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ORIGINAL ARTICLE

Similar renal outcomes in children with ADPKD diagnosed by screening or presenting with symptoms

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Abstract Autosomal dominant polycystic kidney disease (ADPKD) in children is sometimes considered to be a benign condition, with morbidity manifesting in adulthood. Therefore, diagnostic screening of children at risk is controversial. The aim of our study was to to compare the manifestations of ADPKD in children diagnosed by postnatal ultrasound (US) screening versus those presenting with symptoms. This was a retrospective chart review of children with ADPKD assessed in a single centre between 1987 and 2007. Age and reason for diagnosis were noted, and children were separated into two groups: (1) those diagnosed on the basis of family-based screening; (2) those presenting with a symptom. The two groups were compared for renal size, number of cysts, estimated glomerular filtration rate (eGFR), the presence of hypertension and microalbuminuria. In the 47 children with ADPKD (21 females) from 33 families who satisfied the enrollment criteria, mean (standard deviation) age at referral and last follow-up was 7.2 (4.4) and 12.9 (5.1) years, respectively, and the mean follow-up duration was 5.7 (3.6) years. Diagnosis was based on postnatal US screening in 31 children, whereas 16 were diagnosed after presenting with symptoms. The proportions of children with nephromegaly, hypertension, microalbuminuria and decreased eGFR, respectively, were similar in both groups. Based on these results, we conclude that renal-related morbidities, including hypertension and microalbuminia, do occur in children with ADPKD and at a similar frequency in those diagnosed after presenting with symptoms and those diagnosed upon postnatal screening. We suggest that at-risk children should have regular checks to detect hypertension. Moreover, affected children may benefit from novel therapies to minimise cystic disease progression.

Keywords Autosomal dominant polycystic kidney disease · Microalbuminuria · Chronic kidney disease · Hypertension · Screening · Children · Nephromegaly

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is a common genetic disorder, with an incidence of 1:400–1000, characterised by progressive growth of renal cysts manifested by nephromegaly, often leading to end-stage kidney disease (ESKD). It is associated with intracranial arterial aneurysms, cardiac valvular defects and cysts in the liver, spleen and pancreas [1]. The mean age at death in the present era of renal replacement therapy in ADPKD is 59 years, and the main cause of death is cardiovascular

disease including intra- and extracranial aneurysms [2–4]. ADPKD is caused by mutations in either *PKD1* (85%) or *PKD2* (15%). The identification of these genes and the drive to elucidate functions of encoded proteins, polycystin-1 and polycystin-2 are providing the basis for novel therapies to slow cyst growth, with some trials already ongoing in adults with ADPKD [1, 5].

Ideally, treatments for both the primary renal lesion (i.e cystogenesis) and complications (e.g. systemic hypertension) would be commenced before severe and irreversible damage occurs. ADPKD in children is sometimes considered to be a benign condition, with morbidity manifesting in adulthood. Therefore, screening children of affected adults to establish the diagnosis is controversial. Nevertheless, ADPKD lesions may originate as early as the fetal period [6–8]. In the study reported here, our aim was to compare the manifestations of ADPKD in children diagnosed by postnatal ultrasound (US) screening with those in children who presented with symptoms.

Methods

Starting with a comprehensive Nephrology Database, all records of children referred to our tertiary Paediatric Nephrology unit at Great Ormond Street Hospital between 1987 and 2007 with a clinical suspicion of ADPKD were analysed. We first excluded children with cystic kidneys with other diagnoses associated with renal cysts, including tuberous sclerosis (TS) [9], autosomal recessive PKD [10], oral-facial digital syndrome type 1 [11], hypomelanosis of Ito [12] and renal cysts and diabetes syndrome [13]. A diagnosis of childhood ADPKD was accepted when three or more cysts were visualised on US scans and there was either a positive familial history [14, 15] or a lack of evidence of other cystic disease, as outlined above. One of our index cases (who had multiple cysts in each kidney) had no family history, consistent with a de-novo mutation, as reported in about 10% of patients with ADPKD [16].

