



### Correlates of Steady-State Haematocrit and Hepatosplenomegaly in Children with Sickle Cell Disease in Western Nigeria

*Correlations Entre le Taux d'Hématocrite Basal et l'Hepatosplenomégalie Chez des Enfants Présentant la Drépanocytose à l'Ouest du Nigeria*

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#### ABSTRACT

**BACKGROUND:** Sickle cell disease is a common genetic disorder in Nigeria.

**OBJECTIVES:** To determine the steady state haematocrit, liver size and spleen size in children with sickle cell disease and the factors that influence them.

**METHODS:** This was a retrospective study of children with sickle cell disorders who attended the anaemia clinic of the Children's Outpatient Department, University College Hospital, Ibadan between the years 2000–2009. Relevant data extracted from their case notes included socio- demographic variables, haemoglobin phenotype, steady state haematocrit and liver and splenic sizes. Means were compared with t-test and correlation tested with Pearson correlation. Statistical significance was set at  $p < 0.05$ .

**RESULTS:** A total of 415 (Male: female ratio 1.1:1) children were studied and 385 (92.8%) and 30 (7.2%) of the children were of haemoglobin (Hb) SS and Hb SC phenotypes respectively. Their ages ranged from 0.5–17 years with a mean (SD) of 7.3(4.4) years. Mean (SD) steady state haematocrit for children with HbSC was 28.3(4.5) % and significantly higher than 24.1 (3.7) % in HbSS. Mean steady state haematocrit was also higher in children from higher than lower socio-economic classes. There was a negative correlation of haematocrit with age, with hepatomegaly and splenomegaly. Steady state hepatomegaly occurred more frequently in HbSS than in HbSC.

**CONCLUSION:** Haemoglobin phenotype, age and socio-economic status have some modifying influences on the steady-state features of sickle cell disease in Nigerian children. In addition, increasing liver and spleen sizes seem to be related to a decreasing haematocrit. *WAJM 2012; 31(2): 86–91.*

**Keywords:** Sickle cell; steady-state; haematocrit; hepatosplenomegaly.

#### RÉSUMÉ

**CONTEXTE:** La drépanocytose est une affection génétique fréquente au Nigeria.

**OBJECTIFS:** déterminer le taux d'hématocrite basal, la taille du foie et de la rate chez des enfants présentant la drépanocytose et les facteurs influençant ces paramètres.

**MÉTHODES:** Il s'agit d'une étude rétrospective d'enfants présentant une drépanocytose suivis à la consultation pour anémie au département de soins externes de pédiatrie de l'Hôpital Universitaire d'Ibadan entre 2000 et 2009. Les données appropriées recueillies de leur dossier médical étaient : les variables socio démographiques, le phénotype de l'hémoglobine, le taux d'hématocrite basal et la taille du foie et de la rate. Les moyennes ont été comparées en utilisant le test de Student et les corrélations ont été étudiées par le test de Pearson. Les tests étaient statistiquement significatifs pour  $p < 0.05$ .

**RÉSULTATS:** Au total 415 enfants ont été étudiés avec un sex ratio masculin: féminin de 1,1:1 ; l'hémoglobine avait le phénotype HbSS dans 385 cas (92.8%) et HbSC dans 30 cas (7.2%). L'âge variait de 0.5 à 17 ans avec une moyenne de 7,3 ans (écart type: 4.4). Le taux moyen (écart type) d'hématocrite à l'état basal de 28.3% (4.5) chez les cas d'HbSC était significativement plus élevé que chez les cas d'HbSS avec 24.1% (3.7). Le taux moyen d'hématocrite à l'état basal était aussi plus élevé chez les enfants de couches socio économiques favorisées que chez ceux des couches socio économique défavorisées. Il y'avait une corrélation négative entre le taux d'hématocrite d'un côté et l'âge, l'hépatomégalie et la splénomégalie de l'autre. Une hépatomégalie à l'état basal était plus fréquente en cas d'HbSS qu'en cas d'HbSC.

