Risk Factors for Renal Injury in Children With a Solitary Functioning Kidney

WHAT'S KNOWN ON THIS SUBJECT: A reduced nephron number is associated with glomerular hyperfiltration, resulting in renal injury such as hypertension, proteinuria, and chronic kidney disease. Patients with a solitary functioning kidney have an increased risk of dialysis in early adulthood.

WHAT THIS STUDY ADDS: This study demonstrates that a subset of children with a solitary functioning kidney progress toward renal injury during childhood. Risk factors for renal injury are ipsilateral anomalies of the kidney and urinary tract and small renal length.

abstract

OBJECTIVE: The hyperfiltration hypothesis implies that children with a solitary functioning kidney are at risk to develop hypertension, proteinuria, and chronic kidney disease. We sought to determine the presenting age of renal injury and identify risk factors for children with a solitary functioning kidney.

METHODS: We evaluated 407 patients for signs of renal injury, defined as hypertension, proteinuria, an impaired glomerular filtration rate, and/or the use of renoprotective medication. Patients were subdivided on the basis of type of solitary functioning kidney and the presence of ipsilateral congenital anomalies of the kidney and urinary tract (CAKUT). The development of renal injury was analyzed with Kaplan-Meier analysis. Risk factors were identified by using logistic regression models.

RESULTS: Renal injury was found in 37% of all children. Development of renal injury increased by presence of ipsilateral CAKUT (odds ratio [OR] 1.66; \( P = .04 \)) and age (OR 1.09; \( P < .001 \)). Renal length was inversely associated with the risk to develop renal injury (OR 0.91; \( P = .04 \)). In all patients, the median time to renal injury was 14.8 years (95% confidence interval 13.7–16.0 years). This was significantly shortened for patients with ipsilateral CAKUT (12.8 years, 95% confidence interval 10.6–15.1 years).

CONCLUSIONS: Our study determines independent risk factors for renal injury in children with a solitary functioning kidney. Because many children develop renal injury, we emphasize the need for clinical follow-up in these patients starting at birth. Pediatrics 2013;131:e478–e485

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KEY WORDS: kidney, hypertension, chronic renal failure, proteinuria, child

ABBREVIATIONS

CAKUT — congenital anomalies of the kidney and urinary tract
CI — confidence interval
eGFR — estimated glomerular filtration rate
OR — odds ratio
SDS — SD score
SFK — solitary functioning kidney

Drs Westland and Kurvers contributed equally to this work.

All authors are responsible for concept and design of the study; analysis and interpretation of data; drafting or revising of the article; and final approval of the article as submitted.

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More than 3 decades ago, Brenner and coworkers described their hyperfiltration theory after experiments in rats with subtotal renal mass reduction. Reducing the functional nephron number changed glomerular hemodynamics in remnant nephrons and resulted in a vicious cycle of glomerular hyperfiltration and glomerulosclerosis. Renal injury due to this hyperfiltration presents as hypertension or proteinuria during the early stages but may eventually end in chronic kidney disease. Approximately 900,000 nephrons per kidney are formed in humans with a wide interindividual variation. Nephrogenesis terminates before birth, without the possibility of postnatal nephron formation. Low nephron numbers have been described in patients with hypertension, providing evidence for the hyperfiltration hypothesis in humans. However, methods that could confirm the hyperfiltration hypothesis in humans through in vivo measurement of nephron number are not yet available.

Children with a solitary functioning kidney (SFK) have renal mass reduction during an extended period, and this may allow study of the consequences of glomerular hyperfiltration in humans. Indeed, we previously showed that 32% of children with an SFK developed renal injury around 10 years of age. In addition, a recent study demonstrated that 20% to 50% of the study young adults with a congenital SFK required dialysis by the age of 30 years, leading to the advice to monitor all patients with an SFK from childhood. To guide the timing and frequency of clinical follow-up, information is needed on the age at which renal injury presents and on clinical factors that differentiate between children with and without renal injury.