The cohort was divided in two groups: children with a history of ADPKD in one of their parents, who were asymptomatic at diagnosis and identified by postnatal US screening (group 1), and children who presented with symptoms (group 2). Case notes were reviewed for family history, pre- or postnatal presentation features, renal US reports, number and size of cysts, estimated glomerular filtration rate (eGFR) and the presence of complications, such as hypertension and microalbuminuria at presentation and at last follow-up. Children were generally seen in clinics every other year when blood pressure (BP), albumin excretion and US scans were evaluated. Plasma creatinine results were available in only seven children with ADPKD at diagnosis and in 33 at last follow-up, reflecting a lack of consensus between physicians whether to measure this parameter. The eGFR was calculated from plasma creatinine and patient height using the Schwartz–Haycock formula [17], with a k value of 33, which is specific for our laboratory [18], and patients were classified according to chronic kidney disease (CKD) stages [19].

US reports were assessed for kidney length as well as for the presence, number and size of renal cysts. If >10 cysts were present in either kidney, the patient was reported to have "multiple cysts".

Kidney length was defined as the average of the longitudinal diameter of the right and left kidney in each patient and related to age-matched normal ranges [20]. The renal growth of our cohort was calculated by applying a linear fit to a plot of the kidney length from all of the patients (regression line), and the slope of this regression line was compared to the slopes of the normal ranges [20]. Unilateral nephromegaly was defined as being present when one kidney was of a normal length and the other was >2 standard deviations (SD) versus the controls. At presentation, only 19 patients had an exact kidney size from our radiology department. The others were referred with the US-based report without an exact kidney size.

Hypertension (or borderline hypertension) was defined as being present when systolic (SBP) and/or diastolic blood pressure (DBP) were >95th percentile (or between the 95th and 75th percentile) for gender-, age- and height-matched children on at least three measurements [21]. Children with previously diagnosed hypertension who were on antihypertensive therapy were also labelled "hypertensive". Microalbuminuria was defined as being present when the spot urine albumin/creatinine ratio was ≥30 mg/g (3.4 mg/mmol) [22].

Numerical data were expressed as the mean (SD) and median (range), with differences between the two groups determined by the Student *t* test. The proportions between certain subgroups were compared with the chi-square test or, when at least one of the groups had ≤10 individuals, the Fishers exact test. Significance was defined as $p<0.05$.

Results

Overview of the ADPKD cohort

Eighty children were identified with a possible diagnosis of ADPKD (Fig. 1). Thirty-three were excluded from further analysis. Of these, 19 were siblings of ADPKD patients but had overtly normal US scans. In five additional children, other diagnoses had eventually been made: one each with hypomelanosis of Ito, oro-facial-digital syndrome type 1 and renal cysts and diabetes syndrome and two with cystic

