ORIGINAL ARTICLE

Haematological and clinical profile in Nigerian sickle cell disease patients with and without chronic kidney disease

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ABSTRACT

Background: Sickle cell disease (SCD) has adverse effects on the kidneys which impact on clinical outcome.

Objectives: To study and compare some clinical and haematological profiles in SCD patients, with and without chronic kidney disease (CKD).

Methods: Prospectively, 92 SCD patients were investigated and stratified into those with CKD (creatinine clearance ≤60ml/min) and those without (creatinine clearance≥60ml/min). Socio-demographic data, clinical and haematological parameters were documented and compared in the two groups as well as with gender stratification, using the student's t-test.

Results: The crises frequency and transfusion history (in males) together with the corrected reticulocyte count (in females) were significantly different in SCD patients with CKD, compared to those without (p values<0.05).

Conclusion: Kidney disease significantly influences some clinical and haematological parameters in patients with SCD, which could impact on survival.

Keywords: *Corrected reticulocyte count, transfusion history, vaso-occlusive crises*

DISCLOSURES: NIL

INTRODUCTION

Sickle Cell Disease, SCD, is a genetic disorder which is prevalent in parts of Africa, Mediterranean, South-East Asia and Middle Eastern regions of the world.[1] The asymptomatic carrier state of the disease, HbAS, confers some protection against severe falciparum malaria infection; as such it constitutes a 'driver' in the continued presence of the sickle (S) gene in these populations.[2] Previous studies, have identified sickle cell anaemia, HbSS, and sickle haemoglobin co-existing with haemoglobin C, HbSC, as the two common presentations of SCD in Nigeria.[3,4]

The SCD patients in the course of their disease may develop crises which are usually precipitated by exaggerated intravascular red blood cell polymerization and sickling (usually with vascular obstruction). Crises are interspersed by variable periods of apparent reduction in intravascular red cell sickling, known as steady states.[5,6] Vascular occlusion is the hallmark of vaso-occlusive crises in SCD and multiple end organ damage, including chronic kidney disease, CKD, have been documented as possible complications.[7]

Kidney dysfunction in SCD represents a huge burden and a major determinant of survival.[8] Haematopoiesis in health is driven by the glycoprotein hormone erythropoietin, produced mainly by the kidneys. In kidney disease, erythropoietin level falls progressively with decline in renal function and this has profound effects on normal haematopoiesis.[9]

This study was aimed at reviewing and comparing some haematological and clinical parameters in male and female Nigerian SCD patients, with and without CKD.

METHODOLOGY

The study was prospective, over a period of 7months. Patients included confirmed consenting cases of steady state (in steady clinical conditions prior to recruitment) SCD patients. Steady state was defined as no manifest crisis for at least 4weeks after the last episode, 3 or more months after the last blood transfusion and no febrile episode for at least 2weeks. They were regular attendees of sickle cell clinic at the Haematology Out-patient Clinic of our hospital. Subjects with massive oedema or ketosis, those already on dialysis and those on drugs such as co-trimoxazole, probenicid or cephalosporins (known to reduce creatinine tubular secretion or interfere with the alkaline picrate assay (Jaffé's Reaction) for the serum creatinine assay), were excluded.[10] Ethical approval was sought and obtained from the Institution Review Board and all subjects gave informed consent.

Relevant clinical information were captured in a case record form for each participant, including the initials, age, gender, weight, hospital number, frequency of vaso-occlusive crises (VOC) in 1year, history of transfusion(s) in the preceding 2years and a brief drug history. Full Blood Count (FBC) was carried out with the aid of a sysmex coulter counting machine while reticulocyte percentage was done following standard methodology.[11]

Corrected reticulocyte count was calculated using the formula:[12]

$$\frac{\text{Observed Reticulocyte (\%) X Measured Packed Cell Volume (PCV)}}{\text{Appropriate Normal Packed Cell Volume (PCV)}}$$

