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RESEARCH ARTICLE
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The prevalence of Sickle Nephropathy among children with Sickle Cell Disease

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ABSTRACT

Background: Children with SCD might be at higher risk of progressive renal damage. Hyperfiltration and microalbuminuria are the main criteria of early sickle nephropathy. Urine albumin to creatinine ratio (ACR) is an effective screening tool for detection of sickle nephropathy.

Objective: to assess the prevalence of sickle nephropathy among children with sickle cell anemia using Urine albumin to creatinine ratio (ACR).

Methods: This study included 23 children with HbSS (SCA) and 22 patients with HbSβ0 thalassemia of age 1 to 18 years; forty-five apparently healthy children of comparable age and sex were taken as a control group. All patients were in steady state and had normal kidney functions. All subjects were subjected to full clinical assessment and urine ACR measurements.

Results: The study group showed male sex predominance (m/f ratio 3:2). They were aged 1 to 18 years old with mean age 11.0±3.5 years. Their Mean age at diagnosis was 1.33 ±1.02 years in homozygous SS patients and 1.46 years ± 1.07 years in SB thalassemia patients. Thirty-eight (86%) patients had history of consanguineous marriage and 25 (55.5%) had similar condition in the family. The frequency of CNS vasculopathy among the study group was 20%. Microalbuminuria was present in 33.33% of all study subjects. Seven out of 23 homozygous SS children had microalbuminuria (30.4%) vs. 8 out of 22 with SB-thalassemia (36.4%). Mean ACR was twice higher in the study group compared with the control group (p = 0.002). Mean urine specific gravity was 1019.08±4.17mg/g creat in SS group vs. 1017.14±5.16 in SB thalassemia group (p=0.170). Mean A/C ratio was 25.56±20.95 mg/g among sickle SS group of patients vs. 31.09±30.91 among sickle beta thalassemia group of patients (p=0.617)

Conclusions: ACR is higher in children with SCD than in controls. Microalbuminuria is a common finding in children with SCD. Children with SB-thalassemia might be at higher risk of sickle nephropathy.

Keywords: *Sickle cell disease, Children, Microalbuminuria, Urine ACR measurements*

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INTRODUCTION

Sickle cell disease (SCD) is an autosomal recessive disease affecting various body systems, characterized by chronic hemolytic anemia, painful vasoocclusive events and organ damage. Sickle nephropathy (SN) is referred to as renal affection in sickle cell disease patients, raising the morbidity and mortality rates of these patients. Those with homozygous sickle cell disease are more likely to experience renal affection than those with trait or sickle beta thalassemia [1].

Patients with SCD should have regular yearly screening for sickle nephropathy. Long-term hyperfiltration causes proteinuria and kidney damage, which leads to glomerulosclerosis and renal failure. [2]. Children were deemed to have renal insufficiency if their total serum creatinine concentrations were higher than upper limits of normal for age.

Thus early screening for renal disease is very crucial in early detection of sickle nephropathy before disease progression (3). In this study we aimed to assess the role of albumin creatinine ratio (ACR) measurements in the detection of early sickle nephropathy in SCD children.

METHDOLOGY

This was a case-control study that included forty-five patients with SCD aged from 1 to 18 years old who presented to the Hematology Clinic for medical follow-up in the period from April 2020 to March 2021. The study group showed male sex predominance {60% males (n=30) and 40% females (n=15)}. Their mean age was 11.0±3.5 years and they were diagnosed as SCD based on conventional clinical and hematologic criteria. Their Mean age at diagnosis was 1.33 ±1.02 years in homozygous SS patients and 1.46 years ± 1.07 years in sickle beta thalassemia patients. Thirty-eight (86%) patients had history of consanguineous marriage, 25 (55.5%) had similar condition in the family. All enrolled patients were in steady state and proved to have Normal renal functions. Patients with Sickle trait, those with impaired renal functions and those with hypertension were excluded from the study. Further 45 apparently healthy subjects with matching age and sex were included and served as a control group.

An informed consent was obtained from the legal guardians before the enrollment in the study. The study protocol was approved by the Ethical Committee of Cairo University, according to the Institutional Committee for the Protection of Human Subjects and adopted by the 18th World Medical Assembly, Helsinki, Finland. Clinical data and the most recent laboratory data was collected by reviewing medical records as well as patient interviewing where detailed history-taking and thorough clinical examinations were carried out.