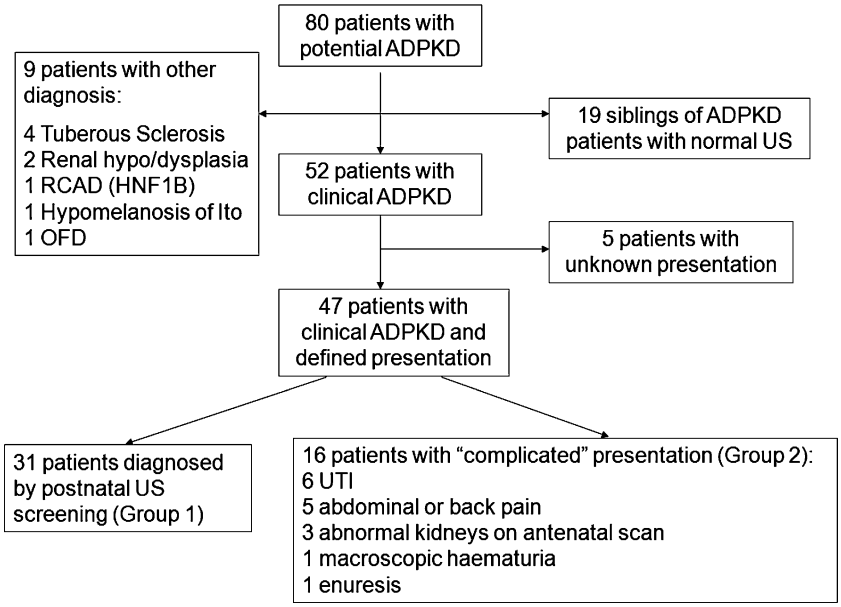

Fig. 1 Overview of the paediatric patient cohort with autosomal dominant polycystic kidney disease (*ADPKD*). *RCAD* renal cysts and diabetes syndrome, *OFD* oral-facial digital syndrome type, *US* ultrasound scan, *UTI* urinary tract infection

dysplastic kidneys. Four others had cystic kidneys associated with TS and accordingly excluded to preserve the purity of the final ADPKD cohort. In five children, the mode of presentation was not documented, and these were also excluded from the analysis. The final cohort comprised 47 children from 33 overtly unrelated families, of whom 46 had a positive family history of ADPKD. Only one child, presenting with bilateral, markedly cystic kidneys, had a negative family history with both parents having a normal US scan when assessed in their third decade of life.

Mean (SD) ages at referral and last follow-up were 7.2 (4.4) and 12.9 (5.1) years, respectively, and the follow-up duration was 5.7 (3.6) years (Table 1). Survival was 100%.

Thirty-one children were asymptomatic and diagnosed by postnatal US screening based on their family history (group 1), whereas 16 presented with symptoms (group 2) comprising antenatal enlarged, echobright kidneys (n=3), urinary tract infection (n=6), abdominal, back or loin pain (n=5), macroscopic hematuria (n=1) and enuresis (n=1).

Gender distribution was similar in both groups (p=0.47): 21 were female (14 from group 1 and 7 from group 2) and 26 were male (17 from group 1 and 9 from group 2).

Mean age (SD) was similar in both groups at presentation (p=0.31) and at last follow up (p=0.49): 7.7 (4.4) and 12.4 (5.8) years for group 1 and 6.3 (4.3) and 11.1 (6.3) years for group 2, respectively. The average length of follow-up was 5.8 (3.6) and 5.6 (3.7) years, respectively (Table 2).

Table 1 Clinical features of the paediatric patient cohort with autosomal dominant polycystic kidney disease at presentation and at last follow-up

Clinical features	Total	
	At presentation	At last follow-up
Mean age (SD), years	7.2 (4.4)	12.9 (5.1)
Median age (range), years	8.3 (0.0–14.1)	14.8 (1.3–19.8)
Mean (SD) follow-up duration, years	5.7 (3.6)	
Kidney length	n=19	n=47
0–2 SD	12 (63%)	22 (47%)
>2 SD	7 (37%)	25 (53%)
Unilateral nephromegaly	n=19	n=47
	3 (16%)	12 (26%)
Multiple cyst	18 (38%)	38 (81%)
Hypertension	3 (6%)	7 (15%)
Borderline hypertension	0 (0%)	7 (15%)
Microalbuminuria	8 (17%)	17 (36%)
Estimated glomerular filtration rate	n=7	n=33
<90 ml/min/1.73 m²	1 (14%)	13 (39%)

Unless given otherwise, the number of patients (n) was 47 at presentation and at last follow-up. Where otherwise, the exact number of patients is given

Table 2 Clinical features of group 1 versus group 2 ADPKD patients at presentation and at last follow-up