A 24-hour urine collection was done for all subjects and venous blood was drawn for serum creatinine estimation. Both Urinary and Serum creatinine estimations were done using the Jaffe's Method [13] while creatinine clearance was calculated using the standard formular.[13,14] Chronic kidney disease was defined as creatinine clearance <60ml/min, following the Kidney Disease Quality Output Initiative (KDQOI) classification system, and patients were, thereafter, stratified into those with CKD (creatinine clearance <60ml/min) and those without (creatinine clearance >60ml/min) and into males and females, while their clinical and laboratory parameters were compared. [15]

The Statistical Package for Social Sciences version 17.0 (SPSS Inc. Chicago IL) and Microsoft Excel 2007 computer soft-wares were used for all data analyses. Clinical and haematological parameters were expressed as means and standard deviations and compared in the two groups of SCD patients (stratified according to gender) using the student's t-test, p-*value* <*0.05* was considered significant.

RESULTS

A total of 46 SCD patients had CKD, (12 males and 34 females). Table 1 shows the means of age, clinical and laboratory parameters in male and female patients with CKD, stratified into HbSS and HbSC haemoglobin types. The mean ages of male HbSS and HbSC patients were 27.00 years and 37.00 years, respectively, while it was 24.00 years and 32.00 years, respectively for female patients. There were no significant differences in the evaluated parameters in male and female HbSS and HbSC patients with CKD, p>0.05 (Table 1).

Table 1. Mean values of parameters (and SD) in SCD patients with CKD (*N=46*)

Parameters	**Male(N=12)**		**Female(N=34)**		**t-Test**		**p-Value**	
	HbSS(11)	HbSC(1)	HbSS(26)	HbSC(8)	M/F (HbSS)	M/F (HbSC)	M/F (HbSS)	M/F (HbSC)
Age(years)	27.00±7.13	37.00±5.02	24.00±6.44	31.88±9.00	1.26	0.54	0.22	0.61
CrCl(ml/min)	44.55±12.36	34.00±8.15	44.54±10.05	47.88±8.32	0.00	-1.57	1.00	0.16
PCV(L/L)	22.68±4.84	28.00±6.20	22.86±4.14	30.85±1.98	-0.11	-1.36	0.91	0.22
WBC(x 10^9/L)	13.31±7.67	4.20±3.14	10.92±6.11	6.14±2.31	0.89	-0.75	0.39	0.48
Platelets(x 10^9/L)	279.61 ±93.13	140.00 ±46.06	264.70 ±137.72	189.9 ±179.40	0.33	-0.26	0.75	0.80
Corrected Retics (%)	1.99±0.80	1.24±0.58	1.65±0.69	1.70±0.36	1.31	-1.22	0.20	0.26
Crises (*per year*)	3.91±1.58	3.00±1.40	3.12±1.75	2.00±1.51	1.30	0.62	0.20	0.55
Transfusion History (in 2years)	1.00±0.78	0.00±0.00	0.46±0.81	0.00±0.00	1.87		0.07	

Table 2 shows the means of age, clinical and laboratory parameters in male and female patients without CKD, stratified into HbSS and HbSC haemoglobin types. A total of 46 SCD patients (23 males and 23 females) were without CKD. The mean ages of male HbSS and HbSC patients were 25.91years and 31 years, respectively, while it was 26.06 years and 24.14years, respectively for female patients. There were no significant differences in the evaluated parameters in male and female HbSS and HbSC patients without CKD, *p>0.05* (Table 2).

