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ORIGINAL ARTICLE

Correlation between hypertrophy and risk of hypertension in congenital solitary functioning kidney

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Abstract

Purpose Solitary functioning kidney (SFK) may be associated to hypertrophy, hypertension and chronic kidney disease. We evaluated blood pressure (BP) of children with congenital SFK comparing agenesis to multicystic dysplastic kidney (MCDK) and correlated BP profiles with renal dimensions of affected and contralateral kidney.

Methods We compared 40 patients with MCDK, grouped for either treatment options (A: conservative vs B: nephrectomy) or involution time (A1: before 4 years-of-age vs A2: persistence-of-MCDK), to 10 unilateral agenesis (C). Patients were evaluated with ultrasound, scintigraphy, office-ambulatory BP monitoring.

Results Compensatory hypertrophy was demonstrated in most of the subjects, without differences between subgroups, with an increase over time ($p < 0.001$). A1-C showed an overall percentage of hypertrophy significantly higher than A2-B (83%–88% vs 70%–73%, respectively; $p = 0.03$); moreover, cumulative risk to develop hypertension in A1-C is significantly higher compared to A2-B in office and ambulatory BP monitoring ($p = 0.03$). Insufficient dipping in systolic and/or diastolic BP was found in 82% children, without differences between subtypes.

Conclusions Patients with a small/absent dysplastic kidney have an increased risk to develop hypertrophy and hypertension compared to patients with a large residual, regardless of nephrectomy. ABPM revealed absent dipping in most patients with SFK, warning further investigations in apparently not symptomatic patients.

Keywords Congenital solitary functioning kidney · Multicystic dysplastic kidney · Hypertension · Renal hypertrophy

Introduction

Solitary functioning kidney (SFK) can be a consequence of a wide range of congenital and acquired renal pathologies, ranging from agenesis and multicystic dysplastic kidney (MCDK) to post-nephrectomy conditions following congenital anomalies of the kidney and urinary tract or malignancies. SFK is strongly associated to contralateral hypertrophy during childhood [1], alongside with hypertension, microalbuminuria and chronic kidney disease [2, 3], possibly correlated with glomerular hyperfiltration. Hypertension and microalbuminuria may occur at an early stage and could evolve in impairment of glomerular filtration rate (GFR) in the long term [4].

Ambulatory blood pressure monitoring (ABPM) is a useful modality in the diagnosis and management of hypertension, able to detect also masked hypertension [5]. A recent systematic review demonstrated that MCDK is not associated with hypertension [6]; however, according to the authors, the results may have been hampered by limited patient numbers and heterogeneous design of the studies. Moreover, more recently, other studies reported renal impairment or insufficiency in long term follow-up [7]. All the above-mentioned results highlight the presence of a complex and controversial field, possibly not fully understood.

In the current study, we specifically aimed to investigate whether different aetiologies of congenital SFK could increase hypertensive risk in childhood; besides, we also wanted to understand if either different treatment options

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could influence the course of the disease or there is a predisposition related to the dimension and eventually involution time of the affected kidney during childhood.

To do so we evaluated blood pressure (BP) profiles of children with congenital solitary functioning kidney using both office blood pressure (BP) and ABPM. Furthermore, we compared agenesis to MCDK, further grouped for either involution time or treatment options, and investigated any correlation between renal dimensions of affected and contralateral kidney and pressure profile.

Materials and methods

Study subjects

We considered for this study all patients referred to our Urology Outpatient Clinic from March 2015 to March 2017 for follow-up for solitary functioning kidney. Since many patients were already followed up at our institution before the selected timeframe, we considered they entered the study at the time of their first ultrasound in our clinic and follow-up was defined as the latest ultrasound date in our database. Eligible subjects were children with a congenital SFK, who had not been treated with antihypertensive agents before inclusion in the study. We obtained informed consent from subjects and their parents. All procedures performed were in accordance with the ethical standards and with the Helsinki declaration and its later amendments.