Clinical features	Group 1 (screening)		Group 2 (symptoms)		p=comparison between the 2 groups	
	At presentation	At last follow-up	At presentation	At last follow-up	At presentation	At last follow-up
Mean age (SD), years	7.7 (4.4)	12.4 (5.8)	6.3 (4.3)	11.1 (6.3)	0.31	0.49
Median age (range), years	8.5 (0.9–14.1)	15.0 (1.3–13.5)	6.7 (0.0–13.9)	13.9 (1.5–17.3)	NA	NA
Mean (SD) follow-up duration, years	5.8 (3.6)		5.6 (3.7)		0.87	
Kidney length	n=13	n=31	n=6	n=16		
0–2 SD	9 (69%)	15 (48%)	3 (50%)	7 (44%)	0.87	0.78
>2 SD	4 (31%)	16 (51%)	3 (50%)	9 (56%)		
Unilateral nephromegaly	n=13	n=31	n=6	n=16		
	3 (23%)	9 (29%)	0 (0%)	3 (19%)	NA	NA
Multiple cyst	12 (39%)	26 (84%)	6 (38%)	12 (75%)	0.94	0.96
Hypertension	2 (6%)	5 (16%)	1 (6%)	2 (13%)	NA	0.74
Borderline hypertension	0	4 (13%)	0 (0 %)	3 (19%)	NA	NA
Microalbuminuria	4 (13%)	9 (29%)	4 (25%)	8 (50%)	0.29	0.44
Estimated glomerular filtration rate	n=4	n=21	n=3	n=12		
<90 ml/min/1.73 m²	1 (25%)	9 (43%)	0 (0 %)	4 (33%)	NA	0.59

NA, Not applicable

Group 1, Children with ADPKD diagnosed by postnatal US screening; group 2 children with ADPKD diagnosed after presenting symptoms (group 2)

Unless given otherwise, n=31 group 1 patients and n=16 group 2 patients. Where otherwise, the exact number of patients is given

Of the 47 patients, eight had imaging performed to assess for intracranial aneurysms, but all scans were normal.

Renal ultrasound

At presentation, the majority of children (63%) had normal-sized kidneys with 16% unilateral nephromegaly. However, the cohort had accelerated kidney growth relative to the normal population (p<0.001) (Fig. 2), and at the last follow-up 53% had enlarged kidneys and 26% had unilateral nephromegaly (Fig. 3). Similarly, only 38% had multiple cysts at presentation, but 81% presented multiple cysts at last follow-up (Table 1). Mean (SD) cyst diameter was 2.2 (1.2) cm. Two patients had a solitary cyst in the liver, and one patient had a solitary cyst in the pancreas.

The proportions of patients with uni- or bilateral nephromegaly or multiple cysts were similar in both groups (Table 2).

Blood pressure

Hypertension was noted in 6 and 15% of the patients at presentation and at last follow-up, respectively (Table 1). There was no statistically significant difference between the groups (p=0.74) (Table 3). However, no one had borderline hypertension at presentation, and 15% had reached this stage at the last follow-up.

Microalbuminuria

Eight (17%) and 17 (36%) of patients had microalbuminuria and at presentation and last follow-up, respectively (Table 1). Again, this was comparable in both group (p=0.44).

Renal function

Of the patients, 39% had a decreased eGFR at the last follow-up, and this was similar in both groups (p=0.59). One patient, diagnosed by US screening, had reached ESKD at last follow-up.

Discussion

Diagnostic screening, especially genetic testing, of children with a family history of ADPKD remains controversial, in part because establishing the diagnosis may cause psychological stress and affect the ability to obtain life or medical insurance [23] and in part because there is currently an absence of effective treatment preventing ADPKD cyst formation and growth. Furthermore, it would appear that there is a perception in the medical community that ADPKD is generally a rather benign condition in children.

