Pediatric Nephrology
https://doi.org/10.1007/s00467-022-05870-1

ORIGINAL ARTICLE

Severe parental phenotype associates with hypertension in children with ADPKD

Nathalie Demoulin[1,2] · Elliott Van Regemorter[1,2] · Karin Dahan[3] · Charlotte Hougardy[3] · Johann Morelle[1,2] · Valentine Gillion[1,2] · Nadejda Ranguelov[2,4] · Nathalie Godefroid[2,4]

Received: 20 September 2022 / Revised: 19 December 2022 / Accepted: 19 December 2022

Abstract

Background Early detection of hypertension in children with autosomal polycystic kidney disease (ADPKD) may be beneficial, but screening children at risk of ADPKD remains controversial. We investigated determinants of hypertension in children with ADPKD to help identify a subgroup of children at risk of ADPKD for whom screening for the disease and/or its complications would be more relevant.

Methods In a retrospective study including consecutive children with ADPKD aged 5–18 years and followed at Saint-Luc Hospital Brussels between 2006 and 2020, we investigated the potential association between genotype, clinical characteristics and parental phenotype, and presence of hypertension. Hypertension was defined as blood pressure > P95 during 24-h ambulatory monitoring or anti-hypertensive therapy use. Parental phenotype was considered severe based on age at kidney failure, Mayo Clinic Imaging Classification and rate of eGFR decline.

Results The study enrolled 55 children with ADPKD (mean age 9.9 ± 2.2 years, 45% male), including 44 with a *PKD1* mutation and 5 with no mutation identified. Nine (16%) children had hypertension. Hypertension in children was associated with parental phenotype severity (8/27 (30%) children with severe parental phenotype vs. 1/23 (4%) children with non-severe parental phenotype ($p = 0.03$)) and height-adjusted bilateral nephromegaly (6/9 (67%) children with bilateral nephromegaly vs. 3/44 (7%) children without bilateral nephromegaly ($p < 0.001$)).

Conclusions Severe parental phenotype is associated with higher prevalence of hypertension in children with ADPKD. Hence, children of parents with severe ADPKD phenotype may be those who will most benefit from screening of the disease and/or yearly BP measures.

Keywords *PKD1* · ABPM · Nephromegaly · Autosomal dominant polycystic kidney disease

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease and the fifth-leading cause of kidney failure [1]. Progressive development of numerous cysts leads to kidney enlargement and progressive reduction of kidney function, with half the patients reaching kidney failure by age 60 [2]. ADPKD is genetically heterogeneous and caused by mutations of *PKD1* and *PKD2*, and more rarely of *IFT140*, *GANAB*, *DNAJB11*, and *ALG9* [3–6]. *PKD1* mutations are associated with a more severe kidney phenotype than *PKD2* mutations, and *PKD1* truncating allele mutations are more severe than *PKD1* non-truncating allele mutations [3, 7].

ADPKD has long been considered an adult condition. However, children with ADPKD may develop hypertension

Nathalie Demoulin and Elliott Van Regemorter contributed equally

✉ Nathalie Demoulin
nathalie.demoulin@saintluc.uclouvain.be

1 Division of Nephrology, Cliniques Universitaires Saint-Luc, Brussels, Belgium

2 Institut de Recherche Expérimentale Et Clinique, UCLouvain, Brussels, Belgium

3 Centre de Génétique Humaine, Institut de Pathologie et de Génétique, Gosselies, Belgium

4 Department of Pediatrics, Cliniques Universitaires Saint-Luc, Brussels, Belgium

Published online: 16 January 2023

in about 20% of cases, as well as impaired urine concentration ability, proteinuria, macroscopic hematuria, glomerular hyperfiltration, and increased left ventricular mass [8–15]. Furthermore, hypertensive ADPKD children have significantly larger kidneys and a higher left ventricular mass [16–19].

Early detection and treatment of hypertension in children with ADPKD could potentially slow disease progression and prevent complications such as left ventricular hypertrophy [18]. Children with ADPKD and hypertension may be those who will most benefit from targeted therapies [20]. However, screening children at risk of ADPKD is often a dilemma for both parents and physicians [21, 22]. Here, we analyzed the clinical characteristics, parental phenotype, and familial genotype associated with hypertension in affected children. These determinants could potentially identify a subgroup of children at risk of ADPKD for whom screening for the disease and/or its complications would be more relevant.

