Congenital versus acquired solitary kidney: is the difference relevant?

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Abstract

Background. Serious concerns have risen during the last decades regarding the potential role of solitary kidney (SK) in promoting systemic hypertension, proteinuria and glomerulosclerosis. The aim of the study was to assess mid- and long-term outcome of children with SK, with special highlight on the differential functional outcome of congenital and acquired forms of SK.

Methods. Ninety-seven patients (43 females) aged from 2.9 to 25 years with radiologically normal SK were divided into two groups depending on whether they had a congenital (CSK, n = 44) or an acquired SK (ASK, n = 53). Mean follow-up time with SK was 8.3 ± 3.2 and 9.1 ± 4.4 years, respectively (P = NS). Blood pressure (BP), glomerular filtration rate (GFR) measured by inulin clearance, and microalbuminuria were assessed in all patients.

Results. Two children (2%), one in each group, had systemic hypertension confirmed by 24-h ambulatory BP monitoring, and 17 (17.5%) had a significant microalbuminuria (8 in CSK and 9 in ASK, P = NS). The overall mean GFR was 100.6 ± 15 mL/min/1.73 m² and was found to be inversely correlated with age and follow-up time. Seven children had a GFR <80 mL/min/1.73 m², all had been nephrectomized in early childhood. Interestingly, GFR was higher in CSK than in ASK group (107.2 vs. 95.2 mL/min/1.73 m², P < 0.01) and was negatively related to follow-up time only in the latter but not in the former group.

Conclusions. In the light of these results, it appears that renal function in children with SK is well preserved in short and medium term, but it seems to decline gradually with longer periods of follow-up, particularly in ASK, thus assuming a better functional adaptation in CSK. Both conditions remain yet risky and predispose children to a greater incidence of hypertension and renal impairment in later life. Thereby, careful screening should be proposed throughout childhood to detect early signs of glomerular hyperfiltration and prevent its progression to more serious complications.

Keywords: acquired solitary kidney; congenital solitary kidney; glomerular filtration rate; hypertension; microalbuminuria

Introduction

During the last three decades, solitary kidney (SK) has drawn a lot of attention as a potential promoter of systemic hypertension, proteinuria and glomerulosclerosis. Such concerns have emerged from revolutionary findings in experimental models of renal mass reduction [1–3], supported by an increasing number of clinical observations [4–8]. It has been demonstrated that following renal ablation in rats, the remnant kidney undergoes a series of structural and functional changes involving both glomerular and tubular components [9,10]. This adaptive response, com-
monly known as ‘compensatory renal hypertrophy’ (CRH), is indisputably of considerable benefit by mitigating the decrease in the total glomerular filtration rate (GFR) that would otherwise occur. However, the counterpart of this phenomenon is an ongoing glomerular overload, with high capillary pressure and sustained glomerular hyperfiltration, eventually leading to proteinuria, elevated vascular resistance and accelerated glomerular sclerosis [1–3]. Thus, the long-term effect of these compensatory mechanisms seems to be more deleterious, predisposing to a higher risk of systemic hypertension and premature renal damage [11–13]. In humans, published data on long-term outcome of SK remain scarce, and results are somewhat controversial [14–23]. Even rarer are the reports that address the separate clinical course of congenital and acquired forms of SK [24–27]. CRH has been described in both conditions, but its onset is much more abrupt in the latter, thrusting the remaining nephrons to immediately overcome the sudden loss in renal function. This could possibly lead to more rapid glomerular overload and accelerate even more the process of glomerulosclerosis and renal scarring. Thus, the purpose of this study was to assess the differential behaviour of congenital and acquired SK in terms of functional adaptation and long-term outcome, using reference methods for GFR measurement.

