Retrospective study to identify risk factors for chronic kidney disease in children with congenital solitary functioning kidney detected by neonatal renal ultrasound screening

Adela Urisarri, MD, PhD,a Marta Gil, MD,b Natalia Mandiá, MD,b Luis Aldamiz-Echevarria, MD, PhDc, Roca Iria,a Domingo González-Lamuño, MD, PhDd, María-Luz Couce, MD, PhDa,*

Abstract

To evaluate the prognostic significance of factors frequently associated with a reduction in renal mass, such as prematurity, low birth weight, and congenital anomalies of kidney and urinary tract (CAKUT), in patients with solitary functioning kidney (SFK) and investigate signs of early renal injury due to glomerular hyperfiltration damage or dysplasia in the remaining kidney.

Retrospective observational study of congenital SFK diagnosed and followed at a tertiary care hospital over a period of 10 years in which 32,900 newborns underwent routine neonatal abdominal ultrasound screening. We analyzed age at diagnosis, sex, gestational age, anthropometric measurements at birth and prenatal and neonatal ultrasound findings, in addition to follow-up data corresponding to imaging findings (ultrasound, micturating cystourethrogram, dimercaptosuccinic acid renal, and scintigraphy), ipsilateral CAKUT, compensatory hypertrophy, and renal injury in the form of albuminuria, blood pressure, and estimated glomerular filtration rate (eGFR).

In total, 128 congenital SFK cases were detected (1 per 257 live births). Of these, 117 (91.4%) were diagnosed by neonatal ultrasound screening and 44.5% of these had been previously identified by prenatal ultrasound. Neonatal ultrasound had a specificity of 100% and a sensitivity of 92.1%. Forty-five patients (35.2%) had ipsilateral CAKUT and the most common type was urinary collecting system anomalies (75.5%). Over a median follow-up of 6.3 years (1–10 years), compensatory renal hypertrophy was observed in 81 patients (63.7%), most of whom had ipsilateral CAKUT (76.1% vs 56.6% of patients without ipsilateral CAKUT). Albuminuria and hypertension were observed in 3.12% and 5% of patients, respectively, and both were associated with ipsilateral CAKUT (P < .05). In addition, 75% of albuminuria cases (P = .031), 83.3% of hypertension cases (P = .004), and 100% of decreased eGFR cases (P = .031) were significantly associated with CAKUT (renal parenchymal anomaly category), being the strongest predictor of GFR the presence or absence of CAKUT.

Neonatal ultrasound screening is useful for the early diagnosis of SFK. The presence of ipsilateral CAKUT should be evaluated in all patients with SFK as congenital anomalies of the renal parenchyma are associated with a poorer prognosis. Because morbidity from CAKUTs may not develop until adulthood, patients should be closely followed throughout life.

Abbreviations: BMI = body mass index, BP = blood pressure, BW = birth weight, CAKUT = congenital anomalies of kidney and urinary tract, CKD = chronic kidney disease, DMSA = dimercaptosuccinic acid, eGFR = estimated glomerular filtration rate, GA = gestational age, MCKD = multicystic dysplastic kidney, SFK = solitary functioning kidney.

Keywords: albuminuria, CAKUT, chronic kidney disease, hypertension, prematurity, renal injury

1. Introduction

Children with a solitary functioning kidney (SFK) have at least a 30% reduction in renal mass. According to the Brenner hyperfiltration theory, a reduced number of nephrons could cause hemodynamic changes in the remaining glomeruli, leading to glomerular hypertension and an increased glomerular filtration rate (GFR).1-2 Although these changes seem to reflect a positive adaptive response, patients with unilateral renal agenesis and a normal contralateral kidney are at an increased risk of proteinuria, hypertension, and renal insufficiency and hence require close long-term follow-up and strategies to preserve optimal function in the remnant kidney.

