ORIGINAL ARTICLE

Risk of Wilms' tumour with multicystic kidney disease: a systematic review

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Background: Children with multicystic kidney disease (MCKD) are increasingly managed conservatively and are followed up throughout childhood because they are perceived to be at increased risk of developing Wilms' tumour. With this risk still poorly defined and somewhat controversial, the strategy and the duration of follow up do not seem to be based on evidence.
Methods: Systematic review of the literature for all published cohort studies (prospective and retrospective) of children diagnosed to have unilateral MCKD and managed conservatively. Exclusion criteria: bilateral MCKD, nephrectomy (not for malignancy) during the follow up period. We estimated for children with MCKD the probability of developing Wilms' tumour during the follow up period, with 95% CI using the Poisson distribution.
Results: From 26 reviewed studies, no cases of Wilms' tumour developed in 1041 eligible children. The mean probability of a child with unilateral MCKD to develop Wilms' was therefore nil, with a 97.5% upper CI estimated at 0.0035 (or 3.5 per 1000 children).
Conclusion: The development of a national or a European registry for children with MCKD would increase the precision of their risk estimate to develop Wilms' tumour. In the meantime, there is no evidence to support any of the different modalities for following up these children by ultrasound, if indeed such a strategy is necessary.

More children with multicystic kidney disease (MCKD) are being now diagnosed antenatally, with an estimated incidence of 1:4300 live births.[1] In view of the high incidence of structural abnormalities in the affected as well as in the contralateral kidney, they undergo postnatal uroradiological investigations. In the absence of complications, they are increasingly managed conservatively, but because of the perceived long term risk of hypertension and renal neoplasms, mainly Wilms' tumour, they are also followed up throughout childhood.[1–5] With the risk of renal neoplastic degeneration in these children still poorly defined and somewhat controversial,[1 5 6] the strategy and the duration of follow up do not seem to be based on evidence. The guidelines to monitor by ultrasound are not uniform and still debated: from a frequency of every three months to biannually and for a duration of up to eight years or until adulthood.[1–5 7 8] In addition, even when the spontaneous involution (in approximately 40% of cases) is documented on ultrasound scan and most units cease imaging studies at that point, there may still be a theoretical risk of malignant degeneration, even in late adulthood.[9–11]

More epidemiological information is needed to properly assess and quantify this risk for a scientifically robust and consistent planning of the surveillance strategy. The prospective data collected by the American MCKD Registry was published in 1993 and did not show any case of neoplasm in the reported 260 children, but no further data have been published since that time.[5]

We therefore undertook a literature search to try to estimate the epidemiology of malignant kidney degeneration in children with MCKD.

METHODS

We undertook a systematic review of the literature for all published cohort studies (prospective and retrospective) of children diagnosed to have unilateral MCKD, using PubMed, Embase, SumSearch, and the Cochrane databases. Search strategy: ''multicystic dysplastic kidney'' [MESH] AND (''cohort studies'' [MESH] OR ''prospective studies'' [MESH] OR ''retrospective studies'' [MESH] OR ''follow-up studies'' [MESH] OR ''outcome'' OR ''complications''). From the retrieved results, we only analysed the studies where the children were managed conservatively and followed up for Wilms' tumour as an outcome. We also only included histologically confirmed Wilms' tumour as outcome, when reported. As bilateral MCKD is invariably lethal and unilateral MCKD is associated with a favourable outcome,[12] we excluded from this study children who had bilateral MCKD. We also excluded those who underwent nephrectomy (not for malignancy) during the follow up period.

As the follow up time for each individual child was not available, the incidence rate of renal neoplasia could not be computed. We therefore estimated for children with MCKD the probability of developing Wilms' tumour during the follow up period, with 95% confidence intervals (95% CI) using the Poisson distribution for rare and independent events.

RESULTS

Twenty six studies published between 1986 and 2004, totalling 1219 children with unilateral MCKD, were reviewed. Nephrectomy (not for malignancy) was carried out in 178 children, who were therefore excluded from the review. The final number of children with unilateral MCKD who were treated conservatively and followed up was therefore 1041 (table 1). At least 653 of them were diagnosed antenatally.

The earliest patients were followed up since 1975.[3] Eight studies did not report the duration of follow up, while the mean duration of follow up in 18 studies ranged from 1.25 to 6.5 years, with a maximum of 23 years of follow up.

Throughout the follow up period, none of these 1041 children developed histologically confirmed Wilms' tumour. The mean probability of these children to develop this malignancy (Poisson distributed counts) was therefore nil,