Table 2. Mean values of parameters (and SD) in SCD patients without CKD (*N=46*)

Parameters	**Male(N=23)**		**Female(23)**		**t-Test**		***p-Value***	
	HbSS(22)	HbSC(1)	HbSS(16)	HbSC(7)	M/F (HbSS)	M/F (HbSC)	M/F (HbSS)	M/F (HbSC)
Age(years)	25.91±7.89	31.00±12.25	26.06±6.09	24.14±4.67	-0.65	1.19	0.95	0.29
CrCl(ml/min)	90.45±26.63	87.40±12.90	84.88±16.51	84.29±7.80	0.74	0.52	0.46	0.61
PCV(L/L)	24.93±5.01	33.04±7.92	24.79±3.08	32.63±2.31	0.10	0.11	0.92	0.92
WBC(x 10^9/L)	12.04±4.42	7.02±2.36	10.99±4.53	6.07±1.51	0.72	0.85	0.48	0.41
Platelets (x 10^9/L)	250.95 ±110.20	194.80 ±72.09	319.00 ±112.54	221.42 ±168.82	-1.86	-0.33	0.07	0.75
Corrected Retics. (%)	2.10±0.54	1.65±0.70	2.30±0.82	1.74±0.54	-0.91	-0.24	0.37	0.81
Crises(per year)	2.86±1.70	1.20±1.10	2.38±1.26	1.43±0.98	0.97	-0.38	0.34	0.71
Transfusion history(in 2 years)	0.41±0.59	0.00±0.00	0.44±0.63	0.14±0.38	-0.14	-0.83	0.89	0.14

ABBREVIATIONS *CrCl - Creatinine clearance*

PCV - Packed cell volume
WBC- White cell count
Corrected Retics – Corrected reticulocyte count
M/F – Male/Female

A total of 12 male SCD patients had CKD while 23 did not (Table 3). There were statistically significant differences in the means of creatinine clearance, frequency of crises and transfusion history in male patients with and without CKD ($p<0.05$, Table 3). There were no significant differences in the means of PCV, WBC, platelet count and corrected reticulocyte count in the two population of patients ($p>0.05$, Table 3).

Table 3. *Comparison of means and SD of parameters in Male SCD patients with and without CKD (N=35)*

Parameters	CrCl < 60(12)	CrCl > 60(23)	t-Test	*p-Value*
CrCl (ml/min)	43.67±12.18	89.89±24.50	-6.17	0.00*
PCV (L/L)	23.12±4.87	26.43±6.34	-1.61	0.12
WBC(x 10^9/L)	12.55±7.78	11.11±4.54	0.73	0.47
Platelets(x 10^9/L)	268.00±97.52	240.56±105.37	0.77	0.45
Corrected Retics. (%)	1.93±0.79	2.01±0.58	-0.39	0.70
Crises (per year)	3.83±1.53	2.56±1.72	2.22	0.03*
Transfusion history (in 2 years).	0.92±0.79	0.33±0.56	2.65	0.01*

Abbreviations:
CrCl - Creatinine clearance
PCV - Packed cell volume
WBC - White cell count
Corrected Retics – Corrected reticulocyte count
**statistically significant p-value*

A total of 34 female SCD patients had CKD, while 23 did not (Table 4). There were statistically significant differences in the means of creatinine clearance and corrected reticulocyte count in female patients with and without CKD (*p<0.05*, Table 4). Correspondingly, there were no significant differences in the means of PCV, WBC, platelet count, crises frequency and transfusion history in the two population of patients (*p>0.05*, Table 4).

Table 4. Comparison of means and SD of parameters in female SCD patients with and without CKD (*N=57*)

Parameters	**CrCl < 60(34)**	**CrCl > 60(23)**	**t-Test**	**p-Value**
CrCl (ml/min)	45.32±9.66	84.70±14.23	-12.46	0.00*
PCV(L/L)	24.74±5.07	27.17±4.64	-1.84	0.07
WBC(x 10^9/L)	9.82±5.83	9.49±4.47	0.23	0.82
Platelets(x 10^9/L)	289.14±149.11	247.30±136.07	-1.08	0.28
Corrected Retics. (%)	1.66±0.63	2.13±0.78	-2.49	0.02*
Crises(per year)	2.85±1.74	2.09±1.24	1.82	0.08
Transfusion History (in 2 years).	0.35±0.73	0.35±0.58	0.03	0.98

Abbreviations
CrCl - Creatinine clearance
PCV - Packed Cell Volume
WBC - White Blood Cell count
Corrected Retics – Corrected reticulocyte count
**statistically significant p-value*

DISCUSSION

Our population of SCD patients, with and without CKD appeared to represent a fairly uniform group, as no significant difference was noted in any of the evaluated parameters within the two groups, when compared by gender (Tables 1 and 2).