It has been shown that nephrogenesis ends in the 36th week of gestation3,4 and that no new nephrons are formed in the postnatal period.4 The number of glomerular units per kidney varies widely in humans, with figures ranging from 200,000 to over 2,500,000.1,5 As prematurity interrupts nephrogenesis, premature newborns may have a decreased nephron number. Moreover, intrauterine growth restriction can cause fetal reprogramming, which could have a profound effect on the
development of kidneys and other organs.\(^{[7]}\) In one study of intrauterine growth retardation, a reduced nephron number at birth in low birth weight (BW) infants was identified as an indicator of altered kidney development.\(^{[4]}\)

SFK is an important subgroup of congenital anomalies of the kidney and urinary tract (CAKUT),\(^{[10]}\) which are the main causes of chronic kidney disease (CKD) in childhood.\(^{[9]}\) CAKUT are classified into 3 groups: renal parenchymal anomalies, migration and fusion anomalies, and urinary collecting system anomalies. During nephrogenesis, reciprocal inductive interactions controlled by a gene regulatory network occur between the metanephric mesenchyme and the ureteric bud.\(^{[10]}\) Disruption during nephrogenesis results in a wide spectrum of renal and urinary tract malformations, explaining why about 40% of children with SFK have associated congenital kidney anomalies. A low nephron number or impaired nephron function due to alterations during nephrogenesis places patients with CAKUT at a high risk of stage 2 to 5 CKD. Other studies have found more favorable outcomes, which is the opposite of what might be expected according to the Brenner hypothesis.\(^{[11,12]}\)

Follow-up studies of children with SFK are scarce and most have been conducted in children who have undergone unilateral nephrectomy,\(^{[11-14]}\) that is, in children without congenital SFK. In addition, evidence suggests that prognosis may vary depending on whether the patient has congenital or acquired SFK.\(^{[15]}\) We performed a retrospective study of congenital SFK cases diagnosed at our hospital over a period of 10 years to investigate the potential prognostic impact of factors associated with additional renal mass reduction.

2. Patients and methods

2.1. Study design

This retrospective observational study was conducted to evaluate cases of SFK diagnosed in newborns at a tertiary university hospital over a period of 10 years (January 2007–December 2016). The study protocol was approved by the Research Ethics Committee of Santiago-Lugo (2017/576). Written informed consent was obtained from the parents or legal guardians of all the patients included.

SFK was diagnosed by routine prenatal ultrasound performed at 12, 20, and 32 weeks gestational age (GA) and/or by routine neonatal ultrasound performed by neonatologists within the first 7 days of life within the hospital’s neonatal screening program. All diagnoses are confirmed by renal scintigraphy and patients are followed-up to the age of 18 years by the hospital’s pediatric nephrology unit, which is the reference unit for the area.

2.2. Population

Of the 32,900 newborns evaluated during the 10-year study period, 128 were diagnosed with congenital SFK and followed at our unit.

The following diagnostic and follow-up data were recorded and analyzed for all 128 patients:

- Age; sex; GA (weeks); GA classification (preterm [≤ 36 + 6 weeks], full-term [37–41 + 6 weeks], or post-term [≥ 42 weeks]); family history of kidney disease and type; birth length; BW classified as low (< 3rd percentile), appropriate (3rd–97th percentile), or high (> 97th percentile) according to Carrascosa’s charts;\(^{[16,17]}\) prematal (12, 20, and/or 32 weeks GA) and postnatal ultrasound results (within first 7 days of life).
- Systolic and diastolic brachial blood pressure (BP) classified using the charts from the Task Force Report on high BP in children and adolescents.\(^{[18]}\) High BP was defined as systolic and/or diastolic BP above the 95th percentile according to gender, age, and height on repeated measurements.
- Urine and blood parameters. Albuminuria was classified as normoalbuminuria (< 30 mg/g creatinine), microalbuminuria (30–300 mg/g creatinine), or macroalbuminuria (> 300 mg/g creatinine). Estimated GFR (eGFR) was classified as stage I (> 90 mL/min/1.73 m² with renal parenchymal damage), stage II (90–60 mL/min/1.73 m²), stage III (60–30 mL/min/1.73 m²), stage IV (30–15 mL/min/1.73 m²), or stage V (< 15 mL/min/1.73 m²). Renal injury was defined as the persistent presence of hypertension and/or severely increased albuminuria and/or a significantly impaired eGFR.
- Imaging studies (micturating cystourethrography, dimercapto-succinic acid [DMSA] renal scintigraphy). CAKUT based on imaging test results was classified into 3 groups: renal parenchymal anomalies (renal hypodysplasia, defined as a kidney size < 50% of average size; multicystic dysplastic kidney [MCKD], defined as changes in the renal parenchyma with associated renal cysts; renal agenesis); migration anomalies (kidney ectopia); and urinary collecting system anomalies (mild [grade I–II] or severe [grade III–V] vesicoureteral reflux, ureteropelvic junction obstruction, ureterovesical junction obstruction, posterior urethral valves, ureterocele, or duplicated pyeloureteral system. Finally, the presence or absence of compensatory hypertrophy, defined as an increase in renal size over the 95th percentile for height, was established according to Gavela et al’s charts.\(^{[19]}\)