Table 1 Conservatively managed unilateral MCDK

First author	Year	No. of children (antenatal diagnosis)	Follow up range, (mean) [median] years	Wilms' tumour
Pedicelli[10]	1986	9 (3)	NA	0
Gordon[1]	1988	23 (18)	(1.25)	0
Vinocur[3]	1988	19 (5)	0.16–8.4 (2.8)	0
Martin[14]	1990	15 (NA)	NA	0
Shimada[15]	1990	5 (5)	NA	0
Orejas[16]	1992	12 (12)	0.1–14 (5.3)	0
Tohda[17]	1992	14 (NA)	NA	0
Rickwood[18]	1992	39 (39)	NA	0
Wacksman[5]	1993	260 (most)	<5	0
Strife[4]	1993	48 (28)	(2.5)	0
al Khaldi[12]	1994	30 (30)	0.2–7 (2.4)	0
Cigna[19]	1997	16 (NA)	<7	0
Rottenberg[20]	1997	55 (most)	0.16–5.75 (2.6)	0
John[21]	1998	27 (27)	1–11.6 (4.9)	0
Perez[7]	1998	37 (most)	(3.5)	0
Kessler[22]	1998	19 (18)	0.25–5 (3.8)	0
Sukthankar[8]	2000	70 (70)	0.1–13.8 (5.3)	0
Feldenberg[23]	2000	35 (NA)	0.1–23 (6.5)	0
Matsumoto[24]	2001	46 (96%)	1.3–8.8 (4.5)	0
Oliveira[2]	2001	20 (20)	0.6–7.6 (2.8)	0
Fanos[25]	2001	21 (21)	2	0
Aubertin[26]	2002	73 (73)	NA	0
Kis[27]	2002	94 (NA)	NA	0
Metcalfe[28]	2002	4 (NA)	NA	0
Okada[29]	2003	10 (10)	1.4–10.4 [3.5]	0
Kaneyama[30]	2004	40 (NA)	(5.3)	0
Total		1041		0

NA, not available.

with a one sided 97.5% upper CI of 0.0035 (or 3.5 per 1000 children). Using the calculation method for the maximum probability for events which have not occurred (3/N), that maximum probability was quite similar, estimated to be 0.0028 (or 2.8 per 1000 children).[13]

DISCUSSION

This study focused on the risk of Wilms' tumour in children with MCKD, excluding nephroblastomatosis which could be found incidentally in infants at postmortem examination for unrelated causes. We only include unilateral cases of MCKD as bilateral cases have a spontaneous high mortality rate.[12] Although the paper by Gordon and colleagues[1] had mentioned two cases of Wilms' tumour,[31 32] these were not included in our study as they remained unconfirmed histologically when reviewed by a well known histopathologist in an editorial:[33] the photomicrograph in the first report was more suggestive of cystic differentiation within Wilms' tumour rather than tumour in a multicystic dysplastic kidney,[31] and the absence of any illustration or information concerning the histology of the kidney or the tumour in the second report[32] made impossible the confirmation of the type of malignancy.[33]

The results of this systematic review are reassuring, showing that the mean probability of a child with unilateral MCKD to develop Wilms' tumour is nil, with a 97.5% upper CI estimated at 0.0035 (or 3.5 per 1000 children). This is comparable to the published data by the American MCKD Registry in 1993 which showed no case of neoplasm in the reported 260 children.[5] These findings are more reassuring than the mathematically cited risk of Wilms' in MCKD estimated to be 3–10 per 10 000 MCKD, or 3–10 times higher than in the general population (1 per 10 000), where the underlying calculations involved several assumptions and were not population based.[7]

This review had a number of inherent weaknesses. The 26 studies were not homogeneous. They were reported over a span of 18 years. With antenatal ultrasonography not available in the earlier years and its diagnostic accuracy progressively improving since its early use, it is likely that selection bias has occurred. In addition, antenatally diagnosed cases of MCKD (with variable degree of accuracy throughout the study period) were grouped together with other postnatally diagnosed cases (such as children with an abdominal mass), although the natural history and the prognosis for malignancy might not be similar between these two groups. Another weakness in this systematic review is that the duration of follow up varied widely between the 26 studies and the frequency of ultrasonography surveillance on follow up was very variable too.

Publication bias and reporting bias may also have occurred, as only a few studies have looked at and reported outcomes

What is already known on this topic

- Children with MCKD are followed up throughout childhood by ultrasound because of the perceived risk of developing Wilms' tumour, although this risk is poorly defined and somewhat controversial
- The strategy and the duration of monitoring by ultrasound is widely variable, and not based on solid evidence

What this study adds

- The results of this systematic review of cohorts including 1041 children are reassuring, showing that the mean probability of a child with unilateral MCKD to develop Wilms' is nil, in contrast to the previous mathematically calculated risk

of MCKD in a systematic manner, in comparison to virtually all the cases of renal neoplasm associated with MCKD being isolated case reports. As obviously many more series of children with MCKD have never been reported, the true number and proportion of children with MCKD who did not develop neoplasia is likely to be even much higher, making the estimated maximum incidence rate of neoplasm in MCKD even lower. As it is likely that a significant percentage of unilateral renal agenesis are in fact MCKD which involute, the true incidence of MCKD is likely to be even higher than currently reported, resulting in an even lower risk of malignancy than theoretically calculated.[6 10]

The precision estimate of this risk could be refined further. While further information from the American registry would be very helpful, a national, or a European registry for children with MCKD needs to be developed, with systematic and uniform prospective long term follow up of affected children. Further breakdown of cases between those diagnosed antenatally and those diagnosed later may also clarify any differences in the natural history or prognosis for malignant degeneration between these two subgroups. Such long term cohort studies are likely to be difficult: with Wilms' tumour being relatively rare, a very large number of children with MCKD will need to be prospectively followed up for a very long period, well into adulthood, with the inherent risk of loss to follow up. An easier and more pragmatic solution involving a more reasonable sample size would be a case-control study. Cases would be children from the Wilms' tumour registry available nationally and throughout Europe, and suitable controls would be chosen with precautions in the design to minimise possible selection bias.

In the meantime, there is no evidence to support any of the different modalities for following up these children by ultrasound, if indeed such a strategy is necessary.

Competing interests: none declared

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