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Rev Chil Pediatr. 2020;91(1):51-57
DOI: 10.32641/rchped.v91i1.1274

ORIGINAL ARTICLE

Characterization of kidney complications in patients with sickle cell anemia

Caracterización de las complicaciones renales en pacientes con anemia de células falciformes

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Received: 11-6-2019; Approved: 01-10-2019

What do we know about the subject matter of this study?

Sickle cell nephropathy is a common complication of sickle cell disease that includes tubular and glomerular renal disorders, which normally appear in adulthood with microalbuminuria and glomerulosclerosis.

What does this study contribute to what is already known?

We detected findings of sickle cell nephropathy since the infant stage, mainly glomerular hyperfiltration, microalbuminuria, acute kidney injury, high blood pressure, and hyposthenuria. The presence of pulmonary hypertension or dilated cardiomyopathy has been observed more frequently in patients with sickle cell nephropathy.

Abstract

Sickle cell nephropathy (SCN) is a poorly studied complication of pediatric patients. It appears in different forms, including glomerulopathy, and tubulopathies. **Objective:** To describe acute and chronic renal complications in patients with sickle cell anemia (SCA). **Patients and Method:** Retrospective study. Pediatric patients with confirmed diagnosis of sickle cell disease were included who had a nephro-urology study. Hemoglobin electrophoresis pattern, presence and type of renal involvement, and presence of cardiac involvement were recorded. Bivariate analysis was performed to compare patients with and without SCN. **Results**: 79 patients were included, 59.5% of them were men, and the most frequent electrophoresis pattern was Hb-SS (60.9%). The SCN occurred in 70% of patients with an average age of 114 months (RIQ 65-157). The most frequently observed alterations were glomerular hyperfiltration, microalbuminuria, acute kidney injury, arterial hypertension, and hyposthenuria. In the bivariate analysis, an abnormal echocardiogram result was presented more frequently in patients with SCN (84.8% vs. 54.3% p = 0.01), as well as more frequent use of nephrotoxic drugs (74.5% vs. 54.2% p = 0.07). **Conclusions:** Our findings suggest that sickle cell nephropathy may occur at an early age, where glomerular hyperfiltration is very common. Cardiopulmonary complications in patients with SCA may be related to the presence of SCN.

Keywords:
Sickle Cell Anemia;
Proteinuria;
Renal failure;
sickle cell nephropathy

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How to cite this article: Rev Chil Pediatr. 2020;91(1):51-57. DOI: 10.32641/rchped.v91i1.1274

Introduction

Sickle cell anemia (SCA) is an autosomal recessive blood disorder of high prevalence[1]. SCA is produced by mutations on chromosome 11 (11p15.4) that cause a structural alteration in the hemoglobin subunit β[1,2] and lead to the production of Hemoglobin S (Hb S)[1]. The characteristic of this hemoglobin is the formation of polymers when tissue hypoxia, hyperosmolarity, and acidosis occur, changing the membrane and deforming the red blood cells[3]. Erythrocytes with polymerized hemoglobin are rigid and crescent-shaped[2], which leads to hemolysis and recurrent vaso-occlusive crises in small-caliber vessels, generating ischemia and tissue inflammation that causes painful crises, increased susceptibility to infection, and even organ damage.

Among the complications secondary to SCA are renal complications, known as sickle cell nephropathy (SCN)[2,3]. SCN comprises both glomerular and tubular alterations, including hematuria, hyposthenuria, tubular disorders, and both acute and chronic kidney failure. These findings can appear early in the pediatric age[2-4], increasing morbidity and mortality[5]. Unfortunately, there are few studies that evaluate the presence of SCN at an early age and what risk factors are associated with its development[2]. The objective of this study is to describe the prevalence of SCN, risk factors, and its characterization in a pediatric population with SCA.

Patients and Method

Data collection

Retrospective cohort study that reviewed the electronic medical records of pediatric patients seen at the General Hospital of Medellin between 2009 and 2017. We included patients with a confirmed diagnosis of sickle cell disease with and without sickle crises who had undergone some nephro-urology study.