Materials and methods

Patient characteristics — children

This retrospective study included children aged 5–18 years old with ADPKD seen consecutively at the pediatric outpatient clinic at Cliniques universitaires Saint-Luc (Brussels, Belgium) between January 1, 2006 and September 30, 2020. The diagnosis of ADPKD was established if patients had at least one kidney cyst and a positive family history [14, 22]. Prenatal diagnosis of ADPKD was defined by the presence of hyperechogenic fetal kidneys, bilateral nephromegaly, and/or at least one kidney cyst on prenatal ultrasound. Patients presenting a de novo *PKD1* or *PKD2* mutation were excluded.

Clinical data extracted from patient records included demographics, context of ADPKD diagnosis, personal or familial genotype, presence of urological complications and hypertension, estimated glomerular filtration rate (eGFR), proteinuria, and ultrasonographic kidney measures. Hypertension was determined as diurnal and/or nocturnal mean systolic and/or diastolic blood pressure (BP) > 95th percentile during 24-h ambulatory BP monitoring (ABPM) or use of anti-hypertensive therapy. Nocturnal dipping was absent when the nocturnal BP fall was inferior to 10% of daytime values on ABPM [23]. Notably, our center has been performing ABPM routinely in pediatric ADPKD patients only for the last 2–3 years [14, 20, 21]. GFR was estimated according to the revised Schwartz formula [24]. Nephromegaly was defined according to height-adjusted percentiles (kidney length > 97.5th percentile) [25].

Molecular genetic testing was performed in the child or affected family members for clinical purposes, using LR-PCR based Sanger sequencing for *PKD1* gene, Sanger sequencing for *PKD2* gene, multiplex ligation probe amplification (MLPA), and/or targeted next-generation sequencing (NGS) panel. Bioinformatic analysis of NGS data enables the detection of germline single nucleotide variants, small insertion-deletions, and copy number variants. The detected variants were interpreted and classified (classes 1 to 5), according to the ACMG guidelines [26].

Patient characteristics — parents

A severe phenotype in the affected parent was defined as kidney failure before age 55 years and/or Mayo Clinic Imaging Classification (MCIC) classes 1C to 1E and/or eGFR (CKD-EPI) loss superior to 5 ml/min/1.73 m^2 per-year (with at least 3 eGFR values available) [27–30].

The study was conducted in accordance with the principles of the Declaration of Helsinki and received approval from the Saint-Luc Hospital's Ethical Committee (2020/09JUL/364).

Statistical analysis

Baseline characteristics of ADPKD children, parental phenotype (including MCIC class), and familial genotype (*PKD1* truncating vs. non-truncating mutation) were compared between children with and without hypertension. Baseline characteristics were also studied according to parental kidney severity. Additionally, the characteristics of children according to their age group at inclusion (≥ 5 and < 13 years vs. ≥ 13 and < 18 years) were compared in order to assess a potential age bias to the presence of hypertension. Continuous data was examined and tested for normality and parametric or non-parametric tests used in consequence. Fisher's exact test was used for categorical variables and Student's *t*-test for continuous variables. Statistical significance was set at $p < 0.05$.

Results

Fifty-five children with ADPKD (42 pedigrees) were included in the study. Mean age at the initial outpatient visit was 9.9 ± 2.2 years, and 45% were males (Table 1). ADPKD was diagnosed at a mean age of 6.0 ± 4.8 years, in the setting of familial screening in 28 (51%) cases; evaluation for hypertension, abdominal pain, hematuria or urinary tract infection in 22 (40%) cases; and prenatal screening in 5 (9%) cases. Estimated GFR was ≥ 90 ml/min/1.73 m^2 in all children, and > 140 ml/min/1.73 m^2 in 4 (8%) cases. The urinary protein-creatinine ratio (PCR) was superior to 0.2 g/g on 2 distinct samples in 3 (5%) cases (ages 8, 10, and 12 years), with orthostatic proteinuria excluded when relevant.