Materials and methods

Patients
Between January 1991 and March 2008, 127 children with a single functioning kidney were referred to the Paediatric Nephrology Unit at Edouard Herriot Hospital in Lyon, for functional renal work-up. Each patient had at least one GFR measurement by inulin clearance. Twenty-eight children were excluded because of evidence of structural and/or parenchymal abnormalities in the remnant kidney. Such anomalies included vesicoureteric reflux (n = 7), megaureter (n = 6), parenchymal hypercineogenicity and dysplasia (n = 6), ureteropelvic junction obstruction (n = 3), posterior urethral valves (n = 3), neurogenic bladder (n = 2), and duplication of the collecting system (n = 1). Two more children were excluded because of associated nephropathy diagnosed prior to investigation (i.e., a nephropathy in one child and tuberculosis in the other). The remaining 97 children with echographically ‘normal’ SK (Table 1) were divided into two groups according to whether they had a congenital (CSK) or an acquired solitary kidney (ASK). The CSK group enrolled 44 patients with unilateral renal agenesis (URA, n = 21) or multicystic dysplastic kidney (MCDO, n = 23). None of these children had a history of urinary tract infection prior to investigation. The diagnosis was established mostly prenatally or discovered by chance on abdominal ultrasound carried out for another reason. The ASK group included 53 patients who underwent unilateral nephrectomy in childhood for a renal tumour (n = 41) or urological structural abnormality with complicated clinical course prior to surgery (n = 12), at a mean age of 2.9 ± 2.7 years (range: from 12 days to 10.7 years). At the time of nephrectomy, all children had normal contralateral kidneys on ultrasonography and functional imaging.

Formal evaluation by the institution’s ethical committee and informed consent were waived because of the retrospective nature of the study.

Methods

The data were collected from medical records at the last clinical and functional assessment (i.e., most recent inulin clearance). For each patient, a standardized Z-score was determined for height, body weight (BW) and body mass index (BMI) from the mean of the general population [28]. Blood pressure (BP) measurements were recorded by an oscillometric device regularly calibrated against an auscultatory method. The mean value of three consecutive readings in resting state was then compared with BP standards based on gender, age and height [29]. Hypertension was defined as systolic and/or diastolic BP greater than or equal to the 95th percentile for age, sex and height on at least three different occasions [29], or as the use of antihypertensive drugs.

GFR was measured by inulin clearance using a continuous infusion of inulin after a prime dose of 30 mg/kg BW (Inutest 25%, Fresenius Kabi, Graz, Austria), starting early in the morning at 0800 h after an overnight fast. Water diuresis was induced by oral ingestion of 5 mL/kg BW of water during the first hour, followed by 3 mL/kg BW every 30 min. Four urine samples were collected by spontaneous micturation at 30-min intervals, and blood samples were drawn midway through each urine collection period. Measurements of plasma and urine inulin were performed using an enzymatic procedure [30]. The clearance values, expressed in millilitre per minute per 1.73 m² body surface area (BSA), were obtained from the mean values of the four clearance periods. The GFR was considered normal for a solitary kidney when inulin clearance was ≥80 mL/min/1.73 m² BSA.

Microalbuminuria was measured by immunoturbidimetry in a second voided morning urine sample and was expressed as urinary albumin-to-creatinine concentration ratio (alb/crea) with the upper normal limit set to 2 mg/mmol [31].

Ultrasonographic measurements of renal size were unfortunately missing from most of the medical charts at the last assessment. Furthermore, reported measurements were often performed by different operators; therefore, available data on renal length could not be reliably analysed.

Statistics

Descriptive analysis was done using means and standard errors for continuous variables and percentages for qualitative ones. Normality of continuous variable distribution was tested using the Kolmogorov–Smirnov test. When the hypothesis of normality was verified, Student’s parametric test was used for comparison between the two groups, as well as Pearson’s parametric test for correlation between continuous variables. When the hypothesis was not verified, the Wilcoxon and Spearman non-parametric tests were respectively used for comparison and correlation studies. Qualitative variables were compared using chi-square test. Linear regression analysis was carried out to establish relationships between parameters of interest. A P-value of <0.05 was considered statistically significant. The data were analysed using SAS software (version 9.1; SAS Institute Inc, Cary, NC, USA).

Results

Patient characteristics

Clinical and functional data of the 97 patients are summarized in Table 2. There were 54 male patients and 43 females. The mean age was 10.3 ± 4.3 years (median: 10.0, range: 2.9–25.5), and the mean follow-up time with SK—expressed

| Table 1. Patient distribution according to the cause of solitary kidney |
|-------------------------|-------------------------|
| Congenital single functioning kidney | 44 |
| Unilateral renal agenesis | 21 |
| Dysplastic multicystic kidney | 23 |
| Unilateral nephrectomy | 53 |
| Urologic structural abnormalities | 12 |
| Vesicoureteric reflux | 5 |
| Megaureter | 3 |
| Ureteropelvic junction obstruction | 2 |
| Duplicated collecting system | 2 |
| Unilateral renal tumour | 41 |
| Wilms’ tumour | 32 |
| Neuroblastoma | 5 |
| Clear cell carcinoma | 2 |
| Multilocular cystic nephroma | 2 |
| Total | 97 |
as ‘years at risk’—was 8.7 ± 3.9 years (median: 8.1, range: 1.5–21.2). There was a male predominance in the CSK group (68%). Other demographic characteristics were comparable between the two groups, except for age, as patients with acquired SK were relatively older than those in the CSK group (12.0 ± 4.5 vs. 8.3 ± 3.2 years, respectively, P \(<\) 0.01), but the average follow-up time with SK was similar in both groups (9.1 ± 4.4 and 8.3 ± 3.2 years, respectively, P = NS).