Our study, which is not epidemiological in design, confirms that nephromegaly, decreased kidney function,

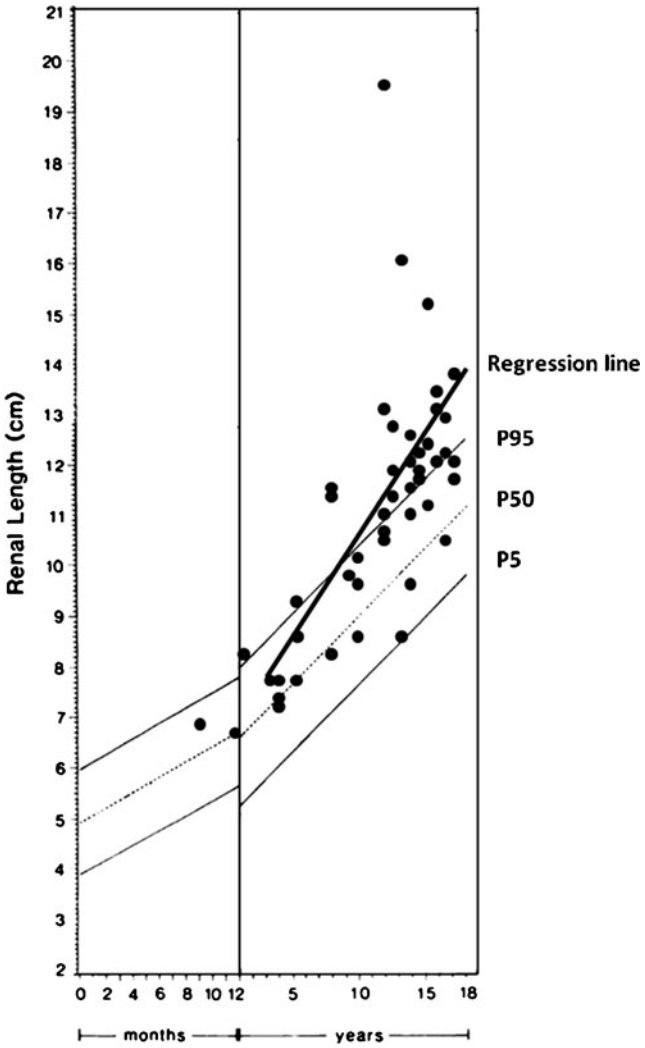

Fig. 2 Average kidney length in each patient at last ultrasound (US) scan. *Solid circles* Average kidney length of each patient at last US scan, *top, middle and bottom lines* the 95th, 50th and 5th centiles for age based on published percentiles [19] used in our hospital. Adapted from [19] to accommodate nephromegaly of ADPKD patients (original graph limited at 13 cm). Regression line (*line in bold*) was calculated using a linear fit of the most recent kidney length of all the patients as a total line, and the slope of this regression line was compared to the slopes of the normal ranges. The cohort had accelerated renal growth, as assessed by renal lengths, relative to the normal population ($p<0.001$)

hypertension and microalbuminuria can indeed occur in children with ADPKD. It is therefore the first study to highlight the fact that complications in children with ADPKD diagnosed by postnatal US screening and those diagnosed in children with ADPKD based on symptoms are similar.

Indeed, because all of the cases were assessed at a tertiary Paediatric Nephrology centre, one could contend that there had been a bias towards more severely affected patients. To account for this potential bias, we separated those children diagnosed solely because of their at-risk status and without overt symptoms from those who presented with overt symptoms, thereby obtaining two patient subgroups. It was striking that the proportions of cases with nephromegaly, decreased kidney function, hypertension and microalbuminuria were similar between the groups. Notably, at last follow-up, the child with the fastest progression, reaching ESKD at the age of 17 years, had been diagnosed by screening. Moreover, the three patients who were diagnosed antenatally and who were aged 1.5, 2.4 and 5.1 years, respectively, at last follow-up had normal BP and normal eGFR. However, all of three had microalbuminuria. Boyer et al. reported that 73% of 26 children who were diagnosed in utero or at day 1 of life were asymptomatic after a mean follow-up duration of 76 months [7] and that only two of the 26 reached CKD stage 4 at a mean age of 19 years.