The KIMONO (Kidney of MONofunctional Origin) study aims to determine the age of presentation of renal injury in children with an SFK. In addition, we identify clinical risk factors for the development of renal injury.

METHODS

Patients

All children with an SFK and renal follow-up at 2 pediatric renal centers (VU University Medical Center, Amsterdam, and Radboud University Nijmegen Medical Centre, Nijmegen) in the Netherlands were included in this retrospective longitudinal cohort study (enrollment period 1992–2011). Part of this cohort has been previously described. An SFK was identified by the unilateral absence of (functional) renal tissue on ultrasound or on renal scintigraphy. Children with an acquired SFK as a result of renal malignancy (n = 17) were excluded because of potential confounding effects from the use of nephrotoxic chemotherapy. Also, children with an estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 m² from birth (n = 11) and children who died before reaching the age of 1 year (n = 17) were excluded. All remaining 407 patients with an SFK were included in the study.

To identify differences between the 2 causes of an SFK, patients were divided into categories: congenital SFK or acquired SFK. A congenital SFK can be due to unilateral renal agenesis/aplasia or to a multicystic dysplastic kidney. An SFK is acquired when children undergo nephrectomy secondary to congenital anomalies of the kidney and urinary tract (CAKUT) such as pelviureteric junction obstruction, posterior urethral valves, or vesicoureteral reflux, as well as to acute pyelonephritis or renovascular disease.

Because patients with SFKs often have additional CAKUT, which would imply an additional risk of chronic kidney disease, a subdivision was made in patients with or without ipsilateral CAKUT (ie, on the side of the SFK). CAKUT were identified by renal ultrasound in all patients and, on indication, by voiding cystourethrogram (n = 303, 74%) and/or renal scintigraphy (n = 330, 81%).

Measurements

Birth weight was obtained by chart review and divided into 5 different groups: <2500 g (n = 56, 15%), ≥2500 to <3000 g (n = 63, 17%), ≥3000 to <3500 g (n = 111, 30%), ≥3500 to <4000 g (n = 87, 23%), and ≥4000 g (n = 56, 15%). BMI (kg/m²) was calculated from weight and height. In addition, SD scores (SDSs) were calculated based on gender, age, and ethnicity according to the Fifth Dutch Growth Study.

Blood pressure was measured with the use of automated oscillometric devices with an appropriate cuff size. To minimize the effect of stress, the lowest reading of blood pressure was used. Hypertension was defined as a persistent presence of a systolic blood pressure and/or diastolic blood pressure ≥95th percentile corrected for age, gender, and height.

Proteinuria was defined as a protein/creatinine ratio >0.2 mg/mg (≥22.6 mg/mmol) in children >2 years of age and as >0.5 mg/mg (≥56.6 mg/mmol) for children <2 years of age. Microalbuminuria was defined as a urinary albumin level of >30 to 300 mg/24 h in timed collected urine samples or as a urinary albumin/creatinine ratio of >30 to 300 mg/g in a spot (morning) sample. We aggregated data on the presence of proteinuria and microalbuminuria by using the term “proteinuria.”

Creatinine (μmol/L) was measured enzymatically, and an eGFR was calculated by using the Schwartz equation (eGFR = k × height/serum creatinine).
Renal length was measured by renal ultrasound, proteinuria, an impaired eGFR, or use of renoprotective medication. Because medication (ie, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, \(\beta\)-adrenoceptor antagonists, and calcium antagonists) could be a potential confounder in the determination of hypertension as well as proteinuria and eGFR, the use of this “renoprotective” medication was separately obtained. Even though renoprotective medication does not influence the progression of renal disease in children with CAKUT, the use of renoprotective medications was used as a surrogate marker of clinically relevant hypertension and/or proteinuria.

Renal injury was defined as hypertension, proteinuria, an impaired eGFR, or the use of renoprotective medication.

Renal length was measured by renal ultrasound and expressed as an SDS. Finally, relapsing urinary tract infections (ie, \(\geq 2\) during follow-up) were noted in all patients.

