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RESEARCH ARTICLE

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Congolese children with sickle cell trait may exhibit glomerular hyperfiltration: A case control study

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Background: The prevalence of sickle cell trait is extremely high in sub-Saharan Africa. Recent studies have reported the impact of sickle cell carriers on renal function. However, data on renal abnormalities in children with sickle cell trait in this part of the world are unknown. In this report, we assess the glomerular function of children with sickle cell trait (SCT).

Methods: A case control study was conducted to assess the glomerular function in 43 Congolese children with sickle cell trait (Hb-AS) matched for age to 65 children with sickle cell anemia in steady state (Hb-SS) and 67 normal controls (Hb-AA).

Results: There was a significant difference in the blood pressure levels between the Hb-AS group vs Hb-SS group (P<.05). The estimated glomerular filtration rate (eGFR) corrected for body surface area was increased in Hb-AS group compared to Hb-AA group, but there was no significant difference between the two groups (P=.48). At the same time, the eGFR was decreased, but no significantly so, in the Hb-AS group compared to the Hb-SS group (P=.19). The proportion of children with Hb-AS (16.3%) who had hyperfiltration was higher compared to the proportion (6.1%) found in the Hb-AA group, but lower compared to the proportion found in the Hb-SS group (30%). However, in both situations, the difference was not statistically significant. No case of proteinuria was detected in children with Hb-AS.

Conclusion: It appears that at least one of six children with SCT had hyperfiltration. The findings could form a basis for further studies on this renal physiology among SCT individuals in Africa.

KEYWORDS

children, Democratic Republic of Congo, proteinuria, renal hyperfiltration, sickle cell trait

1 | INTRODUCTION

Sickle cell trait (SCT) is a physiological condition in which individuals have one copy of normal beta globulin gene and another copy of sickle variant gene. This situation leads to the production of heterozygous Hb-AS.[1] SCT occurs commonly in the malarial regions with intense transmission.[1] This geographical location is due to the fact that the presence of Hb-AS confers a resistance to severe forms of malaria.[1,2]

In the world, it is estimated that 300 million of people have the sickle cell trait (SCT). In 2010, 5 476 407 (IQR: 5 290 779-5 679 288) heterozygous AS neonates were born in the world.[2] Different migrations have promoted the expansion of the gene in other parts of the world.[3] In United States, the sickle cell trait varies from 7% to 10% among African descendants.[4-9] The higher concentration of this sickle cell trait is found in Africa, in the Mediterranean region and the Middle

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West.[10] sub-Saharan Africa accounts for about 64% of newborns trait carriers.[2]

In the Democratic Republic of Congo (DRC), the prevalence of SCT is extremely high and the sickle hemoglobin beta globin gene is carried by 25%-30% of the population.[11] Recent population-based studies have calculated the prevalence of SCT to range from 17% to 23% in Congolese neonates and the incidence to be approximately 489 745 (IQR: 455 733-524 014) newborns per year.[2,12,13]

Sickle cell trait is considered as an asymptomatic condition with no increased morbidity and mortality in individuals.[10,14,15] The children with Hb-AS living in endemic malaria area have some resistance to falciparum malaria infection.[16,17] However, recent studies have associated complications due to the presence of the hemoglobin S.[18-23] To these complications, the kidney is also an organ of considerable impact on the clinical course of individuals with SCT.[24-26] A recent study in the United States showed that the SCT may be associated with the higher risk of kidney disease in young adult African Americans, suggesting a genetic predilection.[27,28] Individuals with SCT are at high risk due to inadequate detection of renal complications in the general population.

Despite this high prevalence of the SCT in the general population and the renal high risk in sub-Saharan Africa, information about renal complications in pediatric population with SCT are unknown. This situation presents the opportunity to investigate the early detection of these renal complications especially in children with SCT and if possible, their prevention in our midst. In this report, we assess and compare the glomerular function of children with SCT compared to normal children (Hb-AA) and children with Sickle Cell Anemia (SCA) in steady state (Hb-SS) living in Kinshasa, DRC.

2 | MATERIALS AND METHODS

2.1 | Ethical consideration

Since all participants were minors, their legal guardians provided consent for their study participation. This consent procedure was reviewed and approved by the National Ethical Committee of the Public Health School of the University of Kinshasa, Kinshasa, DRC.