2.3. Methods

Recumbent length was measured with a length board and weight was measured using a manual baby scales. These measurements were made by specialized personnel for these patients in all cases. Body mass index (BMI) was calculated as weight (kg)/height\(^2\) (m\(^2\)) and classified as normal weight (3rd–85th percentiles), overweight (> 85th–95th percentiles), or obesity (> 95th percentile) according to Hernández’s charts.\(^{[20]}\) BP was measured using oscillometric devices and high BP was confirmed by auscultation and/or ambulatory BP monitoring.

Albumin concentrations in first-morning urine were measured using bromocresol green. Serum creatinine was analyzed using the kinetic Jaffe method and eGFR was estimated using the Schwartz formula [K [constant] × height [cm]/serum creatinine [mg/dL]].

Renal ultrasound was performed using a 2.5-MHz probe (GE Voluson Expert 730 Ultrasound System; GE Healthcare, Spain). Micturating cystourethrography was performed using the Optima XR646 digital radiography system (GE Healthcare), and results were classified according to grading system presented in the International Reflux Study in Children.\(^{[21]}\) DMSA renal scintigraphy was performed using a Brivo NM615 collimator (GE Healthcare), and results were evaluated on the scale formulated by Goodrich.\(^{[22]}\)

2.4. Statistical analysis

Statistical analysis was performed using R Core Team (2017), version 3.4.0. In order to evaluate the significance of the difference between qualitative variables, we used the Fisher’s...
exact test, and the Benjamini–Hochberg correction was applied to adjust the \( P \)-values. Only \( P \)-values under .05 were considered significant. We also used a stepwise AIC (Akaike information criterion)-based regression method to identify risk factors for renal injury.

### 3. Results

The 128 congenital cases of SFK detected corresponded to an overall incidence of 1 case per every 257 live births. The most common SFK phenotype was a full-term (106/128, 82.8%) newborn male (82/128; 64%) of appropriate BW for GA (93/128, 73%) without a family history of kidney disease (94/128, 73.4%) or associated ipsilateral CAKUT (83/128, 65%). The kidney diseases detected in the family were nephrolithiasis (15.6%), renal agenesis (6%), and renal hypoplasia, vesicoureteral reflux, and glomerular disease (5%).

Fifty-seven (44.5%) of the 128 cases of SFK were detected by prenatal renal ultrasound and confirmed by neonatal abdominal ultrasound and 60 (46.8%) were detected by routine neonatal ultrasound screening. The remaining 11 cases (8.6%) were diagnosed during the ultrasound investigation of other underlying diseases in the postnatal period. Eight of these cases were detected within the first year of life. All diagnoses of SFK were confirmed by renal scintigraphy. The functioning kidney was the right kidney in 60.9% of cases. Seventy-five (58%) of the 128 patients had renal agenesis and 53 (42%) had MCKD. All of the patients in whom CFK was diagnosed outside the neonatal period had MCKD (Table 1).

Overall, neonatal ultrasound had as specificity of 100% and a sensitivity of 92.1%. Sensitivity was 100% for renal agenesis and aplasia and 82.8% for MCKD. The respective positive and negative predictive values were 100% and 99.9%.

Forty-five patients (35.1%) had ipsilateral CAKUT, which corresponded to urinary collecting system anomalies in 75.5% of cases. Vesicoureteral reflux was the most common malformation, present in 21.8% of the population.

