Risk stratification for children with a solitary functioning kidney

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In the last decade, it has become widely accepted that living with just 1 kidney may be harmful for that solitary functioning kidney (SFK) [1]. This deterioration is explained by the hyperfiltration hypothesis from Prof. Brenner [2], which states that a reduction in the number of nephrons will result in glomerular hyperfiltration in the remaining nephrons. This hyperfiltration starts a vicious cycle of glomerular hypertension, hypertrophy, and injury, which results in systemic hypertension, albuminuria, and glomerulosclerosis with a further reduction in nephron numbers.

Kidney donation is the most common cause of living with an SFK, and even though the absolute risk after kidney donation is limited, the risk for kidney failure is indeed increased [3]. However, not every kidney donor has the same risk for kidney failure. To assist in estimating an individual's risk for kidney failure after kidney donation, online calculators are available. These calculators take into account risk factors for kidney failure such as age, sex, race, obesity, and diabetes.

Children may present with an SFK as a consequence of a congenital non-functioning kidney or after nephrectomy, for instance due to malignancy. Being born with an SFK exposes glomeruli to a much longer period of hyperfiltration, and has been associated with kidney injury starting in childhood [4] and a higher risk of kidney failure later in life than after kidney donation [5]. Unfortunately, risk stratification within the group of SFK patients is not yet possible, as factors that differentiate between high and low risk groups need to be better established and the prediction model that was developed in a single study should be improved and confirmed extensively

[6]. With the increasing interest in the subject, however, and the increase in size of the cohorts described, it is to be expected that such a good prediction model and a risk calculator may be developed in the coming years.

Risk stratification

In recent years, the issue of risk stratification for kidney injury in the follow-up of children with an SFK has been addressed by several authors. Similar to risk factors for chronic kidney disease (CKD) [7], such risk factors can be grouped into four categories: genetic factors (risk alleles), perinatal factors (e.g., low birth weight and premature birth), additional kidney or urinary tract abnormalities (such as vesico-ureteral reflux or the absence of kidney hypertrophy), and additional hits to the kidney (e.g., urinary tract infections (UTIs) or obesity) (Table 1). In addition to these risk factors, the degree and period of hyperfiltration, and thereby the age of the patient, plays an important role.

Patient characteristics such as sex and ethnicity could be involved. Most studies showed no association between sex and risk for kidney injury in SFK patients [4, 6, 8–12]. One notable exception is the study by Alfandary et al. in which male adolescents with SFK had a threefold higher risk of kidney injury compared to female patients [11].

In the current edition of this journal, Matsell et al. have identified that the subtype of congenital SFK may also be a risk factor for kidney injury, with a higher risk in patients with unilateral renal agenesis (URA) compared to children with a multicystic dysplastic kidney (MCDK) [20]. This is in line with the previous report from Sanna-Cherchi et al., who showed that the chance of needing dialysis at the age of 30 years was higher for patients with URA (~40%) compared with MCDK (~20%) [5]. Previous studies have also suggested that the risk for kidney injury is higher in patients with acquired than congenital SFK [19]. Both findings strengthen the hypothesis that the cause of SFK is an important determinant of the risk for kidney injury.

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Table 1 Potential risk factors for kidney injury in children with SFK

Risk factor	Magnitude	References
Patient characteristics		
Male sex	0.8–4.4	[4, 6, 8–12]
Ethnicity	n/a	n/a
Duration of hyperfiltration		
Older age (per year)	1.1	[4, 9, 13–18]
Cause of SFK		
Acquired vs. congenital SFK	n/a	[19]
URA vs. MCDK	2.1–2.7	[5, 6, 20]
Genetic factors		
Risk alleles	n/a	n/a
Perinatal factors		
Premature birth	2.0	[6]
Low birth weight	2.1–2.7	[4, 6]
Additional kidney or urinary tract abnormalities		
Smaller SFK size (per SDS)	1.1	[4, 6, 11, 12, 17, 21, 22]
Additional CAKUT	1.7–13	[4–6, 11, 12, 17, 20, 23–26]
Additional hits to the kidney		
Nephrotoxic drug use	n/a	n/a
Urinary tract infections	1.6–6.7	[4, 6, 12, 26]
Obesity	1.4–15	[10–12, 23, 24, 27]
Smoking	1.5	[11, 23, 27]
Diabetes	4.4	[18, 28, 29]
Hypertension	n/a	[17, 18, 28, 29]
Cardiovascular disease	5.6	[18]
Pregnancy	2.4	[30, 31]

