Sickle Cell Nephropathy in the Pediatric Population

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Abstract

Background: Compared to the past, patients with sickle cell disease (SCD) currently live longer due to improvements in diagnosis and comprehensive care. Due to these advances, long-term chronic complications pose a greater challenge in the management of patients with SCD. In particular, sickle cell nephropathy (SCN) is associated with significant morbidity and mortality across all age groups. Furthermore, SCN is an understudied condition with relatively few symptoms and therefore requires close surveillance. In this review, we sought to explore the epidemiology, natural history, and treatment options for SCN with an emphasis on the pediatric population. **Summary:** SCN invariably begins in childhood with evidence of structural changes detected as early as infancy. These indolent changes can progress undetected to advanced chronic kidney disease by late adolescence or early adulthood. The risk factors for progression are not well

defined, but significant albuminuria (which is also the most common presentation in childhood) is a key factor in progression. One of the main challenges in understanding SCN in children is the poor correlation between estimated and measured glomerular filtration rates. Another challenge is the lack of large-scale longitudinal studies that track the clinical outcomes of pediatric patients over time. Several studies aim to identify early biomarkers of SCN in children, as albuminuria presents only following significant chronic damage. The utility of angiotensin converting enzyme inhibitors and hydroxyurea in treating albuminuria is addressed here as well as novel treatments that may be of benefit.

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Introduction

Sickle cell nephropathy (SCN) is a well-defined group of renal abnormalities associated with an increased risk for morbidity and mortality in patients with sickle cell disease (SCD) [1, 2]. We will review different aspects of SCN with an emphasis on the pediatric population.

Brief Overview of SCD

SCD is a severe monogenic condition that affects millions of people worldwide, predominantly in malaria-endemic countries where the sickle cell mutation evolved as a protective response [3–6]. In the United States, SCD affects 1 in every 365 black births [4].

SCD is a clinical syndrome caused by a point mutation of the hemoglobin subunit beta gene found on chromosome 11p15.4 [7, 8]. The most common and severe form of SCD is sickle cell anemia (SCA), which is caused by the homozygous inheritance of the sickle gene [8, 9]. Other forms of SCD are shown in Table 1.

The pathology of SCD is due to the polymerization of red blood cell (RBC) hemoglobin in low oxygen tension states, hyperosmolarity, and/or acidosis [1, 3, 8]. Hemoglobin polymerization alters both the structure and function of RBC membranes resulting in recurrent microvascular vaso-occlusion, ischemia-reperfusion injury, and hemolysis [3, 8, 10, 11]. Hemoglobin polymerization also leads to the abnormal expression of adhesion molecules on vascular endothelium and RBCs [3, 8, 10, 11]. These sequelae ultimately contribute to systemic inflammation [3, 8, 10, 11].

The advent of newborn screening, early comprehensive care, and effective treatments has significantly improved survival in SCD [12, 13]. As a result, the chronic manifestations of recurrent end organ damage, such as SCN, have become a significant issue.

Epidemiology

Approximately 16–27% of children with SCD have chronic kidney disease (CKD) as defined by Kidney Disease: Improving Global Outcomes (KDIGO) criteria [14–19]. However, most of the cited studies were cross-sectional in nature. There is a clear need for large longitudinal studies to accurately determine the age of onset and risk factors for the development of pediatric SCN.

Risk factors that have been associated with the development of pediatric SCN are older age, early severe anemia, severe hemolysis, Central African Republic sickle haplotype, elevated blood pressure for age, priapism, and hyperuricemia [1, 13, 17, 19–24].

Once patients with SCD progress to a glomerular filtration rate (GFR) of <60 mL/min, the mean survival time is 4 years [13, 22]. There is lack of studies examining the effects of pediatric SCN on morbidity and mortality during childhood due, in part, to the fact that most adverse manifestations of SCN occur in adults.

