Early Diagnosis of Solitary Functioning Kidney: Comparing the Prognosis of Renal Agenesis and Multicystic Dysplastic Kidney

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Abstract

Background

Individuals with congenital solitary functioning kidney (SFK) are at an increased risk of kidney damage. According to some studies, the risk is higher in unilateral renal agenesis (URA) than in unilateral multicystic dysplastic kidney (UMCDK). We hypothesized that with early detection of children with URA and UMCDK, there would be no difference in the presence of hypertension, proteinuria, and reduced glomerular filtration rate (GFR) between URA and UMCDK.

Methods

Based on a long-term follow-up protocol, we evaluated a cohort of 160 children followed from birth for SFK (84 with URA and 76 with UMCDK) detected by prenatal or routine neonatal ultrasound screening. Hypertension, proteinuria and elevated GFR were monitored as markers of kidney damage. We compared the characteristics and outcomes of the subgroups of children with URA and UMCDK.

Results

GFR was reduced in 42 (26.2%) children, of whom 41 showed only mild reduction. Hypertension and proteinuria were found in 22 (13.8%) and 14 (8.8%) children, respectively.

Combined kidney damage was present in 57 (35.6%) children. The UMCDK and URA subgroups differed in GFR at final examination, with UMCDK patients being significantly more likely to have normal GFR compared to URA patients (82% vs 67%; p = 0.039).

Conclusions

One third of the children showed signs of SFK damage, albeit mild. Patients with URA had reduced GFR significantly more often than those with UMCDK, but did not differ in the rates of hyperfiltration injury or congenital anomalies of the kidneys and urinary tract (CAKUT) in SFK.

Introduction

In children, 30–50% of chronic renal failure cases are caused by congenital anomalies of the kidneys and urinary tract (CAKUT) [1, 2]. The risk of kidney damage is mainly present in children with bilateral kidney anomalies or solitary functioning kidney (SFK), especially if SFK is associated with CAKUT, such as high-grade vesicoureteral reflux (VUR) or obstructive defects. However, individuals with congenital SFK without associated CAKUT also have a higher risk of renal function decline over their lifetime than those with both kidneys. Published papers are inconsistent as to whether already in childhood this risk is significant [3] or low [4, 5, 6]. Similar discrepancies are seen in the presence of hyperfiltration injury to the solitary kidney (hypertension, increased proteinuria). One explanation for the differences in the prognosis of a solitary kidney in children is the difference in selecting the initial patient population; for example, whether

SFK was diagnosed only at the onset of clinical problems or prenatally. The present study followed children with unilateral renal agenesis (URA) and unilateral multicystic dysplastic kidney (UMCDK) with only the contralateral functioning kidney. The cohort is specific in that the children with SFK were diagnosed in the neonatal period based on both prenatal and routine postnatal ultrasound (US) screening. Although the quality of prenatal US screening continues to improve, it is still not sufficiently sensitive in detecting URA. Thus, children with asymptomatic URA, who would likely improve the prognosis of patients with SFK, may go undetected for a long time and are not included in the population studied.

The study aimed to determine the frequency of congenital solitary kidney damage in children followed from birth for URA or UMCDK. We hypothesized that children with SFK in the cohort would have a good prognosis regarding kidney damage because the defect was detected early and preventive measures were taken from birth. Another objective was to identify the characteristics that distinguish the URA subgroup from the UMCDK subgroup and whether the frequency of SFK damage is different in these subgroups. Although a worse prognosis for URA is reported in the literature [7, 8], we assumed that because of the early detection of children with asymptomatic URA, there would be no difference in the presence of hypertension, proteinuria and reduced glomerular filtration rate (GFR) between URA and UMCDK patients. Based on the findings, we planned to optimize the follow-up protocol for children with SFK.

Material and methods

Patients

Using a long-term follow-up protocol, we evaluated a cohort of patients followed at our center between 2000 and 2023 for a congenital SFK caused by URA or UMCDK. Some of these patients (46 out of 160) had been enrolled in our earlier prospective multicenter study entitled Renal Parenchymal Thickness in Children with Solitary Functioning Kidney [9]. The current cohort of patients included all children with URA or UMCDK identified by prenatal or postnatal US screening. In the Czech Republic, prenatal US screening is performed as part of recommended gynecological procedures in all pregnant women and is covered by insurance. With regard to renal defects, screening at 20–22 and then at 30–32 weeks' gestation is essential. In addition to regular prenatal US screening, US screening for renal defects is performed in all newborns aged three to four days in our center.