The diagnosis of "solitary kidney" was based on the unilateral absence of functional renal tissue based on absent/dysplastic renal parenchyma at ultrasound confirmed with no functional renal tissue at scintigraphy (< 10% tracer uptake at Tc99m-DMSA scintigraphy). We defined "renal agenesis" the absence of pre-natal visualization of the kidney or, if pre-natal data were not available, absent visualization of the kidney at first ultrasound. All renal agenesis were confirmed with absence of any renal tissue at scintigraphy. For each patient we reviewed medical charts, collected anthropometric data, including age, sex, side of the solitary functioning kidney, presence and eventually gestational age of prenatal diagnosis, presence of any other disease. To have a homogeneous population, we decided to exclude from the analysis patients who showed systemic diseases, such as diabetes, known hypertension or increased body mass index (BMI), or pathologies of contralateral kidney.

The common protocol of investigation consists of ultrasound scan (US) and scintigraphy. US follow-up was planned usually at birth, 3, 6, 12 months and yearly thereafter. Scintigraphy was performed at minimum 6 months of age to avoid radiation exposure at an early age. Cystourethrogram was performed in any patient with dilatation of the urinary tract or in case of urinary tract infections; if any other urinary pathology was detected, patients were subsequently excluded according to exclusion criteria listed above.

Study subjects had a congenital solitary functioning kidney due either to unilateral renal agenesis or multicystic dysplastic kidney. As differences in the aetiology of a solitary functioning kidney may influence clinical outcome [8], sub-analyses between solitary functioning kidney types were additionally performed and patients were thus divided in three different groups: group A patients with MCKD followed with conservative treatment, group B patients undergone nephrectomy for MCKD and group C with renal agenesis from birth. Group A was further divided in A1, patients with a spontaneous involution of residual dysplastic kidney within 4 years and A2 patients with a persistence of the multicystic kidney beyond 4 years. In this specific group of patients, indication for nephrectomy was the presence of a mass effect due to a large non-functioning kidney since patients with hypertension or other pathologies were already excluded in the inclusion phase. In case of persistence of a remnant above 50 mm beyond 4 years of age possible nephrectomy was discussed with parents.

A further analysis was performed according to size of affected kidney, thus dividing patients with a small MCDK/absent (A1 and C) from those with a large MCDK, either treated conservatively (A2) or surgically with nephrectomy (B).

Blood pressure measurements

Office BP was measured with an automated oscillometric device (Dinamap Pro 100, GE Healthcare, Little Chalfont, UK) using an appropriately sized cuff. Measurements were performed after 5 min rest for each child, 2 different measures 5-min distance one from the other. We used the mean of BP measurements to calculate standard deviation (SD) scores (i.e., *Z*-scores) for office BP, which were based on normal values for age, gender, and height [9]. If elevated BP was suspected on the basis of oscillometric readings, confirmatory measurements were obtained by auscultation [10].

ABPM was performed with an oscillometric device (Spacelabs Healthcare, model 90217, Snoqualmie, WA, USA) and an appropriately sized cuff on the non-dominant arm. BP was measured every 20 min during the day, and every 30 min during the night. Based on diary information provided by the subject and his/her parents, daytime was individually defined. Considering the young age of the participants, only recordings with 60% of the expected number of readings were included for analysis. For each subject, ABPM SD scores based on gender and height were calculated for mean systolic and diastolic BP using reference data of healthy children. According to recently published AAP guidelines [10], hypertension was defined as a mean systolic and/or diastolic office BP or 24-h ABPM SD score ≥ 1.96

(95th percentile), whereas elevated blood pressure was considered as a mean systolic and/or diastolic office BP or 24-h ABPM SD score ≥ 1.64 (90th percentile) but < 1.96 (95th percentile). Masked hypertension was defined by abnormal values detected at ABPM with normal office BP measurement. Furthermore, we calculated the dipping status as [(daytime BP − nocturnal BP)/daytime BP]. Insufficient dipping was defined as a drop of less than 10% in mean systolic and diastolic nocturnal BP compared to daytime BP [11].

Renal length was determined by abdominal ultrasound and SD scores were calculated using data from healthy two-kidney controls [5]. Compensatory hypertrophy was defined as a renal length SD score ≥ 1.96 (95th percentile). During the follow-up, the measurements of each patient ware collected, and therefore, stratified according to patient age (0–4, 5–15, 17–34, 34–52, 53–94, 95–153 months respectively).

Serum creatinine (mg/dL) was measured using an enzymatic method and GFR was estimated with the Schwartz equation (eGFR), which has been shown to be reliable for children with a solitary functioning kidney [12], and an impaired eGFR was defined as an eGFR < 60 mL/min/1.73 m^2.