2.2 | Study design and population

The study was conducted in two health facilities in Kinshasa, the University Hospital of Kinshasa (Division of Division of Haemato-Oncology and Nephrology, Department of Paediatrics) and the Sickle cell center of Yolo. These hospitals provide most of the non-private pediatrics beds in Kinshasa for sickle cell patients.

Children aged 3-18 years with sickle cell trait were selected among the family of patients with sickle cell disease regular monitoring in these two health facilities. For each case, at least one normal child (Hb-AA) and homozygous sickle cell child (Hb-SS) matched for age, sex, and place of residence were recruited into the study. All sickle cell children (Hb-SS) were free of pain for at least 30 days not hospitalized or transfused for at least 100 days prior the study.

The following clinical and laboratory information were collected and analyzed: (i) demographic characteristics, (ii) blood pressure, (iii) creatinine, uric acid, and urea, and (iv) proteinuria.

2.3 | Data and sample collection

The following formula was used to estimate the minimum size of the study population: $n=Z^2pq/d^2$. n=sample size; Z=confidence level at 95% (1.96); p=proportion of the target population with microalbuminuria. There was no previous renal data in pediatric population with SCT in Africa. However, the chronic kidney disease prevalence of 1.5%, found recently among high school students of Kinshasa, was the reference value for this study.[29] q=proportion of the target population without the characteristic of the study population (0.985) and d=degree of accuracy (0.05). The minimum sample size was estimated at 22 children. Each child with SCT was matched with one or two control AA-child and one or two control SS-child for age and place of residence.

2.4 | Laboratory analysis

Children were excluded by appropriate clinical and laboratory investigations when they presented prior known proteinuria, hypertension, diabetes, HIV, HCV, renal, and cardiovascular diseases. We also excluded children with previous blood transfusion in the 3 months prior to the study.

Five 10 mL of blood sample were collected in all subjects. Sickle cell screening was performed using isoelectric focusing (IEF) technique with the Multiphor II apparatus (GE Healthcare, Little Chalfont, England) at the Laboratory of Haematology of Centre Médical Monkole of Kinshasa. The separation of different hemoglobin (F, A, S, and other types of hemoglobin) was obtained after application on thin-layer home-made agarose gel containing ampholytes pH 6-8 (ref.2117-003; Pharmalyte pH 6.7-7.7; GE Healthcare).

Five milliliters of blood were drawn in EDTA tubes by venipuncture in lithium heparin specimen bottles. The plasma separated from the blood by centrifugation was used for estimation of creatinine using the endpoint Jaffe reaction, uric acid using Folin method, and urea using diacetylmonoxime. No dietary restrictions were imposed. These tests were performed in the Clinical Biochemistry Laboratory of the University Hospital of Kinshasa.

2.5 | Diagnosis of renal dysfunction

The diagnosis of glomerular dysfunction was defined as the presence of at least one of these following criteria: (i) the diagnosis of hyperfiltration, (ii) diagnosis of renal failure, and/or (iii) presence of positive dipstick. The diagnosis of chronic kidney disease was defined as an estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m^2.[30]

Blood pressure (BP) was measured in the sitting position after 5 minutes of relaxation and was measured twice in left arm using a calibrated sphygmomanometer for pediatric patients (WelchAllyn,

Hechingen, Germany) at heart level, by trained personnel. The definition of normal BP, hypertension, or hypotension had been based on age- and height-specific percentiles.[31]

Normal BP was defined as average systolic and diastolic BP below the 90th percentile for age, gender, and height. Hypertension was defined as average systolic or average systolic or average diastolic BP greater than the 95th percentile for age, gender, and height. Hypotension was defined as BP<5th percentile for age and height.

For estimated glomerular filtration rate determination, creatinine clearance standardized to body surface area (BSA) was calculated for children (<20 years) using formula of Schwartz 1976[32]: Creatinine clearance, mL/min/1.73 m²=(0.55×height, cm)/(serum creatinine, mg/dL).

Body surface area (BSA; m²) was calculated using the DuBois and DuBois formula: 0.007184×body weight (kg)^{425}×height (cm)^{725}.[33]

Hyperfiltration was defined as a GFR >140 mL/min/1.73 m².[34]

Children were considered to have renal insufficiency if their total serum creatinine concentrations were greater than upper limits of normal for age and sex established by Schwartz et al.[32] in 1976.