**CONCLUSION:** Le phénotype de l'Hémoglobine, l'âge et le statut socio économique modifient le taux basal d'hématocrite chez les enfants présentant une drépanocytose au Nigeria. En plus, une augmentation de la taille du foie et de la rate semble être liée à une baisse du taux d'hématocrite. *WAJM 2012; 31 (2): 86–91.*

**Mots clés:** Drépanocytose; état basal; hématocrite; hépatosplenomégalie.

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Abbreviations:

## INTRODUCTION

The term sickle cell disease (SCD) covers a group of genetically inherited conditions in which pathology may be attributed to the presence of sickle haemoglobin. The five principal genotypes of sickle cell disease are homozygous sickle cell disease (SS disease), sickle cell haemoglobin C disease (SC disease), sickle cell- $\beta^0$  thalassaemia ( $S\beta^0$  thalassaemia), sickle cell- $\beta^+$  thalassaemia ( $S\beta^+$  thalassaemia) and sickle cell  $\beta^+$  thalassaemia ( $S\beta^+$  thalassaemia).<sup>1</sup> It is particularly common among people whose ancestors come from sub-Saharan Africa, India, Saudi Arabia and Mediterranean countries.<sup>2</sup> The predominant variant of sickle cell disease in Nigeria is SS disease or haemoglobin SS (HbSS) which is estimated to be by the World Health Organization to have a prevalence of about 20 per 1000 live births. This translates into about 150 000 children born annually with sickle-cell anaemia in Nigeria.<sup>2</sup>

Sickle cell disease is characterized by chronic haemolytic anaemia and the clinical course of affected children is typically associated with intermittent episodic acute events, often referred to as "crises".<sup>3</sup> However, persons suffering from sickle cell disease are not ill most of their lives but rather in a steady-state. It is important to have knowledge of the steady state profile of these patients for a number of reasons. Steady state data provide a baseline status that could be useful in describing the usual clinical course of the illness and therefore also in defining perturbations caused by intercurrent complications. In this context, baseline data are therefore required to inform evidence-based decisions regarding appropriate management of children with sickle cell disease. Baseline data are also useful in counselling with caregivers about the clinical course of the condition and in comparing similar information from other populations.

Reports on the steady state profile and the factors that influence them are few.<sup>4,5</sup> Clinical reports on children with sickle cell disease in Nigeria focus mainly on complications of the condition.<sup>6</sup> Also, the few available reports that make

reference to some steady state features have been largely limited to HbSS children, excluding those with HbSC.<sup>4,5</sup> The objectives of this study were therefore to determine the steady state haematocrit and to describe the pattern of clinical hepatosplenomegaly in children with sickle cell disease including those with HbSS and Hb SC. The influences of age, sex, haemoglobin phenotype and socio-economic class on the above listed steady state features were also studied.

## SUBJECTS, MATERIALS AND METHODS

This was a retrospective study of children with sickle cell disease aged less than 18 years seen at the Children's Outpatient Clinic of the University College Hospital, Ibadan, Nigeria between the years 2000 and 2009. Haemoglobin phenotype of all patients was established by haemoglobin electrophoresis at a pH of 8.6 at the haematology laboratory of the hospital. It involved data extraction from case notes of children aged 0 to 17 years and entry onto case record forms. Demographic variables extracted included age, sex and educational levels and occupations of their parent. The families were classified into socio-economic groups using a combined score derived from the occupation and maximum educational level of both parents (or their substitutes) as described by Oyedeji.<sup>7</sup>

Clinical and laboratory data obtained were haemoglobin phenotype, steady-state haematocrit and steady state liver and spleen sizes palpable below the costal margins. The liver size was measured along the mid-clavicular line and the splenic size along the longest axis. Routinely, haematocrits and liver and spleen measurements are taken on every clinic visit in our centre. Steady-state observations used for this study were those obtained when patients were not in the midst of or recovering from acute events and had not been transfused within four months.<sup>8</sup> An average of 2 measurements taken on consecutive clinic visits usually about 6 weeks apart was taken as the steady state figure. Data were entered into a micro-

computer and analyzed with SPSS version 15.0. Means were compared using t-test and risks estimated using Odd ratio and 95 % confidence intervals (CI). Correlation of continuous variables was done using Pearson's correlation. Statistical significance was set at  $p < 0.05$ .