Statistics

All statistical analyses were performed using GraphPad Prism version 6 software (GraphPad Software, La Jolla California USA). Continuous values are expressed as mean (± SD) in case of a normal distribution and as median [interquartile range (IQR)] in case of non-normal distribution. Differences were analysed using the independent samples *t* test. In case of non-normality, a non-parametric test (Mann–Whitney *U* test) was performed. Qualitative variables are expressed as percentage and were compared using the Chi-square test. The risk of hypertrophy and hypertension were determined using cumulative risk analysis, according to the Kaplan–Meier method. Log-rank tests (Mantel–Cox test) were used for comparison between different groups. A p value < 0.05 was considered statistically significant in all analyses.

Results

Patient characteristics

The study sample consisted of 50 patients, 40 (80%) with a congenital solitary functioning kidney due to multicystic kidney and 10 (20%) with a unilateral renal agenesis. From the first group, 15 (30% of the total) had a complete involution of the MCK before 4 years of age and thus belonged to group A1, 14 (28% of the total) had a persistence of the dysplastic kidney beyond 4 years and thus belonged to group A2, 11 (22% of the total) undergone nephrectomy and were assigned to group B.

Mean age at the time of study was 9.5 (± 4.2) years; most of the children were referred at our clinic at birth and mean follow-up was 8.3 (± 5.7) years. The vast majority of subjects were male (64%). For all patients, mean height, weight, and BMI were all within − 2 SD and + 2 SD when compared to reference population data [13]. For all patient characteristics, no differences were identified between the subgroups of patients (Table 1). The solitary functioning kidney was mainly located on the left side (54%) and it demonstrated

Table 1 Patients demographic

	All patients	Group A1 MCDK involuted	Group A2 MCDK persistent	Group B nephrectomies	Group C agenesis	*p* value
Age	9.5 (4.2)	9.8 (3.8)	9.9 (4.0)	9.7 (4.5)	8.4 (5.1)	0.8*
Male/female ratio	32/18	11/4	9/5	7/4	5/5	0.9°
BMI	17 (3)	18 (5)	17 (2)	19 (4)	19 (2)	0.4*
Side solitary kidney left/right ratio	27/23	9/6	5/9	5/6	8/2	0.2°
eGFR (mL/min/1.73 m^2)	80.60 (12.22)	94.30 (0.49)	82.31 (7.23)	77.26 (10.03)	83.67 (7.77)	0.1*
Length SD score (months)						
0–4	3.4 (1.9)	3.2 (1.8)	3.4 (1.7)	2.5 (2.2)	3.9 (2.0)	0.1–0.9§
5–15	2.3 (1.0)	2.1 (0.9)	2.1 (0.8)	2.3 (1.0)	2.7 (1.1)	0.6–0.9§
17–34	2.4 (1.0)	2.7 (0.4)	1.7 (0.5)	1.7 (0.7)	3.0 (1.1)	0.1–0.9§
35–52	3.6 (1.0)	3.7 (0.5)	3.7 (1.0)	2.8 (1.0)	3.9 (1.4)	0.5–0.9§
53–94	5.1 (1.3)	4.6 (0.9)	5.1 (1.2)	4.4 (1.3)	5.9 (1.4)	0.1–0.9§
95–153	6.0 (0.7)	5.9 (0.7)	5.5 (0.9)	6.3 (0.5)	6.5 (0.3)	0.8–0.9§

Data are presented as mean (standard deviation) unless otherwise specified. *p* values represent differences between groups: *ANOVA test, °Chi-square contingency test, §Tukey multiple comparison test

MCK multicystic kidney, *BMI* body mass index, *GFR* glomerular filtration rate, *SD* standard deviation

compensatory hypertrophy in the clear majority of the subjects (Fig. 1).

In group B, nephrectomy was performed at 3.0 (±2.3) years with a mean of 51.7 (±10.8) mm of the MCDK and 73.2 (±12.6) mm of the contralateral. All intra-operative and histological analysis confirmed the diagnosis. All post-operative courses were uneventful.