**Blood pressure**

BP values fell into the normal range for most patients without any significant difference between the two groups (Table 2). Two patients were treated for hypertension at the time of the last assessment. The first, a 12-year-old boy with a right MCDK discovered incidentally on abdominal ultrasonography and no other known cardiovascular risk, had a systolic hypertension confirmed by 24-h ambulatory blood pressure monitoring (ABPM) and was treated with an angiotensin-converting enzyme (ACE) inhibitor. The other patient was a young girl nephrectomized in early childhood for a renal tumour (stage IV neuroblastoma). She had ABPM-confirmed mixed hypertension associated with chronic renal failure and persistent microalbuminuria. She was treated with an angiotensin receptor blocker (ARB). Nine other children exhibited high systolic and/or diastolic BP above the 95th percentile for age, gender and height at the time of investigation but had normal BP values on further follow-up (BP controlled by an auscultatory method on an outpatient basis).

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Values are expressed in mean ± SD. SK, solitary kidney; CSK, congenital solitary kidney; ASK, acquired solitary kidney; SDS, standard deviation score; BMI, body mass index; BP, blood pressure; GFR, glomerular filtration rate; Alb/crea, albumin-to-creatinine ratio; NS, not significant.

*Years at risk with a solitary kidney.

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<th>Table 3. Hypertension, microalbuminuria and renal impairment in children with solitary kidney</th>
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SK, solitary kidney; CSK, congenital solitary kidney; ASK, acquired solitary kidney; ABPM, ambulatory blood pressure monitoring; GFR, glomerular filtration rate; Alb/crea, albumin-to-creatinine ratio; NS, not significant.

*Children having at least one functional anomaly (i.e. hypertension and/or microalbuminuria and/or low GFR).

*Systolic and/or diastolic blood pressure ≥95th percentile for age, gender and height, confirmed by ABPM.

Fig. 1. Scatter plot showing inverse relationship between GFR and age (r = -0.332, P = 0.0009). GFR, glomerular filtration rate.

Fig. 2. Inverse relationship between GFR and follow-up time, i.e. years at risk (r = -0.234, P = 0.02); GFR, glomerular filtration rate.
Microalbuminuria
The mean alb/crea ratio was 2.3 ± 4.6 mg/mmol (median: 1.2, range: 0.1–27.7) and was comparable between the two groups (Table 2). Seventeen patients (17.5%) had an alb/crea ratio above the threshold of 2 mg/mmol (Table 3), eight in CSK and nine in ASK group of whom six had significant microalbuminuria on at least two previous evaluations.

Glomerular filtration rate
The mean overall GFR was 100.6 ± 15.0 mL/min/1.73 m² BSA. Seven patients (7.2%) had a GFR <80 mL/min/1.73 m² BSA at the last assessment, ranging from 62 to 78 mL/min/1.73 m² BSA. All had undergone unilateral nephrectomy in early childhood because of a renal tumour and had a constantly low inulin clearance on repeated renal workups since surgery with an increased microalbuminuria in four of them including the young girl with systemic hypertension.

When comparing both groups, GFR was found to be higher in CSK than in ASK (107.2 ± 13.4 vs. 95.2 ± 14.1 mL/min/1.73 m² BSA, respectively, P < 0.001).

Linear regression analysis revealed a negative correlation in the study population between GFR and age on the one hand (Figure 1), and between GFR and follow-up time (i.e. years at risk) on the other (Figure 2). An inverse relationship was also found between GFR and follow-up time only in the ASK but not in the CSK group (Figure 3). The same negative trend was observed between GFR and age, but the correlation did not reach statistical significance in either group (ASK: r = -0.257, P = 0.06; CSK: r = -0.094, P = 0.54). GFR was not found to be related to BMI or any other clinical or biological parameter.