Thorough history taking was obtained including age, sex, diagnosis, consanguinity, other affected siblings, similar family condition, history of disease related complications e.g. Stroke , Avascular Necrosis, Pulmonary hypertension , leg ulcers, cholelithiasis…etc, history of concomitant medical conditions e.g. viral hepatitis (as HCV), age of disease onset, duration and frequency of transfusion, duration and frequency of hospitalization and history of drug therapy e.g. hydroxyurea, and type and dosage of chelation therapy received. A complete physical examination was performed for all patients by assessing anthropometric measurements, vital signs, presence of pallor, jaundice, etc..

Laboratory Examination: Urine analysis and A/C ratio: urine analysis and urinary A/C ratio were performed for all patients. Urine Samples were collected aseptically midstream sample, voided directly into a sterile container. Assessing A/C ratio; considering microalbuminuria when A/C ratio ranged from 30-300 mg/dl but if A/C ratio was >300 mg/dl gross albuminuria is considered. (4).

Other laboratory variables: including complete blood picture with blood indices, reticulocytic count, liver enzymes (ALT and AST), HCV serology, serum ferritin and lactate dehydrogenese (LDH) were retrieved from the patients' medical records.

Estimated Glomerular Filteration Rate (eGFR) Assessment: Schwartz eGFRs were calculated using the new Schwartz estimating equation (5) ,

(10) . eGFR=0.413∗(Height cm÷ Scr mgdL) or eGFR=36.2∗(Height cm÷Scr umolL).

Data was coded and entered using the statistical package SPSS version 22. Data was summarized using mean and standard deviation for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between groups were done using unpaired t test in normally distributed quantitative variables while the non-parametric Mann-Whitney test was used for non-normally distributed quantitative variables. P-values less than 0.05 were considered as statistically significant.

RESULTS

Forty five children with SCD were included in the study group. The frequency of CNS vasculopathy as evidenced by abnormal TCD findings showed that 9 patients (20%) had abnormal TCD findings and were at risk of stroke. General characteristics of the studied patients are illustrated in table 1.

TABLE 1: Laboratory Results of the studied SCD cases (n=45):

Characteristics	Study group (n=45)	
	Number	Percentage
Gender (n, %): Male Female	 27 18	 60% 40%
Genotype: Homozygous SS (SCA) Sβ thalassemia	 23 22	 51.1% 48.9%
Risk of stroke (TCD)	9	20%
TCD : Low Conditional (170-184cm/sec) High Conditional (185-199cm/sec) Abnormal (>200cm/sec)	 2 5 2	 4.4% 11.1% 4.4%
	Mean± SD	Range
Height (cm)	132.62±18.18	90-164
Weight (kg)	32.5±12.19	11-65
BMI (Kg/m2)	17.87±3.55	12.73-28.9

Other SCD related complications among the study group are shown in table (2). The most frequent complications detected among our cohort were recurrent infections (17.8%), followed by ACS (11.1%) and active HCV infection (11.1%).

TABLE 2: SCD complications among the study group:

Variable	All patients (n=45)	SS group (n=23)	Sβ group (n=22)
Acute chest syndrome	(5) 11.1%	2 (8.7%)	3 (13.6%)
Pulmonary HTN	4 (8.9%)	1 (4.3%)	3 (14.3%)
Recurrent infections	8 (17.8%)	2 (8.7%)	6 (27.3%)
Avascular necrosis of the hip	6 (13.3%)	3 (13%)	3 (13.6%)
Osteoporosis & fractures	5 (11.1%)	2 (8.7%)	3 (13.6%)
Gall bladder stones	1 (2.2%)	1 (4.3%)	0
Limb weakness	1 (2.25%)	1 (4.3%)	0
HCV PCR positive	6 (13.3)	4 (17.4%)	2 (9.1%)

Laboratory data of the study population are illustrated in table (3). Almost all cases (n=44) were on hydroxyurea with doses ranging from 15 to 37 mg/kg/day and 50% were receiving iron chelator (Deferasirox) with doses ranging from 7 to 28 mg/kg/day.