**Statistical Methods**

Statistical analyses were performed by using SPSS 19.0 (SPSS Inc, Chicago, IL). Values are expressed as mean and SD for continuous variables and percentages for qualitative variables. Differences were analyzed with the independent-samples \(t\) test for continuous variables. In case of non-normality, a log transformation using the natural logarithmic was performed before analysis. Qualitative variables were compared by using the \(\chi^2\) test. Data on the variables of renal injury (blood pressure, urinary protein excretion, and eGFR) were considered to be within normal range when missing. The development of renal injury was determined by using survival analysis, according to the Kaplan-Meier method. For every patient, the starting point was considered to be the day of birth. The end point was defined as the date at which a patient first showed signs of renal injury. Subsequent to this end point, the analysis was right censored. Log-rank tests were used for comparison between different groups.

Logistic regression models were used to determine risk factors for the development of renal injury. Univariate analysis to explore associations with renal injury was performed for the following variables: type of SFK, ipsilateral CAKUT, side of SFK (left/right), prenatal diagnosis, birth weight, BMI SDS (linear), relapsing urinary tract infections, and renal length SDS (linear). Because birth weight was a categorical variable, we considered the category with the lowest incidence of renal injury as the reference group. We included all variables with a \(P\) value of \(\leq 0.10\) for additional analysis. Also, gender and age (linear) were simultaneously added. In addition, multivariate associations were explored by using a backward (Wald) elimination strategy \((P < .10\) for inclusion and \(P > .157\) for removal\(^{20}\)) in the final model. Finally, differences were considered to be statistically significant at \(P < .05\) in all analyses.

**RESULTS**

**Patient Characteristics**

The KIMONO study cohort consisted of 407 patients, 223 with a congenital SFK (55%) and 184 with an acquired SFK (45%) (Table 1). The SFK was identified by prenatal ultrasound in 176 (43%) subjects. For the remaining children, the SFK was identified after renal ultrasound due to the development of symptoms (eg, urinary tract infection, signs of renal injury, abdominal pain, or palpable abdominal mass) or by chance during an abdominal ultrasound for non–urinary tract indications.

The mean age at last follow-up was 9.0 years (SD 6.0 years) (Table 2). Children with an acquired SFK were older than children with a congenital SFK \((P = .001)\). Ipsilateral CAKUT were present in 137 (34%) patients and more frequently found in the acquired-SFK group than in the congenital-SFK group \((P = .001)\). Relapsing urinary tract infections occurred in 33% of patients (Table 2), with a higher incidence in the acquired-SFK group than in the congenital-SFK group \((P < .001)\). The overall mean renal length SDS \((n = 389)\) was 2.8 (SD 2.6).

**Renal Injury**

One hundred fifty-one (37%) patients met the criteria for renal injury, defined as hypertension, proteinuria, an impaired glomerular filtration rate, or the use of renoprotective medication, at a mean age of 6.4 years (SD 5.9 years). At follow-up, renal injury was more frequently identified in the acquired-SFK group than in the congenital-SFK group \((P = .002\); Table 3). Children with ipsilateral CAKUT demonstrated a higher proportion of renal injury than did children without ipsilateral CAKUT (49% vs 31%, respectively; \(P < .001\)). After dividing patients into quartiles according to renal length, children with the
TABLE 2 Clinical Characteristics of the KIMONO Study Cohort

