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Renal Involvement in Patients with SS and SC Sickle Cell Disease Followed at the Clinical Hematology Department of Aristide Le Dantec Hospital

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Abstract

Introduction: Renal complications are frequent and often early in patients with major sickle cell syndromes. However, the existing literature on this topic remains limited. The aim of this study was to screen for renal abnormalities and to describe the epidemiological, clinical, and paraclinical profiles of SS and SC sickle cell patients followed at Aristide Le Dantec Hospital (HALD). **Patients and Methods:** This was a cross-sectional, descriptive, and analytical study conducted over five months in the Clinical Hematology and Nephrology departments at HALD. All regularly followed SS and SC sickle cell patients were included. Each patient underwent a full clinical examination, urine dipstick test, and serum urea and creatinine measurement. Renal ultrasound was systematically performed. Data were analyzed using SPSS version 18. **Results:** Thirty-two patients were screened. Sixteen patients had renal involvement, representing a hospital prevalence of 50%. The average age of the patients was (32.21 ± 12.29) years with a sex ratio of 0.77. Fourteen patients (87.5%) were SS and two (12.5%) were SC. Clinically, six patients (37.5%) were hypertensive, twelve (75%) had clinical anemia, and two patients (12%) had renal-type edema. Fourteen patients (87.5%) had proteinuria ≥ 0.5 g/24h. Leukocyturia and hematuria were found in 36.4% and 12.5% of cases, respectively. Four patients had renal failure, including one at stage 4. Renal biopsy was performed in four patients and revealed focal segmental glomerulosclerosis in one patient, minimal change disease in two patients, and glomerular congestion in one patient. High blood pressure was the only poor prognostic factor found in

our study. **Conclusion:** Our study supports international recommendations for the systematic screening of renal abnormalities in sickle cell patients with urine dipstick testing and GFR estimation. The high prevalence in our study necessitates early screening and management strategies for patients with major sickle cell syndromes.

Keywords

Proteinuria, Renal Failure, SS Sickle Cell Disease

1. Introduction

Sickle cell disease is an autosomal recessive hereditary disorder caused by a hemoglobin abnormality resulting from a substitution of glutamic acid by valine. This abnormal hemoglobin (HbS) is responsible over time for numerous complications, including renal involvement [1]. Approximately 300 million people worldwide carry S gene mutation [2], with a prevalence ranging from 10% to 40% in Africa [3]. In Senegal, a 2003 study involving 36 homozygous SS sickle cell patients revealed that 19.4% had chronic kidney disease (CKD) [4], and another study in 2011 reported a prevalence of 54.5% [5]. HbS polymerization is the key pathophysiological event in sickle cell nephropathy, occurring during cellular or tissue hypoxia, oxidative stress, or dehydration. The mutated beta-globin chains of the HbS molecule form tetramers, altering RBCs into crescent or sickled shapes with increased rigidity [6]. The renal medulla is the primary site of injury in sickle cell nephropathy, where the vasa recta are exposed to a uniquely hypoxic, acidic, and hypertonic environment. These factors promote sickling, leading to vascular congestion, ischemia, infarction, and chronic loss of glomerular and tubular function. Sickling in the vasa recta also impairs countercurrent exchange, causing reduced urine-concentrating ability (hyposthenuria), which can present as polyuria and nocturia, even in childhood [7]. Moreover, free heme release during hemolysis induces oxidative stress through reactive oxygen species generation, lipid peroxidation, and depletion of antioxidants such as glutathione, affecting HMOX1 and SOD2 activity. Inflammatory pathways play a significant role, involving leukocyte adhesion through VCAM-1 and ICAM-1; activation of proinflammatory cytokines, such as TNF-α, IL-1β, and IL-6; and complement system activation [8]. In summary, Sickle cell nephropathy is caused by a multifactorial etiology involving genetic, molecular, and cellular mechanisms. HbS polymerization [9], hemolysis-induced endothelial dysfunction, endothelial activation and inflammation, several genetic modifiers (variants in APOL1, MYH9, HMOX1, HBA1, and HBA2), medullary ischemia, early glomerular hypertrophy and hyperfiltration [10]. Few comprehensive studies have been conducted on renal involvement in sickle cell disease in Senegal. Therefore, we conducted this study to screen for renal complications in SS and SC sickle cell patients followed in the clinical hematology department of Aristide Le Dantec Hospital (HALD), and to describe their epidemiological,

clinical, and paraclinical characteristics, as well as identify associated risk factors.

2. Patients and Methods

This was a cross-sectional, descriptive, and analytical study conducted from July 1st to November 30th, 2016, in the Nephrology Department of HALD. All regularly followed SS and SC sickle cell patients were included. Written informed consent was obtained from all patients or their legal guardians. Data were collected using a standardized form that included sociodemographic information (age, sex, marital status, ethnicity, residence, education level, occupation) and medical history (age at diagnosis, type of sickle cell disease, number of vaso-occlusive crises per year).

All patients underwent a full clinical examination, urine dipstick testing, serum urea and creatinine measurement, and renal ultrasound to assess kidney size and differentiation. GFR was calculated using the MDRD formula.