In infancy, SFK was confirmed by DMSA static renal scintigraphy and was defined as 100% unilateral function.

The exclusion criterion was having diseases other than CAKUT that could affect renal function in the neonatal period, such as sepsis or perinatal asphyxia.

Indicators of kidney damage

The indicators of kidney damage were reduced GFR and signs of hyperfiltration injury, that is, hypertension and proteinuria. The category of combined kidney damage comprised children with any of the above indicators, that is, reduced GFR or hypertension or proteinuria.

The GFR was calculated using two formulas based on the child's serum creatinine level, height, age and sex, namely the Schwartz formula [10, 11] and CKiDU25 [12]. In children aged two years or older, GFR < 90 mL/min/1.73 m^2 was considered reduced and GFR < 60 mL/min/1.73 m^2 was considered moderately reduced. The reduced GFR category included children whose GFR was found to be reduced using both formulas. According to the KDIGO guidelines, long-term GFR < 90 mL/min/1.73 m^2 is referred to as stage 2 chronic kidney disease (CKD 2) and GFR 60–89 mL/min/1.73 m^2 as stage 3 chronic kidney disease (CKD 3). In children younger than two years of age, GFR was assessed according to the National Kidney Foundation recommendations [11].

Casual oscillometric blood pressure (BP) measurements were obtained in all children during regular outpatient visits. In addition, some patients older than five years (65 out of 160) underwent 24-hour ambulatory BP monitoring (ABPM). Hypertension was defined as BP ≥ 95th percentile for the sex, age and height of the child [13] at casual measurement and BP ≥ 95th percentile for the sex and height of the child at ABPM [14]. Children with hypertension at casual BP measurement underwent ABPM and had other secondary causes of hypertension excluded.

Proteinuria was assessed by calculating the urine protein-creatinine ratio (uPCR) and/or urine albumin-creatinine ratio (uACR) in early morning urine samples. Proteinuria was defined as uPCR > 20 mg/mmol and/or uACR > 3 mg/mmol in children aged two years or older and as uPCR > 50 mg/mmol and/or uACR > 10 mg/mmol in children younger than two years [15].

Children with hypertension and repeated proteinuria or albuminuria were treated with ACE inhibitors or angiotensin receptor blockers. These children were categorized as having hypertension or proteinuria, even though their BP or urine proteins were controlled with medication.

Risk factors

Following on from previous studies on congenital SFK, we investigated the following risk factors: sex, SFK side, immaturity (preterm birth before 37 weeks' gestation), low birth weight (< 2500 g), GFR at initial examination, SFK length, CAKUT in SFK, urinary tract infection (UTI), body mass index (BMI) at final examination, hypertension, proteinuria/albuminuria, and urinary beta-2 microglobulin (U-B2M).

SFK length was measured by US and classified into percentile intervals according to the mean kidney length by age, as described by Akhavan et al. [16].

CAKUT in the solitary kidney was diagnosed by US and, in selected patients, by MAG3 diuretic renal scintigraphy to detect pelviureteric junction obstruction (PUJO) and by micturating cystourethrography (MCUG) to detect VUR. Indications for MCUG were SFK ureteral dilatation on US, SFK length below the 5th percentile, or UTI.

UTI was defined as the presence of pyuria and significant bacteriuria.

BMI was assessed using national reference charts for sex and age [17] and categorized as normal, overweight (> 85th percentile and ≤ 97th percentile) and obese (> 97th percentile).

The indicator of tubular injury was U-B2M, with levels above 0.202 mg/L being considered elevated by our laboratory.

