

RENAL STATUS OF CHILDREN WITH SICKLE CELL DISEASE IN ACCRA, GHANA

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SUMMARY

Introduction: In West Africa, the prevalence of sickle cell disease (SCD) is 2%. The disease adversely affects growth, development and organ function including the kidneys. There is however a dearth of information about the renal status of SCD children in Ghana.

Objectives: To assess the renal status of children with SCD in steady state.

Design: A cross-sectional case-control study.

Setting: Paediatric Sickle Cell Clinic, Korle Bu Teaching Hospital, Accra.

Participants: Cases-357 SCD cases and 70 of their HbAA sibs as controls.

Methods: Documentation of their socio-demographic data, clinical data and dipstick urinalysis findings, and renal ultrasonography on selected participants.

Results: The mean [SD] age was 7.18 [3.15]yrs for cases and 5.16[3.28]yrs for controls. The genotypes were Hb SS (76.7%), Hb SC (21.8 %), and Hb Sp^{thal} (1.4%). Urinalysis showed leucocyturia in 12.6% versus 5.7% ($\chi^2=62.5$ and the $p=0.000$), isolated proteinuria in 2.8% versus 1.43% ($\chi^2=10.01$ and $p=0.001$) haematuria in 2.6% versus 0% ($\chi^2=9.233$, $p=0.002$) and nitrites in 2.2% versus 1.4% ($\chi^2=16.3$, $p=0.02$) of cases and controls respectively. The youngest SCD case with proteinuria was 2yrs. old. Proteinuria prevalence increased with age, occurring in 5.7% of cases aged 9-11yrs. and 20.6% of cases aged 12yrs. Two-thirds of the proteinuria cases were aged 9-12yrs., of whom 50% were aged 12yrs. Renal ultrasound findings were normal in all those examined.

Conclusion: Urinary abnormalities suggesting nephropathy occur early in SCD patients in Ghana. Routine dipstick screening at clinic visits countrywide would help early detection and prompt intervention to limit renal impairment.

Keywords: Kidney, Sickle Cell Disease, Children, and Ghana.

INTRODUCTION

Extensive research and understanding of SCD in the last century has informed management for better health outcomes.^{1,2} Early screening with appropriate follow-up and support has led to prolonged and improved quality of life. SCD prevalence in Ghana has remained at 2% and the trait 25% in the population.^{3,4} Glomerulosclerosis has been identified as the commonest renal pathology in SCD patients. Chronic renal failure (CRF), a known cause of death in adults with SCD is often the end stage manifestation of asymptomatic nephropathy in childhood.^{5,6}

Among the challenges in the management of renal complications of SCD are identifying early indicators, reducing glomerular damage and progression to end stage renal failure. Studies have been carried out in children in the sub region and beyond to assess renal status with varied outcomes depending on the indicator used.^{6,7} The relatively higher glomerular filtration rate (GFR) of children with SCD together with tubular secretion of creatinine result in low serum creatinine levels especially in sickle cell anemia patients. Thus biochemical indices like creatinine, urea and electrolytes have been essentially within the normal range in SCD children with renal complications and imminent renal failure, while proteinuria has been identified to be persistent and to increase progressively with severity of renal damage.⁷⁻⁹

Ghana's national neonatal screening program is yet to start, therefore children with the disease are diagnosed late. This means that organ impairment including renal, may already have set in before diagnosis, increasing the risk for development of disease complications leading to increased morbidity and mortality. However, there is a dearth of information on this in Ghana, hence the need for this study. This study sought to find the extent to which renal damage and impaired renal function occur in children with SCD in Ghana, using non-invasive methods.

It also sought to establish the impact, if any, of early diagnosis of sickle cell disease on renal status of patients who are on regular clinic follow-up, and the reason for the diagnosis being made in the first place.

