Low prevalence of hypertension in children with renal cysts and diabetes syndrome is the hallmark of the disease

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Research Article

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Abstract

Cystic kidney diseases such as autosomal recessive or dominant polycystic kidney disease (ARPKD and ADPKD) are associated with high prevalence of arterial hypertension. On the contrary, studies on hypertension in children with renal cysts and diabetes (RCAD) syndrome caused by abnormalities in the *HNF1B* gene are rare. Therefore, the aim of our study was to investigate the prevalence of hypertension in children with RCAD syndrome due to HNF1B gene abnormalities and to search for possible risk factors for development of hypertension.

Data on all children with genetically proven RCAD syndrome from three pediatric nephrology tertiary centers were retrospectively reviewed (office blood pressure (BP), ambulatory blood pressure monitoring (ABPM), creatinine clearance, renal ultrasound, echocardiography, albuminuria/proteinuria). Hypertension was defined using the current ESH 2016 criteria and/or by the use of antihypertensive drugs.

Thirty-two children with RCAD syndrome were investigated. Three children received ACE-inhibitors for hypertension and/or proteinuria. Hypertension was diagnosed using office BP in 22% of the children (n = 7) In the 7 performed ABPM 1 child (14%) was diagnosed with hypertension. Creatinine clearance, proteinuria, albuminuria, body mass index, enlargement or hypodysplasia of the kidneys and prevalence of *HNF1B*-gene deletion or mutation were not significantly different between hypertensive and normotensive children.

Conclusion: Hypertension is rare in children with RCAD syndrome. The low prevalence of hypertension seems to be the hallmark of the disease.

Introduction

What is known:

Arterial hypertension is a common complication in children with polycystic kidney diseases.

What is new

Hypertension is a rare clinical manifestation of children with renal cyst and diabetes (RCAD) syndrome. The low prevalence of hypertension seems to be the hallmark of children with RCAD syndrome.

Cystic kidney diseases belong to the most common structural kidney abnormalities with autosomal dominant polycystic kidney disease (ADPKD) being the most common one and autosomal recessive polycystic kidney disease (ARPKD) being the most severe with high morbidity and mortality [1, 2]. Both polycystic kidney diseases are associated with high prevalence of arterial hypertension in childhood. Elevated blood pressure is documented in 35% of children with ADPKD [3, 4] and in 75% of children with ARPKD [2]. By contrast, studies on hypertension in children with renal cysts and diabetes (RCAD)

syndrome due to *HNF1B* gene abnormalities are lacking. Adult patients with RCAD syndrome show a variable prevalence of hypertension ranging from 7% to 80% [5 - 7]. Only one pediatric study investigating patients with *HNF1B* mutations showed normal mean blood pressure (BP) in comparison to healthy children. Other pediatric studies on patients with RCAD syndrome did not give any data on BP or arterial hypertension.

Therefore, the aim of our study was to investigate the prevalence of hypertension in children with RCAD syndrome due to *HNF1B* gene abnormalities and to search for possible risk factors for its development.

Methods

Subjects

A total of 32 children (20 boys and 12 girls) with RCAD syndrome were retrospectively analyzed using the medical records of three tertiary pediatric nephrology centres in Prague, Jena, and Munich. The inclusion criteria were genetically proven RCAD syndrome (whole *HNF1B*-gene deletion or pathogenic variant of the *HNF1B*-gene in combination with presence of any renal anomaly) and office BP data. Children with CKD stage 5 were excluded from the study. The median age was 3.0 years (range 0.3-18.5 years). The *HNF1B*-gene deletion was found in 72 % of patients and a pathogenic variant of the *HNF1B*-gene in 28 % of patients. Renal ultrasound was pathological prenatally in 48 % of patients and postnatally in 52 % of children. The median age at diagnosis was 3.0 years (range 1 day – 18 years).

Antihypertensive medication

Three (9%) children received ACE-inhibitors for hypertension and/or proteinuria. No child received any other antihypertensive medication at the time of the study.

Office blood pressure measurement

Office BP was measured using an oscillometric device Omron and hypertension (HT) was defined as systolic and/or diastolic BP ≥ 95th percentile according to the current ESH guidelines [8] and/or the use of antihypertensive medication.