Table 1. Types of sickle cell disease

Type	Abbreviation
Homozygous sickle gene inheritance	HbSS disease (sickle cell anemia)
Heterozygous sickle gene inheritance with other abnormal variants of hemoglobin	HbSC disease, HbSD disease, HbSE disease, etc.
Heterozygous sickle cell gene inheritance with thalassemia	HbS-beta thalassemia disease

Pathophysiology

The renal medulla is uniquely suited to promote hemoglobin polymerization because of low oxygen tension, hyperosmolarity, and acidosis [1, 2]. Renal medullary vascular stasis promotes the sickling of RBCs and the expression of vascular adhesion molecules on RBCs [1]. This leads to chronic recurrent ischemic-reperfusion injury and infarction of the medulla, with resulting medullary vascular disruption, fibrosis, and hypoperfusion [1, 2, 25].

Due to multiple factors, cardiac output is increased in SCD patients [11, 25]. This results in high renal blood flow and GFR [1, 2, 11, 25]. Nath et al. [25] described this as the “perfusion paradox” – macrovascular hyperperfusion (increased GFR) and microvascular hypoperfusion (reduced medullary perfusion) occurring simultaneously.

Patients with SCD undergo chronic hemolysis. This induces functional endothelial nitric oxide deficiency, thereby impairing appropriate vascular physiologic responses to stress [3, 26, 27]. This is exacerbated by the overexpression of endothelin-1, a powerful vasoconstrictor [1, 25]. Therefore, the kidney is unable to adequately compensate for adverse hemodynamic changes, thus, increasing susceptibility to acute kidney injury (AKI) [3, 25–27]. Chronic hemolysis leads to iron deposition in the kidney, resulting in the proliferation of mesangial cells and interstitial and glomerular fibrosis [1, 28, 29].

Traditionally, SCD was thought to be associated with a low prevalence of hypertension compared to healthy controls [30, 31]. However, masked hypertension is common in pediatric SCD and could contribute to SCN pathophysiology [32, 33]. These processes are summarized in Figure 1.

Fig. 1. Pathophysiology of sickle cell nephropathy. The complex pathophysiology of SCN is a result of the vasculopathy that occurs in SCD. This vasculopathy results in medullary hypoperfusion, glomerular hyperfiltration, and cyclical ischemia-reperfusion in-

juries. Chronic renal exposure to products of hemolysis and masked hypertension contributes as well. These processes initiate and sustain the progression of SCN.

Pathology and Clinical Features in the Pediatric Population

Overview of Pathology

Nephromegaly, caused by hypertrophic glomeruli secondary to glomerular hyperfiltration, is well described in SCN. It is seen in children as young as 7–18 months on ultrasound [34, 35]. Children with SCD may also have diffuse echogenicity and loss of renal cortico-medullary differentiation [34, 36]. On light microscopy, the most commonly described feature of SCN is focal segmental glomerulosclerosis and its variants due to glomerular hyperfiltration [1, 36–40]. However, membranoproliferative glomerulonephritis without immune complex deposits has also been described [40–42]. Unfortunately, there remains a paucity of studies detailing the histology of pediatric SCN. To better understand the natural history of SCN, pediatric renal biopsy studies are needed.

Overview of Clinical Features (Table 2)

Renal Tubular Disease

Hyposthenuria occurs as early as infancy [43, 44]. This is due to renal medullary sickling resulting in the destruc-

tion of the vasa recta [45]. These changes result in the loss of the countercurrent multiplication and exchange system [1, 43, 46]. Hyposthenuria can progress to frank polyuria and enuresis [44]. The other common manifestation of renal tubular disease in pediatric SCN is a distal renal tubular acidosis despite an intact renin-aldosterone system. This typically manifests as hyperkalemia in the setting of stressors (e.g., AKI, dehydration and pain crisis) [1, 42, 43, 47–49]. Renal tubular dysfunction in SCN has not been definitively linked with a progressive decline in renal function.