Follow-up protocol

Children who were diagnosed with URA or UMCDK by prenatal or postnatal US screening were followed in our outpatient nephrology unit. In the case of normal postnatal US findings in the functional kidney, the first appointment was scheduled at approximately three months of age, which included a follow-up US examination and DMSA static renal scintigraphy to confirm the function of only one kidney. At the same time, GFR was measured (using serum creatinine levels) and urine tests were performed, including uPCR and/or uACR. Parents were informed about the symptoms of UTI. In selected children with dilatation of the SFK pelvicalyceal system, antibiotic prophylaxis for UTI was administered until six months of age or until surgery for high-grade VUR. With normal US findings in SFK, the follow-up US scan, urine tests and BP measurements were scheduled at one year of age, then annually until five years of age, and every two years thereafter. The follow-up protocol was similar for all patients but evolved over the years. Initially, proteinuria was monitored, later albuminuria was added, and in the last five years, U-B2M was also measured. Preventive ABPM was performed only in the last 10 years. In the case of any pathological finding (SFK dilatation on US, proteinuria, reduced GFR, hypertension, UTI), check-ups were more frequent. Patients with obstructive SFK defects or high-grade VUR underwent early surgery by consensus of a nephrologist and a urologist. Patients were followed at our center until 18–19 years of age. After that, further follow-up was recommended, either by a general practitioner or, if kidney damage was suspected, by a specialist, usually an adult nephrologist.

Statistical analysis

Two independent samples were compared using Fisher's exact test (qualitative data) and Mann–Whitney U-test (numerical and ordinal data).

Risk factors for reduced GFR and hypertension were assessed with odds ratio (OR) and 95% confidence interval (95% CI). The former was calculated by logistic regression. In addition, multivariate logistic regression was used to assess risk factors for reduced GFR and hypertension. In both cases, the model included the following variables: sex, BMI, immaturity, low birth weight, recurrent UTI, hypertension, proteinuria, elevated U-B2M, SFK side, SFK length at one year of age, GFR at initial examination, and severe CAKUT. The model was developed using the forward stepwise method (likelihood ratio).

All tests were performed at a significance level of 0.05.

Statistical analyses were performed with IBM SPSS Statistics 23.0 (Armonk, NY: IBM Corp.).

Results

The entire cohort comprised 160 children with congenital SFK who met the inclusion criteria. Their mean age at final examination was 10.4 years (median 10.1 years, SD 5.47 years). Detailed clinical data of the patients are shown in Table 1.

Table 1
Clinical and laboratory characteristics of all children with congenital SFK at the beginning of the follow-up

n = 160	Count	%
Sex - male/female	101/59	63.1/36.9
Immaturity	10	6.3
Low birth weight	12	7.5
Prenatal diagnosis	87	54.4
Etiology		0.5
UMCDK	76	47.5
URA	84	52.5
SFK side		
right	84	52.5
left	76	47.5
CAKUT in SFK	29	18.1
Severe CAKUT	11	6.9
CAKUT type		
hydronephrosis	4	13.8
megaureter	7	24.1
ADPKD	1	3.4
PUJO	2	6.9
duplex kidney	1	3.4
VUR	14	48.3
Other anomalies	36	22.5
CNS	1	2.8
female genitals	3	8.3
male genitals	9	25.0
GIT	4	11.1
cardiac	7	19.4
cardiac, male genitals	1	2.8

n = 160	Count	%
musculoskeletal	9	25.0
musculoskeletal, male genitals	1	2.8
musculoskeletal + mixed	1	2.8
US - SFK length, 3 months of age		
below p50	9	6.2
p50-75	14	9.7
p75-95	64	44.1
above p95	58	40.0
US - SFK length, 1 year of age		
below p50	5	3.2
p50-75	13	8.3
p75-95	62	39.7
above p95	76	48.7
GFR - initial		
normal	151	94.4
mildly reduced	9	5.6

As for the etiology of SFK, there were 76 children with UMCDK (47.5%) and 84 children with URA (52.5%). Prenatally, SFK was detected in 54.4% of children; the others were diagnosed during postnatal US examination.

CAKUT in the solitary kidney was seen in 18.1% of children, with VUR being the most common anomaly (48.3%). Eleven children (6.9%) had severe CAKUT; of whom nine were indicated for surgical management of the SFK defect. Five children underwent ureteral reimplantation for grade 3–4 VUR or refluxing megaureter, two were operated for obstructive megaureter, and two underwent pyeloplasty for PUJO.