Renal measurements

Compensatory hypertrophy was confirmed by mean SD-scores calculated at different time points and it did not differ among the groups (Table 1; $p=0.1$–0.9; 2-way ANOVA with Tukey multiple comparison test), but it increased with time ($p<0.001$; 2-way ANOVA). However, if we consider each patient separately, patients belonging to groups A1 and C showed an overall percentage of hypertrophy, namely SD scores above 1.96, significantly higher than those in groups A2 and B (Fig. 1: 83% and 88% vs 70% and 73% respectively; $p=0.03$, Chi-square test).

Blood pressure measurements

Office blood pressure

Overall, mean office BP was 101/65 (±12/±8) mmHg. No groups showed pathologic increase in mean systolic and diastolic office BP SD scores (Table 2). However, based on reference data for office hypertension, cumulative risk to develop elevated BP or hypertension is significantly higher in groups A1 and C compared to A2 and B (53% and 60% vs 14% and 18%, respectively; $p=0.03$, Mantel–Cox test, Fig. 2), with an overall risk of 36%. Of those, 4 in group A1 had elevated BP and 2 in group A2, B and C. Moreover, the analysis according to size of affected kidney patients demonstrated that patients with a small/absent kidney had a significantly increased risk to develop hypertension compared to patients with a large residual dysplastic kidney ($p=0.003$, Mantel–Cox test).

Ambulatory blood pressure monitoring

Mean 24-h ABPM in all subjects was 110/64 (±9/±7) mmHg. Mean 24-h ABPM SD scores for systolic and diastolic BP are listed in Table 2. SD scores for 24-h ABPM were higher in children with a small/absent kidney than in children with a large non-functioning kidney. Isolated daytime and nocturnal ABPM SD scores are additionally presented in Table 2. These differences were confirmed in nocturnal ABPM SD scores, even though nocturnal diastolic SD score had no significant difference among study groups.

ABPM identified 24-h hypertension or elevated BP in 23 (46%) children in total; similarly to office BP findings, cumulative risk to develop hypertension was higher in groups A1 and C (53% and 70% respectively) compared to groups A2 (35%) and B (27%) (Fig. 2), with an increased risk for patients with small/absent kidney ($p=0.02$ compared to large MCDK, Mantel–Cox test). As a consequence,