Table 1 Clinical characteristics of children with ADPKD of the CUSL cohort ($N=55$)

Characteristics	Value	*N*
Demographics		
Age at visit — years	9.9 ± 2.2	55
Gender — males	25 (45)	55
Race — White/Black/MENA	45 (82)/1 (2)/9 (16)	55
Birth weight — g	3087 ± 748	51
Diagnosis of ADPKD		
Age at diagnosis — years	6.0 ± 4.8	55
Circumstance — prenatal/screening/symptomatic[1]	5 (9)/ 28 (51)/22 (40)	55
Diagnosis before age 18 months	15 (27)	55
Genetic testing in family[2]/child	49 (89)/17 (31)	55
Genetic testing in children — NGS/Sanger	7 (13)/10 (18)	55
Familial mutation — *PKD1* truncating	32 (65)	49
Familial mutation — *PKD1* non-truncating	12 (24)	49
Familial mutation — no mutation detected	5 (10)	49
Urological complications of ADPKD		
History of urinary tract infection	14 (25)	55
History of enuresis[3]	6 (11)	55
History of macroscopic hematuria	5 (9)	55
Hypertension[4]	9 (16)	55
Anti-hypertensive treatment	7 (13)	55
Age at treatment initiation — years	8.3 ± 4.5	7
24-h ambulatory blood pressure monitoring performed	27 (49)	55
Age at 24-h ABPM — years	11.0 ± 3.9	27
Diurnal hypertension (> P95)	5 (19)	27
Nocturnal hypertension (> P95)	6 (22)	27
Diurnal and nocturnal hypertension (> P95)	5 (19)	27
Nocturnal dip abolished	18 (67)	27
Echocardiography performed	19 (35)	55
Age at echocardiography — years	12.8 ± 3.0	19
Mitral valve prolapse/LVH	0 (0)/0(0)	19
Laboratory results		
eGFR — ml/min/1.73 m^2	119 ± 24	52
eGFR impairment/hyperfiltration[5]	0 (0)/4 (8)	52
PCR > 0.2 g/g (twice)	3 (5)	55
Urinary osmolality/age — mOsm/kg/year	825 ± 212/9.2 ± 4.6	42
Kidney ultrasound		
Unilateral/bilateral kidney enlargement based on height-adjusted PC	21 (40)/9 (17)	53
Presence of at least 1 kidney cyst ≥ 30 mm	12 (22)	54

Results are presented as number and percentage (%) or mean ± standard deviation (SD)

N number of children with data available, *MENA* Middle Eastern and North African, *NGS* next generation sequencing, *ABPM* ambulatory blood pressure monitoring, *P95* 95th percentile, *LVH* left ventricular hypertrophy, *eGFR* estimated glomerular filtration (Schwartz formula), *PCR* urinary protein creatinine ratio, *PC* percentile

[1]Evaluation of hypertension, abdominal pain, hematuria or urinary tract infection

[2]In at least one of the affected family members

[3] ≥ 5 years old

[4]Treated and/or pathologic 24-h ambulatory blood pressure measurement (> P95)

[5]eGFR > 140 ml/min/1.73 m^2

Familial genotyping had been performed for clinical purposes in 49/55 cases: 32, 12, 0, and 5 children were from families with a *PKD1* truncating mutation, a *PKD1* non-truncating mutation, a *PKD2* mutation, and with no mutation detected, respectively. *PKD1* mutations are detailed in Supplementary Table 1. Genotyping was performed using Sanger sequencing and next-generation sequencing targeted cystic panel in 10 and 7 children, respectively. No additional pathogenic variants of non-*PKD1* and -*PKD2* genes were found in the 7 children who had a ciliopathy NGS panel performed.

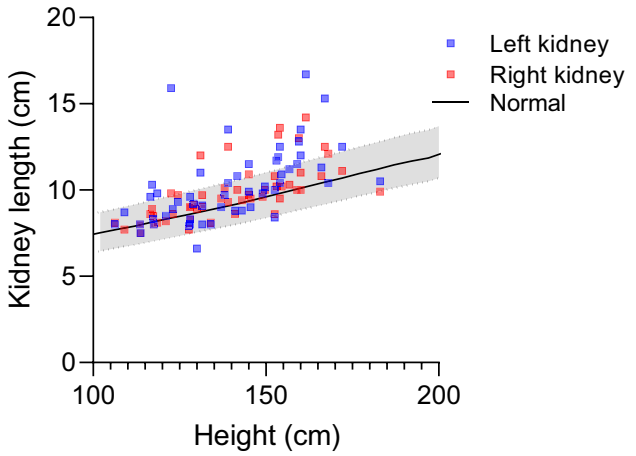

Fig. 1 Kidney length according to height at visit. Blue and red dots/curves represent left and right kidney measures, respectively. Grey curve represents control kidney lengths percentile 2.5–97.5 (grey area), (data extracted from Obrycki, 2022; ref. 25); Spearman's rank correlation coefficient $r=0.79$ for right kidney ($p<0.001$). and $r=0.69$ for left kidney ($p<0.001$)