<table>
<thead>
<tr>
<th></th>
<th>SFK, Total (N = 407)</th>
<th>Congenital-SFK Group (n = 223)</th>
<th>Acquired-SFK Group (n = 184)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, %</td>
<td>265 (65)</td>
<td>147 (66)</td>
<td>118 (64)</td>
<td>.71</td>
</tr>
<tr>
<td>Left-sided SFK, %</td>
<td>202 (50)</td>
<td>114 (51)</td>
<td>88 (48)</td>
<td>.51</td>
</tr>
<tr>
<td>Age at last follow-up, y</td>
<td>9.0 (6.0)</td>
<td>7.8 (5.6)</td>
<td>10.5 (6.0)</td>
<td>.001</td>
</tr>
<tr>
<td>Ipsilateral CAKUT, %</td>
<td>137 (34)</td>
<td>59 (26)</td>
<td>78 (42)</td>
<td>.001</td>
</tr>
<tr>
<td>Vesicoureteral reflux, %</td>
<td>61 (15)</td>
<td>24 (11)</td>
<td>37 (20)</td>
<td>.01</td>
</tr>
<tr>
<td>&gt;1 CAKUT, %</td>
<td>30 (7)</td>
<td>11 (5)</td>
<td>19 (10)</td>
<td>.04</td>
</tr>
<tr>
<td>Urinary tract infection, %</td>
<td>133 (33)</td>
<td>45 (20)</td>
<td>88 (48)</td>
<td>.001</td>
</tr>
<tr>
<td>Systolic blood pressure, SDS</td>
<td>0.4 (1.0)</td>
<td>0.4 (0.9)</td>
<td>0.3 (1.0)</td>
<td>.71</td>
</tr>
<tr>
<td>Diastolic blood pressure, SDS</td>
<td>0.5 (1.1)</td>
<td>0.5 (1.0)</td>
<td>0.6 (1.1)</td>
<td>.33</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m²</td>
<td>101 (30)</td>
<td>104 (28)</td>
<td>98 (32)</td>
<td>.06</td>
</tr>
<tr>
<td>Renal length, SDS</td>
<td>2.8 (2.9)</td>
<td>3.0 (2.6)</td>
<td>2.5 (2.7)</td>
<td>.43</td>
</tr>
<tr>
<td>Birth weight, kg</td>
<td>3.2 (0.8)</td>
<td>3.2 (0.8)</td>
<td>3.3 (0.7)</td>
<td>.23</td>
</tr>
<tr>
<td>BMI, SDS</td>
<td>0.2 (0.8)</td>
<td>0.1 (0.4)</td>
<td>0.5 (1.2)</td>
<td>.01</td>
</tr>
</tbody>
</table>

Data are presented as No. of patients (%) or mean (SD). For continuous variables, clinical parameters from last follow-up are shown. P values represent differences between congenital-SFK and acquired-SFK groups.

TABLE 3 Renal Injury According to Type of SFK

<table>
<thead>
<tr>
<th></th>
<th>SFK, Total (N = 407)</th>
<th>Congenital-SFK Group (n = 223)</th>
<th>Acquired-SFK Group (n = 184)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal injury</td>
<td>151 (37)</td>
<td>88 (31)</td>
<td>63 (45)</td>
<td>.002</td>
</tr>
<tr>
<td>Hypertension</td>
<td>107 (26)</td>
<td>49 (22)</td>
<td>58 (32)</td>
<td>.04</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>79 (19)</td>
<td>29 (13)</td>
<td>50 (27)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>eGFR &lt;60 mL/min/1.73 m²</td>
<td>25 (6)</td>
<td>9 (4)</td>
<td>16 (9)</td>
<td>.05</td>
</tr>
<tr>
<td>Renoprotective medication</td>
<td>80 (20)</td>
<td>37 (17)</td>
<td>43 (23)</td>
<td>.09</td>
</tr>
</tbody>
</table>

Data are presented as No. of patients (%). P values represent differences between congenital-SFK and acquired-SFK.

The smallest SFK (SDS <1.1) had a higher incidence of renal injury than did children with the largest SFK (SDS >4.2) (50% vs 34%, respectively; P = .022).

Hypertension was found in 107 (26%) patients, with a higher proportion in the acquired-SFK group (P = .039; Table 3). Patients developed hypertension at a mean age of 4.9 years (SD 5.4 years). No differences in systolic or diastolic blood pressure SDS were found between the acquired-SFK and congenital-SFK groups. Patients with hypertension were more likely to have proteinuria and an impaired eGFR and more often used renoprotective medication than did patients without hypertension (35% vs 14%, 16% vs 3%, and 62% vs 5%, respectively; P < .001).