Hematuria

Microscopic hematuria is common in pediatric SCN with cross-sectional studies reporting a prevalence of up to 30% [42]. Hematuria in SCN is usually left sided, caused by increased pressure in the longer left renal vein due to compression by the aorta and superior mesenteric artery [1, 50]. This causes medullary capillary congestion with extravasation of RBCs into the tubular lumen or rupture of the submucosal capillaries of the renal pelvis [1, 50]. Macroscopic hematuria is a potentially life-threatening complication that may occur from renal papillary ne-

Table 2. Clinical manifestations of sickle cell nephropathy

Distal tubular dysfunction
Hypothenuria
Partial distal renal tubular acidosis
Proximal tubular hyperfunction
Increased secretion of creatinine
Increased reabsorption of phosphate
Hematuria
Renal papillary necrosis
Glomerular hyperfiltration
Higher than normal estimated glomerular filtration rate
Proteinuria
Tubular proteinuria
Focal segmental glomerulosclerosis and its variants
Membranoproliferative glomerulonephritis
Recurrent clinical and sub-clinical acute kidney injury
Increased risk for recurrent urinary tract infections
Chronic tubulointerstitial disease
Decline in glomerular filtration rate and progression to end-stage renal disease
Increased susceptibility to renal medullary carcinoma

erosis secondary to vaso-occlusion. This condition may require urgent treatment with hydration and bicarbonate [1, 51, 52].

Albuminuria

Several studies have suggested that 16–27% of children with SCD have albuminuria [14, 44, 53, 54].

Albuminuria in SCN has been linked to widening of the inter-podocyte pore radius and reduction of total podocyte pores due to sickled RBCs causing endothelial activation and inflammation [55]. Furthermore, hemoglobin dimers released during hemolysis promote albuminuria by inhibiting the reuptake of albumin in the proximal tubule [56]. Levels of albuminuria in SCN also correlate with hemolysis and markers of tubular injury [24].

Shatat et al. [57] retrospectively examined 353 children with SCD and microalbuminuria and found that older age, higher bilirubin, and lower HbF levels were associated with albuminuria over time. Albuminuria >500 mg/g and nephrotic syndrome have been associated with progression to end-stage renal disease (ESRD) in adulthood in more than one study [58, 59].

Chronic Kidney Disease

Advanced CKD in SCN occurs primarily in adults. Powars et al. [22] demonstrated this in a 25-year prospective study involving 725 patients with SCD followed from childhood. The median age of onset was 23.1 years in SCA

[22]. This study found that a decline in GFR was associated severe anemia, hematuria, albuminuria, and nephrotic syndrome [22]. More recently, McPherson et al. [19] examined 410 children in a cross-sectional study and found that age correlated negatively with GFR. The most advanced CKD stage recorded in this study was KDIGO stage 2 [19]. There are no data in SCD pediatrics detailing the rate of fall in GFR over time and how this correlates with factors such as albuminuria or progression to ESRD.

Acute Kidney Injury

Baddam et al. [60] examined 197 admissions for vaso-occlusive crisis (VOC) in children with SCD (age 8–18 years) and found that 17% were associated with AKI (KDIGO criteria) [61]. They also found that lower hemoglobin and increased exposure to ketorolac were correlated with AKI risk [60]. These findings suggest a role for recurrent VOC and AKI in the development of SCN [62]. This is supported by data from adult SCD patients in France, which demonstrated sub-clinical kidney injury as shown by elevated urine neutrophil gelatinase-associated lipocalin levels during VOC despite an unchanged serum creatinine [63]. No similar study has been performed in the pediatric population.

Management

Current guidelines for managing SCN as outlined by an expert panel convened by the National Heart, Lung and Blood Institute are mostly based on low-quality evidence [7]. The expert panel has called for further research into SCN [7].

Early Detection and Monitoring in the Pediatric Population

Early detection and monitoring are key to managing this condition because of the chronic progressive nature of SCN [1, 13, 22, 35]. The tools available for this are limited.