Anomalies of other organs were found in 22.5% of children. The most frequent were anomalies of the male genitals (hypospadias, seminal vesicle cysts, cystic testicular dysplasia, cryptorchidism, Zinner syndrome) and the musculoskeletal system (vertebral anomalies, polydactyly, cutaneous syndactyly, radial club hand, nail patella syndrome). Cardiac anomalies included atrial septal defect, ventricular septal defect, and pulmonary stenosis. Gastrointestinal tract (GIT) anomalies included diaphragmatic hernia, GIT duplication, esophageal atresia, and anorectal atresia. Female genital anomalies included

obstructed hemivagina and ipsilateral renal anomaly syndrome, bicornuate uterus, double uterus, and vaginal septum. One child with a central nervous system anomaly had agenesis of the corpus callosum and colpocephaly.

Compensatory renal hypertrophy, monitored by measuring SFK length during US examination, was present in 40% of children aged three months and 48.7% of one-year-old children.

The initial GFR was reduced in 5.6% of children (minus 1 to 2 SDs from the mean) and normal in the rest of the cohort. No children had severely reduced GFR in the first months of life (less than minus 2 SDs).

Kidney damage in the entire cohort

Table 2 shows the results for all children at the end of follow-up.

Table 2
Clinical outcomes in all children with congenital SFK

n = 160	Count	%
GFR - final		
normal	118	73.8
mildly reduced	41	25.6
moderately reduced	1	0.6
BMI		
normal	117	73.1
overweight	29	18.1
obesity	14	8.8
UTI	30	18.8
Recurrent UTI	10	6.3
Hypertension	22	13.8
Proteinuria/albuminuria	14	8.8
U-B2M		
not assessed	37	23.1
elevated	18	11.3
normal	105	65.6
US - SFK length, final		
below p50	4	2.5
p50-75	10	6.3
p75-95	47	29.7
above p95	97	61.4
Antihypertensives	21	13.1
Combined kidney damage	57	35.6

Renal function decline

Although GFR was reduced in a total of 42 children (26.2%), the reduction was mild (CKD 2) in 41 of them and moderate (CKD 3) in only one child (0.6%), a patient with UMCDK.

Hyperfiltration injury

Hypertension was observed in 22 children (13.8%) and proteinuria in 14 children (8.8%).

Combined kidney damage was present in 57 children (35.6%).

Other indicators

Elevated BMI was found in 26.9% of children, with 18.1% being overweight and 8.8% being obese.

UTI developed in 18.8% of children, of whom 6.3% had recurrent UTI.

Some patients in the cohort (76.9%) also had U-B2M assessed. The indicator of tubular injury was elevated in 11.3% of children; patients with severe CAKUT had significantly more often elevated U-B2M than the others ($p = 0.0004$).

Compensatory renal hypertrophy was present in 61.4% of children at the end of follow-up.

In patients with UMCDK, involution of the multicystic kidney was monitored by US examination and confirmed in 79.4% of children with a mean age of 3.45 years.

Comparison of the UMCDK and URA subgroups

The numbers of children in the two subgroups was comparable (Table 1), as was the mean age, which was 10.34 years (SD 5.50) for UMCDK and 10.53 years (SD 5.48) for URA ($p = 0.782$). Table 3 shows a statistical comparison of the clinical characteristics of the two subgroups. The UMCDK and URA subgroups differed in three characteristics: GFR at final examination, prenatal diagnosis, and the presence of UTI. Patients with UMCDK were statistically significantly more likely to have normal GFR values than those with URA (82% vs 67%, $p = 0.039$). Children with UMCDK were statistically significantly more likely to have their renal defects detected prenatally (80% vs 31%, $p < 0.0001$). UTI was statistically significantly more frequent in patients with UMCDK than in those with URA (26% vs 12%, $p = 0.025$). No other significant differences were found. There was no difference in hyperfiltration injury (hypertension, proteinuria) or combined kidney damage. Finally, there was no significant difference in the presence of CAKUT.