Twenty-four-hour proteinuria was performed in patients with dipstick proteinuria ≥ 2+. Urine microscopy was performed for patients with hematuria or leukocyturia, and urine culture was done when nitrites or leukocytes were detected. Therapeutic aspects were noted.

Operational definitions included:

- Proteinuria was considered significant when it was greater than two crosses on the urine dipstick test and ≥0.5 g/24h on quantitative measurement.
- Leukocyturia was considered significant when it was greater than one cross on the urine dipstick test and >10,000/ml on hemogramme.
- Hematuria was considered significant when it was positive on the urine dipstick test and >10,000/ml on hemogramme.
- CKD was defined as GFR < 60 ml/min/1.73m^2 for more than three months.
- Urine density was considered normal (eusthenuria) if values were between 1.010 and 1.030 g/ml. Hyposthenuria was defined as density < 1.010 g/ml.
- Hypersthenuria was defined as density > 1.030 g/ml.
- Urine pH was considered normal when it was between 7 and 7.5.
- Vaso-occlusive crisis is a painful episode that ranges from mild to severe and can occur in any part of the body, but commonly affects the extremities, back, and chest.

Data were analyzed using SPSS v18. Means and percentages were compared using Student's t-test, chi-square test, or Fisher's exact test where applicable.

3. Results

Forty-five records were reviewed, of which 13 were excluded. A total of 32 patients were included, 16 of whom had renal involvement, representing a prevalence of 50%. The mean age of patients with renal involvement was (34.18 ± 11.66) years (range: 14 to 58 years). The 40 - 49 age group was the most represented at 31.3%. Among the 16 patients with renal involvement, 9 were women (56.3%) and 7 were men (43.7%). In the population of patients with renal involvement, 14 were SS (87.5%) and 2 were SC (12.5%). Clinically, two patients (12%) had renal-type

edema, 6 (37.5%) were hypertensive, and 12 patients (75%) had mucosal pallor. Two patients had macroscopic hematuria (12.5%). Of the 16 patients with renal involvement, 12 (75%) had proteinuria greater than two crosses on the urine dipstick test. On the urine dipstick test, 11 patients (68.8%) had leukocyturia with two crosses, and 8 patients had microscopic hematuria (Table 1).

Table 1. Clinical results.

Clinical Parameters	Effective	Percentage
Edema	2	12.00
Hypertension	6	37.50
Clinical anemia	12	75.00
Macroscopic hematuria	2	12.00
Proteinuria on urine dipstick test	12	75.00
Leukocyturia on urine dipstick test	11	68.80
Microscopic hematuria on urine dipstick test	8	50.00

Biologically, all patients with renal involvement had biological anemia. The average proteinuria was (1.98 ± 1.99) g/24h. A total of 14 patients (87.5%) had proteinuria ≥ 0.5 g/24h. Leukocyturia was positive in 4 patients (36.4%) with an average of 110,593.27 ± 265,333.40. On the urine dipstick test, 8 of the 16 patients had microscopic hematuria. The average urine pH was 6.03 ± 0.56 (range: 5 to 7.50). Fifteen patients (93.8%) had a pH < 7, and one patient had a pH > 7.50 (6.3%). According to the MDRD formula, the average GFR in the study population was 105.56 ml/min/1.73m^2 body surface area ± 58.10 (range: 19 to 202) (Table 2).

Table 2. Biological results.

Biological Parameters	Effective	Percentage
Anemia	16	100
Proteinuria	14	87.5
Leukocyturia	4	25.0
Microscopic hematuria	2	12.0
Urine pH < 7	15	93.8
Urine pH > 7.5	1	06.3
Renal failure	4	25.0

Nine patients (56.3%) were at stage I, including five with glomerular hyperfiltration. Three patients (18.8%) were at stage II of chronic kidney disease. Four patients had renal failure, including three (18.8%) at stage III and one (6.3%) at stage IV (Figure 1). Three of these patients are male and were all SS profile. Two are over 50 years old, one was 24 years old, and one was 17 years old.

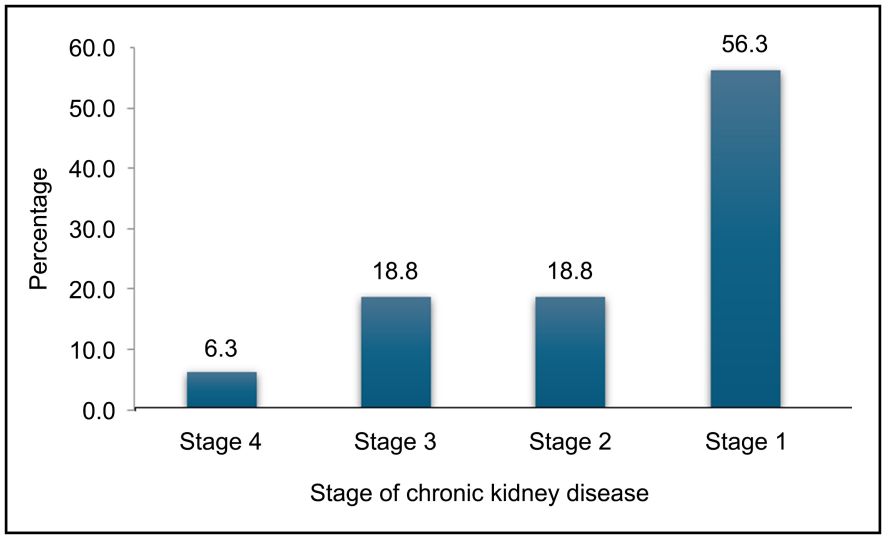

Figure 1. Distribution of patients with renal involvement according to clearance.