All children provided a first morning fresh mid-stream urine sample to detect proteins. Standard urine dipstick screening was performed using Combur® 10 (Roche Diagnostics Gmbh, D-68298 Mannheim, Germany). Patients with urine samples positive for blood, white blood cells, or nitrites were excluded. Children were considered to have proteinuria if three consecutive urinalyses were at least 1+ positive for protein. If proteinuria by dipstick was positive, the measurement of 24-hour quantitative urinary protein was obtained using Esbach method and was collected from each participant.[35]

Hyperuricaemia was defined as a serum concentration as more than 6.5 mg/100 mL.[36]

2.6 | Data management and statistical analysis

Statistical analysis was performed using the statistics software SPSS for windows (15.0 SPSS, Chicago, USA). Data are represented as means±SD when the distribution was normal and median with range when the distribution was not normal. The analysis of Student's *t*-test was used for comparisons of means. Categorical variables were compared using Fischer's exact test. A *P* value <.05 was considered significant. Patients with Hb-AS and without microalbuminuria in both HIV-infected patients and HIV-negative group were compared using Student's *t*-test or *U* Mann-Whitney test for continuous variables, and chi-square or Fisher's exact tests for categorical data.

3 | RESULTS

3.1 | Baseline characteristics of participants

In all, 175 children, of whom 43 heterozygous for the β-globin S gene mutation (Hb-AS), 67 children with normal Hb (Hb-AA), and 65 children suffering from SCA in steady state (Hb-SS), were enrolled in the study. The demographic and baseline clinical characteristics of the participants are shown in Table 1. Distributions of age, sex, weight, height, and BMI use were similar in the three groups.

3.2 | Blood pressure

In this cohort, there was no significant difference in the systolic and diastolic blood pressure levels between the Hb-AS group vs Hb-AA group (Table 2).

Hypertension was a rare event and was found in one of the children with Hb-AS and no case was found in the Hb-AA and Hb-SS groups.

3.3 | Glomerular filtration

3.3.1 | Creatinine

Creatinine was lower, but not significantly so, in the Hb-AS group than in the Hb-AA group. Creatinine was higher in the Hb-AS group than in children with Hb-SS, but the difference between the two groups was not significant (Table 3).

TABLE 1 Characteristics of the study population

Variables	Hb-AS, n=43	Hb-AA, n=67	Hb-SS, n=65	*P*
Age (y)	7.4±3.6[a]	6.7±3.2[a]	7.3±3.3[a]	.44
Weight (kg)	22.8±9.4	21.3±8.4	19.2±6.1	.70
Height (cm)	118.6±23.5	114.8±21.1	112.8±18.5	.37
BMI (kg/m²)	15.7±2.6	15.6±1.9	14.9±2.1	.07

BMI, body mass index.
[a]Age range: 2-13 y.

TABLE 2 Blood pressure according Hb status

Variables	Hb-AS, n=41	Hb-AA, n=67	Hb-SS, n=61	Hb-AS vs Hb-AA	Hb-AS vs Hb-SS
Systolic BP (mm Hg)	100.6±11.0	97.3±11.9	94.9±9.7	0.30	0.03
Diastolic BP (mm Hg)	59.8±8.5	55.8±8.3	55.8±8.3	0.16	<0.001

BP, blood pressure.

TABLE 3 Biological profile of the glomerular function in the study population

Variables	Hb-AS, n=43	Hb-AA, n=67	Hb-SS, n=65	Hb-AS vs Hb-AA	Hb-AS vs Hb-SS
Creatinine (mg/L)	0.54±0.12	0.57±0.12	0.50±0.13	0.41	0.24
eGFR (mL/min/1.73 m²)	120.0±20.5	113.7±24.5	130.5±34.1	0.48	0.19
Uric acid (mg/dL)	3.8±1.4	3.5±1.1	4.4±1.3	0.62	0.02
Urea (mg/dL)	20.9±8.6	22.9±10.1	15.3±8.3	0.50	0.006

eGFR, estimated glomerular filtration rate.

3.3.2 | Creatinine clearance

The eGFR corrected for BSA was increased in Hb-AS group compared to Hb-AA group, but there was no significant difference between the two groups. At the same time, the eGFR was decreased, but no significantly so, in the Hb-AS group compared to the Hb-SS group, (Table 3).

The proportion of children with Hb-AS (16.3%, n=43) who had hyperfiltration was higher compared to the proportion (6.1%, n=67) found in the Hb-AA group, but lower compared to the proportion found in the Hb-SS group (30%). However, in both situations, the difference was not statistically significant.