Therefore, the most important finding of our study is that we found that clinically relevant ADPKD-associated morbidities, such as CKD stage ≥2, hypertension and microalbuminuria, can be present in children who do not present overt symptoms that would otherwise prompt a medical consultation. As such, our results emphasise the need to screen at-risk children in order to instigate appropriate treatment.

Grootendorst et al. describe relevant considerations in screening for CKD [24] that can also be applied to the

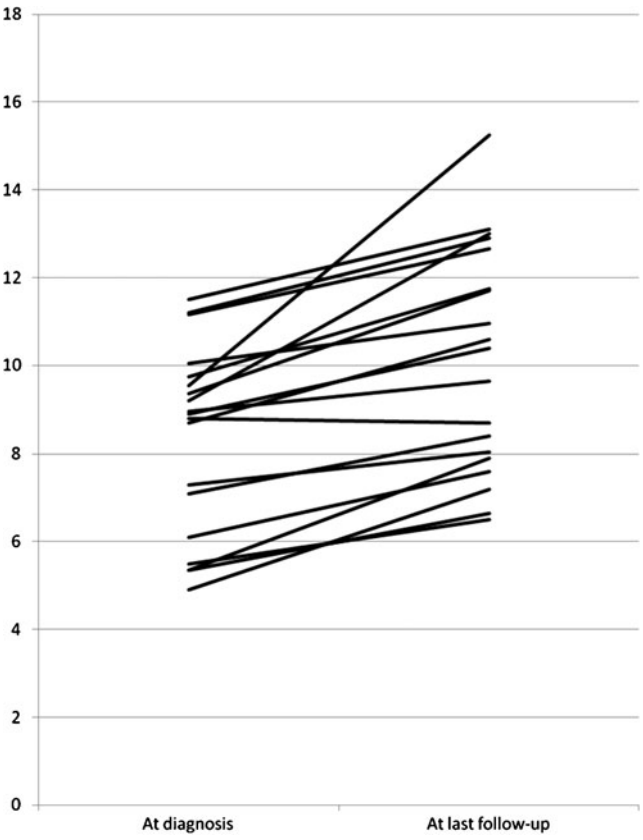

Fig. 3 Average kidney length at presentation and at last follow-up

Table 3 Blood pressure of group1 versus group 2 paediatric patients with ADPKD at presentation and at last follow-up

Blood pressure	Total		Group 1 (screening)		Group 2 (symptoms)		p = comparison between the 2 groups	
	At presentation	At last follow-up	At presentation	At last follow-up	At presentation	At last follow-up	At presentation	At last follow-up
SBP (mmHg)	100±3	108±3	100±3	107±3	100±5	110±5	0.97	0.57
DBP (mmHg)	62±1	65±2	61±1	65±1	62±1	64±1	0.88	0.52
SBP index	0.85±0.03	0.85±0.02	0.85±0.03	0.84±0.02	0.86±0.04	0.88±0.04	0.84	0.35
DBP index	0.78±0.02	0.78±0.02	0.78±0.02	0.78±0.02	0.79±0.02	0.79±0.02	0.84	0.38

SBP, Systolic blood pressure; DBP, diastolic blood pressure

The results are expressed as mean±standard deviation

ADPKD population. Several reports demonstrate that hypertension and albuminuria in adults with ADPKD are associated with progression of the renal disease, with an increased risk for development of cardiovascular disease and mortality [2, 3, 25, 26].