## RESULTS

### Demographics

Four hundred and fifteen children were studied comprising 218 (52.5%) males and 197 (47.5%) females yielding a male: female ratio of 1.1:1. Their ages ranged from 6 months to 17 years with a mean of 7.3 years and standard deviation (SD) of 4.4 years. Haemoglobin phenotype was SS in 385 (92.8%) of the children and SC in 30 (7.2%).

Steady state haematocrit ranged from 15 to 37 % with a mean of 24.4 % and SD of 3.9 % and only 50 (12.0%) of the children had haematocrit levels of 30 percent and above. This comprised 36 (9.4%) of 385 children with haemoglobin SS and 14 (46.7%) of the 30 children with Haemoglobin SC.

### Steady State Haematocrit and its Correlates

Mean steady state haematocrit was higher in Hb SC than in HbSS and also higher in children from higher socio-economic classes (I & II) as shown in Table 1.

There was a negative correlation of steady state haematocrit with splenic size ( $r = -0.121, p = 0.013$ ) and with liver size ( $r = -0.190, p = 0.010$ ). There was also a negative correlation of haematocrit with age in Hb SS children (Figure 1;  $r = -0.274, p = 0.000$ ) but an insignificant correlation in Hb SC children (Figure 2;  $r = 0.224, p = 0.234$ ).

A line graph of trend of haematocrit with age shows that a downward trend of haematocrit with age in HbSS that continued till it reached a nadir at 13–14 years and seems to have started an upward trend at 15 years (Figure 3). A graph segregating this trend into sex revealed that the upward trend in haematocrit from about the age of 15 years was only in males (Figure 4).

**Table 1: Comparison of Steady State Haematocrit with Respect to Sex, Haemoglobin Phenotype and Socio-economic Status**

Variable		N	Mean % Haematocrit (SD)	t	p
Sex	Male	218	24.3 (3.9)	-0.756	0.450
	Female	197	24.6 (3.9)		
	Total	415			
Haemoglobin phenotype	SS	385	24.1 (3.7)	-4.945	0.000*
	SC	30	28.3(4.5)		
	Total	415			
Socioeconomic class	1&2	129	25.4 (3.7)	3.771	0.000*
	3 – 5	286	23.9 (3.9)		
	Total	415			

Mean steady state haematocrits were compared for any differences with respect to gender, haemoglobin phenotype and socio-economic status using t-test. \* Significant at  $p < 0.05$

**Table 2: Prevalence of Clinical Splenomegaly in Different Age Groups**

Age group (years)	HbSS		HbSC		All patients N	Clinical Splenomegaly n (%)
	N	Clinical Splenomegaly n (%)	N	Clinical Splenomegaly n (%)		
<5	128	43 (33.6)	12	3 (25.0)	140	46 (32.9)
5-9	129	42 (32.6)	6	3 (50.0)	135	45 (33.3)
10 – 14	106	34 (32.1)	10	4 (40.0)	116	38 (32.8)
15 – 17	22	3 (13.6)	2	0 (0.0)	24	3 (12.5)
<b>Total</b>	<b>385</b>	<b>122 (31.7)</b>	<b>30</b>	<b>10(33.3)</b>	<b>415</b>	<b>132 (31.8)</b>

Percentage of children with palpable spleens in different age groups presented for all children studied and also separately for Hb SS and HbSC phenotypes

**Table 3: Steady State Palpable Splenomegaly and its Relationship to Sex, Haemoglobin Phenotype and Socio-economic Status**

Variable		n	Palpable Splenomegaly (%)	OR	95% CI
Sex	Male	218	80 (36.7)	1.62	1.06, 2.46*
	Female	197	52(26.4)		
	Total	415			
Haemoglobin phenotype	SS	385	122(31.7)	0.93	0.42, 2.04
	SC	30	10(33.3)		
	Total	415			
Socioeconomic class	1&2	129	33(25.6)	0.65	0.41, 1.03
	3 – 5	286	99(34.6)		
	Total	415			

Prevalence of palpable splenomegaly in children of different genders, haemoglobin phenotypes and socioeconomic classes. \* Odds of splenomegaly marginally greater in males compared to females

**Hepatomegaly and Splenomegaly and their Correlates**

The spleen was palpably enlarged in 132 (31.8%) children with sizes ranging from 2–18 cm and a mean (SD) of 5.4 (3.2) cm below the costal margin. The prevalence of clinically palpable splenomegaly in the different age groups is as shown in Table 2.