Ninety-seven (19%) patients were diagnosed with proteinuria at a mean age of 9.8 years (SD 5.6 years). Proportions of proteinuria were equal between patients with the 2 types of SFK. Patients with proteinuria more often used renoprotective medication (53% vs 12%, respectively; P < .001) and had a higher incidence of an impaired eGFR (20% vs 2%, respectively; P < .001) compared with patients without proteinuria.

To determine the development of renal injury in children with SFK, we performed Kaplan-Meier analyses (Figs 1, 2, and 3). Overall median time to develop renal injury was 14.8 years (95% confidence interval [CI] 13.7–16.0 years). The cumulative proportions to remain free from renal injury at the end of the following intervals were 1 year, 86%; 5 years, 77%; 10 years, 66%; and 15 years, 40%. The cumulative time to remain free from renoprotective medication (ie, a surrogate marker for clinically relevant renal injury) is also presented in Fig 1.

Separate analysis was performed for the congenital-SFK group (median time to develop renal injury 14.9 years, 95% CI 13.5–16.3 years) and the acquired-SFK group (median time to develop renal injury 14.8 years, 95% CI 12.8–16.7 years) (Fig 2). The median time to develop renal injury was similar between the types of SFK (P = .50), whereas patients with CAKUT had a shorter median time to develop renal injury than did patients without CAKUT (12.8 years, 95% CI 10.6–15.1 years, vs 15.9 years, 95% CI 13.9–17.9 years, respectively; P = .006) (Fig 3).

Risk Factor Analysis

Analysis was performed on 357 children who had complete data on all potential risk factors. Univariate analysis (Table 4) showed an association with the development of renal injury and increasing age, acquired SFK, CAKUT, prenatal diagnosis, birth weight <2500 g, history of urinary tract infections, and renal length SDS. There was no association between renal injury and side of the SFK or BMI SDS. Results from the multivariate analysis are shown in Table 5. After adjustments,
increasing age and the presence of ipsilateral CAKUT were shown to be independent risk factors for renal injury (Table 5). In addition, renal length SDS was inversely associated with the risk to develop renal injury. Birth weight <2500 g and a history of urinary tract infections were associated with renal injury, although differences were not statistically significant ($P = .065$ and $P = .083$, respectively). Type of SFK (odds ratio [OR] 1.39, 95% CI 0.85–2.28; $P = .19$) and prenatal diagnosis (OR 0.77, 95% CI 0.82–2.25; $P = .77$) were not shown to be independent risk factors for the development of renal injury.

**DISCUSSION**

The KIMONO study demonstrates that a substantial proportion of children with an SFK develop renal injury during childhood. Kaplan-Meier analysis showed that these children have a median time toward renal injury of $\sim 15$ years. Renal injury development is independent of SFK type but is significantly accelerated when there is additional ipsilateral CAKUT. In addition, insufficient renal hypertrophy can be considered as an independent risk factor for renal injury. Low birth weight and urinary tract infections demonstrate a trend in the association with renal injury.

We previously described a similar incidence of renal injury in a smaller cohort of patients with SFK. Although similar in design, our cohort has doubled compared with the first KIMONO Study, allowing for regression analyses and more robust conclusions. Also, with the use of Kaplan-Meier analysis, this study demonstrates the presenting age of renal injury in these specific patients.

As reported in patients with diabetes, we expected renal injury to occur in the second decade after the onset of glomerular hyperfiltration. Surprisingly, our results illustrate that patients show signs of renal injury during the full age range of childhood. Twenty-three percent of patients already were symptomatic before the age of 5 years. We hypothesize that these are children with a certain degree of (hypo)dysplasia in the SFK, which results in signs at an earlier stage due to a subsequent insufficient nephron endowment or inappropriate renin-angiotensin system activation. Follow-up of children with an SFK should therefore start at a young age. Subsequently, many patients...
with an SFK developed signs in the second decade. This might be a reflection of glomerular hyperfiltration necessary to maintain normal eGFR during ongoing increases in body surface area and associated metabolic demands.