In this series, none of the children with Hb-AS or Hb-AA had renal insufficiency (<90 mL/min/m²). Only eight (12.3%) of the children with Hb-SS had renal insufficiency (<90 mL/min/m²).

3.3.3 | Proteinuria

In this series, no case of proteinuria was detected in children with Hb-AS or Hb-AA, and only one case of proteinuria was detected in a child with Hb-SS.

3.4 | Uric acid

Uric acid levels were higher, but not significantly so, in children with Hb-AS than in Hb-AA subjects. At the same time, uric acid levels were significantly lower in the Hb-AS than in the Hb-SS group (Table 3).

A higher proportion (7.0%) of subjects with hyperuricemia was found among children with Hb-AS compared to (1.5%) children with Hb-AA. A similar proportion (7.7% for Hb-SS vs 7.0% for Hb-AS) of subjects with hyperuricemia was found between the two groups of children. No case of gout was found in the three groups.

3.5 | Urea

Urea levels were lower, but not significantly so, in children with Hb-AS than in Hb-AA subjects. Urea levels were significantly lower in the Hb-AS than in Hb-SS group.

4 | DISCUSSION

The present study is the first attempt to describe and to investigate the renal abnormalities of the SCT in the pediatric population in sub-Saharan Africa. Several types of renal complications have been reported in children with SCT.[37] We studied glomerular function in children with SCT in our midst. An assessment of renal complications from SCT is required because about 18 million people in the DRC are SCT carriers and vulnerable to present these kidney injuries.

Systolic and diastolic BP levels systolic blood pressure of children with Hb-AS were similar to those with normal hemoglobin (Hb-AA). These results are in line with previous observations reported by Adams-Campbell in Nigeria that found no significant difference of blood pressure between the children with Hb-AA and children with Hb-AS.[38] Compared to children with Hb-SS, systolic and diastolic BP levels systolic blood pressure were higher in children with Hb-AS and showed significant difference between both groups. Our findings are in line with the literature that considers SCA as a possible physiopathological condition to explain the lower blood pressure in patients with the disease. The etiology of the lower blood pressure in SCA remains unclear. The literature suggests that the compensatory systemic vasodilatation to increase oxygen delivery may be a possible explanation of this condition in SCA patients.[39] However, further studies are needed to deeply investigate this assumption in pediatric population.

Hypertension was a rare event in our series. Only one child with Hb-AS was found to be hypertensive for diastolic BP. There is a gap in epidemiologic data about hypertension in pediatric population with SCT. In a previous study conducted in adult population, the presence of the gene S was discussed as a possible marker to explain the higher blood pressure in African descendants compared to Caucasian descendants in United States.[38]

The serum creatinine is influenced by muscle mass and GFR. In this study, Hb-AS was compared for age, weight, height, and BMI with the two groups. In our series, creatinine tended to be lower in children with Hb-AS than in Hb-AA subjects, but higher than in children with Hb-SS. In these both cases, there was no statistically significant difference in contrast to three previous studies conducted in Saudi Arabia, in Iraq and in Brazil in their series that found a significant difference in children with SCT compared to the other groups.[37,40,41] Additionally, it is important to specifically note the higher level of creatinine reported in the Iraqi study (0.8±0.1 mg/dL vs 0.5±0.1 mg/dL). This difference could be associated with factors influencing creatinine such as genetic predisposition but should also be related to variations in diagnostic techniques.

As the children with Hb-AS tend to have high eGFR compared to children with Hb-AA, the serum creatinine is lower than expected and may further lowered by particular renal mechanisms in SCT. A polymerization of erythrocytes with hemoglobin S may be due to the extreme hypoxemia, acidosis, hypertonicity, and the dehydration of the

erythrocyte with an increase in the concentration of HbS in the renal medulla. These conditions may transform silent SCT into a syndrome resembling to SCA.[42,43] In addition, specific genetic factors may be discussed in SCT condition and in African population such as apolipoprotein L1 (APOL 1), apolipoprotein L4 (APOL 4), and non-muscle myosin heavy chain 9 (MYH9) gene risk variants.[42,44-47] Consequently, this tendency was decreased compared to corresponding values in Hb-AA group. Thus, an interpretation of serum creatinine must be sensitive to this factor. Values at the upper end of the normal range should raise the index of suspicion for reduced renal function.