TABLE 3: Laboratory Results of the studied SCD cases (n=45):

Variables	Mean± SD	Range
HB in gm/dl	9±1.42	(7-12.3)
HB S %(baseline)	67.06±14.28	(43-98)
TLC (10^3/cmm)	10.63±5.54	9.5 (6.5-13.5)
PLTs (10^3/cmm)	345.2±205.06	266 (169.5-505)
Reticulocytic count %	6.88±4.09	6.8 (3.6-9.6)
Na (mmol/L)	137.91±3.84	(130-148)
K (mmol/L)	4.44±0.48	(3.7-5.5)
Creatinine (mg/dl)	0.48±0.13	(0.27-0.90)
Serum Albumin(g/dl)	4.21±0.64	(3-5.8)
LDH(U/L)	659.04±1610.47	(200-11167)
Variables	Mean± SD	Median(IQR)
BUN (mg/dl)	10.39±4.29	9 (7-12.5)
Total serum bilirubin (mg/dl)	1.99±1.09	1.8 (1.2-2.65)
Direct Serum Bilirubin(mg/dl)	0.34±0.19	0.3(0.25-0.4)
ALT(U/L)	24.82±21.35	18 (13-28)
AST(U/L)	45.08±25.87	39 (28-48.5)
Serum Ferritin Level(ng/ml)	1107.76±778.97	900 (500-1692.5)

Renal assessment

eGFR was calculated for studied children using schwartz formula. The overall mean eGFR in was 144.58±35.89 ml/min/1.73m2 ranging from 76 to 240 ml/min/1.73m2.

Microalbuminuria was present in 15 (33.33%) children among the study group (7/23 (30.4%) with homozygous SS and 8/22 (36.4%) with SB thalassemia (fig.1). Comparative assessment of ACR measurements of the study and control Populations revealed that mean ACR was twice higher in the study group compared with the control group (p = 0.002) (Table 4, fig.2)

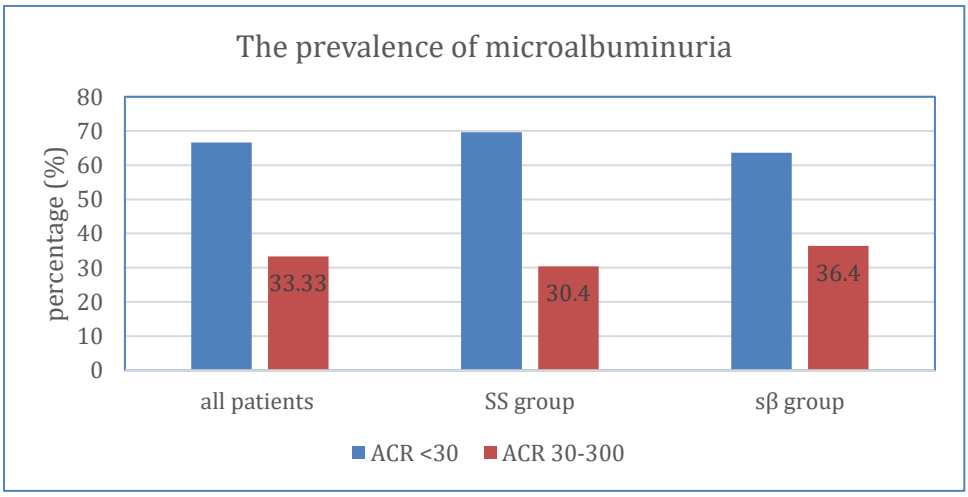

FIGURE 1: the prevalence of microalbuminuria among the study population according to genotype.

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TABLE 4: Comparison of the A/C ratio of the studied patient compared to Control group:

Variable	SCD patients group (n=45)	Control group (n=45)	Tests	
			z	P
Age (yrs): Mean±SD	11.35 ± 3.5	10.82 ± 3.68	0.702	0.485
Gender (n, %):			0.0	1
Male	27 (60%)	27 (60%)		
Female	18 (40%)	18 (40%)		
Urine ACR(mg/g)				
Mean±SD	28.27±26.14	13.33±4.82	-3.103	0.002*
Median(IQR)	18 (12-38)	14 (10-17)		