The prevalence of splenomegaly was higher in HbSC than in HbSS between the ages of 5 and 14 years but it subsequently dropped to zero whilst the drop in HbSS is less dramatic (Table 2). However the number of Hb SC patients older than 14 years in the study population was only two; the zero percent prevalence may therefore not be significant.

Correlates of splenomegaly in the steady state are shown in table 3. Males are 1.62 times as likely to have a palpable splenomegaly compared to females with marginal significance given the 95 per cent confidence interval. There was no significant difference in the likelihood of splenomegaly between children of different socio-economic class and haemoglobin phenotype categories.

Palpable hepatomegaly was present in 367(88.4%) children and the sizes ranged from 2–17 cm below the costal margin with a mean (SD) of 5.4 (2.7) cm. Correlates of hepatomegaly in the steady state are shown in Table 4. Children with HbSS are about 4 times as likely as HbSC children to have hepatomegaly. There was no significant difference in the likelihood of hepatomegaly between children of different genders and different socio-economic classes as categorised.

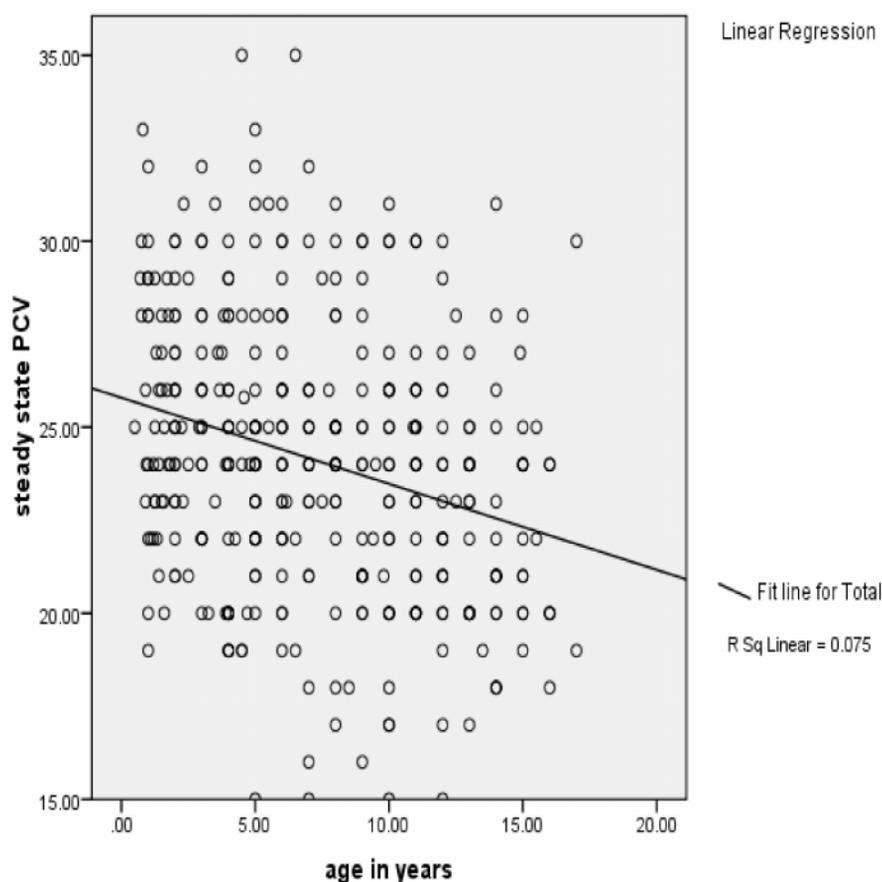
**DISCUSSION**

The mean haematocrit of 24. 1 per cent in Hb SS observed in the present study is close to values observed in previous studies in Nigeria and in the United States.<sup>4,5</sup> However, in addition to previous Nigerian studies most of whom described the steady state features of HbSS, the present study has also reported the steady state hematocrit in HbSC which had a mean value of 28.3 percent. The higher haematocrit in Hb SC compared to Hb SS is in keeping with the more severe clinical course in the latter and documented in literature.<sup>9</sup>