Nine (16%) children had hypertension, of which 8 started anti-hypertensive therapy at a mean age of 8.3 ± 4.5 years. Hypertension was diagnosed using ABPM measures in 6 of the 9 children. None of the hypertensive children had a history of low birth weight. There was an abolition of nocturnal dip in 18/27 (67%) children who underwent ABPM. No mitral valve prolapse or left ventricular hypertrophy was detected at echocardiography performed in 19 children (of whom 5 were hypertensive). Twenty-one (40%) and 9 (17%) children had unilateral or bilateral kidney enlargement according to height-adjusted percentiles (length > 97.5 percentile), respectively. Figure 1 shows the relationship between kidney length and height.

Parental kidney phenotype was severe in 27/50 (54%) cases. Seventeen children had parents reaching kidney failure before age 55. Five parents were either lost to follow-up or deceased. Nineteen of 31 (61%) parents with *PKD1* truncating mutations (mean age 41.4 ± 7.3 years) had a severe phenotype vs. 4/11 (36%) parents with *PKD1* non-truncating mutations (mean age 40.3 ± 6.1 years) ($p=0.18$). Kidney failure was reached before the age of 55 years in 13/31 (42%) parents with *PKD1* truncating mutations vs. 3/11 (27%) parents with *PKD1* non-truncating mutations ($p=0.49$).

The comparison between normotensive and hypertensive children is shown in Table 2. Hypertension was associated with bilateral nephromegaly ($p=<0.001$), severe parental phenotype ($p=0.03$), and parental MCIC classes 1C–1E ($p=0.01$), but not with the presence of truncating vs. non-truncating *PKD1* mutation ($p=0.66$). Table 3 shows that diurnal and nocturnal hypertension, as measured by ABPM, was associated with a severe parental

Table 2 Determinants of hypertension in children with ADPKD

	No hypertension $N=46$	Hypertension $N=9$	*P*-value
Age at visit	9.8 ± 3.2	10.5 ± 3.4	0.61
Gender — males	20 (43)	5 (56)	0.72
Prenatal diagnosis	4/46 (9)	1/9 (11)	1.00
eGFR — ml/min/1.73 m^2	119 ± 26	119 ± 23	0.97
Hyperfiltration[1]	3/42 (7)	1/9 (11)	0.55
Urinary osmolality — mOsm/kg	842 ± 215	742 ± 191	0.25
Unilateral nephromegaly (height-adjusted)	15/44 (34)	6/9 (67)	0.13
Bilateral nephromegaly (height-adjusted)	3/44 (7)	6/9 (67)	**< 0.001**
PCR > 0.2 g/g (twice)	3/46 (7)	1/9 (11)	0.52
Severe parental phenotype[2]	19/41 (46)	8/9 (89)	**0.03**
Parental MCIC 1C–1E	7/29 (24)	5/6 (83)	**0.01**
Familial *PKD1* truncating mutation	28/38 (74)	4/6 (67)	0.66

Results are presented as number out of available data and percentage (%), significant *p*-values are bolded

N number, *eGFR* estimated glomerular filtration (Schwartz formula), *PCR* urinary protein creatinine ratio, *MCIC* Mayo Clinic Imaging Classification

[1] *eGFR* > 140 ml/min/1.73 m^2

[2] Kidney failure before age 55 years and/or MCIC 1C–1E and/or eGFR loss > 5 ml/min/1.73 m^2 per-year

Table 3 Comparison of children with a severe vs. non-severe parental phenotype

	Non-severe parental phenotype[1] $N=23$	Severe parental phenotype[1] $N=27$	*P*-value
Hypertension[2]	1/23 (4)	8/27 (30)	**0.03**
High diurnal BP at 24-h ABPM (> P95)	0/10 (0)	5/13 (38)	**0.05**
High nocturnal BP at 24-h ABPM (> P95)	0/10 (0)	6/13 (46)	**0.02**
Abolition of nocturnal dip at 24-h ABPM	6/10 (60)	9/13 (69)	0.65
Prenatal diagnosis	3/23 (13)	1/27 (4)	0.32
Unilateral nephromegaly (height-adjusted)	6/21 (29)	12/27 (44)	0.37
Bilateral nephromegaly (height-adjusted)	1/21 (5)	7/27 (26)	0.39
Hyperfiltration[3]	1/19 (5)	3/27 (11)	0.63
PCR > 0.2 g/g (twice)	1/23 (4)	3/27 (11)	0.61
Familial *PKD1* truncating vs. non-truncating mutation	14/19 (74)	18/22 (82)	0.71