We evaluated the sociodemographic and clinical characteristics of the patients, the results of the hemoglobin electrophoresis test were recorded, we looked for the presence of high blood pressure (HBP) based on the American Academy of Pediatrics guidelines 2017[6], and the presence of pulmonary hypertension (PH) was verified through echocardiographic findings reported in the last year of follow-up. We considered as PH when the peak flow rate of tricuspid valve regurgitation was higher than or equal to 2.5 m/sec which indirectly corresponds to pulmonary artery pressure higher than 35 mmHg[7]. We also evaluated the pharmacological treatments administered and the need for blood products.

For the diagnosis of SCN, we used the different definitions reported in the literature[3,8], where SCN is considered as the renal involvement secondary to SCA and comprises a wide spectrum of manifestations including any of the following findings: hyposthenuria (specific gravity less than 1,010), proteinuria (higher than or equal to 30 mg/dL), hematuria (higher than or equal to three red blood cells per high-power field of a non-centrifuged urine drop), microalbuminuria (occasional urinary albumin excretion higher than 30 mg/g), altered Doppler imaging of renal vessels, renal papillary necrosis, and altered glomerular filtration rate (GFR)[2,8]. The GFR was calculated using Schwartz formula (GFR= height/Size (cm) x 0.413/plasma creatinine (mg/dL). In patients with impaired kidney function, KDIGO classification[9] was used to stage acute kidney injury (AKI). It was considered glomerular hyperfiltration an increase of GFR over 2 SD of normal for the age as follows: child aged between 6 months and 1 year 117.2 ml/min/1.73m^2, between 1 and 2 years 130.7 ml/min/1.73m^2, and aged over 2 years 145.2 ml/min/1.73m^2 [10].

Statistical analysis

Descriptive statistics were used. The qualitative variables were analyzed as proportions and absolute values and the quantitative ones were described as means and standard deviation or medians and interquartile ranges (IQR) according to data distribution. Normality was assessed using histograms, Q-Q plots, Box-plot, kurtosis, and asymmetry. Subsequently, a bivariate analysis was performed comparing patients with SCN with those without it, using the Chi-square or Fisher test according to the quantity of data in the cells. A $p < 0.05$ value was considered statistically significant. The statistical analysis was performed with the SPSS software version 25.

Ethical considerations

This study was approved by the research committee of the General Hospital of Medellín, and we followed the rules on ethical aspects of research on human beings contained in the resolution 00843 of 1993, issued by the Ministry of Health of Colombia. Also, this study was classified as research without risk for patients.

Results

During a 9-years observation, 119 patients with a confirmed diagnosis of sickle cell disease were seen at the hospital. 40 of them were excluded since they did not undergo any renal studies, remaining 79 patients. More than one hospital admission was recorded in 29 patients (136 events). The median age was 114 months (IQR 75-156) and 59.5% were men. Of the 79 patients included with a diagnosis of sickle cell disease, the elec-

trophoretic pattern was observed in 46 patients, out of which 28 (60.9%) presented Hb SS and 8 of them (17.4%) presented sickle cell trait. The electrophoretic pattern was not recorded in the remaining 33 patients with a known diagnosis of sickle cell disease.

Among the main causes of admission in this series were painful crises (84.8%), hemolytic ones (78.5%), infections (49.4%), and acute chest syndrome (33%) (Table 1). Out of the total patients, 75.9% (IQR 60-79) received red blood cell transfusion during the acute event and only six patients had a chronic hyper-transfusion regime. Among the observed complications, 12.7% of the patients presented HBP, and 34% presented some electrolyte imbalance. An echocardiogram was performed in 62 patients, out of which 59.5% (IQR 47-61) of them presented some abnormality (PH and/or ventricular dilation). Regarding the therapy used for chronic outpatient SCA treatment, 49.4% of patients received hydroxyurea.

SCN occurred in 70% of patients. The age of the first kidney complication detected was 114 months (IQR 65-157). The renal alterations observed were hyposthenuria (11.4%), hematuria (3.8%), and abnormal urine pH (5.1%). When evaluating the presence of microalbuminuria in 21 patients, it was present in 19% of them (Figure 1). The average GFR was 152 ± 36.9 mL/min/1.73m^2. Out of the patients in whom GFR was calculated, the presence of glomerular hyperfiltration was observed in 59.3% of them. Serum creatinine was measured in 73 patients, with a mean of 0.37 ± 0.1 mg/dl. AKI was observed in 10 patients, four of them were classified as KDIGO 1, two as KDIGO 2, and four as KDIGO 3. One patient presented two AKI episodes during the observation period. Out of the total of patients with AKI, serum creatinine values were normalized in 90% of the cases and in one patient, renal function was not assessed.