Mann Whitney test * significant < 0.05

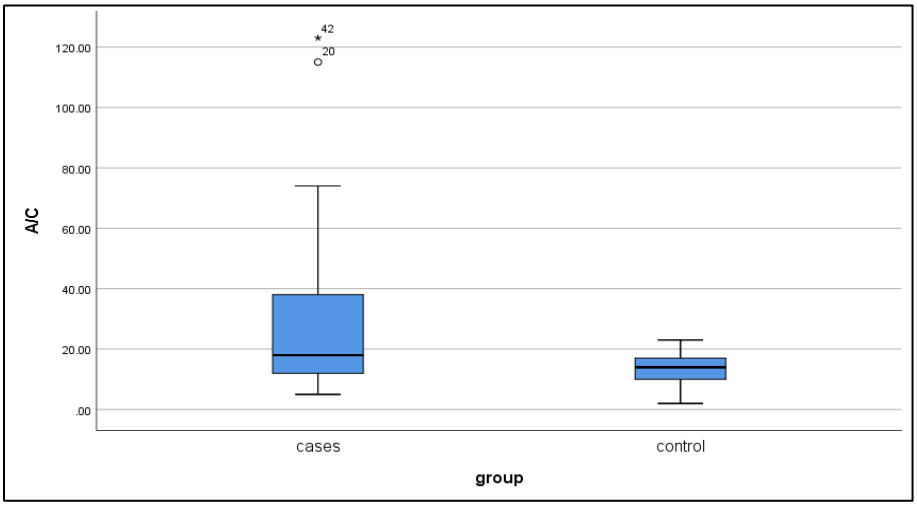

FIGURE 2: Showing A/C ratio among the cases versus control group

Mean urine specific gravity was 1019.08±4.17mg/g creat in Sickle SS group while was 1017.14±5.16 in sickle beta thalassemia group (p=0.170). Mean A/C ratio was 25.56±20.95 mg/g. among sickle SS group of patients while was 31.09±30.91 among sickle beta thalassemia group of patients (p=0.617) (Table 5).

TABLE 5: Urine analysis results among the studied group:

Variables	SS group (n=23)	Sβ group (n=22)	p-value
Urine specific gravity Mean± SD	1019.08±4.17	1017.14±5.16	0.170
Urine ACR(mg/g)	25.56±20.95	31.09±30.91	0.617
Median(IQR)	15 (12.25-34.25)	19 (12-39)	

(MW) Mann whitney test

DISCUSSION

One of the most serious complications among patients with SCD is sickle nephropathy, where hemolysis and vascular occlusion are the primary causes of this disease, which have been explained by a variety of different processes. Proteinuria and albuminuria which are among the markers for renal injury are associated with outcomes in patients with sickle nephropathy and thus helping in early detection of nephropathy before

progression to renal failure (3). In the current study we aimed to assess the prevalence of sickle nephropathy among children with sickle cell anemia using a simple and cheap tool. We studied 45 SCD patients among whom mean creatinine was 0.48(±0.13) mg/dl, denoting hyperfiltration this result matched with Thompson et al. (6) who found that serum creatinine levels were lower in patients with sickle cell disease but still within normal ranges .

In our study, mean ACR of the study group was higher compared to healthy control group. This was in agreement with previous reports (6).

The overall prevalence of microalbuminuria was 33% and based on genotype categorization, the prevalence of microalbuminuria was higher among our patients with SB thalassemia. This also was in line with a previous study (7) , (8) that showed that 47% of SCD patients enrolled in the study had microalbuminuria the majority of them had sickle cell anemia (63.2%) and the rest had sickle thalassemia (36.8%).

There are some limitations to this study: the small sample size, assessment of albumin level only once on early morning urine specimen collected from each of the participating subjects and using using Schwartz formula to calculate the estimated glomerular filtration rate (eGFR). This method overestimates GFR in SCD due to increased tubular excretion of creatinine.

In conclusion, children with SCD had higher mean ACR than healthy subjects. Microalbuminuria is a common finding in children with SCD. The prevalence of microalbuminuria in our study population was high and is similar to previous studies. Children with SB-thalassemia might be at higher risk of sickle nephropathy. Urinary albumin creatinine ratio would be a good and cheap screening tool for sickle nephropathy.

Declarations

Details of funding

None.

Declarations of interest

None

Conflicts of interest

None

Ethics approval

The study was approved by the institutional research ethics committees at Faculty of Medicine, Cairo University .

Consent to participate and publication

Written informed consent was obtained from the patients or their guardians .

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