n/a, not available

Extent of glomerular hyperfiltration

Both the duration and timing of hyperfiltration play an important role in the risk of kidney injury. A longer period of hyperfiltration increases the chance of developing kidney injury in diabetic nephropathy, a well-known cause of hyperfiltration injury, where the duration of diabetes is associated with the risk of developing albuminuria [32]. In addition, older age has been shown to increase the proportion of SFK patients who develop hypertension [4], albuminuria [4, 13–15], and/or abnormal kidney function [16, 17]. The impact of timing has been shown by the fact that the degree of glomerular hyperfiltration was twice as high after early kidney mass reduction when compared to nephrectomy in adulthood [1, 33]. Thus, early kidney mass reduction may increase the risk of kidney injury. During adolescence, kidney function is well known to decline at an increased speed, as has been described in patients with kidney hypodysplasia [34] or with an SFK [4, 23], further increasing the effect of timing (kidney mass reduction before or after puberty) on the risk of kidney injury. The kidney function decline during puberty may be

explained by the rapid growth with the subsequent metabolic demand on the kidney, which the SFK is not able to deliver without a relevant change in glomerular hemodynamics. This increase in glomerular hyperfiltration, and potentially in glomerular hypertension, will lead to more glomerular injury with subsequent albuminuria. Another explanation may be that the increased demand on the kidney unveils the influence of dysplastic nephrons, in line with the findings in patients with hypodysplasia [34]. The latter may also be an explanation for the differences found between URA and MCDK by Matsell et al. [20]. Cause, timing, and duration of the renal mass reduction with subsequent hyperfiltration are all factors that should therefore be considered in the risk stratification.

Genetic factors

Genetic factors contributing to kidney injury in patients with SFK are likely to be risk alleles that, in contrast to highly penetrant disease-causing mutations, are associated with a relatively small increased risk of disease only. In a large meta-analysis of genome-wide association studies of estimated glomerular filtration rate (eGFR) in the general population, 264 loci associated with kidney function were identified [35]. When a selection of 147 of these single nucleotide polymorphisms (SNPs) was combined to calculate genetic risk scores, these scores proved to be associated with an increased risk of CKD and hypertension [35]. Although it is unlikely that similar-sized cohorts of SFK patients will be composed, smaller studies may also identify variants with prognostic value, as illustrated by the results of cohorts of patients with obstructive uropathies suggesting that variants in angiotensin converting enzyme (*ACE2*), angiotensin II type 2 receptor (*AGTR2*), and cadherin 12 (*CDH12*) are associated with the development of kidney injury [36, 37]. Interestingly, the variants in *ACE2*, *AGTR2*, and *CDH12* were not among the 147 SNPs used to calculate genetic risk scores for signs of kidney injury in the general population. This indicates that risk alleles for kidney injury may differ between patients with congenital anomalies of the kidney and urinary tract (CAKUT) and healthy individuals and that the search for additional risk alleles in CAKUT patients may benefit from a hypothesis-free approach.

Perinatal factors

In humans, nephrons are formed until approximately 36 weeks of pregnancy [38]. As a consequence, nephron formation may not be complete in infants born prematurely, and continued nephron development with signs of abnormal morphology has been found in preterm neonates [39]. The inter-individual differences in kidney development that were observed in this study suggested that early (during active nephrogenesis) postnatal exposure to an inflammatory environment [40] or nephrotoxins may play an additional role.