The SCA complications associated with the presentation type of AKI were hemolytic crisis with the need for red blood cell transfusion in all patients, vaso-occlusive crisis in nine out of ten patients, and sepsis in eight out of ten patients. HBP was observed in three out of ten patients with AKI, two of them presented with hypertensive crisis with brain and kidney as target organs, respectively. Echocardiographic changes related to SCA (PH and/or ventricular dilation) were observed in eight out of ten patients.

Table 2 shows the complications grouped according to the clinical behavior of sickle cell disease (71 patients with SCA versus eight patients with sickle cell trait). It can be seen that the presence of hyperfiltration was more frequent in patients with SCA compared with patients with trait (62.1% vs 28.6%). Additionally, the percentage of patients with altered urine sediment was lower in patients with CF compared with patients with sickle cell trait (4.2% vs 37.5%). However, due to the small number of patients in the sickle cell trait group, it is not possible to determine whether this difference is statistically significant.

In the bivariate analysis, comparing patients with SCN with those without it, there were no differences regarding distribution by sex, electrophoretic pattern, red blood cell transfusion, chronic hyper-transfusion regime, and use of hydroxyurea (Table 3). In contrast, an altered echocardiogram result occurred more frequently in patients with SCN (83% vs 53.3%, p = 0.02). Additionally, there was a trend towards higher use of

Table 1. Baseline characteristic of patients with Sickle cell anemia

Characteristic	n	
Sex men n (%)	79	47 (59.5%)
Weight median (IQR)	79	25.5 kg (18-31)
Height median (±SD)	79	126.4 cm (± 21.1)
Age at SCA diagnosis median (IQR)	79	15.5 meses (8-48)
Age at SCN median (IQR)	55	114 meses (75-156)
Hemoglobin electrophoresis pattern n (%)	46	
Hb SS		28 (60.9%)
Hb SC		5 (10.9%)
Hb SB+		4 (8.7%)
Hb SD		1 (2.2%)
Sickel cell trait		8 (17.4%)
Blood transfusion n (%)	79	60 (75.9%)
Chronic hyper-transfusion regime n (%)	79	6 (7.7%)
Painful crises n (%)	79	67 (84.8%)
Hemolytic crises n (%)	79	62 (78.5%)
Sepsis n (%)	79	39 (49.4%)
Acute chest syndrome n (%)	79	26 (32.9%)
CVA n (%)	79	6 (7.6%)
Splenic sequestration n (%)	79	3 (3.8%)
Other complications n (%)	79	25 (31.6%)
Echocardiogram n (%)	61	
Normal		14 (23%)
Abnormal		47 (59.5%)
High blood pressure n (%)	79	10 (12.7%)
Hemoglobin media (±SD)	79	7.5 mg/dL (± 1.97)
Creatinine media (±SD)	79	0.37 mg/dL (± 0.10)
BUN median (IQR)	79	8 (5.9-10.0)
GFR media (±SD)	79	152.4 mL/1.73 m^2/min (± 36,9)
Renal replacement therapy (%)	79	0 (0%)
Death n (%)	79	0 (0%)

SCA: sickle cell anemia; SCN: sickle cell nephropathy; CVA: Cerebrovascular accident; GFR: glomerular filtration rate; Hb: hemoglobin; BUN: blood urea nitrogen.

nephrotoxic drugs in patients diagnosed with SCN (74.5% vs 54.2%, p = 0.07). During the follow-up period, no patients presented chronic kidney disease or need for renal replacement therapy, neither were any deaths reported.

Discussion

This study retrospectively evaluated a cohort of 79 patients diagnosed with SCA, finding a 70% prevalence of SCN, defined as the kidney affectation secondary to SCA that appears with both tubular and glomerular alterations[2,3,8]. The most frequent renal alterations were glomerular hyperfiltration, microalbuminuria, HBP, and AKI.

Current recommendations suggest kidney disease screening from the age of 10 years[11], which contributes to the low detection of SCN during childhood. However, other authors suggest starting screening at an earlier age[12,13]. In our series, the mean detection age of the first renal complication was 114 months (IQR 65-157), similar to that reported in previous studies where the age of detection was between 7 and 9 years of age[12,14]. However, there are reports of early-onset renal complications such as glomerular hyperfiltration diagnosed at 13 months[15] or microalbuminuria at 2.8 years[5,12].