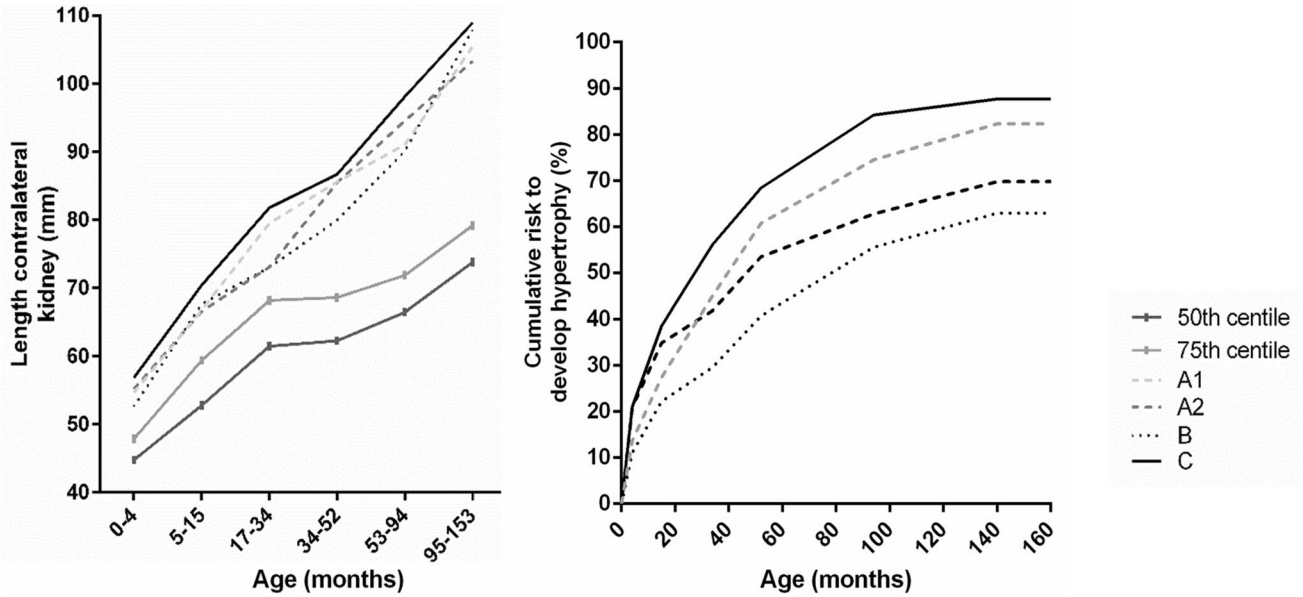

Fig. 1 Solitary functioning kidney hypertrophy: on the left each curve represents the mean of the values per group plus corresponding 50th and 75th centile; on the right the cumulative risk to develop hypertrophy of the solitary kidney. Group A1: multicystic dysplastic kidney involuted within 4 years of age; group A2: multicystic dysplastic kidney persistent beyond 4 years of age; group B: nephrectomies for multicystic dysplastic kidney; group C: kidney agenesis

Table 2 Blood pressure profiles

	All patients	Group A1 MCDK involuted	Group A2 MCDK persistent	Group B nephrectomies	Group C agenesis	*p* value
Office BP values						
Systolic BP SD score	0.64 (0.92)	0.76 (1.02)	0.34 (0.87)	0.64 (0.82)	0.91 (1.09)	NS ($p=0.5$)
Diastolic BP SD score	0.91 (0.75)	1.49 (0.85)	0.65 (0.56)	0.64 (0.35)	0.71 (0.84)	$p=0.004$
ABPM						
Daytime systolic BP SD score	−0.43 (0.84)	0.7 (0.20)	−0.43 (0.3)	−0.7 (0.12)	1.3 (1.89)	$p<0.005$
Daytime diastolic BP SD score	−0.43 (0.36)	−0.6 (0.6)	0.10 (0.09)	−0.5 (0.41)	−0.7 (0.21)	$p<0.005$
Nightime systolic BP SD score	2 (1.60)	1.4 (0.75)	0.6 (1.23)	1.7 (0.32)	4.3 (0.50)	$p<0.005$
Nightime diastolic BP SD score	1.15 (0.57)	0.8 (0.53)	0.9 (1.45)	0.9 (1.53)	2 (2.54)	NS ($p=0.2$)

Data are presented as mean (standard deviation). *p* values represent differences between subgroups by Tukey multiple comparison test

MCDK multicystic dysplastic kidney, *BP* blood pressure, *ABPM* ambulatory blood pressure monitoring, *SD* standard deviation

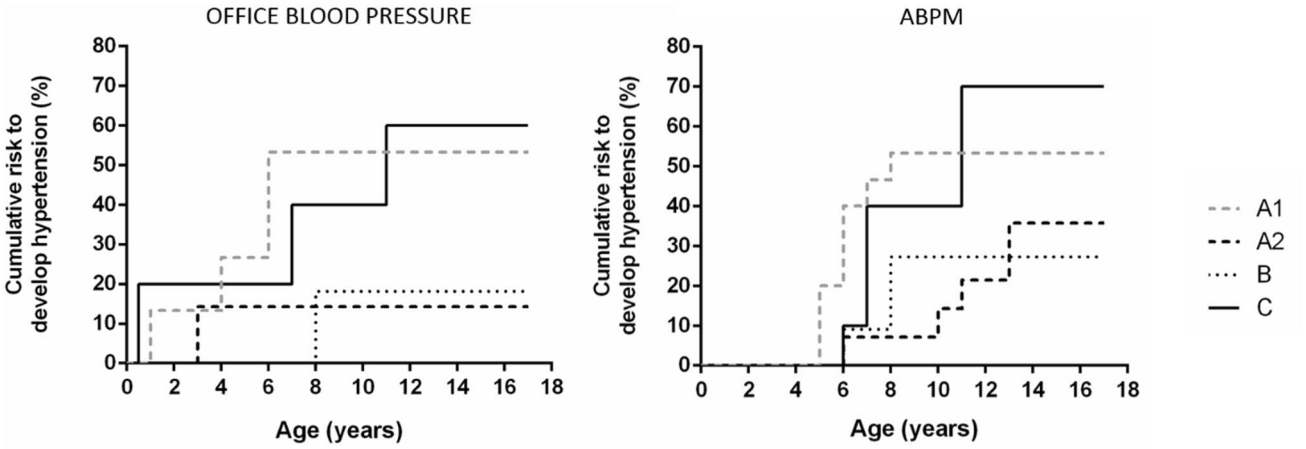

Fig. 2 Cumulative risk to develop hypertension: on the left office blood pressure values; on the right measurements with ABPM. Group A1: multicystic dysplastic kidney involuted within 4 years of age; group A2: multicystic dysplastic kidney persistent beyond 4 years of age; group B: nephrectomies for multicystic dysplastic kidney; group C: kidney agenesis

masked hypertension was identified by ABPM in 3 out of 4 groups.