Discussion
In the late 1980s, Brenner et al. introduced their novel theory on the hyperfiltration injury as the missing link that directly implicates the kidney in the pathogenesis of essential hypertension. Initially based on experimental studies, they assumed the existence of an inverse relationship between the filtration surface area, i.e. total number of glomeruli, and systemic hypertension [11,12]. As mentioned before, renal mass reduction in animal models has been proven to induce a cycle of haemodynamic and structural changes in the residual glomeruli that could ultimately lead to elevated systemic BP, proteinuria and accelerated glomerular sclerosis [1–3,13]. In humans, evidence of this maladaptive response has been highlighted in several clinical observations and post-mortem studies reporting reduced nephron endowment in highly prevalent hypertensive populations [32–34], thus raising serious concerns about long-term outcome of individuals with SK. Initial interest was brought to living kidney donors as their number continues to escalate with the increasing shortage in cadaveric transplants. Overall, in spite of an estimated 20–25% decrease in baseline GFR, renal function in living kidney donors seems to be well preserved over more than 25 years following nephrectomy [35–38]. However, this may not be entirely reassuring for children whose life expectancy is more likely to exceed most periods of follow-up in adult donors and therefore are exposed much longer to hyperfiltration injury.

Another intriguing issue that remains unclear is whether being born with a single kidney or having lost one during childhood would have a differential impact on final renal outcome, especially since large comparative studies are still lacking.

In an attempt to elucidate the aforementioned issues, we conducted a retrospective chart review of 97 children with a radiologically normal SK. The patients were then separated into two groups according to whether they had a congenital or an acquired form of SK. Children in the former group had no history of urinary tract infection prior to investigation in order to obviate any additional renal risk. Despite certain limitations set by the retrospective design of the study, the final results were in line with previous published reports.

There was a male predominance in the CSK group, which is a common observation in congenital conditions of single functioning kidney [39,40]. Systemic hypertension confirmed by means of 24-h ABPM was found in only two patients (2%), one in each group. Higher prevalence was reported by Seeman et al. who found ABPM-confirmed hypertension in, respectively, 7% and 14% of their URA and MCDK patients with normal contralateral kidney [21,22]. Dursan et al. recorded a systemic hypertension in up to 26% of their patients by means of 24-h ABPM (32% with ASK and 22% with URA) [23]. In their report, Mei-Zahav et al. found a mean 24-h, daytime and nighttime systolic BP significantly higher in children with URA or unilateral nephrectomy compared with controls [27], drawing the attention to a potential risk of hypertension in adulthood. In studies based on clinical assessment of BP, the prevalence of hypertension was variable ranging from 0% to 50% [14–17].

Microalbuminuria is another frequent finding in children with SK for it appears to be the earliest [41] and most commonly reported sign of hyperfiltration injury in the literature, with a wide range of prevalence varying from 10% to 75%, with most of the published data based on a single
time-point measurement [15,17,18,24–26]. However, it has been demonstrated that urinary albumin excretion varies considerably on a day-to-day basis [42,43]; thus, most authors recommend that microalbuminuria be measured at least three times to ensure accuracy [44,45]. Moreover, the rate of albumin excretion does not seem to be constant throughout the day [42,46], and therefore, the timing of urine sampling may significantly influence the results. Measurement of albumin/creatinine ratio in a morning urine sample appears to be the most reliable method of screening for microalbuminuria, and it seems to correlate best with 24-h urinary albumin excretion when samples are taken after the first voided morning specimen [47]. In our study, microalbuminuria was measured in all of our patients by determining the alb/crea ratio in the second voided morning specimen, as this sampling time has been found to have an excellent correlation with 24-h albumin excretion [48]. By using this method, 17 children had positive screening for microalbuminuria at the last assessment (17.5%), equally distributed between the two groups. Six of these children (all in the ASK group) had an increased alb/crea ratio recorded on at least two previous functional evaluations, with low GFR in four of them. As for the 11 remaining children, the diagnosis of microalbuminuria has to be considered with caution provided that it has been determined only once on a single measurement and that the possibility of an orthostatic proteinuria cannot be completely ruled out.

