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EDITORIAL COMMENTARY

Acute kidney injury in children with sickle cell disease—compounding a chronic problem

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Abstract In an article recently published in *Pediatric Nephrology*, Baddam and colleagues discuss the relatively underreported clinical problem of repeated episodes of acute kidney injury (AKI) in children with sickle cell disease (SCD). Their report is a cautionary note about the importance of repeated kidney injury on the background of underlying chronic kidney injury and its potential implications on long-term kidney outcome. In children and adults with SCD, this includes the effects of repeated vaso-occlusive crises and the management of these painful episodes with non-steroidal anti-inflammatory drugs. Here we review the scope of kidney involvement in SCD in children and discuss the potential short- and long-term consequences of AKI in children with SCD.

Keywords Sickle cell nephropathy · Vaso-occlusive pain crisis · Acute kidney injury · Non-steroidal anti-inflammatory drugs · Children

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Introduction

In an article recently published in *Pediatric Nephrology*, Baddam and colleagues report an acute kidney injury (AKI) incidence of 17% in children with sickle cell disease (SCD) presenting to the hospital emergency room with vaso-occlusive crisis, of whom 50% developed AKI after being admitted to hospital [1]. In another recently published study, the same research group reported an incidence of AKI of 8% in children with SCD presenting with acute chest syndrome (ACS), characterized by fever and pulmonary infiltrates [2]. As highlighted by the authors in both reports, this kidney injury appears to be an underreported problem in this pediatric patient population. In adults, AKI occurs in 4–10% of SCD patients who have been hospitalized, and in up to 14% of adults with ACS [3, 4]. This high incidence of AKI, however, should not be surprising, given the underlying renal pathology in children with SCD, the effects of vaso-occlusive crisis on this kidney background, and the continued use of non-steroidal anti-inflammatory drugs (NSAIDs) to treat painful crises in this patient population. We present a suggested paradigm of the pathway towards sickle cell nephropathy that includes the potential independent effects of single or repeated episodes of AKI (see Fig. 1).

Sickle cell nephropathy

Sickle cell nephropathy refers to the spectrum of chronic kidney disease (CKD) that results from the effects of repeated episodes of red blood cell sickling in patients with SCD. Some of these sickling episodes manifest silently while others occur as painful vaso-occlusive crises. While most obvious in adults with SCD, children also develop significant long-term, permanent, and progressive kidney injury. This injury affects the glomeruli, leading to global or segmental glomerulosclerosis, glomerular hypertrophy, and duplication of the glomerular basement

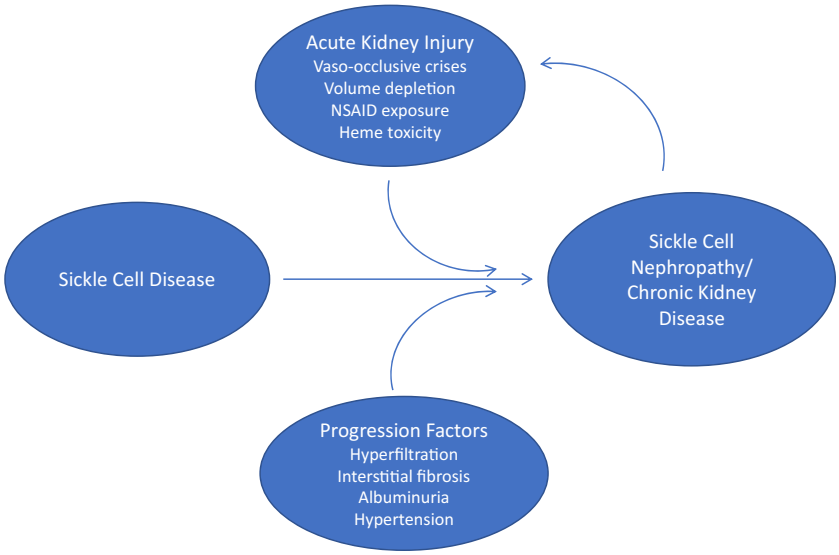

Fig. 1 The putative role of acute kidney injury (AKI) in the progression of sickle cell nephropathy. Progression of chronic kidney disease in sickle cell disease is due to the traditional factors of glomerular hyperfiltration, glomerular hypertrophy and glomerulosclerosis, vascular remodeling, tubular atrophy, and interstitial fibrosis. However, repeated episodes of AKI, resulting from vaso-occlusive crises, volume depletion due to hyposthenuria, and/or the use of non-steroidal anti-inflammatory drugs (*NSAIDS*), are likely important contributors to the development and progression of sickle cell nephropathy