Renal biopsy was performed in 4 patients (25%). Indications included abundant proteinuria in two patients, isolated active urinary sediment in one patient, and abundant proteinuria associated with active urinary sediment in one patient. The biopsy revealed focal segmental glomerulosclerosis associated with moderate atherosclerosis in one patient, minimal glomerular lesion in two patients, and glomerular congestion associated with moderate atherosclerosis of the arcuate artery in one patient.

Therapeutically, fourteen patients (87.5%) received blood transfusions. All patients were supplemented with folic acid and iron. Six patients (37.5%) were on ACE inhibitors. One patient (6.3%) was on hydroxyurea.

We investigated the correlation between the occurrence of renal involvement and age, blood pressure, vaso-occlusive crises, urine pH, and hemoglobin levels (anemia). In our study, elevated blood pressure was the only risk factor associated with the occurrence of renal involvement. (Table 3)

Table 3. Correlation between renal involvement and clinico-biological parameters.

	Renal involvement		P
	Yes n (%)	No n (%)	
Age < 40 ans	10 (62.5)	12 (75.0)	0.450
Age ≥ 40 ans	06 (37.5)	04 (25.0)	
Hb < 8 g/dl	07 (43.8)	04 (25.0)	0.264
PA > 140/90 mmHg	06 (37.5)	01 (06.3)	0.033
Nomber of CVO > 1	12 (75.0)	12 (75.0)	0.999
pH < 7	15 (93.8)	15 (93.8)	0.999

4. Discussion

Studies conducted in Senegal [11], Ghana [12], and Nigeria [13] have focused on glomerular involvement and renal failure. In our study, the prevalence was 50%. This prevalence is significantly higher than that observed in other studies. This high prevalence in our study may be explained by the small cohort size and the fact that we considered all elements of the definition of renal involvement.

In our study, the average age of individuals with renal involvement was (34.18 ± 11.66) years. This relatively young age was also found in several studies conducted in the sub-region. However, in bivariate analysis, there was no significant correlation between patient age and the occurrence of renal involvement, contrary to studies by Dharnidharka and McBurney showing a correlation between age and the occurrence of renal involvement [14].

A high frequency of renal involvement found in women could be explained by the predominance of women in the global and Senegalese population, as well as the socio-economic vulnerability of women, making access to care and medication difficult.

In our study, 6 patients (37.5%) in the population with renal involvement had hypertension. Ndiaye [4] in a study conducted at CHU Le Dantec in a cohort of 36 SS patients found a prevalence of hypertension of 19.44%. This high percentage found in our study could be explained by the statistically significant correlation between hypertension and the occurrence of renal involvement ($P = 0.033$), although several studies have reported that hypertension is rare in sickle cell disease.

In our study, the average hemoglobin level in the population with renal involvement was (8.49 ± 1.52) g/dl. This result was almost similar to those of studies conducted in the sub-region. Although several studies demonstrate a relationship between the occurrence of renal involvement and low hemoglobin levels, in our study, this was not statistically correlated with the occurrence of renal involvement.

Proteinuria was present in 14 patients in our study, representing a prevalence of 43.75%. This was correlated with a proteinuria level ≥ 0.5 g/24h. Our results were relatively similar to those of Fongoro [15] and Dharnidharka [14], but higher than those of McBurney (19% proteinuria) [16] and Ranque (24.94% proteinuria) [17]. These variations in results could be explained by the threshold of proteinuria defined and retained in our study. To avoid overestimating proteinuria, we only considered a level ≥ 0.5 g/24h and eliminated urinary infection by performing urine culture.

Macroscopic hematuria was rarely found in our study (6.25%). This was not the case for microscopic hematuria, which was found in 25% of cases. This hematuria is difficult to interpret as it may indicate glomerular nephropathy or papillary necrosis. Therefore, more specific analyses could have clarified the glomerular or urological nature. However, it indicates a renal complication of sickle cell disease and should be sought in all major sickle cell patients.

Renal failure is the most frequently found complication in sickle cell disease. In our

study, according to the MDRD formula, 4 patients had a GFR < 60 ml/min/1.73m², including 3 patients (18.8%) at stage 3 and one patient (6.3%) at stage 4. No patient was at stage 5. However, other markers of renal involvement, such as glomerular hyperfiltration, proteinuria, and hematuria, were at higher percentages.

5. Conclusion

Our study supports international recommendations for the systematic screening of renal abnormalities in sickle cell patients with urine dipstick testing and GFR estimation. The high prevalence in our study necessitates early screening and management strategies for patients with major sickle cell syndromes.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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