Regarding renal filtration function, most of the published data refer to an overall long-term GFR of 75% to 80% of the normal two-kidney value, with renal insufficiency occurring in 0–30% of cases [17,18,20,25,26], depending mainly on the method applied for estimating GFR, but also on patient selection. By using inulin clearance, the reference test for GFR measurement, we found a well-preserved value of 100.6 mL/min/1.73 m² BSA over an average follow-up of 8.6 years. Seven children (7.2%), however, had a low GFR of <80 mL/min/1.73 m² BSA. All seven had been nephrectomized in early childhood for unilateral renal tumours. Five had high-risk malignancies treated with aggressive protocols with known nephrotoxicity [49–52], associating intensive chemotherapy and local radiation (stage IV nephroblastoma, n = 2) or total body irradiation prior to bone marrow transplantation (stage IV neuroblastoma, n = 3). The two remaining patients, however, had relatively low-risk neoplasia (stage I nephroblastoma and low-grade renal cell carcinoma), both treated with actinomycin D and vincristin, a combination with presumably no adverse renal effect [53,54].

Another interesting finding in our study was the negative correlation between GFR and both age and follow-up time, suggesting a gradual decline in renal function over time. This is in agreement with the observations of Wikstad et al. [15] and Baudoin et al. [19] who noticed that, in adults with SK since childhood, renal function tends to decrease slowly but significantly with increasing follow-up time. A similar reflection was made by Argueso et al. who documented a positive correlation between the likelihood of developing renal insufficiency and years at risk [17]. This can be hardly explained by normal ageing as physiological decline in renal function does not occur before the age of 40 years [55]. It seems rather related to the fact that children with SK from birth or early childhood are prone to much more ‘years at risk’ than adults, especially since CRH has proven to be an age-dependent process with a much more pronounced response in younger ages [56–58], thus predisposing to a higher incidence of glomerulosclerosis and premature renal damage [59].

In the same manner, an inverse relationship between GFR and follow-up time was found only in ASK but not in CSK (Figure 3). Furthermore, children in the latter group had a constantly higher GFR than those in the former, regardless of the duration of follow-up (Figure 4), suggesting that congenital forms of SK might perform better in the long term than acquired ones. Worthy of notice is that the advantage of CSK over ASK held true even after excluding children (n = 7) having received nephrotoxic antimitotic agents with or without radiation therapy (mean GFR: 107.2 vs. 96.8 mL/min/1.73 m² BSA, respectively, P = 0.0002).

One explanation for the significant difference between CSK and ASK is that the adaptive response following congenital nephron deficiency begins much earlier in fetal life at as early as 22 weeks of gestation, and continues to progress throughout childhood [60,61]. On the contrary, surgical removal of renal tissue immediately instigates the remaining nephrons to undergo compensatory changes in order to rapidly overcome the substantial loss in the filtration surface area. Given that mature glomeruli have low mitotic activity, the residual nephrons will adapt by increasing their size exclusively but not their number [1,2], reaching ultimately a maximum level of hypertrophy beyond which a compensatory reaction may no longer be achieved [59]. In fact, studies on renal functional reserve in patients with ASK have often shown a partially or completely blunted response several years following nephrectomy [62–64]. Thus, acquired SK may possibly be more vulnerable to additional stress than congenital forms of SK.

Another possible reason for the difference between the two groups is that the compensatory response to congenital nephron reduction might involve not only cellular hyper-
trophy but also hyperplasia or cellular multiplication. In their animal model, Danton et al. found that ovine fetuses, uninephrectomized during the period of active nephrogenesis, showed by the end of normal gestation a 45% increase in the number of nephrons in their remnant kidneys compared with controls [65]. Given that ovine species have a nephrogenesis pattern similar to that observed in humans, one can assume that in response to congenital renal mass reduction, the remnant kidney would react by enhancing its nephrogenesis, so that by the end of normal gestation, there would be enough nephrons to carry out the function of both kidneys. In support of this hypothesis, Maluf compared a histologically normal congenital SK from an otherwise healthy 27-year-old man with a control kidney from an equal pair and found that the SK was ~1.8 times heavier and had twice as many glomeruli as the control kidney (2.52 × 10⁶ vs. 1.14 × 10⁶, respectively) [66]. More nephrons imply less glomerular hyperfiltration, thus a lower incidence of glomerulosclerosis. Indeed, further studies are needed to confirm these speculations.

Conclusions

Until a few years ago, it was common to admit that one can live just as well with one kidney as with two. This might be true on the short and medium term but surely less certain with longer periods of follow-up since children with solitary kidney, as with any other condition of reduced nephron endowment, are potentially predisposed to a higher risk of hypertension and renal impairment in later life. Careful monitoring throughout childhood is therefore mandatory in order to detect early signs of hyperfiltration injury and prevent its progression to more serious complications [67,68]. This is particularly relevant for those who had their kidney removed in early childhood, irrespective of the cause of nephrectomy.

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Conflict of interest statement. None declared.

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