Table 3
Comparison of the UMCDK and URA subgroups

ETIOLOGY					
variable	UMCDK		URA		p
	n = 76	%	n = 84	%	
GFR - final					
normal	62	81.6	56	66.7	
mildly reduced	13	17.1	28	33.3	0.039*
moderately reduced	1	1.3	0	0	
Sex - male/female	48/28	63.2/36.8	53/31	63.1/36.9	1.000
BMI					
normal	58	76.3	59	70.2	
overweight	13	17.1	16	19.0	0.350
obesity	5	6.6	9	10.7	
Immaturity	3	3.9	7	8.3	0.334
Low birth weight	5	6.6	7	8.3	0.769
Prenatal diagnosis	61	80.3	26	31.0	< 0.0001***
CAKUT in SFK	11	14.5	18	21.4	0.306
Severe CAKUT in SFK	5	6.6	6	7.1	1.000
Other anomalies	14	18.4	22	26.2	0.261
UTI	20	26.3	10	11.9	0.025*
Recurrent UTI	6	7.9	4	4.8	0.520
Hypertension	9	11.8	13	15.5	0.647
Proteinuria/albuminuria	8	10.5	6	7.2	0.579
U-B2M elevation	7	11.7	11	17.5	0.448
SFK side					
right	39	51.3	45	53.6	
left	37	48.7	39	46.4	0.874

*p < 0.05; *** p < 0.001

	ETIOLOGY				
US - SFK length, 3 months of age					
below p50	4	5.6	5	6.8	
p50-75	6	8.5	8	10.8	
p75-95	29	40.8	35	47.3	
above p95	32	45.1	26	35.1	0.245
US - SFK length, 1 year of age					
below p50	3	4.1	2	2.5	
p50-75	7	9.3	6	7.4	
p75-95	27	36	35	43.2	
above p95	38	50.7	38	46.9	0.863
Antihypertensives	12	15.8	9	10.7	0.360
GFR - initial					
normal	71	93.4	80	95.2	
mildly reduced	5	6.6	4	4.8	0.737
Combined kidney damage	22	28.9	35	41.7	0.101
*p < 0.05; *** p < 0.001					

Risk factors for kidney damage

The risk factors for reduced GFR identified by logistic regression are shown in Table 4. A statistically significant protective factor was kidney length on US at three months and one year of age. Compensatory hypertrophy (kidney length above the 95th percentile) at three months of age and at one year of age reduced the odds ratio for reduced GFR to one third (0.356 and 0.330, respectively). Statistically significant risk factors for reduced GFR in the entire cohort were CAKUT (OR = 2.858), severe CAKUT (OR = 9.020), hypertension (OR = 4.320), proteinuria (OR = 6.109), need for antihypertensive/antiproteinuric medication (OR = 3.832), and reduced GFR at initial examination at the beginning of the follow-up (OR = 6.389).

Table 4
Risk (protective) factors for reduced GFR

	GFR-final						
	reduced		normal		OR	(95% CI)	p
	Count	%	Count	%			
Sex - male/female	28 / 14	66.7 / 33.3	73 / 45	61.9 / 38.1	1.233	(0.587; 2.587)	0.710
BMI							
normal	28	66.7	89	75.4			
overweight, obesity	14	33.3	29	24.6	0.652	(0.303; 1.402)	0.312
Immaturity	3	7.1	7	5.9	1.220	(0.301; 4.951	0.723
Low birth weight	3	7.1	9	7.6	0.932	(0.240; 3.618)	1.000
CAKUT in SFK	13	31	16	13.6	2.858	(1.234; 6.620)	0.019*
Severe CAKUT in SFK	8	19	3	2.5	9.020	(2.267; 35.887)	0.001**
UTI	8	19	22	18.6	1.027	(0.418; 2.522)	1.000
Recurrent UTI	4	9.5	6	5.1	1.965	(0.526; 7.338)	0.292
Hypertension	12	28.6	10	8.5	4.320	(1.702; 10.967)	0.003**
Proteinuria/albuminuria	9	21.4	5	4.3	6.109	(1.915; 19.490)	0.002**
U-B2M elevation	6	20.7	12	12.8	1.783	(0.603; 5.268)	0.367
SFK side							
right	23	54.8	61	51.7			
left	19	45.2	57	48.3	1.131	(0.558; 2.293)	0.857