Regarding the electrophoretic pattern, in 33 patients with previous SCA diagnosis and clinical profile compatible with SCA (frequent vaso-occlusive and hemolytic crises, and high transfusion requirement), the result of it was not recorded which represents a limitation of this study. The small size of the groups of patients with SCA and sickle cell trait does not allow us to say that there is a difference in the outcome of SCN. A recent systemic review of patients with sickle cell trait reported no association with kidney complications in the included pediatric studies, but a positive association with proteinuria and chronic kidney disease in adults with sickle cell trait[16].

In addition, some studies report a higher incidence of some manifestation of SCN or younger-onset age in patients with an Hb SS[12,14] electrophoretic pattern. These patients present a more aggressive course of sickle cell disease due to target organ damage secondary to frequent vaso-occlusive crises[8]. A study in the Republic of Congo reported a 30.8% prevalence of glomerular hyperfiltration in children with Hb SS compared with 6.1% in the Hb AA group[17]. In our series, 63.6% of the patients with SCN had electrophoretic Hb SS pattern.

Glomerular hyperfiltration has been described as an early marker of kidney involvement, which contributes to glomerular damage and the development of kidney disease. Among the physiopathological mechanisms, it has been proposed that chronic anemia initially causes renal vasodilation with the consequent hyperperfusion and glomerular hyperfiltration[8], in addition to the polymerization of Hb S in the renal medulla[18]. We observed that 59.3% of the patients presented glomerular hyperfiltration, similar to that reported by King et al (50.8%)[12]. In a study of kidney disease screening in 206 children with SCA, glomerular hyperfiltration was present in 84.95% of them and there was a 92.5% prevalence of Hb SS[14]. It has been described in the literature that Schwartz formula may overestimate GFR and consequently increase the prevalence of glomerular hyper-

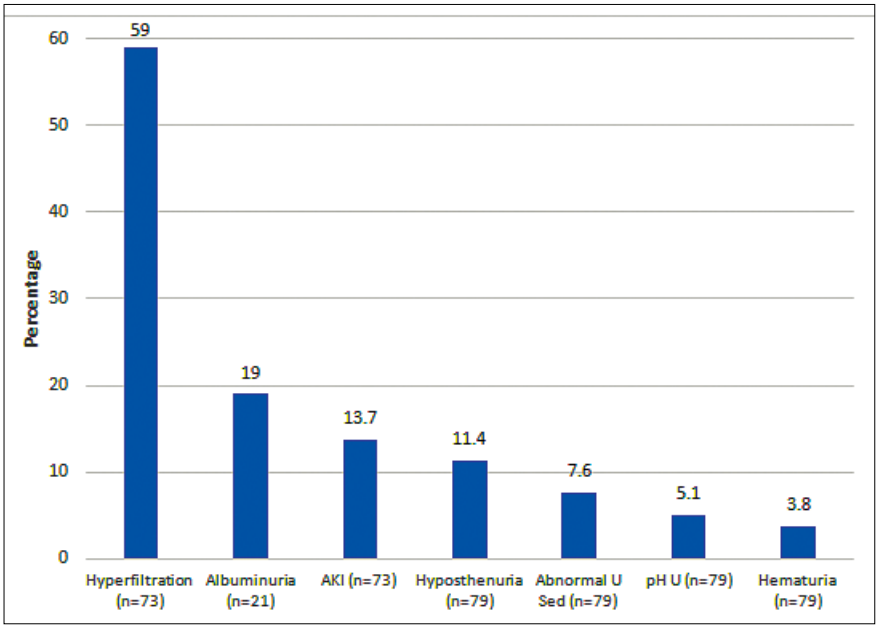

Figure 1. Kidney complications in patients with Sickle cell anemia. AKI: acute kidney injury; U Sed: urine sediment; pHU: urine pH.