Results are presented as number out of available data and percentage (%), significant *p*-values are bolded

N number, *BP* blood pressure, *ABPM* ambulatory blood pressure monitoring, *P*95 95th percentile, *PCR* urinary protein creatinine ratio

[1]Severe parental phenotype defined by kidney failure before age 55 years and/or Mayo Clinic Imaging Classification (MCIC) classes 1C to 1E and/or eGFR loss superior to 5 ml/min/1.73 m^2 per-year

[2]Treated and/or pathologic 24-h ambulatory blood pressure measurement (> P95)

[3]eGFR > 140 ml/min/1.73 m^2 based on Schwartz formula

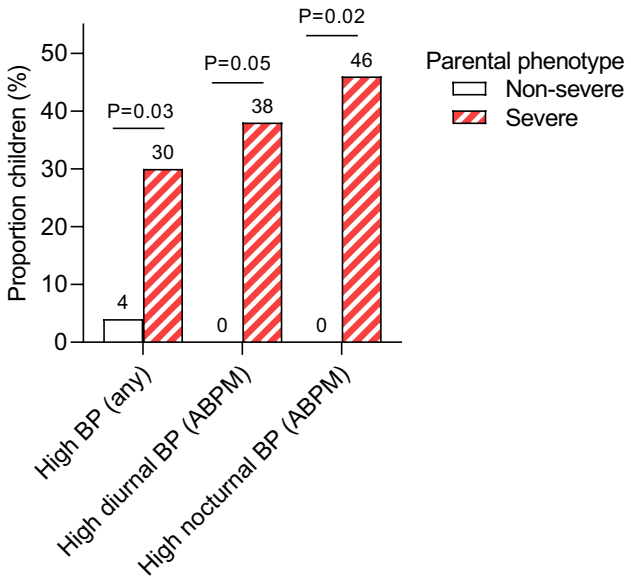

Fig. 2 Proportion of children (%) presenting hypertension, high diurnal BP, or nocturnal BP (> 95th percentile), according to severity of parental phenotype. BP, blood pressure; ABPM, ambulatory blood pressure monitoring

kidney phenotype ($p=0.05$ and $p=0.02$, respectively) (Fig. 2). Abolition of nocturnal dip was, however, not associated with severity of parental phenotype ($p=0.65$). There was no association between hypertension and age groups (≥ 5 and < 13 years vs. ≥ 13 and < 18 years) ($p=0.79$).

Discussion

In a retrospective cohort study, we showed that hypertension was more likely to be present in children with ADPKD whose parents have a severe kidney phenotype than in those whose parents do not have a severe phenotype, based on well-established criteria of age at kidney failure, MCIC class, and rate of decline in eGFR. Our results, if confirmed in larger studies, would suggest that children at risk of ADPKD with parents who present a severe kidney phenotype are those who will most benefit from both screening of ADPKD and/or yearly BP measures.

Diagnosis of hypertension in children with or at risk of ADPKD is important, given its prevalence of approximately 20% in a relatively recent meta-analysis of ADPKD children vs. 4% in the general pediatric population [11, 31]. We similarly found hypertension to be present in 16% of our children with ADPKD. Hypertensive ADPKD children have a more rapid increase in kidney volume and are at risk for faster kidney function decline and left ventricular hypertrophy [17, 18, 20]. Early treatment of hypertension in children with ADPKD may be associated with long-term cardiovascular and kidney benefits.

Identifying factors that worsen ADPKD children's outcome is of great importance to improve the benefit-to-risk ratio of screening and/or therapies [32]. Indeed, screening children at risk of ADPKD is controversial. On the one hand, early diagnosis may lead to interventions on blood pressure and proteinuria control and reduce the psychological burden associated with uncertainty of ADPKD status. On the other

hand, a positive result may be stressful and psychologically detrimental for both children and parents, especially since no curative therapies are yet available, and may have long-term impacts on patients' insuring and financing capabilities.