MATERIALS, SUBJECTS AND METHODS

This was a hospital-based cross-sectional study, conducted over a 4 month period, July to November 2008 at the Department of Child Health, (DCH) Paediatric Sickle Cell Clinic (SCC), Korle Bu Teaching Hospital (KBTH), Accra. A control group was selected to provide a case control comparison for patient's selected. All patients who visited the sickle cell clinic during the study period were eligible for recruitment into the study. Those who were in steady state (defined as reporting to SCC without a fever or any acute illness) and whose parent/guardians gave written informed consent and older (>7years) children who assented to participate in the study were recruited. A sample of their siblings living in the same household within the same age range with confirmed HbAA genotype was recruited to serve as control. Following informed written consent from parents or guardians, 357 children with SCD as cases aged 1-12 yrs and 70 of their genotype Hb AA siblings as controls within the same age range were recruited by purposive sampling.

A structured questionnaire capturing demographic data, genotype, past medical history including age at diagnosis and reason for Hb electrophoresis being done was completed by one of the investigators (CO-Y). Dipstick urinalysis was conducted on freshly voided midstream urine of all recruited participants at the project site using the Combi-Screen 10SL dipstick. Renal ultrasound studies were conducted for all patients who had proteinuria on dipstick testing and a selected sample of patients who had normal urinalysis findings. The sample was selected using the first patient and subsequently every tenth patient identified with normal urinalysis results. All the ultrasound examinations were done by the same radiologist and with the same ultrasound machine. Dipstick measured protein, blood, leucocytes and nitrites in urine. Abdominal ultrasound focused on kidney texture and cortico-medullary differentiation. Ethical Clearance for the study was obtained from the Ghana Health Service Ethics Review Committee.

Data analysis

Data was entered into Access database. Statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS) for Microsoft Windows, 14th students' edition. Continuous variables like age were reported using mean and standard deviation. Bivariate analysis was reported using Chi-squared (χ^2)

and correlation coefficients were calculated for variables of interest and the significance level set at 0.05.

RESULTS

The age and sex distribution of the 427 participants, 357 cases and 70 controls, is shown in Table 1. The genotypes identified were 'SS' (76.7%), 'SC' (21.8%), 'SD' (15.4%) and S β^{thal} (1.4%). All the controls were genotype Hb AA. Of the cases 48.6% were diagnosed with SCD before their 2nd birthday, and 78.5% before their 5th birthday.

Most of them (85.7%) were diagnosed as part of investigations for an acute illness, 10.0% on a health worker's recommendation due to suggestive symptoms and 5.3% by voluntary testing. There were statistically significant differences in dipstick urinalysis findings between cases and controls (Table 2).

Patients with Hb SS phenotype were more likely to present with proteinuria, and to have leucocytes and haematuria. The inter-genotype differences however were not statistically significant. Analysis showed that HbSS cases accounted for 13/21 (57%), 37/45(71%), 6/9(66%) and 8/8 (100%) of the total cases of proteinuria, leucocyturia, haematuria and nitrites respectively among children with haemoglobinopathy.

Participants who presented with only proteinuria had no urinary tract infection by their urine culture report. Figure 1 shows the Dipstick urinalysis by genotype. The prevalence of proteinuria in SCD cases increased with age; the youngest case with proteinuria was 2 years old, and two-thirds of cases with proteinuria were aged 9 to 12 years. Of these, 50% were aged 12years. The distribution of proteinuria according to genotype is show in Figure 2There were 21 cases and 6 controls with proteinuria on dipstick testing.