Median follow-up was 6.3 years (range 1–10 years). Compensatory renal hypertrophy was observed in 81 patients (63.7%). The rates were similar following analysis by GA (57.7% for preterm newborns and 66.6% for full-term newborns) and BW (60.8% for low BW and 65% for appropriate BW). Compensatory renal hypertrophy was more common in patients with ipsilateral CAKUT (76.1% vs 56.6% in patients without ipsilateral CAKUT) but the differences were not significant (Table 2).

Albuminuria or microalbuminuria was detected in 4 patients (3.12%), all of whom were full-term newborns with an appropriate BW and ipsilateral CAKUT \((P = .023)\). Six patients (5%) had hypertension and all of them had ipsilateral CAKUT \((P = .0051)\) and BMI in the range of obesity. Three patients had decreased eGFR (stage III or higher) and 2 of these had associated ipsilateral CAKUT \((P = n.s)\) (Fig. 1).

Finally, we observed that 75% of albuminuria cases \((P = .031)\) and 83.3% of hypertension cases \((P = .004)\) were associated with type 1 CAKUT (renal parenchymal anomalies). A similar association was observed for decreased eGFR \((P = .031)\) (Table 2) (Fig. 2).

We used a stepwise regression method based on AIC to identify the strongest predictors of GFR, systolic and diastolic pressure, and albuminuria, among the variables: age at diagnosis, gestational age, sex, weight, BMI, CAKUT, and compensatory renal hypertrophy. We found that the strongest predictor of GFR was the presence or absence of CAKUT \((\text{Adj } R^2 = 0.03, P = .029)\). The best fitting model for systolic and diastolic pressure was the combination of BMI and CAKUT (systolic: \(\text{Adj } R^2 = 0.156\), BMI

### Table 1

Characteristics of 128 cases of solitary functioning kidney diagnosed over a 10-year period at a hospital with routine neonatal ultrasound screening.

| Detection by ultrasound | Cases (n) (%) | Male sex (%) | Family history (%) | Full-term GA (%) | Appropriate BW for GA NW (%) (n) | Right location RA MCKD (n) |
|-------------------------|--------------|--------------|--------------------|------------------|----------------------------------|-----------------------------|
| Antenatal               | 45 (35.2)    | 64.4         | 35.6               | 28.9             | 2.2                              | 6.7                         |
| First 7 days of life    | 55 (42)      | 61.4         | 26.3               | 87.7             | 72.7                             | 18.8                        |
| Postnatal               | 28 (22)      | 45.4         | 18.2               | 65               | 46                               | 14                          |

\(BW=\) birth weight, \(GA=\) gestational age, \(M=\) male, \(MCKD=\) multicystic dysplastic kidney, \(RA=\) renal agenesis/aplasia.

### Table 2

Main characteristics of patients with solitary functioning kidney (SFK) with and without ipsilateral CAKUT.

| SFK                        | Number (n) (%) | Male (%) | F (%) | LBW (%) | ABW (%) | HBW (%) | Preterm (%) | Full-term (%) | Post-term (%) | Follow-up period, years | Hyper trophy (%) | Micro albuminuria (%) | High BP (%) | \(\text{GFR} \) (%) |
|----------------------------|----------------|----------|-------|---------|---------|---------|-------------|---------------|---------------|------------------------|----------------|------------------------|------------|------------------|
| CAKUT                      | 45 (35.2)      | 64.4     | 35.6  | 28.9    | 68.9    | 2.2     | 22.2        | 77.8          | 0             | 6.8                    | 76.1          | 8.8                    | 13.3       | 6.7              |
| Abnormalities of the renal | 5 (11.1)       | 80       | 20    | 40      | 60      | 0       | 40          | 60            | 0             | 6.7                    | 60            | 60                    | 100        | 60              |
| parenchyma                 |                |          |       |         |         |         |             |               |               |                        |                |                        |            |                  |
| Abnormal migration         | 5 (11.1)       | 100      | 0     | 100     | 0       | 0       | 0           | 100           | 0             | 100                    | 0             | 0                      | 0          | 0                |
| Abnormalities of the urinary collecting system | 35 (77.7) | 71.4 | 26.8 | 31.4 | 65.7 | 2.8 | 22.9 | 77.1 | 0 | 6.3 | 74.2 | 2.8 | 0 | 0 |
| No CAKUT                   | 83 (64.8)      | 63.8     | 36.2  | 15.7    | 74.7    | 9.6     | 13.2        | 85.5          | 1.2           | 5.9                    | 56.6          | 0                      | 0          | 0                |