**Table 4: Steady State Hepatomegaly and its Relationship to Sex, Haemoglobin Phenotype and Socio-economic Status**

Variable		n	Palpable Hepatomegaly (%)	OR	95% CI
Sex	Male	218	196(89.9)	1.36	0.74, 2.47
	Female	197	171(87.2)		
	Total	415			
Haemoglobin phenotype	SS	385	347(90.1)	4.57	2.00, 10.47*
	SC	30	20(66.7)		
	Total	415			
Socioeconomic class	1&2	129	110(85.3)	0.65	0.35, 1.22
	3 – 5	286	257(89.9)		
	Total	415			

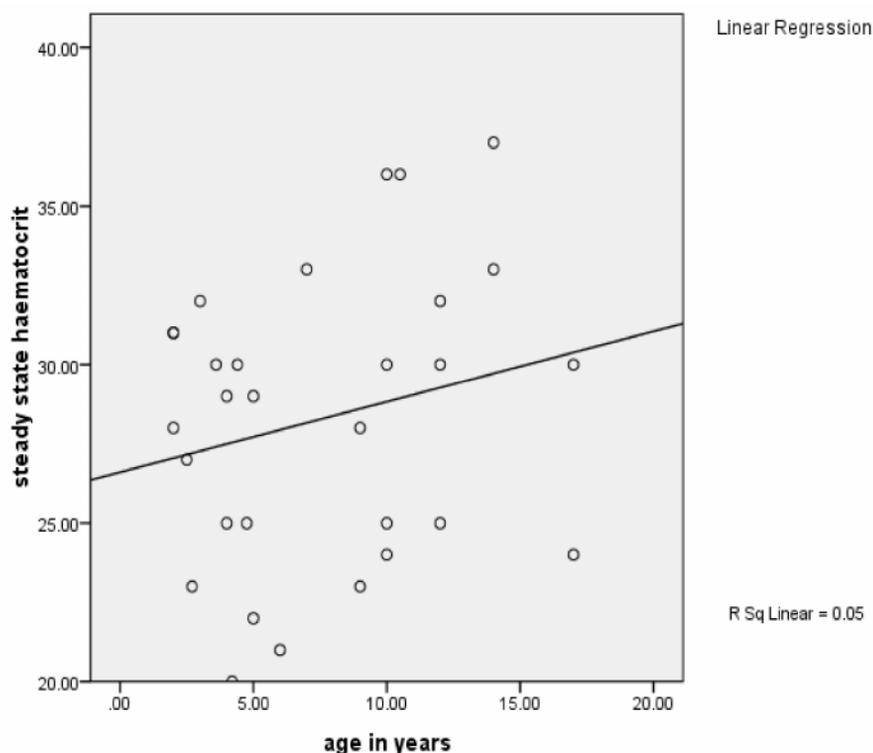
Prevalence of palpable hepatomegaly in children of different genders, haemoglobin phenotypes and socioeconomic classes. \* Odds of splenomegaly greater in Hb SS compared to Hb SC