An alternative to screening would be BP monitoring in all children at risk for ADPKD, whether affected or not, as proposed by the Kidney Disease: Improving Global Outcomes (KDIGO) ADPKD Controversies Conference. KDIGO suggests screening for hypertension from the age of 5 years onward, with an interval of 3 years in cases in which no hypertension is found [22]. A more recent international consensus statement recommends at least yearly BP monitoring in asymptomatic at-risk children, based on a moderate level of evidence [21]. Yearly BP monitoring is indeed non-invasive and would lead to early diagnosis of hypertension in at-risk children. This does, however, represent a burden and cost for the potentially non-carriers. Pros and cons of screening for hypertension in the general pediatric population have also been addressed by the European Society of Hypertension guidelines which recommend BP monitoring starting from the age of 3 years onward, with an interval of 2 years if normotensive [23].

We further showed a significant association between the presence of hypertension and kidney length in our cohort of children with ADPKD, as previously reported in a larger collaborative European study [14]. Previous studies have also shown that increased kidney volume (and cyst volume) measured by ultrasonography or MRI is associated with hypertension in ADPKD children [16, 17, 19, 33]. Nephromegaly is also associated with faster total kidney volume growth [19]. Of note, kidney volumes measured by ultrasonography are slightly smaller than those measured by MRI [19, 33]. We did not have kidney volume measures and defined nephromegaly based on established height-adjusted kidney length percentiles. Indeed, a large multicenter study recently reported that height was the most important determinant of kidney length in children, independently of gender [25]. In children with diagnosed ADPKD, the presence of bilateral nephromegaly may warrant more intensive BP monitoring and ABPM measures.

We were unable to show an association between *PKD1* truncating vs. non-truncating mutation and hypertension in children. We also did not observe the well-known genotype–phenotype correlation in affected parents, probably due to the limited number of patients [7, 34]. Adult ADPKD series also show that mutation class alone cannot be used to predict disease severity at the individual level and that interfamilial variability in phenotypic severity may be important [27, 28, 34]. Prenatal diagnosis was not associated with hypertension either [13]. Lastly, eGFR was not associated with hypertension, probably due to the presence of hyperfiltration in the early stages of ADPKD [11, 13, 14, 21]. Of note, eGFR was estimated using the bedside Schwartz (CKiD) equation, as recommended by the KDIGO guidelines [35] and not the newly-published CKiDU25 equation [36], pending its external validation. In addition, we did not have cystatin C measures in our cohort to improve GFR estimation [36].

The strengths of our study include the consistent and careful recording of studied variables by a single team over the last 15 years and the availability of genotyping in around 90% of families. Also, criteria for severity of adult ADPKD phenotype are well-established [27–30]. We also acknowledge limitations, including moderate sample size, the retrospective design of the study, and the absence of ABPM performed in all children. Our cohort was probably enriched for more progressive ADPKD in view of the monocentric academic center setting with potential referral bias and because children are more likely to undergo screening when their parents have a severe phenotype. Thus, we did not have any *PKD2* families in our cohort. Another limit is the absence of systematic complete genotyping (NGS ciliopathy panel) in all children. Indeed, rare cases of digenic ADPKD with variants in *PKD1* and other cystic genes have been reported in children with severe phenotype [13].

In conclusion, our observations suggest that children of parents with a severe ADPKD phenotype may be those who will most benefit from screening of the disease and/or yearly BP measures.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00467-022-05870-1.

Acknowledgements We wish to thank O. Devuyst and Y. Pirson for their constructive advice and review of the manuscript, as well as P. Harris and SR Senum for their help in the categorization of the *PKD1* variants.

Six of the authors of this publication are members of the European Reference Network for Rare Kidney Diseases (ERKNet).

Author contribution All the authors contributed to the design of the study and review of the manuscript. ND, EVR, and NG wrote the manuscript. JM performed the statistical analysis.

Funding This study was supported by a private grant ("Prix Marlène et Philippe Cloës"), and an unrestricted educational grant from Otsuka Pharmaceuticals (Nathalie Demoulin).

Declarations

Conflict of interest The authors declare no competing interests.