membranes, but also results in interstitial fibrosis, tubular atrophy with loss of peritubular capillaries, and papillary necrosis. In fact, renal biopsies in patients and autopsy studies suggest that focal segmental glomerulosclerosis (FSGS) is the most common cause of renal failure in SCD [5]. The medulla is particularly prone to the effects of red blood cell sickling, and vaso-occlusion due to sickling of red blood cells can cause destruction of the vasa recta and loss of peritubular capillaries. The medulla is relatively hypoxic, and the acidic environment and hyperosmolality further increase the intracellular hemoglobin concentration and decrease oxygen affinity, leading to increased red blood cell sickling. These factors ultimately result in impaired blood flow, microinfarctions, and ischemia. Over time, this leads to remodeling of the medullary vasa recta peritubular capillaries with multilayering of the basement membranes, peritubular capillary loss, interstitial fibrosis and tubular atrophy, and papillary necrosis when severe [6–8]. The clinical manifestations of renal medullary injury include hyposthenuria, polyuria, metabolic acidosis, and hyperkalemia.

Hypoperfusion of the medulla results from infarction, thrombosis, and remodeling of the microvasculature, creating a "perfusion paradox" [8]. There is a concomitant increase in cortical blood flow that has damaging consequences, such as glomerular hyperfiltration, enlargement of the glomeruli, tubular hypertrophy, and enlarged kidneys. The endpoint of this hyperfiltration is glomerular scarring with progressive loss of renal function. Glomerular injury is evident in adults with SCD, with up to 50% of this patient group showing evidence of hyperfiltration and 21–27% having CKD, defined as an estimated glomerular filtration rate (eGFR) of <90 mL/min/1.73 m^2 [9–12]. The prevalence of end-stage renal disease (ESRD) in the adult SCD population has been estimated to be between 4 and 12%, with a mean time to ESRD of 37 years [12, 13]. However, SCD represents only approximately 0.1% of all incident patients with ESRD in the USA [14].

Sickle cell nephropathy in children

Sickle cell nephropathy is also apparent in children with SCD, with glomerular hyperfiltration evident as early as infancy. Glomerular hyperfiltration in children was first described decades ago [15] and has since been confirmed in a number of different cohorts [16–18]. In the original study by Etteldorf and colleagues, children with SCD aged 4–11 years had a significantly higher mean measured glomerular filtration rate (mGFR) (169 mL/min/1.73m^2) than normal controls (128 mL/min/1.73 m^2) [15]. In the BABY HUG trial, a multi-center randomized controlled trial to assess the potential beneficial effects of hydroxyurea in young children with SCD, 176 children aged 9–19 months had a mGFR at baseline of 125 mL/min/1.73 m^2 [16], which was significantly higher than published normal values for the same age group [19]. Interestingly, after 2 years, the mGFR had increased significantly in both the treatment and control groups [17].

Children with SCD may also have evidence of more advanced renal injury, whereby the hyperfiltration, glomerular hypertrophy, and glomerular scarring result in proteinuria. In a cross-sectional study of 410 patients with SCD aged 2–21 (mean age 11) years, 23% had the HbSS form of SCD, with elevated urinary albumin excretion (≥30 mg/g), while other investigators have reported a HbSS prevalence of 16–27% in the childhood SCD population [18, 20, 21].

Further progressive kidney injury and CKD is reflected in a declining and abnormally low GFR. However, data on the prevalence of CKD in childhood SCD are relatively scarce. McPherson Yee reported a CKD (eGFR <90 ml/min/1.73m^2) prevalence of 12% of their cohort of 410 children with SCD [22], using serum creatinine and a modified Schwartz formula to calculate eGFR [23]. Similarly, Bodas et al. recently reported a CKD prevalence of 8% in a cohort of patients with SCD aged 3–17 years, using the same CKD criteria and the same eGFR calculation [24]. The prevalence of ESRD in the pediatric SCD population is also not well described; however, childhood SCD accounts for only 0.3% of incident pediatric ESRD (U.S. Renal Data System 2015 annual data report; https://www.usrds.org/2015/view). The factors that predispose children with SCD to develop CKD are unknown. As in other kidney diseases, persistently elevated blood pressure and the presence of overt proteinuria likely contribute to progressive glomerular scarring and renal fibrosis leading to secondary FSGS. Pediatric SCD patients with underlying CKD may also be at a higher inherent risk of developing AKI due to inadequate renal reserve.