Ambulatory blood pressure monitoring (ABPM)

ABPM was performed in 7 patients because of elevated OBP (n=2) or because of CKD despite of normal OBP (n=5). In the remaining 25 patients ABPM was not performed mainly because of normal office BP. ABPM studies were carried out using oscillometric SpaceLabs 90207 or 90217 monitors (SpaceLabs Medical, Redmont, WA). An appropriate cuff was placed on the non-dominant arm by a physician who also informed the child and parents in detail how to operate the monitoring system. Monitors were programmed to measure BP automatically every 20 min during the day and every 30 min at night. The criteria for omitting BP outliers from ABP recordings were systolic BP >200 and <70 mmHg, diastolic BP >150 and <40 mmHg, and mean arterial pressure (MAP) >200 and <40 mmHg. According to the reference

values by Wuhl et al. [9], data were analyzed by using an individualized daytime and nighttime period according to the individual diaries. Mean systolic and diastolic BP at daytime and nighttime were calculated. The BP index was calculated as mean BP, divided by the 95th percentile that was determined according to the body height and sex of the patient [9]. For children with body height <120 cm the 95th percentile was used for children with body height 120 cm. Ambulatory HT was defined as systolic and/or diastolic mean BP at daytime and/or nighttime ≥95th percentile.

Urinary excretion of albumin and protein

Freshly voided urine (first morning urine) was obtained for quantitative measurement of total protein (Biuret method), albumin (turbidimetry) and creatinine (enzymatic). Pathological albuminuria was defined as albumin/creatinine ratio >3 mg/mmol creatinine and proteinuria as protein/creatinine ratio >22 mg/mmol creatinine [10].

Renal function

Chronic kidney disease (CKD) stages 1 – 4 according to the K-DOQI guidelines were detected [K-DOQI] using estimated glomerular filtration rate according to the Schwartz formula using serum creatinine (enzymatic method) and body height [11]. Children with CKD stage 5 were excluded from the study.

Renal ultrasonography

Data on renal ultrasound findings were collected (cysts, renal length, dysplasia, dilation of renal pelvis). Kidney lengths were analysed, compared with normal standards and expressed as SDS [12].

Echocardiography

Echocardiogram (standard two-dimensional echocardiogram (GE/Wingmed system 5, Vivid 7, Horten, Norway) was performed in 8 children on the same day as the office BP measurement (according to the recommendations of the American Society of Echocardiography) [13]. Left ventricular mass (LVM), was calculated according to the formula of Devereux from the left ventricular internal dimension at end diastole, interventricular septal thickness and left ventricular posterior wall thickness [14]. Left ventricular mass was indexed to height2.7 (left ventricular mass index LVMI) to account for body size [15]. Left ventricular hypertrophy (LVH) was defined as LVMI ≥95th percentile for normative pediatric LVMI data [16].

Extra-renal findings

The extra-renal findings (maturity onset diabetes of the young - MODY, hypomagnesemia or liver abnormalities) and medical history data such as birth weight or oligohydramnios were collected retrospectively from the medical charts.

Statistical analysis

The data were analysed by using the STATA software package. SDS values of hypertensive and normotensive patients were investigated by using the Mann-Whitney U test. Values with $p<0.05$ were considered statistically significant.

Results

Office blood pressure measurement

Seven out of 32 patients (22 %) were regarded as hypertensive on the basis of the office BP measurements or by the use of antihypertensive drugs. All hypertensive children had stage 1 hypertension. Three patients had isolated diastolic hypertension, three patients combined systolic and diastolic hypertension and no child had isolated systolic hypertension. One patient on ACEI therapy had normal office BP values. Among children with CKD stage 2 – 4 (n=11) 36% were hypertensive on contrary to 14% in children with CKD stage 1 and normal eGFR (p=0.13).

Ambulatory blood pressure monitoring

Only one patient from seven measured children (14%) was found to have hypertension defined by ABPM. He had borderline isolated night-time diastolic hypertension with a diastolic BP of 65 mmHg (95^{th} percentile 65 mmHg). He had also hypertension defined by office BP. One patient had white-coat hypertension, no patient showed masked hypertension and five children were normotensive both by ABPM and office BP.