The means of VOC and transfusion requirements were significantly higher in male SCD patients with CKD than those without (Table 3). VOC is usually an acute event which could be triggered by recognizable stressors, including infection, dehydration, physical exertion and acidosis.[16] Subjects with CKD are known to be prone to infections, mainly due to an impairment in the humoral and cellular components of the immune system, effect of age and co-mobidities.[17] The increased risk of infection may thus account for the higher rate of VOC observed in them. More so, CKD (in the polyuric phase) may predispose to dehydration, which is a trigger for the development of crisis in SCD.

The frequency of crises is known to be higher in SCD patients with more severe disease and worse clinical outcome.[18] Our report is in agreement with this observation, as well as with the report of Platt, *et al,* in African-Americans, in which pain frequency was reported to be a predictor of early death.[19] It, therefore, may appear that pain frequency in our SCD patients with CKD may have implications on survival. This will, however, need to be confirmed by follow-up survival studies in our SCD patients with CKD.

Our observation that SCD patients with CKD had a higher transfusion history, compared to those without, was in agreement with the report of Lucio Luzzato, that identified a marked increase in transfusion requirement with the occurrence of complications in SCD.[20] The increased transfusion requirement in our population of SCD patients with CKD may be due to the fall in erythropoietin levels with the development of CKD.[9] Such increase in transfusion demand may further worsen the morbidity in these patients because of the attendant risks of iron overload and transfusion transmissible infections, which therefore, calls for aggressive management of nephropathy in SCD.

Our female SCD patients showed a significant difference in the corrected reticulocyte count between those with CKD and those without (Table 4). The blunted reticulocyte response may be due to the decline of erythropoietin in CKD, which stimulates erythropoiesis.[9] Since a similar observation was not made in male patients with and without CKD (Table 3), it would appear that our female SCD patients showed a more profound suppression of marrow response to anaemia than male patients. The reason for this discrepancy was, however, not clear from this study and could be a subject for further research.

Anaemia has been identified as a significant predictor of morbidity and hospitalization in CKD.[21,22] In recognition of this, the KDQOI recommends the evaluation for anaemia in all patients with CKD.[15] Even though our SCD patients (both males and female) with CKD had lower haematocrit than those without, these were not statistically significant (Tables 3 and 4). This is contrary to the report of Okocha, *et al*, who noted a significant decline in steady state PCV with increasing number of complications in SCD subjects.[23]

Anyaegbu, *et al*, in a report involving 74 cohorts of HbSS subjects in steady state, noted that the white cells, particularly, neutrophils, correlated well with clinical outcome.[24] Our study did show a higher WBC in male and female SCD patients with CKD, compared to those without, though this difference was not statistically significant.

Platelets have been increasingly reported to play a significant role in the pathogenesis of VOC in SCD, mainly through its interaction with cells of the endothelial wall, along with white cells and sickled red cells.[25] Some studies have even documented platelet count as a predictor of clinical outcome in SCD.[26] Even though the platelet counts appeared higher in our male and female patients with CKD, this difference was not significant (Tables 3 and 4).

CONCLUSION

The frequency of crises, transfusion requirements and reticulocyte response to anaemia showed significant variations in our SCD populations, with CKD, compared to those without. These findings have huge implications on morbidity of SCD as well as patient survival; therefore, universal screening for nephropathy (which may be done with simple and universally available tests such as urine analysis) is advocated with a view to enabling early detection and appropriate management to forestall deterioration in renal function, which tends to worsen some clinical and laboratory parameters in patients with this disease.

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