*p < 0.05; **p < 0.01

		GFR-final					
US - SFK length, 3 months of age							
≤ p95	27	77.1	60	54.5			
> p95	8	22.9	50	45.5	0.356	(0.148; 0.852)	0.018*
US - SFK length, 1 year of age							
≤ p95	29	70.7	51	44.3			
> p95	12	29.3	64	55.7	0.330	(0.153; 0.710)	0.003**
Antihypertensives	11	26.2	10	8.5	3.832	(1.490; 9.859)	0.007**
GFR - initial							
reduced	6	14.3	3	2.5			
normal	36	85.7	115	97.5	6.389	(1.520; 26.846)	0.011*
*p < 0.05; **p < 0.01							

Subsequently, the risk factors for reduced GFR were then evaluated using multivariate logistic regression. The results are shown in Table 5. The final model comprised two significant risk factors and one significant protective factor. The former were hypertension (OR = 9.335) and proteinuria (OR = 15.113). The protective factor was kidney length at one year greater than the 95th percentile (OR = 0.112).

Table 5
Risk (protective) factors for reduced GFR – multivariate logistic regression

Variable	OR	(95% CI)	p
Proteinuria/albuminuria	15.113	(2.429; 94.022)	0.004**
Hypertension	9.335	(2.106; 41.385)	0.003**
US - SFK length, 1 year of age	0.112	(0.032; 0.391)	0.001**
**p < 0.01			

Risk factors for hypertension

Table 6 shows the risk factors for hypertension. GFR at initial examination (OR = 16.875) and severe CAKUT (OR = 4.159) were found to be statistically significant risk factors. Table 7 shows the risk factors identified by multivariate logistic regression. In the final model, there were two significant factors, namely BMI (OR = 5.487) and GFR at initial examination (OR = 13.815), both of which are risk factors. Patient overweight or obesity increases the odds of developing hypertension, as does reduced GFR at initial examination.

Table 6
Risk (protective) factors for hypertension

	Hypertension						
	yes		no		OR	(95% CI)	p
	Count	%	Count	%			
Sex -male/female	16 / 6	72.7 / 27.3	85/53	61.6 / 38.4	1.663	(0.612; 4.515)	0.352
BMI							
normal	13	59.1	104	75.4			
overweight, obesity	9	40.9	34	24.6	0.472	(0.186; 1.302)	0.124
Immaturity	1	4.5	9	6.5	0.683	(0.082; 5.668)	1.000
Low birth weight	1	4.5	11	8.0	0.550	(0.067; 4.483)	1.000
CAKUT in SFK	7	31.8	22	15.9	2.461	(0.900; 6.731)	0.081
Severe CAKUT in SFK	4	18.2	7	5.1	4.159	(1.107; 15.624)	0.047*
UTI	3	13.6	27	19.6	0.649	(0.179; 2.354)	0.769
Recurrent UTI	2	9.1	8	5.8	1.625	(0.322; 8.207)	0.629
Proteinuria/albuminuria	3	13.6	11	8.0	1.809	(0.462; 7.080)	0.414
U-B2M elevation	3	23.1	15	13.6	1.900	(0.468; 7.708)	0.404
SFK side							
right	13	59.1	71	51.4			
left	9	40.9	67	48.6	1.363	(0.547; 3.397)	0.647
US - SFK length, 3 months of age							
≤ p95	13	68.4	74	58.7			

*p < 0.05; *** p < 0.001

			Hypertension				
> p95	6	31.6	52	41.2	1.523	(0.543; 4.266)	0.464
US - SFK length, 1 year of age							
≤ p95	11	50.0	69	51.5			
> p95	11	50.0	65	48.5	1.062	(0.431; 2.616)	1.000
GFR - initial							
mildly reduced	6	27.3	3	2.2			
normal	16	72.7	135	97.8	16.880	(3.840; 74.100)	0.0002***
*p < 0.05; *** p < 0.001							

Table 7
Risk factors for hypertension – multivariate logistic regression

Variable	OR	(95% CI)	p
BMI (normal vs overweight, obesity)	5.487	(1.525; 19.743)	0.009**
GFR - initial	13.815	(1.468; 130.040)	0.022*
*p < 0.05; ** p < 0.01			

Discussion

The present study evaluated the presence of SFK damage in children mostly followed “preventively” based on prenatal and neonatal US screening findings at a single nephrology center and compared the outcome of URA and UMCDK. Combined prenatal and neonatal US screening allows for the earliest possible diagnosis of SFK, early follow-up and early treatment of both CAKUT in SFK and proteinuria and hypertension. To the best of our knowledge, only one study has been published on congenital SFK diagnosed by combined prenatal and postnatal US screening, which did not compare the prognosis of URA and UMCDK [18].