Risk factors for hypertension

The data on risk factors for development of hypertension are given in Table 1. In summary, no one from the investigated risk factors for hypertension were significantly different in hypertensive in comparison to normotensive children with RCAD syndrome

Echocardiography

No child from eight investigated children (three hypertensive and five normotensive) had left ventricular hypertrophy.

Discussion

Arterial hypertension is present in more than 90% of perinatal diagnosed ARPKD patients [2] and in 35% of children with ADPKD [3, 4]. In contrast to this high prevalence of hypertension in children with polycystic kidney diseases, the frequency of hypertension in children with RCAD syndrome is not known. Our study is the first systematic investigation of blood pressure and hypertension in children with RCAD syndrome. We could demonstrate that hypertension is rare in children with RCAD syndrome. Only 14-22% of children with HNF1ß mutation presented with arterial hypertension, detected by office BP or by ABPM, mainly those with decreased eGFR, i.e. chronic kidney disease stages 2–4.

In adults with RCAD syndrome the data on prevalence of hypertension are very heterogeneous. Several studies demonstrated prevalence ranging from 0% to 80% [5 - 7, 17]. A French study on 27 adult patients showed a very low prevalence of hypertension of only 7% [5]. These authors stated, that this low prevalence of hypertension - together with the slowly progressive kidney function is the hallmark of the RCAD disease [5]. By contrast, an even smaller Brazilian study showed a prevalence of hypertension of 80% adults with RCAD syndrome [7]. Dubois-Laforgue et al. reported in one of the largest cohort studies on more than 200 adults a prevalence of 58% of hypertension in patients with RCAD syndrome. The CKD stages 3-5 were the most important risk factors associated with elevated BP. The analysis showed a trend for more hypertension in patients with HNF1ß-mutations in comparison to patients with HNF1B-deletion [6]. In our study, a numerically higher prevalence of hypertension was noted in children with CKD stages 2-4 (36%), compared to those patients with CKD stage 1 and normal renal function (14%). Thus it seems that the prevalence of hypertension in patients with RCAD syndrome depends mainly on the stage of CKD, eGFR and somewhat age of the patients (higher prevalence in adults than in children).

The prevalence of hypertension 14-22% in our children with RCAD is considerably lower than in children with ARPKD (75%) [2] or ADPKD (35%) [3, 4]. The reason for this large discrepancy could be the amount of cystic degeneration of the kidneys being the biggest in patients with ARPKD. Those patients demonstrate the highest prevalence of hypertension and decreased GFR. By contrast, patients with RCAD syndrome have usually normal sized or small kidneys with only small cysts and show a low prevalence of arterial hypertension. This low prevalence of hypertension seems to be the hallmark of this disease in children as it has been stated in adults [5]. Therefore, RCAD syndrome resembles more congenital anomalies of the kidney and urinary tract (CAKUT), where the prevalence of hypertension is also very low [18].

So far, there are no studies dealing primarily with BP or hypertension in children with RCAD syndrome. Thomas et al. investigated patients with *HNF1B* (n=4) and *PAX2* gene mutations from the CKiD (Chronic Kidney Disease in Children) study and stated that children with HNF1B and PAX2 gene mutations have normal blood pressure. [19]. Unfortunately, they did not indicate the prevalence of hypertension in this cohort. Only the BP percentiles were mentioned (62^{nd} and 69^{th} for systolic and diastolic BP), which were normal. Other larger studies did not show data on the prevalence of HT or on BP levels [20 - 27]. The relatively low prevalence of hypertension in our cohort and the fairly normal BP in the very small cohort from the CKiD study underline that there is a low prevalence of hypertension among children with RCAD syndrome. This low prevalence seems to be the hallmark of this genetic multisystem disease [5] and is similar to autosomal dominant tubulointerstitial kidney disease [28]. Indeed, one subtype of ADTKD is caused by deletion/mutation of the *HNF1B* gene (named HNF1B-ADTKD). Moreover, both diseases are primarily tubular diseases which show in general a low prevalence of arterial hypertension.