Hypertension is a well-recognised complication of ADPKD in adults, often being present before the onset of ESKD. It is probably in part mediated by renin over-expression within cystic kidneys [26, 27]. It has recently been reported that hypertensive children with ADPKD are also at risk for nephromegaly, increased left ventricular mass index (LVMI) and decreased renal function [25, 28–30]. The increase of LVMI even occurs in patients with borderline hypertension (75th and 95th percentile) and may be ameliorated by therapeutic blockade of the renin–angiotensin system [25]. These findings suggest that cardiovascular involvement, which is currently the main cause of death in ADPKD adults, starts very early in the course of ADPKD [2–4]. Seven (15%) of our paediatric cohort were found to have hypertension and seven (15%) had borderline hypertension at the last follow-up, which is consistent with findings from previous studies [7, 31]. The rate of hypertension among our patient cohort was lower than that reported in a number of other studies, which was around 30% [28, 32]. This may be related to the fact that these other studies used either home BP recordings or ambulatory blood pressure monitoring (ABPM), while we assessed office measurements. If this were to be the reason accounting for the difference, our findings emphasise the need to perform ABPM in order to better diagnose and treat hypertension.

Azurmendi et al. showed that even modest increases in albuminuria in adults with ADPKD are associated with subtle markers of renal (urine monocyte chemoattractant protein-1 levels) and vascular (carotid intima-media thickness) damage [33]. Seventeen (36%) of patients were found to have microalbuminuria at the last follow-up, and this was comparable in both groups. Shamshirsaz et al. reported overt proteinuria in 34% of 153 patients with a diagnosis of ADPKD between 18 months and 18 years and in 45% of 46 patients diagnosed before the age of 18 months [34].

Hypertension and microalbuminuria are modifiable risks factors and can be managed with optimal BP treatment and the early initiation of treatment with angiotensin-converting enzyme inhibitors (ACEi), as has been shown for adult patient populations [25, 35]. Consequently, more attention should be paid for monitoring the BP and albumin excretion in these children, with the aim of minimising the cardiovascular risks.

It was striking that more than half (53%) of our patient cohort had an increased average renal length >2 SD versus the age-matched controls at last follow-up and that the renal growth of our cohort was significantly increased compared to that of the normal population. Because nephromegaly in adults with ADPKD positively correlates with the progression of renal excretory failure [36, 37], clinical trials with the aim of reducing kidney cyst growth are currently underway in this population [1, 38–41]. The availability of proven effective treatment would clearly affect the indication for diagnostic screening of at-risk children.

In contrast, the proportion of children with CKD stage ≥2 was higher (39% for the entire cohort) than that found in most other studies which report normal renal function in the vast majority of children with ADPKD [8, 15, 42]. This apparent discrepancy may be explained by the fact that the commonly used Schwartz–Haycock formula overestimates GFR in CKD. Indeed, Schwartz et al. recently revised their originally published k-factor because of exactly this problem [43]. To account for this, we used a "k factor" specific for our unit and derived from Cr51–EDTA GFR measurements in order to obtain a more accurate estimate of GFR in the CKD population [18].

In accordance with the definition of our study cohort, we had excluded 19 siblings with normal renal US scans and due to the lack of facilities for *PKD1*/*PKD2* mutation testing and/or linkage analyses, we could not definitively assign an "affected" or "non-affected" status. According to a recent large study, only about 10% of genetically affected

individuals aged 15–29 years lack cysts on US scans [14], while no comparable data exist for children <15 years. The proportion of "missed" affected siblings may be even lower in our study, as there is some concordance with respect to age of onset within families [44]. Moreover, the mean age (SD) of the 19 sibling was 18.8 (3.1) years, and the US scan showed normal-sized kidneys without any cysts.

In summary, our results reveal that clinically relevant manifestations can indeed occur in children with ADPKD, even in those without overt symptoms. We believe that our data provide strong support for the need to screen children with a family history of ADPKD in order to monitor their BP and urine albumin measurement and to start appropriate treatment aimed at minimising the cardiovascular risks. Furthermore, because overt nephromegaly can develop in children with ADPKD, these children may be candidates for novel therapies to slow cyst growth.

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Disclosures None

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