GFR is usually estimated in pediatrics using the modified Schwartz formula, which incorporates height and enzymatically measured serum creatinine [64]. In the double-blinded, randomized controlled BABY HUG trial, investigators looked at the effect of hydroxyurea on renal function in infants [65]. Comparing estimated GFR (using the Schwartz formula) to quantitative GFR measurements in 176 infants between the ages of 9 and 19 months, the investigators found that the Schwartz formula significantly overestimated GFR [35]. Patients with SCD have proximal tubule hyperfunction resulting in increased se-

Table 3. Biomarkers investigated for use in sickle cell nephropathy

Proposed potential markers for early detection and monitoring progression of SCN
Urine microalbumin/creatinine ratio
Urine total protein/creatinine ratio
Urine N-acetyl-beta-D-glucosaminidase (NAG) [24, 89]
Urine kidney injury molecule-1 [24, 89]
Urine ceruloplasmin [90]
Urine free hemoglobin [29]
Urine nephrin [91]
Plasma soluble FMS-like tyrosine kinase-1 (sFLT-1) [92]
Plasma cystatin C [89, 93]
Measured glomerular filtration rate using iothexol clearance [94]
Markers with conflicting or negative data on association with proteinuria in SCN
Urine neutrophil gelatinase-associated lipocalin (NGAL) [63, 89, 95]
Urine transforming growth factor beta (TGFβ) [63, 89, 95]
Urine liver-type fatty acid binding protein (L-FABP) [89]
Urine endothelin-1 [24]

cretion of creatinine [1, 66, 67]. Furthermore, the Schwartz formula was validated in children with low GFRs and not in children with high normal GFRs as it occurs in SCN [35]. Given these issues, CKD may need to be redefined in SCN using criteria for a decline in estimated GFR from baseline [19]. This would require a consistent method of routine GFR measurements starting from a predetermined baseline age.

Current guidelines for the management of SCN do not specify how early or how often screening for albuminuria should occur [7]. Studies have detected albuminuria as early as 4 years old [68, 69]; however, 7 years old is widely considered the typical age of onset of albuminuria [14, 44]. This needs to be better clarified. Furthermore, there is evidence that by the time albuminuria develops, significant renal damage has already occurred [69]. Novel and current biomarkers (Table 3) have been proposed as alternatives for early detection of pediatric SCN, but these too suffer from lack of longitudinal studies.

Current Therapies for SCN (Table 4)

Current guidelines for the management of pediatric SCN recommend (1) the initiation of angiotensin converting enzyme inhibitors (ACEi) for renal complications, regardless of blood pressure and (2) renal replacement therapy when indicated [7]. There are few clinical trials to support these recommendations.

Pharmacologic Therapies

A recent, phase 2, multicenter trial evaluating the effects of oral losartan on 36 children and adults with SCN showed a significant decline in albuminuria after 6 months

of treatment with the greatest benefits seen in patients with macroalbuminuria [70]. There was no significant reduction in GFR, but 3 patients came off losartan early due to low GFR [70]. The benefits of ACEi on albuminuria in SCN have been described in children and adults [38, 71–73]. A retrospective study of 37 patients with SCN (age 3–20 years) found that ACEi resolved microalbuminuria in 56% of cases, but its use was limited by hyperkalemia [16]. No studies have demonstrated a sustained benefit of ACEi or losartan in terms of progression of CKD in SCN.

Hydroxyurea, an anti-metabolite used to reduce the frequency of SCD VOC, has been studied in SCN. Hydroxyurea increases HbF levels that inhibit the polymerization of HbS [7, 70, 73–76]. However, its use is hampered by concerns of myelotoxicity and waning effectiveness over time [7, 74, 76–78]. A 2-year, phase 3 randomized clinical trial using the BABY HUG cohort evaluated the effect of hydroxyurea versus placebo on measured GFR in 193 infants and found no significant effect [65]. The investigators report ongoing observational follow-up of their cohort to evaluate the effect of hydroxyurea on the prevention of albuminuria [65]. However, there is observational and trial data in the pediatric SCN population that suggests that hydroxyurea may reduce albuminuria [16, 70, 73].

The treatment of SCN is difficult due to its complex pathophysiology. The treatment of masked hypertension and how this affects SCN is a potential area of research. Novel therapies may need to be developed and multi-drug therapy might need to be employed. For example, endothelin receptor antagonists have robust reno-protective effects in SCA mice but human studies are pending [79].