In our analysis, it was very difficult to discover risk factors for hypertension in the few hypertensive children with RCAD syndrome due to the very low number of hypertensive patients (n=7). We did not find any statistically significant marker associated with arterial hypertension. The only trend for higher prevalence of hypertension was CKD stages 2-4. This finding is in line with published data from the

largest adult cohort study demonstrating CKD stages 3-5 being the only risk factor for the development of hypertension [6]. In adult and pediatric patients with ADPKD the kidney size is positively associated with BP and patients with larger kidney size have higher risk of hypertension [4, 29, 30]. In our cohort of children with RCAD syndrome, only 10% of children had enlarged kidneys, a percentage similarly low to the prevalence of hypertension. Furthermore, more children (40%) had small kidneys or unilateral renal agenesis that do not cause hypertension.

In conclusion, we have demonstrated that children with renal cyst and diabetes syndrome have a low prevalence of arterial hypertension.This seems to be the hallmark of the disease in children.

List Of Abbreviations

ABPM Ambulatory blood pressure monitoring

ACEI angiotensin-converting enzyme inhibitor

ADPKD autosomal dominant polycystic kidney disease

ADTKD autosomal dominant tubulointerstitial kidney disease

ARPKD autosomal recessive polycystic kidney disease

BP blood pressure

CAKUT congenital anomalies of the kidney and urinary tract

CKD chronic kidney disease

HNF1B hepatocyte nuclear factor 1β

HT hypertension

LVH left ventricular hypertrophy

LVMI left ventricular mass index

MODY maturity onset diabetes of the young

RCAD renal cysts and diabetes syndrome

Declarations

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Availability of data and material: Not applicable

Authors´ contributions: TS and UJK made substantial contributions to the conception and design of the work. TS collected, analyzed and interpreted the clinical data and wrote the manuscript, FW, BW and FF collected the clinical data. KH, RK and BLS collected clinical data and wrote part of the manuscript and VG made the statistical analyses.

Ethics approval: The present study was conducted in accordance with the principles outlined in the Declaration of Helsinki with approval from the Ethics Committee of LMU Munich and CHU Prague. Formal written informed consent could not be obtained from the patients' parents or patients due to the retrospective design of the study.

Consent to participate: N/A

Consent for publication: N/A

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Tables

Table 1 Biochemical, clinical and renal ultrasound data in normotensive and hypertensive children with renal cyst and diabetes syndrome

	All patients (n=32)	Normotensive patients (n=25)	Hypertensive patients (n=7)	P value
Age (years)	3.0 (0.3-18.5)	2.9 (0.3-18.5)	3.9 (2.9-18.4)	0.16
Sex (boys)	29 %	30 %	28%	0.89
CKD stages 2 – 4	34 %	28 %	57 %	0.15
Creatinine clearance (ml/min/1.73m2)	90 (8-19)	90 (8-193)	68 (13-142)	0.12
Proteinuria (mg/mmol creatinine)	26 (3-104)	27 (3-82)	25 (7-104)	0.58
Pathological proteinuria (>40 mg/mmol creatinine)	58 %	58 %	57 %	0.97
Albuminuria (mg/mmol creatinine)	1.2 (0-44)	1.0 (0-44)	2.9 (0.5-12.6)	0.58
Pathological albuminuria (>3.0 mg/mmol creatinine)	40 %	36 %	50 %	0.55
BMI (kg/m^2)	16.7 (12.9-26.5)	17.2 (12.9-26.5)	16.0 (14.4-24.2)	0.98
HNF1 gene deletion	72 %	76 %	57 %	0.32
Left kidney length (SDS)	-0.9 (-5.1 to 2.5)	-0.6 (-5.1 to 2.5)	-1.1 (-2.0 to 0.0)	0.34
Right kidney length (SDS)	-0.8 (-3.6 to 2.1)	-0.7 (-3.3 to 2.1)	-0.8 (-3.6 to 0.0)	0.36
Enlarged kidneys	10 %	13 %	0 %	0.36
Small kidney(s) or kidney agenesis	40 %	42 %	33 %	0.71
Oligohydramnios	18 %	14 %	29 %	0.39
SGA	10 %	13 %	0 %	0.35
MODY	13 %	9 %	25 %	0.48
Hypomagnesemia (<0.70 mmol/l)	53 %	56 %	43 %	0.78
Liver abnormalities	22 %	24 %	14 %	0.51

Data are given as median (range) or as relative frequency

CKD chronic kidney disease

BMI body mass index

SGA small for gestational age

MODY maturity onset diabetes of the young