history of maternal glucose intolerance, and a broader family history of renal malformation, the current patient was tested for mutations and found to be normal.

ACKNOWLEDGMENTS

I thank the patient's parents, both physicians, for permitting and for checking details of the case presentation, Dr Rose deBruyn (Great Ormond Street Hospital for Children NHS Trust, London, UK) for providing ultrasound images, Dr Coralie Bingham and colleagues (Peninsula Medical School, Exeter, UK) for excluding *HNF1β* mutation and Professor Peter Maxwell (Belfast City Hospital, UK) and Dr Frederick Tam (Imperial College London, UK) for helpful discussion at The Renal Association, which hosted a *Kidney International* Forum in Belfast, UK, in April 2005, at which this case was presented. I acknowledge grant support from Action Medical Research, Biotechnology and Biological Sciences Research Council, Kidney Research Aid Fund/Kids Kidney Appeal, Medical Research Council, National Kidney Research Fund and the Wellcome Trust.

REFERENCES

1. Kim EK, Song TB. A study on fetal urinary tract anomaly: antenatal ultrasonographic diagnosis and postnatal follow-up. *J Obstet Gynaecol Res* 1996; **22**: 569–573.
2. Liebeschuetz S, Thomas R. Unilateral multicystic dysplastic kidney. *Arch Dis Child* 1997; **77**: 369.
3. Hiraoka M, Tsukahara H, Ohshima Y *et al.* Renal aplasia is the predominant cause of congenital solitary kidneys. *Kidney Int* 2002; **61**: 1840–1844.
4. Potter EL. *Normal and Abnormal Development of the Kidney*. Year Book Medical Publishers Inc.: Chicago; 1972 pp 1–305.
5. van Eijk L, Cohen-Overbeek TE, den Hollander NS *et al.* Unilateral multicystic dysplastic kidney: a combined pre- and postnatal assessement. *Ultrasound Obstet Gynecol* 2002; **19**: 180–183.
6. Burgler W, Hauri D. Vital complications in multicystic kidney degeneration (multicystic dysplasia). *Urol Int* 1983; **38**: 251–256.
7. Oliveira EA, Silva AC, Rabelo EA *et al.* Spontaneous improvement of hypertension in multicystic dysplastic kidney: a case report. *Pediatr Nephrol* 2002; **17**: 954–958.
8. Liapis H, Doshi RH, Watson MA *et al.* Reduced renin expression and altered gene transcript profiles in multicystic dysplastic kidneys. *J Urol* 2002; **168**: 1816–1820.
9. Kuwertz-Broeking E, Brinkmann OA, Von Lengerke HJ *et al.* Unilateral multicystic dysplastic kidney: experience in children. *BJU Int* 2004; **93**: 388–392.
10. Narchi H. Risk of hypertension with multicystic kidney disease: a systematic review. *Arch Dis Child* 2005; **90**: 921–924.
11. Barrett DM, Wineland RE. Renal cell carcinoma in multicystic dysplastic kidney. *Urology* 1980; **15**: 152–154.
12. Narchi H. Risk of Wilms' tumour with multicystic kidney disease: a systematic review. *Arch Dis Child* 2005; **90**: 147–149.
13. Woolf AS, Price K, Scambler PJ, Winyard PJD. Evolving concepts in human renal dysplasia. *J Am Soc Nephrol* 2004; **15**: 998–1007.
14. John U, Rudnik-Schoneborn S, Zerres K *et al.* Kidney growth and renal function in unilateral multicystic dysplastic kidney disease. *Pediatr Nephrol* 1998; **12**: 567–571.
15. Winyard PJD, Nauta J, Lirenman DS *et al.* Deregulation of cell survival in cystic and dysplastic renal development. *Kidney Int* 1996; **49**: 135–146.

16. Douglas-Denton R, Moritz KM, Bertram JF *et al.* Compensatory renal growth after unilateral nephrectomy in the ovine fetus. *J Am Soc Nephrol* 2002; **13**: 406–410.
17. Feldenberg LR, Siegel NJ. Clinical course and outcome for children with multicystic dysplastic kidney. *Pediatr Nephrol* 2000; **14**: 1098–1101.
18. Scott JES. Fetal, perinatal, and infant death with congenital renal anomaly. *Arch Dis Child* 2002; **87**: 114–117.
19. Argueso LR, Ritchey ML, Boyle Jr ET *et al.* Parognosis of patients with unilateral renal agenesis. *Pediatr Nephrol* 1992; **6**: 412–416.
20. Duke V, Quinton R, Gordon I *et al.* Proteinuria, hypertension and chronic renal failure in X-linked Kallmann's syndrome, a defined genetic cause of solitary functioning kidney. *Nephrol Dial Transplant* 1998; **13**: 1998–2003.
21. Gonzalez E, Gutierrez E, Morales E *et al.* Factors influencing progression of renal damage in patients with unilateral renal agenesis and remnant kidney. *Kidney Int* 2005; **68**: 263–270.
22. Shibata S, Shigeta M, Shu Y *et al.* Initial pathological events in renal dysplasia with urinary tract obstruction *in utero*. *Virchows Arch* 2001; **439**: 560–570.
23. Lynch SA, Wright C. Sirenomelia, limb reduction defects, cardiovascular malformation, renal agenesis in an infant born to a diabetic mother. *Clin Dysmorphol* 1997; **6**: 75–80.
24. Chugh SS, Wallner EI, Kanwar YS. Renal development in high-glucose ambience and diabetic embryopathy. *Semin Nephrol* 2003; **23**: 583–592.
25. Kolatsi-Joannou M, Bingham C, Ellard S *et al.* Hepatocyte nuclear factor 1β: a new kindred with renal cysts and diabetes, and gene expression in normal human development. *J Am Soc Nephrol* 2001; **12**: 2175–2180.
26. Gresh L, Fischer E, Reimann A *et al.* A transcriptional network in polycystic kidney disease. *EMBO J* 2004; **23**: 1657–1668.