Furthermore, ABPM data on dipping status are shown in Fig. 3. Insufficient dipping in systolic and/or diastolic was found in 82% children, without differences between solitary functioning kidney types.

Discussion

Detection of MCDK is increasing due to ameliorated diagnostic tools, especially routine foetal and post-natal ultrasound scans. Current practice of management is conservative in the absence of complications, but the long term risk of hypertension and renal neoplasia is unclear and warrants long term follow-up throughout childhood [14] and eventually adulthood.

Hypertrophy of solitary functioning kidney is a well described entity, especially in the setting of contralateral MCDK where it has been correlated to involution of the MCDK after 2 years of age. In this context, contralateral hypertrophy has been reported to vary from 77 to 90% depending of inclusion criteria in different studies [1, 15]. In the present study, patients who had early spontaneous involution of MCDK or agenesis had greater contralateral kidney growth compared to patient who have a large residual dysplastic kidney. During foetal life, the SFK may show hypertrophic growth likely explained by compensatory nephron formation during nephrogenesis, that is loss after birth [16]. Pathways leading to pathologic renal hypertrophy afterwards could lie on a variety of mechanisms: MCDK involution may invoke changes either in renal innervation [17] or in a humoral substance that controls renal hypertrophy [18], or otherwise a persistent dysplastic kidney may

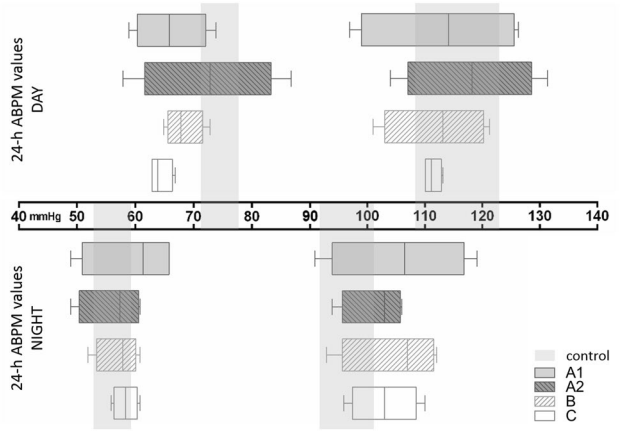

Fig. 3 24-h ambulatory blood pressure monitoring in solitary functioning kidney. Graph shows the absence of dipping in most of the patients compared to age-matched reference for age. Group A1: multicystic dysplastic kidney involuted within 4 years of age; group A2: multicystic dysplastic kidney persistent beyond 4 years of age; group B: nephrectomies for multicystic dysplastic kidney; group C: renal agenesis

act as a "vascular steal" that prevents contralateral growth [19]. In addition, renal growth factors in the beginning of life could outweigh the influence of the MCDK kidney, as even in non-pathological kidneys much growth occurs in the first few years of life. Moreover, even though the complete absence of nephrons, was initially described as a characteristic of MCDK, most recent studies report the presence of some functional renal tissue [20]. The above-mentioned mechanisms could explain, all or in part, why the presence of a large MCDK could "prevent" hypertrophy in the normal contralateral kidney.