References

1. Torres VE, Harris PC, Pirson Y (2007) Autosomal dominant polycystic kidney disease. Lancet 369:1287–1301. https://doi.org/10.1016/S0140-6736(07)60601-1
2. Chebib FT, Torres VE (2016) Autosomal dominant polycystic kidney disease: Core Curriculum 2016. Am J Kidney Dis 67:792–810. https://doi.org/10.1053/j.ajkd.2015.07.037
3. Cornec-Le Gall E, Torres VE, Harris PC (2018) Genetic complexity of autosomal dominant polycystic kidney and liver

diseases. J Am Soc Nephrol 29:13–23. https://doi.org/10.1681/ASN.2017050483
4. Cornec-Le Gall E, Alam A, Perrone RD (2019) Autosomal dominant polycystic kidney disease. Lancet 393:919–935. https://doi.org/10.1016/S0140-6736(18)32782-X
5. Besse W, Chang AR, Luo JZ, Triffo WJ et al (2019) *ALG9* mutation carriers develop kidney and liver cysts. J Am Soc Nephrol 30:2091–2102. https://doi.org/10.1681/ASN.2019030298
6. Senum SR, Li YSM, Benson KA, Joli G et al (2022) Monoallelic IFT140 pathogenic variants are an important cause of the autosomal dominant polycystic kidney-spectrum phenotype. Am J Hum Genet 109:136–156. https://doi.org/10.1016/j.ajhg.2021.11.016
7. Cornec-Le Gall E, Audrézet MP, Chen JM, Hourmant M et al (2013) Type of PKD1 mutation influences renal outcome in ADPKD. J Am Soc Nephrol 24:1006–1013. https://doi.org/10.1681/ASN.2012070650
8. Ho TA, Godefroid N, Gruzon D, Haymann JP et al (2012) Autosomal dominant polycystic kidney disease is associated with central and nephrogenic defects in osmoregulation. Kidney Int 82:1121–1129. https://doi.org/10.1038/ki.2012.225
9. Selistre L, de Souza V, Ranchin B, Hadj-Aissa A, Cochat P, Dubourg L (2012) Early renal abnormalities in children with postnatally diagnosed autosomal dominant polycystic kidney disease. Pediatr Nephrol 27:1589–1593. https://doi.org/10.1007/s00467-012-2192-y
10. Cadnapaphornchai MA (2015) Autosomal dominant polycystic kidney disease in children. Curr Opin Pediatr 27:193–200. https://doi.org/10.1097/MOP.0000000000000195
11. Marlais M, Cuthell O, Langan D, Dudley J, Sinha MD, Winyard PJ (2016) Hypertension in autosomal dominant polycystic kidney disease: a meta-analysis. Arch Dis Child 101:1142–1147. https://doi.org/10.1136/archdischild-2015-310221
12. Reddy BV, Chapman AB (2017) The spectrum of autosomal dominant polycystic kidney disease in children and adolescents. Pediatr Nephrol 32:31–42. https://doi.org/10.1007/s00467-016-3364-y
13. Gimpel C, Bergmann C, Mekahli D (2021) The wind of change in the management of autosomal dominant polycystic kidney disease in childhood. Pediatr Nephrol 37:473–487. https://doi.org/10.1007/s00467-021-04974-4
14. Massella L, Mekahli D, Paripović D, Prikhodina L et al (2018) Prevalence of hypertension in children with early-stage ADPKD. Clin J Am Soc Nephrol 13:874–883. https://doi.org/10.2215/CJN.11401017
15. Marlais M, Rajalingam S, Gu H, Savis A, Sinha MD, Winyard PJ (2019) Central blood pressure and measures of early vascular disease in children with ADPKD. Pediatr Nephrol 34:1791–1797. https://doi.org/10.1007/s00467-019-04287-7
16. Fick-Brosnahan GM, Tran ZV, Johnson AM, Strain JD, Gabow PA (2001) Progression of autosomal-dominant polycystic kidney disease in children. Kidney Int 59:1654–1662. https://doi.org/10.1046/j.1523-1755.2001.0590051654
17. Cadnapaphornchai MA, McFann K, Strain JD, Masoumi A, Schrier RW (2008) Increased left ventricular mass in children with autosomal dominant polycystic kidney disease and borderline hypertension. Kidney Int 74:1192–1196. https://doi.org/10.1038/ki.2008.397
18. Cadnapaphornchai MA, McFann K, Strain JD, Masoumi A, Schrier RW (2009) Prospective change in renal volume and function in children with ADPKD. Clin J Am Soc Nephrol 4:820–829. https://doi.org/10.2215/CJN.02810608
19. Cadnapaphornchai MA, Masoumi A, Strain JD, McFann K, Schrier RW (2011) Magnetic resonance imaging of kidney and cyst volume in children with ADPKD. Clin J Am Soc Nephrol 6:369–376. https://doi.org/10.2215/CJN.03780410