Table 4. Current therapies for sickle cell nephropathy

Clinical finding	Recommended management
Gross hematuria	Mild: bed rest and hydration [1, 2] Severe: rule out other coagulopathies, pain management, epsilon amino-caproic acid, intervention as indicated (embolization, nephrectomy) [2]
Proteinuria >300 mg/24 h	Referral to a nephrologist [7] Consider kidney biopsy [2] Angiotensin converting enzyme inhibitors regardless of blood pressure [7]
Anemia in CKD	No reliable data – erythropoietin and hydroxyurea as indicated or tolerated and involve hematologist closely to determine best hemoglobin target and dosing of medications
Decline in glomerular filtration rate	Referral to a nephrologist [2, 7] Comprehensive CKD management Initiation of renal replacement therapy when indicated [2, 7] Kidney transplant if available [2, 7]

Non-Pharmacologic Therapies

The evidence for the non-pharmacological therapies in SCN is sparse. In particular, chronic blood transfusions early in childhood have been shown to be reno-protective in children [15], but it is not clear how long this effect lasts. Adequate fluid intake is thought to reduce the risk for recurrent AKI in SCD [1, 2]. It has been suggested that maintaining 1.2 mL/kg/h urine output per day using oral hydration would be ideal [2]; however, the evidence to support this is weak.

Anemia in SCN with Advanced CKD

Patients with SCD have relative erythropoietin deficiency, which is worsened by advanced CKD [42]. Data regarding the management of anemia in pediatric SCN with a GFR <60 mL/min are lacking. Most of the data on erythropoietin use in SCN is in adults because of the degree of CKD required to produce anemia. Current expert opinion recommends using erythropoietin with hydroxyurea to target a hemoglobin of 10–10.5 mg/dL while avoiding a hematocrit rise of greater than 1–2% per week to avoid triggering VOC [27, 80–83].

Dialysis and Transplant

There are limited data on pediatric SCD patients with ESRD because this typically occurs in adult SCD patients with a mean age of 41 years [1, 22, 84]. According to data obtained from the North American Pediatric Renal Trials and Collaborative Studies in 2008, only 0.5% of all pediatric patients registered in the dialysis arm of their database ($n = 7,037$) had SCN [85]. Mortality in pediatric patients with SCD and ESRD has not been described. Data

on how intra-dialytic parameters affect outcomes in pediatric SCN with ESRD are also sparse, although it is assumed that excessive ultrafiltration may promote sickling [86]. There are no guidelines on anemia and iron management in SCN with ESRD, although the lower hemoglobin target of 8–9 mg/dL has been suggested [83, 86]. Unlike in SCD, the effect of hydroxyurea on SCN with ESRD is not well studied. Expert opinion suggests that there could be an advantage of peritoneal dialysis over hemodialysis due to lower ultrafiltration rates and the absence of an extracorporeal low oxygen tension circuit [86]. Because of the very small numbers of pediatric SCN patients with ESRD, it is difficult to assess outcomes with confidence.

Similarly, pediatric SCN kidney transplant studies are rare. Warady and Sullivan [85] examined 10 kidney transplants in 9 pediatric patients with SCN. They reported patient survival rates of 89% and a 1-year graft survival rate of 89% [85]. However, among adults, patients with SCN are much less likely to be listed for or receive a kidney transplant compared to age and race matched controls [84]. This is thought to be due to overall poor health and high panel reactivity due to prior transfusions [87]. It is unclear if this is the same situation observed in pediatric patients. Furthermore, although kidney graft survival in pediatric SCD patients at 1 year was good, Warady and Sullivan [85] reported 21 acute rejection episodes in 7 of the 9 SCN patients. Pediatric SCN specific kidney transplant protocols need to be developed, but this is hampered by the small number of transplants performed in this population.

Conclusion

SCN is a complex condition with diverse clinical presentations. Because early damage invariably occurs in childhood, identifying and addressing risk factors for progression is key. A unique staging system for pediatric SCN is needed to better identify opportunities for intervention. Drugs approved for the prevention of frequent VOC need to be investigated for their role in preventing SCN. Kidney biopsies in pediatric SCN will add to our understanding of its pathophysiology. Longitudinal prospective cohorts such as the Sick Cell Clinical Research and Intervention Program will provide a wealth of clinical data to answer the pertinent questions in SCN [88].

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