Renal length has been linked to glomerular filtration rate and creatinine clearance [21]. Hypertrophy could be a sign of glomerular hyperfiltration, which in the long term, could lead to renal insufficiency as postulated by Brenner et al. in the 1980s in the 'hyperfiltration theory' [4]. In their studies, subtotal renal mass reduction resulted in hypertension, proteinuria and glomerulosclerosis due to glomerular hyperfiltration in remnant nephrons in rats. Moreover, compensatory hypertrophy was found in the remnant kidney [22]. More specifically, consequences of renal mass reduction in glomerular/tubular haemodynamic seems to be related to age at which nephron mass is reduced. A loss early in life incurs greater risk of renal and cardiovascular disease than loss of a kidney later in life [23]. In humans, association between reduced number of nephrons and elevated arterial pressure has been demonstrated by Keller et al. in patients with primary hypertension [24]. In addition, a recent study demonstrated that a relatively high percentage of young adults with a congenital SFK required dialysis by the age of 30 years [25]. In our study, we did not report evidence of glomerular hyperfiltration, but we reported an increased cumulative risk to develop hypertension in small/absent kidney groups, namely the two with higher cumulative incidence of hypertrophy, both for office BP pressure measurements and ABPM.

Whether nephrectomy could have a role in hypertension is still debate. Some authors hint that prophylactic nephrectomy in infancy would be most unlikely to protect individuals against hypertension [26]. On the other side, a retrospective analysis of a cohort of hypertensive paediatric patients from Schlomer et al. suggests that the removal of poorly or non-functioning kidneys has curative effects on hypertension [27]; moreover, in a subsequent paper, Kumar et al. confirmed that recently diagnosed hypertension in MCDK could be cured with early nephrectomy [28]. Our results seem to suggest that hypertension is more correlated with the original size of the affected kidney and the subsequent hyperplasia of the contralateral rather than with the suggested treatment: the large non-functioning kidneys result in lower risk irrespectively of treatment, causing it to be more the natural disease history to play a role in this risk. The eventual prognostic importance of obtained results in our opinion would deserve a more detailed quantification in further longitudinal study. Moreover, current guidelines suggest ABPM application in high-risk populations and by doing so chronic kidney disease, diabetes mellitus, aortic coarctation, solid organ transplantation patients are specifically included [10]. Based on our findings, we suggest that routine performance of ABPM should be considered also in children and adolescents with congenital SFK with undetected hypertension to determine if abnormal circadian BP patterns are present, which may indicate increased risk for target organ damage.

It is important to underline that our cohort of patients has been selected among those, referred to our urologic clinic for MCDK, diagnosed usually before birth and selected not to have any pathological change in the contralateral kidney and thus not having additional renal risk factor than MCDK. However, independently to MCDK natural history and management, up to 82% of patients included in the study with SFK had hypertension either open or masked, and ABPM was more accurate to detect hypertension compared to office BP, as already reported by others to be a relatively more frequent finding in children compared to adults [29].

It could be argued that a significant percentage of unilateral renal agenesis cases are in fact MCKD which involute. The present study demonstrates that actually agenesis behaves similarly to small MCDK in respect of risk to develop contralateral hypertrophy and hypertension. Whether or not contralateral hypertrophy remains in adulthood and its correlation with hypertension is not known. What has been recently confirmed is the correlation between high BP values over time (i.e., BP trajectories) in children

and increased risk of cardiovascular disease in adulthood [30] or masked hypertension in adults and adverse cardiovascular profile [31]. Longer follow-up in adults with MCDK would allow exploration of this possibility.

Limit of this study were various. ABPM was performed in patients with unknown BP profile, possibly including solitary functioning kidney patients with hypertension in this study. Furthermore, we did not perform ABPM studies in age-matched healthy controls, but we compared our ABPM results with well-established reference values. Since many patients were already followed up at our institution before the selected timeframe and thus have not been subjected to a full assessment at the time of the study, we were not able to analyse data on either birth-weight or proteinuria, which both have been shown to correlate with impaired renal function in solitary functioning kidney [32, 33]. Finally, the generalizability of our findings may be limited due to the relatively small number of subjects included.

In conclusion, the understanding of the natural history and pathophysiological consequences of MCDK has shifted the attention from the affected kidney to the contralateral hypertrophic solitary kidney. Patients with a small/absent kidney have an increased risk to develop hypertrophy and hypertension compared to patients with a large residual dysplastic kidney. Most patients with a congenital solitary functioning kidney develop insufficient dipping, which could be associated with a poor cardiovascular outcome in the long term. Treatment does not seem to influence the progression towards hypertensive state and thus, if nephrectomy should be performed for other indications, patients still maintain a risk of hypertension. ABPM has been demonstrated to be fundamental when evaluating a solitary functioning kidney, allowing to detect early subclinical changes, such as masked hypertension, warning further investigations in apparently not symptomatic patients.

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