**Fig. 1: Scatter Plot showing Relationship between Age and Steady State PCV in HbSS Children**

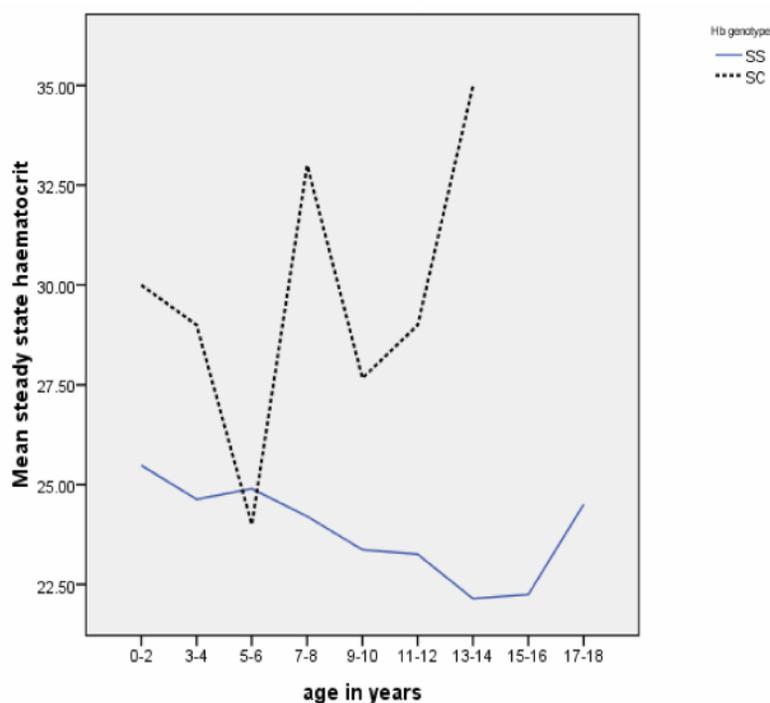
The increased prevalence of hepatomegaly in HbSS children compared to HbSC is similar to findings in adults<sup>10</sup> and may reflect a more intense chronic haemolytic process in the HbSS patients compared to HbSC and which also explains the higher haematocrit in HbSC patients.

Chronic hepatomegaly has been associated with increased clinical severity scores and significantly lower Hb F levels in HbS children indicating its usefulness as an index of a more severe clinical course.<sup>11</sup> The negative relationship between hepatomegaly and haematocrit observed in our study may therefore be considered a consequence of a more severe disease manifesting as co-existence of higher prevalence of hepatomegaly and worse degree of anaemia. In addition, keeping in mind the role of HbF in reducing the polymerisation of deoxyhaemoglobin,<sup>12</sup> the reduced haematocrit may also be a result of increased haemolysis in patients with hepatomegaly. However, the use of *Cajanus cajan*, an anti-sickling agent, has been associated with a reduced frequency of severe painful crises as well as reduced frequency of hepatomegaly without a concomitant increase in haematocrit levels.<sup>13</sup> The relationship between anaemia and hepatomegaly may therefore not be entirely a function of disease severity. It is therefore worthwhile studying in more detail interactions that might exist between anaemia and hepatomegaly keeping in mind the multifactorial nature of hepatomegaly in SCD. This negative correlation between hepatomegaly and haematocrit has however not been previously reported elsewhere but to the best of our knowledge has not been sought for. There is need for more studies especially in tropical Africa to confirm this finding. The negative correlation of splenomegaly with haematocrit supports findings by Adeodu and Adekile<sup>14</sup> who observed lower mean haematocrit in patients with persistent gross splenomegaly (PGS) compared those without. The natural history of sickle cell anaemia in North America is such that recurrent infarction causes regression of the spleen and by 8–10 years, autosplenectomy has



Insignificant correlation between age and steady state haematocrit in Hb SC children.  $r = 0.224$ ,  $p = 0.234$

**Fig. 2: Scatter Plot showing Relationship between Age and Steady State Haematocrit in HbSC Children**



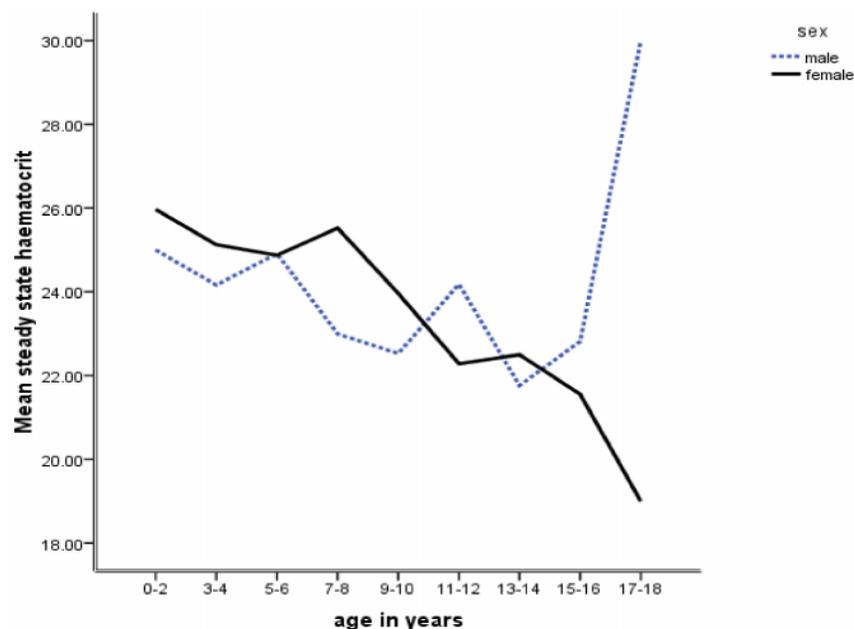
Line graphs of mean steady state haematocrit with age in 2 year class intervals for haemoglobin SS (SS) and haemoglobin SC