\(\text{GFR}=\) glomerular filtration rate, \(<60 \text{mL/min/1.73m}^2\), \(\text{ABW}=\) appropriate birth weight, \(\text{BP}=\) blood pressure, \(\text{CAKUT}=\) congenital anomalies of the kidney and urinary tract, \(\text{F}=\) female, \(\text{HBW}=\) high birth weight, \(\text{LBW}=\) low birth weight, \(\text{M}=\) male, \(\text{SFK}=\) solitary functioning kidneys.
P value = 6.3e-05, CAKUT P value = .0098; diastolic: Adj $R^2$ = 0.064, BMI P value = 0.021, CAKUT P value = .034). In albuminuria, the strongest predictors were the age at diagnosis and CAKUT (Adj $R^2$ = 0.11, age at diagnosis P value = .0036, CAKUT P value = .0094).

4. Discussion

We analyzed clinical, biochemical, and imaging data corresponding to 128 patients with SFK born in a tertiary care hospital to investigate potential prognostic factors and assess the importance of early diagnosis. All the patients underwent routine prenatal and neonatal ultrasound screening and were followed for a mean of 6.3 years.

The incidence of SFK over the 10-year study period was 1 case per 257 live births, which is higher than rates reported elsewhere. In a systematic review of unilateral renal agenesis, Westland et al[23] calculated an incidence of 1 case per 2000 births, while in an analysis of data from 13 European registries, Winding et al[24] found an overall rate of 1 case of MCKD per 2427 births. It is difficult to estimate the incidence of SFK in the general population, since many patients remain asymptomatic into adulthood. Prenatal ultrasound screening detected just 45% of subsequently confirmed cases of SFK in our series, providing further evidence that prenatal detection rates are generally low.[25] One reason proposed to explain these low detection rates is the fact that ultrasound features of adrenal glands or intestinal loops during gestation can mimic renal tissue, causing confusion and misdiagnosis.[26] Although neonatal ultrasound detected SFK in the vast majority of patients in our series, it missed 8.6% of cases, which were all MCKD. We believe that this is probably because it is easier to detect a missing kidney than anomalies in the renal parenchyma.

According to the hyperfiltration theory,[11,21] children with SFK have a high risk of developing long-term hypertension, albuminuria, and reduced GFR in the long-term. Although this theory is accepted worldwide, it has only been demonstrated in experimental animal models, as it is not yet possible to count nephrons in vivo or to measure single-nephron GFR in human. Nevertheless, patients with a single kidney would constitute a human model of a 50% reduction in renal mass. It has been shown that compensatory renal function in solitary kidneys reaches a GFR of 75% of the estimated total value for both kidneys,[27-29] indirectly demonstrating hyperfiltration in the remaining glomeruli. Compensatory growth in response to the loss of a contralateral kidney also indirectly supports the compensatory hyperfiltration theory, with reports of solitary kidneys reaching a volume of up to 180% the volume of a healthy kidney.[30] Since the consequences of compensatory hyperfiltration and final kidney size may be related to the number of functional nephrons, it may be necessary to identify risk factors for nephron number reduction. In the present study we assessed whether factors that predispose to a reduced nephron number,[31] such as prematurity, low BW for GA, and CAKUT, might be associated with changes in SFK size. We found that 63.7% of patients developed compensatory hypertrophy, and the rates were similar when the data were analyzed by GA and BW. Compensatory hypertrophy, however, was more common in patients with ipsilateral CAKUT. One study of ex vivo human samples showed that glomerular size increased with a decreasing number of nephrons; accordingly, an adequate number of nephrons may protect against glomerular hypertrophy.[32] Since the number of nephrons in a single human kidney can vary from 200,000 to over 2,500,000,[3,26] it could be hypothesized that children with a single kidney without ipsilateral CAKUT might have an adequate number of nephrons capable of assuming excessive function in addition to less compensatory hypertrophy. On the other hand, one of the possible explanations why an ipsilateral CAKUT is associated with compensatory hypertrophy more is probably because even in the single kidney some of the nephrons can have developmental issues further reducing the number of