The main finding was that one third of the cohort showed signs of SFK damage, albeit mild, even though CAKUT in SFK was relatively rare. When comparing URA and UMCDK, there was a difference in the frequency of reduced GFR, but no difference in any other characteristic. The study highlights the importance of regular GFR monitoring in children with SFK.

Impaired SFK function, defined by GFR below 90mL/min/1.73m^2 in the study, was found in a not negligible proportion (26.2%) of the entire cohort (mean follow-up of 10 years). On the other hand, only one child (0.6%) had moderately reduced GFR (CKD3); the others showed only mild GFR reduction (CKD2). When comparing the results with those of recent studies, the frequency of reduced GFR in our cohort is comparable to a study by Marzuillo et al. who reported reduced GFR in 21.4% of children [6]. Patients in our cohort have better GFR than those in the SOFIA study, in which 28% of children had CKD2, 3% had CKD3 or worse, and 1% required renal transplantation [8]. By contrast, in a systematic review by Hutchinson et al., where GFR < 90mL/min/1.73m2 indicated pathological renal function, only 8.4% of children had “worsened renal function”. However, it is not specified how the authors assessed “worsened renal function” in the studies included in the review [4]. We chose to consider GFR < 90mL/min/1.73m2 as impaired renal function in our study as we believe that even individuals with mildly reduced GFR deserve long-term monitoring by a nephrologist. Since we are aware that the Schwartz formula for calculating GFR may underestimate GFR in some adolescent patients, GFR was also assessed using the CKiDU25 equation, and only individuals with both GFR values < 90mL/min/1.73m2 were categorized as having reduced GFR.

The frequency of hyperfiltration injury in the entire cohort was similar to that in the review by Hutchinson et al. and earlier studies [19]. In the present study, 13.8% of children had hypertension and 8.8% had proteinuria. The observed frequency of hypertension was higher due to the fact that 40.6% of the children in our cohort had their BP assessed by ABPM in addition to casual measurements. Of the 22 hypertensive patients, five had only nocturnal hypertension, which is impossible to detect without ABPM. Although according to the Italian Society of Pediatric Nephrology consensus recommendations, ABPM should not be used preventively in all children with a SFK [19], we intend to continue preventive ABPM for the time being based on our results.

One of the main objectives of the present study was to compare the outcome of children with URA and UMCDK. Some authors reported a worse outcome for URA than for UMCDK [7, 8]. We hypothesized that this may be due to selection bias and that with our approach of diagnosing SFK by both prenatal and routine postnatal US, providing us with approximately equal numbers of URA and UMCDK cases in the cohort, the prognosis of URA would not be worse. However, this assumption was not confirmed. Although there was no statistically significant difference in the incidence of hypertension or proteinuria between URA and UMCDK patients, we did demonstrate a difference in GFR at final examination. Individuals with URA were statistically significantly more likely to have mildly reduced GFR, which was surprising given the absence of other differences. Both Matsell et al. and Groen in ’t Woud et al. report CAKUT in SFK as a reason for the higher risk of kidney damage in URA compared to UMCDK. In the present study, children with URA had more frequent CAKUT in SFK than those with UMCDK, but this difference was not statistically significant. UTI was even more frequent in patients with UMCDK. The explanation for the slightly worse renal function in children with URA could be different embryonic development. Kidney agenesis manifests itself in earlier stages of development, while defects occurring later tend to be less severe. URA results from the failure of the ureteric duct to contact and/or induce the metanephric

mesoderm [20]. Studies involving conditional gene targeting in mice have pinpointed specific genes critical for normal kidney development, which have homologous counterparts linked to mutations in humans, such as SALL1, EYA1, PAX2 or RET [21], particularly those associated with URA. The impact of such gene mutations can be widespread, affecting the contralateral kidney and leading to extrarenal anomalies. In a rat model of unilateral renal agenesis, the contralateral kidney undergoes hypertrophy, but there is a reduced number of nephrons with hypertrophic glomeruli [22]. This may potentially account for the lower GFR observed in our subgroup of URA patients. The appearance of fetal multicystic dysplastic kidneys suggests a disruption in established kidney induction after it has already initiated affecting normal branching morphogenesis [23]. This scenario would more plausibly explain the development of a contralateral kidney, and there is a greater likelihood that it will be normal. Thus, the pathogenesis of these two conditions appears to be distinct, implying potential differences in outcomes.