The eGFR was increased in Hb-AS group compared to Hb-AA group and decreased compared to Hb-SS group without significant difference ($P>.05$). The study conducted in Iraq by al-Naama et al.[41] found significant difference in eGFR between the groups of children with Hb-AS and normal controls with Hb-AA. In this Iraqi study, the mean age of study population is comparable to our series (7 years). We therefore speculate that BMI and associated genetic factors such as α-gene mutation status, HbF level, co-inheritance of β-thalassaemia in these population may significantly affect measured parameters and may explain this difference.

In this study, glomerular dysfunction is found to be pronounced. Hyperfiltration was present in 17% of children with Hb-AS and in 30% of children with Hb-SS. Different studies reported similar observations.[48-50] The hyperfiltration may be caused by a polymerization of hemoglobin S in the renal medulla.[42,43] Quantification of inulin clearance in a timed urine collection and nuclear medicine based techniques such as iohexol or technetium-99-m-labeled diethylenetriaminepentaacetic acid (DTPA) remain the optimal method for assessing renal function in the clinical setting and the two methods provide accurate similar results.[51-53] However, these techniques are costly and time-consuming, their feasibility for clinic-based screening of renal function is limited. Furthermore, these two procedures are not available in the DRC. The lack of the appropriate diagnostic tools remains a challenge for assessing renal function of children in resource-limited settings. Creatinine-based estimating formulas such as the Schwartz formula in pediatric population are less expensive and relatively easy to obtain, in our midst. The Schwartz formulas are noninvasive estimation of GFR and had similar correlation coefficients with the DTPA-GFR (0.3). However, these estimations have some limitations when compared with gold standard techniques. Increased creatinine secretion due to hyperfiltration or tubular dysfunction may overestimate the GFR.[54] Additionally, another bias may be an above-normal proximal tubular secretion of creatinine and decreased muscle mass found in children suffering from SCA.[55]

Persistent proteinuria should be considered as a precursor of progression to advanced stages in chronic renal failure. Proteinuria detected by dipstick was found in one child with Hb-SS cohort. This child showed clinical and laboratory evidence of secondary nephrotic syndrome. For technical reasons, we were not able to measure microalbuminuria or ratio of albumin to creatinine at the time of the study as proposed by various authors. Non-availability of appropriate diagnostic tools remains a bottleneck to be addressed when the prevalence of proteinuria in children with SCT in resource-limited settings should be assessed. The true prevalence of proteinuria was probably less than what was indicated in our result especially as the renal inability to concentrate urine occurs usually in children with SCT.[10] In this condition, reagent strip analysis probably underestimates the presence of proteinuria in this study; microalbuminuria was not done to confirm that proteinuria was present in children tested negative for proteinuria with a dipstick method. In previous studies, the prevalence of proteinuria significantly increased when microalbuminuria was assessed.[37]

In this study, uric acid levels of children with Hb-AS were similar compared to children with Hb-AA, but significantly lower compared to children with Hb-SS. This difference between children with Hb-AS and children with Hb-SS may be explained by hemolysis process, leading to increased bone marrow activity and renewal of nucleic acids in Hb-SS subjects.[56] Our observation is similar to reports from Saudi Arabia and Iraq.[40,41]

Urea level was similar between children with Hb-AS and Hb-AA. This observation is not in line with the results reported by al-Ali in Saudi Arabia and Al-Naama in Iraq.[40,41] This difference could be associated with factors influencing urea level such as genetic predisposition but should also be related to variations in diagnostic techniques. However, this value was slightly lower in children with Hb-SS than in children with Hb-AS. This trend has also been reported from a previous study in Iraq.[41]

5 | CONCLUSION

In this study, it appears that one on six children with SCT had hyperfiltration which is a major indicator of renal function disturbance. Glomerular hyperfiltration occurs early before decreased creatinine clearance and the appearance of microalbuminuria. We do neither know the consequence of this hyperfiltration, nor do we know if the estimating equations adequately predict hyperfiltration in this setting. The hyperfiltration reported here did not meet statistical significance. A limitation was the use of Schwartz equation to estimate GFR which is well known to overestimate GFR. However, the findings from this study are quite important and could form a basis for further studies on this renal physiology among SCT individuals in sub-Saharan Africa.

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AUTHORS' CONTRIBUTIONS

MNA, FLB, and NMN conceived and designed the study protocol; MNA carried out the clinical assessment; MNA, FBL, and NMN analyzed and interpreted these data. MBE and MNA drafted the

manuscript; NMN, RMN, JLGE, and RNM critically revised the manuscript for intellectual content. All authors read and approved the final manuscript. MNA is guarantor of the paper.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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