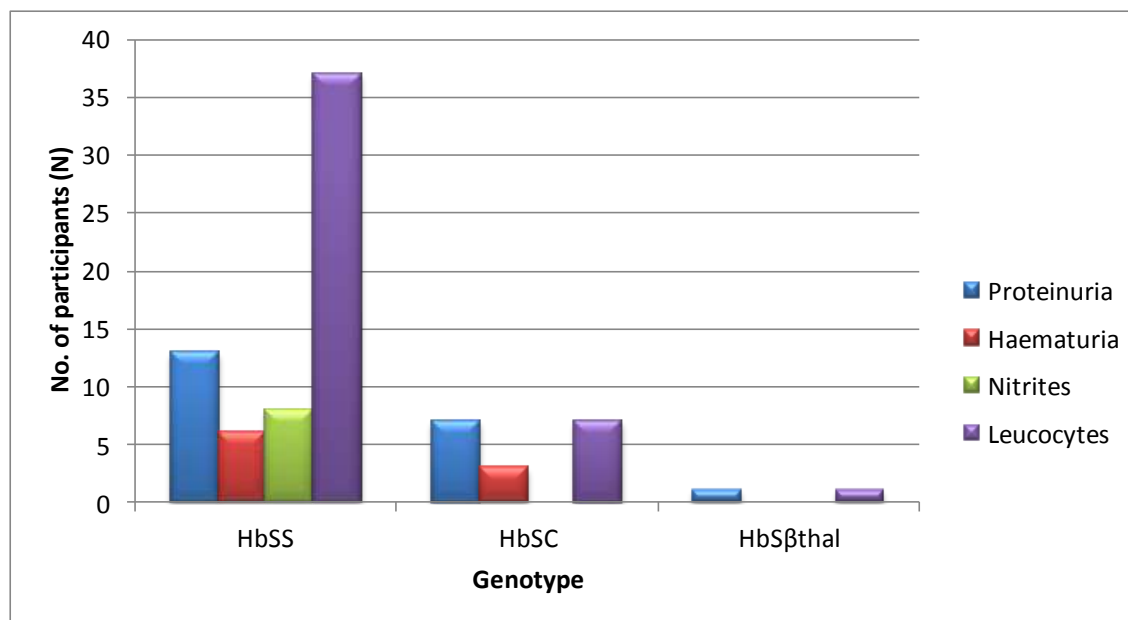
Regarding the amount of proteinuria, of the cases, 11 (52.4%) had trace proteinuria, 7 (33.3%) had 30mg/dl of proteinuria, 2 (9.5%) had 100mg/dl of proteinuria and 1(4.8%) had 500mg/dl of proteinuria. Thus 95.2% of cases with proteinuria had microalbuminuria (20-100 mg/dl); while 4.8% had macroalbuminuria(>200mg/dl). All the controls had only trace proteinuria. There was a statistically significant difference in the amount of proteinuria between the cases and controls. The study found 47.6% of cases compared with 0% controls having between 30mg and 500mg of proteinuria (p = 0.001).

Table 1 Age and sex distribution of 427 participants

Age in years	Sickle Cell Disease Cases n=357		HbAA Controls n=70		Total	
	Male n (%)	Female n (%)	Male n (%)	Female n %	Male n (%)	Female n (%)
1<2	7 (2.0)	2 (0.6)	10 (14.3)	1 (1.4)	17 (4.0)	3 (0.7)
2-<5	48 (13.4)	32 (9.0)	11 (15.7)	13 (18.6)	59 (13.8)	45 (10.5)
5-<9	67 (18.8)	63 (17.6)	9 (12.9)	15 (21.4)	76 (17.8)	78 (18.3)
9-12	66 (18.7)	72 (20.1)	8 (11.4)	3 (4.3)	74 (17.3)	75 (17.6)
Total	188 (52.7)	169 (47.3)	38 (54.3)	32 (45.7)	226 (52.9)	201 (47.1)
	$\chi^2 = 5.3, p=0.147$		$\chi^2 = 12.3, p=0.006$		$\chi^2 = 12.29, p=0.006$	

Table 2 Dipstick urinalysis findings in participants

Urinalysis findings	Cases n=357		Controls n=70		p- value
	No	(% of total)	No	(% of total)	
Only proteinuria	10	2.8	1	1.43	0.001
Proteinuria + blood only	4	1.12	0	0	0.024
Proteinuria + leucocytes only	3	0.84	3	4.29	0.000
Proteinuria + nitrite only	1	0.28	2	2.86	0.001
Proteinuria+blood+leucocytes	3	0.84	0	0	0.014
Leucocytes only	33	9.24	0	0	0.000
Blood + leucocytes only	2	0.56	0	0	0.145
Nitrite + leucocytes only	4	1.12	0	0	0.024
Nitrite only	3	0.84	0	0	0.014
No abnormality	285	79.83	64	91.43	0.000
Total	357	100.00	70	100.00	