**Fig. 3: Trend of Mean Steady State Haematocrit with Age**

occurred.<sup>15</sup> On the contrary we observed a relatively stable prevalence of palpable spleen, occurring in about a third of patients until 15 years of age before it starts dropping. This is similar to the pattern reported in Tropics including Nigeria where splenomegaly tends to persist beyond 10 years; a phenomenon attributed to malaria.<sup>16</sup> We also observed a higher prevalence of splenomegaly in HbSC than HbSS between 5 and 14 years. This is probably due to more intense sickling of red blood cells in the splenic microcirculation in patients with HbSS compared to HbSC resulting in splenic infarction and fibrosis more in the former group of patients than the latter.

In the cooperative study of sickle cell disease in the United States, West *et al* observed a slight but upward trend of haematocrit with age in children with HbSC.<sup>8</sup> In our study, although we also found an overall upward trend in HbSC with age, it was not statistically significant probably because of the relatively small number of HbSC patients in our study compared to theirs. The downward trend of hematocrit with age in our patients with HbSS until the age of 12–14 years has not been reported in other African countries. It is also different from findings in a study in Jamaica where total haemoglobin levels fell from 6 months to 15 months after which no age related changes occurred till 6 years which was the upper age limit of the study.<sup>17</sup> The decreasing haematocrit with age in our patients may represent an inadequate erythropoietic response to growth in childhood in the face of probable nutritional deficiencies. Further studies, are required to confirm our findings and elucidate the underlying mechanisms. The upward trend in boys that started at about 15 years of age is in keeping with the known increase of haemoglobin concentration in boys at puberty due to androgen effects.<sup>18</sup>

Although not based on controlled studies, Serjeant reported a widespread clinical impression that patients from higher socioeconomic background have milder clinical manifestations of sickle cell disease.<sup>19</sup> Okany and Akinyanju<sup>20</sup> observed that the frequency of bone pain crisis was lower in patients from higher socio-economic classes. They also observed a fall in the mean haemoglobin



Graph of mean steady state haematocrit in male and female Hb SS children

**Fig. 4: Trend of Mean Steady State Haematocrit with Age in HbSS Children**

levels with decreasing socio-economic classes in adolescents and adults although not statistically significant. Our study revealed a statistically significant higher mean haematocrit in children from higher socio economic classes than in children from lower classes; this supports the believed improved clinical course conferred by a higher socioeconomic status. This advantage is probably due to better education of their parents, nutritional intake, better health promotional activities and easier access to medical care. Improvement in the social circumstances of children with SCD therefore has a potential for promoting their state of health.

### Conclusion

This study has shown important correlates of some steady state features of SCD in Nigerian children. Haemoglobin phenotype, age and socio-economic status seem to have some modifying influences on the steady features of sickle cell disease in Nigerian children. In addition, increasing liver and spleen sizes seem to be related to a decreasing haematocrit. Also, the steady state haematocrit in haemoglobin SS disease follows a downward trend with increasing age until about 15 years when it turns upward in boys. There is need

for further studies to better evaluate this phenomenon.

### Limitation

In assessing the liver and spleen sizes, concurrent ultrasonographic measurements would have been more accurate but not done.

**Conflict of Interest:** None

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