Most publications report CAKUT as a risk factor for reduced GFR in solitary kidneys, whether URA or UMCDK. In our entire cohort, CAKUT was also a risk factor, but hypertension and proteinuria were statistically more significant risk factors. The fact that CAKUT was diagnosed early in our patients and severe CAKUT was surgically treated in time may have mitigated the power of this risk factor.

While other authors reported CAKUT in 23.2–46% of SFK cases [3, 5–8, 18], the proportion in the present study was relatively low at 18.1%. This may be explained by the large number of children with asymptomatic SFK in our cohort. The most common CAKUT to SFK tends to be VUR, which needs to be diagnosed by MCUG. We performed this examination only in selected children (SFK length below the 5th percentile, urinary tract dilatation, UTI) and thus may not have detected all SFK cases with VUR. However, our practice of performing MCUG is in line with recent recommendations [19].

An unpleasant finding was that 26.9% of the children in our cohort were overweight or even obese. Increased BMI was a statistically significant risk factor for hypertension. It was not shown to be a risk factor for reduced GFR, but this fact was probably influenced by the relatively short follow-up, with a mean of 10 years. Pediatricians and pediatric nephrologists should pay attention to the prevention of obesity in children with SFK, as it is a modifiable risk factor.

We do not expect neonatal US screening of CAKUT to be extended to all newborns to improve URA detection. In our country, such screening is optional and only 63% of all neonatal units perform it on their own initiative. The emphasis must be on the best possible prenatal US screening. Even children with normal US findings in SFK benefit from early referral to a pediatric nephrologist; the first screening should be performed between two and three months of age and should include US measurement of SFK length. Compensatory hypertrophy of SFK at three months and one year of age was a protective factor for reduced GFR in our cohort, consistent with observations by other authors [5, 24, 25]. Currently, it is not considered necessary to confirm the function of only one kidney by DMSA static renal scintigraphy when the US findings are typical of URA or UMCDK. However, in addition to urine testing, the initial nephrologic evaluation should include GFR estimation by measuring serum creatinine levels and educating parents about the symptoms of UTI to allow for early diagnosis and treatment. The frequency of US scans of SFK

established in the study has proven beneficial and will be continued, as will antibiotic prophylaxis for UTI in selected patients with CAKUT in SFK and close collaboration with a pediatric urologist to indicate early surgical management of CAKUT. The children in the cohort continue to undergo preventive ABPM as part of a prospective study. We hypothesize that in our patients, GFR was favorably influenced by early treatment of hypertension and proteinuria.

In conclusion, this study has contributed to knowledge about congenital SFK by finding that even in a cohort followed from birth, with a large proportion of asymptomatic SFK cases, one third of the children showed signs of SFK damage. In most of them, however, the damage was mild. Patients with URA had significantly more often reduced GFR compared to those with UMCDK, but did not differ in hyperfiltration injury or the frequency of CAKUT in SFK.

Declarations

Author contributions

HF followed the patients throughout the study, collected and analyzed the data and drafted the manuscript. KB contributed substantially to the development and design of the study, participated in writing and reviewing the manuscript. OS followed selected patients throughout the study, interpreted the urological data and contributed to the Discussion section. JH participated in the patient follow-up and data collection, and contributed to the Discussion section. KL was responsible for statistical data analysis. KC contributed to the Discussion section. All authors reviewed and approved the final version.

Ethical approval

This study involving human participants was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of the University Hospital Olomouc and the Faculty of Medicine and Dentistry, Palacky University Olomouc (reference number: 139/23).

Consent to participate / consent for publication

Informed consent was obtained from the parents or legal representatives of the participants.

Conflict of interest

The authors have no relevant financial or non-financial interests to disclose.

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