We found a higher incidence of renal injury in the acquired-SFK group than in the congenital-SFK group. Nevertheless, our multivariate analysis and Kaplan-Meier analysis demonstrated that the development of renal injury is independent of SFK type. We therefore suggest that the impaired renal outcome in acquired SFK is caused by the older age and the higher incidence of CAKUT, which are risk factors for renal injury.

Although the effect was small, we show that insufficient compensatory renal hypertrophy implies a greater risk to develop injury. This might be caused by inadequate nephron numbers and/or dysplastic components in the smaller SFK. Birth weight is another potential risk factor that should be considered during clinical follow-up. Although our model could not fully substantiate low birth weight as an independent risk factor for renal injury, other studies have associated lower birth weight with a decreased nephron number. Such studies could provide evidence for a combination of the developmental origins of health and disease hypothesis and the hyperfiltration hypothesis in children with an SFK.

Studies on long-term outcomes of children with an SFK have conflicting results. In addition, it is often stated that children with an SFK are not expected to develop renal damage, because most long-term follow-up surveys on kidney donors show an excellent prognosis. However, hyperfiltration is much more pronounced when renal mass reduction occurs earlier in life, which makes these situations (SFK in childhood versus uninephric kidney donors) not comparable. Moreover, the excellent prognosis of kidney donors could result from the stringent screening before donation.

Our results are complementary to survival analyses by Sanna-Cherchi et al on renal outcome in adults with different types of CAKUT. They demonstrated that adults with a congenital SFK show a high incidence of end-stage renal disease at 30 years of age. As a consequence, their findings emphasize the lifelong need for regular follow-up of individuals with an SFK. Coberi et al propose annual laboratory tests for kidney function, urinary analysis, and blood pressure measurement in children with ipsilateral CAKUT and the same regimen every 2 years for children without ipsilateral CAKUT. If the latter remain asymptomatic until puberty, the follow-up is expanded to once every 3 to 5 years. However, our results may implicate at least annual follow-up of children with SFK until adulthood.
Our results should be interpreted with respect to the retrospective study design. First, to minimize potential overestimation of renal injury, we considered missing data to be in the normal range. Second, our cohort is followed at 2 tertiary medical centers, which might implicate selection bias. However, multivariate analysis of renal injury for all children with a prenatal diagnosis, as the best surrogate marker of an unbiased group of SFK, did not reach statistical significance. Third, we were unable to determine the direct effect of glomerular hyperfiltration on the development of renal injury as this can only be measured in animal studies. One morphometric study on glomerular size indeed has reported an increased glomerular volume in patients with a congenital solitary kidney, indicating glomerular hyperfiltration. Nevertheless, other potential causes for renal injury must be considered in the interpretation of our data. Fourth, blood pressure was measured by using oscillometric devices, which may overestimate the proportion of children with hypertension and, consequently, the proportion of renal injury. Our retrospective design also hampered us in determining the influence of white coat hypertension and other causes of hypertension in our cohort. Nevertheless, our results are in line with studies on hypertension in SFK by using ambulatory blood pressure monitoring. Finally, because our markers for renal injury are indirect and therefore may be somewhat insensitive, we emphasize the need for new markers for early renal damage. Fibroblast growth factor 23 and cystatin C have been identified as promising markers in SFK.

**CONCLUSIONS**

The KIMONO study demonstrates that a substantial proportion of children with an SFK develop renal injury during childhood. This risk to develop renal injury is independent of SFK type but increases with the presence of ipsilateral CAKUT, age, and a small renal length. Identification of these risk factors is important, together with regular follow-up of blood pressure, proteinuria, and eGFR. Because renal injury in SFK may develop from infancy on, clinical follow-up of every child with an SFK should start at birth.

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