**Figure 1** Dipstick urinalysis findings by genotype

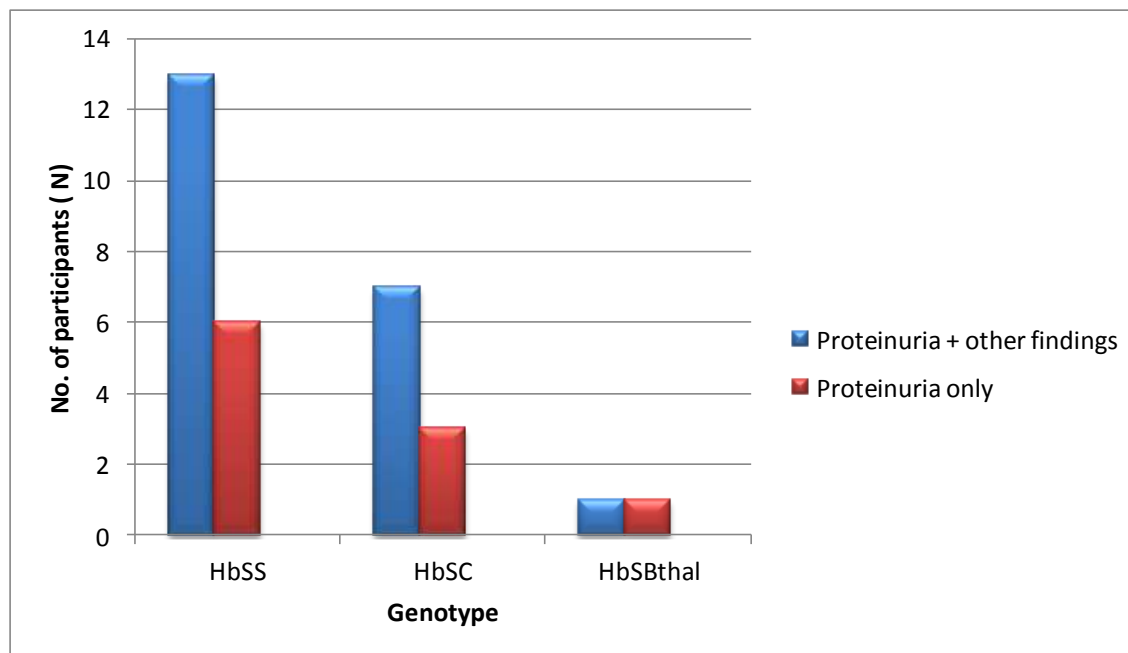


Figure 2 Distribution of proteinuria by genotype of participants

In addition, 5(83.3%) of the six controls with proteinuria had other findings suggestive of urinary tract infection; three had leucocyturia, and two had nitrites. Their urine cultures confirmed urinary tract infections for which appropriate treatment was given. All the participants who had renal ultrasound had normal kidney sizes and cortico-medullary differentiation. There was no correlation between age at diagnosis of sickle cell disease and proteinuria ($r = 0.02$, $p = 0.76$).

DISCUSSION

A number of studies have shown that proteinuria is the earliest sign of renal disease in SCD patients.^{5,9,10} Sickle cell nephropathy is known to start in children as microalbuminuria progressing to macroalbuminuria and then subsequent decline of renal function and creatinine clearance.^{11,12} Our finding that proteinuria was more common among genotype HbSS than HbSC cases is in keeping with that of other studies.^{5,12} The prevalence of proteinuria in the SCD patients in this study was observed to increase with age and the increase was significant after 9 years of age as others have found^{12,14,15}. Our prevalence 9.4% was lower than the 14.3% found by Datta et al 2003¹² or the 24% found by McBurney in 2002.¹⁴ However, our highest prevalence was 21.1% among children aged 12years, and this age actually accounted for one third of the children with proteinuria. We therefore speculate that including older children in the study may have increased the prevalence of proteinuria to within the higher range recorded by these workers.