![Figure 1. Incidence of albuminuria and hypertension in patients with solitary functioning kidney associated or not with ipsilateral congenital anomalies of the kidney and urinary tract (CAKUT). CAKUT = congenital anomalies of the kidney and urinary tract.](image-url)
functional nephrons causing the remaining to hypertrophy. Although in our observational study we found that compensatory renal hypertrophy was more common in patients with ipsilateral CAKUT than in those without CAKUT, large longitudinal follow-up studies are needed to explore clinical outcomes in patients with different types of SFK.

The incidence of albuminuria, hypertension, and decreased eGFR over the median follow-up period of 6.3 years (3%, 5%, and 1.6%, respectively) is consistent with previous reports. This low overall incidence can probably be explained by the fact that manifestations of renal injury in SFK tend to increase with age, with most cases occurring after 25 years of follow-up, ie, in adulthood. It should be noted, however, that all the patients with proteinuria, hypertension, and decreased GFR in our series had associated CAKUT (mostly renal parenchymal anomalies), and patients with SFK and ipsilateral CAKUT have been found to have a higher incidence of renal injury and earlier manifestation of symptoms. It should be also noted that manifestations of CKD were less common in patients with other types of CAKUT (urinary collecting system anomalies in most cases), indicating that not all congenital abnormalities affecting the kidneys and urinary tract have the same impact on prognosis, and that renal parenchymal anomalies appear to be associated with a higher risk of early CKD. Finally, it is worth mentioning that preterm and/or low BW newborns who display more rapid growth on weight charts have been found to have an increased risk of developing metabolic syndrome later in life. In our series, 40% of hypertensive patients were preterm newborns and

![Figure 2. Incidence of albuminuria, hypertension, and decreased estimated glomerular filtration rate (eGFR) in patients with solitary functioning kidney associated or not with type 1 congenital anomalies of the kidney and urinary tract (renal parenchymal anomalies). eGFR = estimated glomerular filtration rate.](image)
had a BMI in the range of obesity, strongly suggesting that weight management should be an integral part of follow-up.

The main limitations of the study are that it is a retrospective study, it is a relative short follow-up for a slow disease, so does not clearly reflect the impact of reduced number of nephrons and that not all cases have the same evolution time. However, this study implies a neonatal screening of a large number of cases, allowing early identification of the risk factors associated with kidney damage in the SFK. Detection of CAKUT during childhood should be followed by lifetime monitoring of the patient, using age-appropriate guidelines. Attention to risk factors and renoprotection may maintain adequate renal function throughout life.

In conclusion, we consider that universal neonatal ultrasound screening by highly qualified staff may be an extremely useful tool for the early diagnosis of SFK. Early detection of associated risk factors, in particular other types of CAKUT, is also important since they can predispose to CKD. Close follow-up of patients with SFK and associated ipsilateral CAKUT, in particular renal parenchymal anomalies, is also necessary for the early detection of microalbuminuria, hypertension, and decreased eGFR. Whether due to dysplasia or glomerular hypertension damage in the remnant kidney, renal injury in the form of hypertension and/or proteinuria was observed in up to 5% of children with congenital SFK in our series. Finally, early initiation of CKD treatment is essential to slow progression to end-stage renal failure.

Author contributions

Conceptualization: Marta Gil, Natalia Mandía, María-Luz Couce.

Data curation: Marta Gil.

Formal analysis: Natalia Mandía, Iria Roca.

Funding acquisition: María-Luz Couce.

Investigation: Domingo González-Lamuño.

Methodology: Natalia Mandía, Luis Aldámirz-Echevarría, Domingo González-Lamuño.

Software: Iria Roca.

Supervision: Marta Gil, Luis Aldámirz-Echevarría, Iria Roca, Domingo González-Lamuño, María-Luz Couce.

Writing – original draft: Adela Uríasari, Natalia Mandía.

Writing – review & editing: María-Luz Couce.

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