Sickle cell nephropathy and AKI

In adults with SCD, AKI has been identified in 4–13.6% of hospitalized patients and is associated with increased mortality in those admitted to the intensive care unit [25]. Even though there has been a steady growth of AKI literature in pediatric populations over the last decade, little is known regarding the epidemiology of AKI in children with SCD. The recent retrospective study by the Lebensburger group revealed an AKI incidence of 8% in 149 pediatric patients admitted for acute chest syndrome using the Kidney Disease Improving Global Outcomes (KDIGO) serum creatinine-based definition, and AKI was associated with an increased hospital length of stay [2]. An accompanying article by Baddam and colleagues from the same institution in Alabama (USA) and using the same definition showed that AKI occurred in 17% of 197 pediatric admissions for pain crisis over a 2-year period and that there was an independent association of AKI with increased length of stay [1].

The true incidence of AKI in pediatric SCD patients may in fact be underestimated from these two retrospective studies [1, 2] due to a lack of available data on baseline serum creatinine in several patients and inconsistent monitoring of creatinine values during admission. In addition, serum creatinine may be an inaccurate marker of GFR in SCD due to the relatively high proximal tubular secretion of creatinine found in this population [26]. Interestingly, a recent adult study showed that even in patients with a normal creatinine level during a pain crisis, acute tubular injury likely occurs, as evidenced by a more than twofold rise in urinary neutrophil gelatinase-associated lipoprotein excretion [27].

The etiology of AKI in the children in these two studies [1, 2] is likely due to a number of causes, such as repeated hypoxic–ischemic episodes to the kidney associated with vaso-occlusive crises and, as highlighted by Baddam et al. [1], by higher exposure to NSAIDs. Although the degree of NSAID use at home was difficult to assess due to the retrospective nature of the study [1], the investigators found that the total days and doses of intravenous ketorolac received after admission was associated with the development of AKI. As renal injury progresses in patients with SCD, glomerular perfusion is maintained through compensatory vasodilation and a decrease in renal vascular resistance. These effects are mediated in part through the local production of prostaglandins, which are increased due to medullary ischemia [28]. Studies in adult patients with SCD support a role for prostaglandins in maintaining a normal GFR, as treatment with indomethacin results in a significant decrease in GFR [26, 29]. In addition, NSAID use is common in children with SCD [30], without evidence to support its benefit compared to other less nephrotoxic options [31]. Similarly, the use of NSAIDS in children hospitalized for various other reasons, including dehydration due to gastroenteritis, was associated with a significant increase in the incidence of AKI [32, 33]. Therefore, it is not surprising that hemodynamic-mediated AKI secondary to NSAIDs, a potential modifiable risk factor, is relatively common in this population, especially as SCD patients are often at higher risk of volume depletion at the time of presentation due to their inherent reduced urine concentrating ability. Another contributing factor includes potential toxic tubular effects of hemoglobin released through hemolysis during a sickle crisis. In children admitted with both vaso-occlusive pain crises and acute chest syndrome, an association was found between a larger drop in hemoglobin and AKI [1, 2].

AKI and CKD association

In adults, a large systematic review and meta-analysis showed that patients with a single episode of AKI had a significantly higher risk of developing CKD and ESRD compared to patients without AKI exposure [34]. In addition, several adult studies have demonstrated a dose–response relationship between AKI and CKD, including a higher risk of CKD in those with more severe AKI and also in those with repeated episodes of AKI [35–37]. Several pediatric observational studies have also shown a high proportion of CKD in survivors of AKI, ranging from 10 to 69%, but these studies have focused on populations without primary kidney disease [38–44]. Although the etiology of AKI varies in most of these studies, Menon and colleagues identified that nephrotoxic AKI in children increases the risk of CKD at 6 months of follow-up [44]. The contribution of single or repeated episodes of AKI towards the development of CKD specifically in patients with SCD is largely unknown. However, based on the association

of AKI and CKD found in several adult and pediatric studies to date, there is rationale to suggest a link in SCD patients as well (see Fig. 1). As pointed out, until recently, AKI in patients with SCD has been largely underreported. With a strong signal of AKI coming from smaller retrospective studies, it is evident that larger prospective longitudinal studies in pediatric SCD are needed to properly determine the burden of AKI and to assess how much AKI has a role in the development of early CKD in this vulnerable population.

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