Severity of Proteinuria in SCD patients

In terms of severity of proteinuria the majority had microalbuminuria. This is consistent with the findings of Alvarez and colleagues.¹¹ They however had a higher proportion (17.4%) of their patients with macroalbuminuria and the upper- age- limit was 18 years. Our lower upper- age- limit of 12 years may account for the disparity in proportions since proteinuria from sickle cell nephropathy, like diabetic nephropathy, worsens with age. The younger the age-group, the more likely it is that one will observe more microalbuminuria. Our finding that proteinuria in the controls was only trace and that all but one of the controls who had proteinuria also had other signs of urinary tract infection suggests that proteinuria in these controls was due to infection and not intrinsic renal pathology, unlike the SCD cases.

Haematuria

It was not surprising that haematuria was encountered in a similar proportion of HbSS 3.3% of the total number of patients and HbSC (2.2%) of the total number of cases and no controls, as unlike proteinuria, this manifestation tends to appear in equal proportions in both genotypes.^{5,19} This is understandably so since the inner medullary sickling and papillary necrosis that is the cause of this phenomenon occurs in all who carry the Hb S gene. As expected none of the participants with genotype AA presented with haematuria. Interestingly none of the patients with $S\beta^{thal}$ had haematuria. This could be because of the small number of cases patients with $S\beta^{thal}$ in the study.

Leucocytes and nitrites

Asymptomatic urinary tract infection may be cause for concern among our patients. Leucocytes and nitrites, known indicators of potential urinary tract infection, were present in more SCD patients than the controls. It is worrying that while none of these children had complained of urinary symptoms and were in fact well and in steady state at the time of the study, as many as 12.6% of them had leucocyturia compared with only 5.7% of controls, and 2.2% of them compared to 1.4% of controls had nitrites. These findings support those of other workers that asymptomatic urinary tract infection is more common among SCD patients than the general population.^{9,17,18} Asymptomatic UTI if not identified and treated early may eventually cause more renal complications. Routine dipstick urinalysis is the key to early detection and treatment to minimize these complications.

Ultrasound findings in children with SCD

All the participants who had renal ultrasound had normal kidney sizes and corticomedullary differentiation. The findings of all SCD patient kidneys duly examined by ultrasound conformed with the findings of Papadaki and colleagues¹⁹ who reported that none of their patients aged below 15 years presented with renal enlargement or poor corticomedullary differentiation. Poor cortico-medullary differentiation was observed only in those older than 15 years in that study.

Awareness of SCD in the population

It is cause for concern that a high proportion (94.7%) of patients were diagnosed as part of investigations for an acute illness or following health worker's recommendation based on suggestive symptoms. While this demonstrates that Ghanaian health workers are well sensitized about the disease, it also implies that the general populace is not. The findings highlight the need for a review of the current advocacy efforts by health and religious bodies to the population. Priority should be placed on intensified public education with emphasis on voluntary Hb electrophoresis for all and opportunities for voluntary testing provided nationwide.

Though it is noteworthy that almost 50% of children with SCD who attend our clinic were diagnosed before 2 years of age, only very early diagnosis and follow up reduce the morbidity and mortality associated with the disease as workers worldwide such as Rahimy and colleagues in Benin²⁰ and other researchers elsewhere have shown^{21, 22} Thus the value of newborn screening cannot be over emphasized. Since 85% of patients were diagnosed as part of diagnostic investigations for illness. Ghanaian children like those in USA, Nigeria, and Jamaica^{1,23,24} are presenting with their first symptoms of SCD early in life and are unfortunately suffer-

ing morbidity before diagnosis. While plans are being put in place for a national neonatal screening program for sickle cell disease in Ghana, it is important to increase the populace awareness and knowledge of sickle cell disease to empower parents to opt for early voluntary testing.

Health workers should be sensitized to recommend Hb electrophoresis instead of sickling test at every opportunity patients have to do haematological investigations, as a negative sickling test result is not synonymous with genotype Hb AA as many in the population wrongly believe. Aggressive testing will go a long way to ensure early diagnosis and early initiation of preventive measures that have been proven to improve quality of life of sickle cell disease patients.

CONCLUSION

Proteinuria at an early age in the Ghanaian child with SCD. Routine dipstick urinalysis should be in the follow-up protocol drawn for the sickle cell clinic especially for children aged 9 years and above. The implementation of the proposed newborn screening programme would help reduce the morbidity associated with renal abnormalities in these children.

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