Table 2. Complications in SCA patients according to the clinical characteristics of the disease

Characteristic		Sickle Cell Anemia (n = 71)	Sickle Cell Trait (n = 8)
Sickel cell nephropathy	(n = 79)	49 (69%)	6 (75%)
Glomerular hyperfiltration	(n = 73)	41 (62.1%)	2 (28.6%)
Albuminuria	(n = 21)	4 (2.2%)	0 (0%)
AKI	(n = 73)	9 (13.8%)	1 (12.5%)
Hyposthenuria	(n = 79)	9 (12.7%)	0 (0%)
Abnormal U sed	(n = 79)	3 (4,2%)	3 (37.5%)
Abnormal urine pH	(n = 79)	4 (5.6%)	0 (0%)
Hematuria	(n = 79)	3 (4.2%)	0 (0%)
HBP	(n = 79)	8 (11.3%)	2 (25%)
Abnormal echocardiogram	(n = 62)	42 (75%)	5 (83.3%)

AKI: acute kidney injury; U Sed: urine sediment; HBP: High blood pressure.

Table 3. Bivariate analysis, according to Sickle cell nephropathy presence

Variable		Sickle cell nephropathy (n = 55)	Sickle cell nephropathy absent (n = 24)	p value
Sex men	n (%)	32 (58.2%)	15 (62.5%)	0.72
Hb SS (n = 46)	n (%)	21 (63.6%)	7 (53.8%)	0.76
Blood transfusion n (%)	n (%)	44 (80%)	16 (66.7%)	0.20
Chronic hyper-transfusion regime	n (%)	5 (9.3%)	1 (4.2%)	0.44
Abnormal echocardiogram (n = 62)	n (%)	39 (83.0%)	8 (53.3%)	0.02
Hydroxyurea chronic therapy	n (%)	29 (52.7%)	10 (41.7%)	0.37
Nephrotoxic drugs	n (%)	41 (74.5%)	13 (54.2%)	0,07

Hb: hemoglobin.

filtration[2]. However, studies conducted in infants with SCA where GFR was calculated through DTPA renal scan, also reported glomerular hyperfiltration[4,15,19].

Regarding other risk factors for SCN, we found that 74.5% of SCN patients received some nephrotoxic drugs. This finding was similar to that reported in a study of 305 children with SCA where the use of NSAIDs was associated with microalbuminuria, (ibuprofen OR 2.3 95%CI 1.4-3.8 p = 0.001, diclofenac OR 2 95%CI 1.2-3.4 p = 0.01)[20]. Another study conducted in 197 pediatric patients with SCA reported an increased risk of AKI in patients who received ketorolac (OR 1.63 95%CI 1.08-2.47)[21]. This finding is explained by the fact that NSAIDs inhibit the prostaglandins action since this blocks the compensatory vasodilation response to ischemia and vasoconstriction leading to a further decrease in renal blood flow during vaso-occlusive crises[21-23].

An incidence between 5% and 18% of AKI has been described in the literature which is multifactorial and self-limiting but associated with higher mortality, multiple organ failure, and longer hospital stay[21,22,24]. Recently, the presence of AKI was assessed in pediatric patients with SCA and vaso-occlusive crisis[21], where AKI appeared in 17% of them. In our study, the prevalence of AKI was 13.7%, and all events occurred during a hemolytic crisis. Among the possible explanations for this association is volume depletion, which is present in patients with hemolytic crises that can lead to an AKI[22].

There is a 24.4% prevalence of PH in children with SCA[25], and it is associated with higher frequency of hemolytic crises, hypoxemia, acute chest syndrome[26], acute CVA, and higher mortality[27]. In our study, the presence of PH and/or ventricular dilation was observed more frequently in patients with SCN. The concomitance of cardiovascular complications and SCN due to hemodynamic changes produced by hemolysis, anemia, chronic hypoxemia, and, subsequently, vasculopathy, is an interesting association described in

adults[27,28] which has not been previously reported in pediatrics. Future studies should explain the reasons for this association.

Limitations

Since this is a retrospective study, exclusion of those patients without complete nephro-urology studies may under- or overestimate the presence of SCN. Also, the unavailability of hemoglobin electrophoresis in the entire evaluated cohort limits the role of the study. There are also limitations arising from conducting a single-center study. We believe that prospective multicenter studies are needed to further evaluate SCN in the pediatric population.

Conclusions

The data available in this cohort of pediatric patients with SCA diagnosis suggest that SCN may occur frequently before the age of 10, as suggested by other authors. We recommend screening for SCN at an earlier age, especially in patients with Hb SS electrophoretic pattern, frequent sickle cell crises, or in the presence of PH-type cardiopulmonary abnormalities and ventricular dilation, which may be associated with SCN.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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