Despite the knowledge that nephrotoxic drugs such as gentamicin or indomethacin can have disrupting effects on kidney development, they are frequently used in neonatal intensive care units [41, 42]. Use of nephrotoxic drugs in premature infants with SFK may have even more detrimental effects and could pose a risk factor for kidney injury in these patients. Low birth weight (< 2500 g) is associated with low nephron numbers [43], and was associated with a risk of kidney injury twice that of children with a normal birth weight in patients with SFK [4, 6]. Prematurity and low birth weight could explain some of the differences in kidney function in children with SFK, and should be considered in risk stratification.

Additional congenital anomalies of the kidney and urinary tract

In a normal cSFK, compensatory growth is expected to start before birth and continue throughout childhood [12, 21, 44, 45]. Before birth, this growth can comprise both hyperplasia (increase in cell number) and hypertrophy (increase in cell size) [46]. The evidence that the absence of compensatory growth is associated with the risk of kidney injury is convincing. Several studies have found that larger SFK size, especially when present at birth, was associated with a lower risk of kidney injury [4, 6, 11, 12, 17, 21, 22] suggesting that a responsive mechanism triggering hyperplasia is very important in dealing with kidney mass reduction. The evidence supporting an association between additional CAKUT of the SFK and kidney injury is also strong, with hazard ratios varying between 1.7 and 13, which is in line with the results reported by Dr. Matsell and colleagues [4–6, 11, 12, 17, 20, 23–26]. The association of additional CAKUT in the SFK with kidney injury may be explained by the fact that these patients are more prone to recurrent UTIs or other events that further decrease the number of nephrons.

Additional hits

In the situation of a reduced nephron number, other exposures that hurt the kidney or increase the demand on the kidney are likely to increase the risk of kidney injury. Such an increased risk has been identified repeatedly for recurrent UTIs [4, 6, 12]. Modifiable risk factors, such as obesity, smoking, or diabetes, should be avoided as much as possible because of their associations with hypertension, albuminuria, and kidney function deterioration [11, 23, 24, 27]. For diabetes, hypertension, and cardiovascular disease, a direct relation with faster development of CKD was shown in patients with SFK [18, 28, 29]. Pregnancy is a period of additional demand on the SFK, which results in a risk for gestational hypertension and preeclampsia that is more than twice that of women with two kidneys [30, 31]. Therefore, careful monitoring of women with an SFK is necessary during pregnancy.

Previously, participation in contact sport has been advised against because of potential kidney trauma to the SFK with potentially devastating consequences. The extremely low incidence of kidney injury caused by sports participation, however, has led to a revision of these guidelines. The potential benefits of sports participation are highly likely to surpass the risks [47].

Clinical implications

The interesting results reported by Matsell et al. provide another step towards further personalizing the care for patients with an SFK [20]. Large cohorts of SFK patients will allow for the development of prediction models that can be used to stratify patients into risk categories. The recently published prediction model developed by Poggiali et al. [6] is an excellent example of what such a model could bring. In its current form, however, the additive value of this prediction model is limited, since the high-risk group is mainly determined by occurrence of multiple UTIs. This information is not yet available in early life and would only allow for adjustment of the follow-up strategy after a second or third UTI has taken place. The same is likely to be done in regular care, since most clinicians would increase follow-up frequency and/or consider treatment in a child with SFK and recurrent UTIs. A prediction model would be especially helpful if it would contain only predictive factors occurring early in life, for instance within the first year, so a tailored follow-up strategy can be initiated from then on. Furthermore, the current model was based on only 18 events in 162 patients. In prediction modelling, a minimum of 10 events per variable (EPV) is usually advised and an EPV ≥ 20 has been advocated to obtain more reliable predictions [48]. Collaborative efforts of research groups will be needed to create and validate prediction models that are applicable in different centers and healthcare settings. If such a prediction model is established, it will likely improve the current recommendations for the follow-up of SFK patients [1, 49], allowing for better and more cost-efficient clinical management. In addition, identification of SFK patients with a high risk of kidney injury facilitates targeted research in these groups, for example regarding innovative biomarkers of kidney injury or future therapies slowing down or even preventing the progression of kidney injury.

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