20. Chapman AB, Guay-Woodford LM (2009) Renal volume in children with ADPKD: size matters. Clin J Am Soc Nephrol 4:698–699. https://doi.org/10.2215/CJN.01410209
21. Gimpel C, Bergmann C, Bockenhauer D, Breysem L et al (2019) International consensus statement on the diagnosis and management of autosomal dominant polycystic kidney disease in children and young people. Nat Rev Nephrol 15:713–726. https://doi.org/10.1038/s41581-019-0155-2
22. Chapman AB, Devuyst O, Eckardt KU, Gansevoort RT et al (2015) Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int 88:17–27. https://doi.org/10.1038/ki.2015.59
23. Lurbe E, Agabiti-Rosei E, Cruickshank JK, Dominiczak A et al (2016) European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. J Hypertens 34:1887–1920. https://doi.org/10.1097/HJH.0000000000001039
24. Gao A, Cachat F, Faouzi M, Bardy D, Mosig D, Meyrat BJ, Girardin E, Chehade H (2013) Comparison of the glomerular filtration rate in children by the new revised Schwartz formula and a new generalized formula. Kidney Int 83:524–530. https://doi.org/10.1038/ki.2012.388
25. Obrycki L, Sarnecki J, Lichosik M, Sopińska M et al (2022) Kidney length normative values in children aged 0–19 years – a multicenter study. Pediatr Nephrol 37:1075–1085. https://doi.org/10.1007/s00467-021-05303-5
26. Richards S, Aziz N, Bale S, Bick D et al (2015) Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 17:405–424. https://doi.org/10.1038/gim.2015.30
27. Irazabal MV, Rangel LJ, Bergstralh EJ, Osborn SL et al (2015) Imaging classification of autosomal dominant polycystic kidney disease: a simple model for selecting patients for clinical trials. J Am Soc Nephrol 26:160–172. https://doi.org/10.1681/ASN.2013101138
28. Lanktree MB, Guiard E, Li W, Akbari P et al (2019) Intrafamilial variability of ADPKD. Kidney Int Rep 4:995–1003. https://doi.org/10.1016/j.ekir.2019.04.018
29. Barua M, Cil O, Paterson AD, Wang K, He N, Dicks E, Parfrey P, Pei Y (2009) Family history of renal disease severity predicts the mutated gene in ADPKD. J Am Soc Nephrol 20:1833–1838. https://doi.org/10.1681/ASN.2009020162
30. Schrier RW, Brosnahan G, Cadnapaphornchai MA, Chonchol M, Friend K, Gitomer B, Rossetti S (2014) Predictors of autosomal polycystic kidney disease progression. J Am Soc Nephrol 25:2399–2418. https://doi.org/10.1681/ASN.2013111184
31. Song P, Zhang Y, Yu J, Zha M, Zhu Y, Rahimi K, Rudan I (2019) Global prevalence of hypertension in children: a systematic review and meta-analysis. JAMA Pediatr 173:1154–1163. https://doi.org/10.1001/jamapediatrics.2019.3310
32. De Rechter S, Bammens B, Schaefer F, Liebau MC, Mekahli D (2018) Unmet needs and challenges for follow-up and treatment of autosomal dominant polycystic kidney disease: the paediatric perspective. Clin Kidney J 11(Suppl 1):i14–i26. https://doi.org/10.1093/ckj/sfy088
33. Breysem L, De Rechter S, De Keyzer F, Smet MH et al (2018) 3DUS as an alternative to MRI for measuring renal volume in children with autosomal dominant polycystic kidney disease. Pediatr Nephrol 33:827–835. https://doi.org/10.1007/s00467-017-3862-6

34. Heyer CM, Sundsbak JL, Abebe KZ, Chapman AB et al (2016) Predicted mutation strength of nontruncating PKD1 mutations aids genotype-phenotype correlations in autosomal dominant polycystic kidney disease. J Am Soc Nephrol 27:2872–2884. https://doi.org/10.1681/ASN.2015050583
35. Levin A, Stevens PE, Bilous RW, Coresh J et al (2013) KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 3:1–150. https://doi.org/10.1038/kisup.2012.73
36. Pottel H, Björk J, Delanaye P, Nyman U (2022) Evaluation of the creatinine-based chronic kidney disease in children (under 25 years) equation in healthy children and adolescents. Pediatr Nephrol 37:2213–2216. https://doi.org/10.1007/s00467-022-05429-0