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Serum Ferritin Levels of Steady State Sickle Cell Anaemia Children in Enugu Southeast Nigeria

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Authors' contributions

This work was carried out in collaboration among all authors. The principal author IEC conceived the work and wrote up the manuscript while authors ANC and CIJ assisted with data and literature collection. All authors read and approved the final write-up.

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ABSTRACT

Background: Serum ferritin(SF), an indicator of body iron stores may be elevated for reasons such as inflammation, chronic haemolysis, and multiple transfusions which all occur frequently in sickle cell anaemia (SCA) patients. Serum ferritin values above 30 µg/dl(300ng/ml) have been said to signify an increase in iron stores. Hyperferritinemia up to ≥500 ng/ml predisposes an individual to haemachromatosis / iron overload. SF values ≥500 ng/ml have been found detectable after twenty blood transfusions and is an indication for iron chelation therapy. The aim of this study is to ascertain the prevalence of elevated SF and identify associated risk factors in a set of Southeast Nigerian SCA children in a steady state.

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Methods: This study regarded elevated iron stores as SF level ≥ 200 ng/ml and classified this as mild (200 to 500ng/ml), moderate (>500 to 1000ng/ml) and severe(>1000ng/ml). Normal values are between (10 and 150 ng/ml) and ≥500 ng/ml as a predisposition to iron overload. SCA children aged 10 months to 17 years in steady state and without notable confounding variables were recruited. Participants were classified into socio-economic classes (SEC), according to Oyedeji. The protocols of research ethics were duly followed. SF was assayed by the enzyme immunoassay using a Mini vidas® device (BioMérieux, France). Standard specimen handling and laboratory operating procedures and the machine and reagent manufacturers' guidelines were adhered to. The Chi Square test or Fisher Exact test were used to compare the categorical variables while the Student's t-tests was used for the numerical variables. The associated risk factors were identified using univariate analysis at 5% level of significance ($p < 0.05$).

Results: Participants were 27 male and 35 female SCA patients who were in steady state. Their mean age was 9.06±4.97 years and 50% were in middle SEC.(50.0%). Mean SF was 517.53±696.78, majority 27(43.5%) had mildly elevated SF levels, 7(11.3%) markedly elevated levels, 17(27.4%) had normal levels but no participant had lower than normal SF levels. Majority (50%) of the participants had haemoglobin F (HbF) levels below 10 while 67.7% had haemoglobin S (HbS) levels above 80%. There was no correlation between SF and HbS, haemoglobin concentration [Hb] or packed cell volume (PCV) but a significant negative correlation existed between SF and and HbF. On comparing the SF of all participants, no statistically significant differences existed between the sexes, SEC, those with frequent (≥3) crises or periodic blood transfusions (≥3) annually, [all (p = >0.05)]. For participants with elevated SF (Table 6), SF levels were more markedly elevated in females, among the lower SEC, and among those with frequent crises and blood transfusion but these differences were also not statistically significant.

Conclusions: In steady state SCA children on periodic blood transfusion, serum ferritin is mostly mildly elevated despite age, gender, socioeconomic class and HbS levels. Low HbF levels may be a risk for elevated serum ferritin.

Keywords: Elevated serum ferritin; risk factors; Sickle cell anaemia; steady state.

1. INTRODUCTION

Sickle cell anemia is the most common genetic disease in populations of African descent [1]. Nigeria has the highest population of SCA patients in the world followed by India and The Democratic Republic of the Congo (DRC). SCA affects 1 to 2% of live births in Nigeria, whereas the heterozygous form can affect 10 to 35% of individuals [2,3]. SCA is characterized by chronic, low grade, on-going haemolysis with episodes of exacerbation (vaso-occlusive and hemolytic crises). The end result of chronic hemolysis is excess serum iron levels [4] since there is both an increase in gastrointestinal absorption of iron to compensate for the resultant anaemia as well as very slow elimination of the iron released [5,6].

Frequently the hemolytic crisis may be severe enough to require urgent blood transfusion therapy with its attendant risk of iron overload since each transfused red blood cell provides about 200 mg of iron [7]. The effectiveness of regular red cell transfusion therapy in reducing the risk of stroke and other complications of SCA has led to increase in its use in the management of children with sickle cell disease [8]. Several studies have reported that the need for blood transfusions following severe anaemia is more in children with SCA than other children [9-12].

Excess serum iron levels lead to complete saturation of transferrin and ferritin followed by binding of iron to other circulating molecules and ultimately parenchymal cells [5,6]. Ferritin is a positive acute phase response protein whose concentrations increase with inflammatory processes. This mars proper interpretation of SF values in the face of widespread infection or inflammation [13]. Thus SF levels may be elevated in SCA as a result of hemolysis, blood transfusion therapy and inflammation [14,15]. SF values above 300ng/ml signify an increase in iron stores [16]. World Health Organisation (WHO) 2018 guideline stated that the risk of iron overload is highest at SF levels >200 ng / ml in children above 5 years-of-age [17] while organic lesions may occur at ferritin levels above 1000 ng / ml. SF gives a reliable estimate of blood transfusion related iron overload [18,19]. SF has also been identified as one of the most important tools in the measurement of iron balance in steady-state sickle cell disease [4]. Yet, there is

paucity of data documenting SF levels in steady state SCA children in our environment. This implies that iron overload with possible organ damage in children with SCA may be under-diagnosed and undertreated. In Nigeria, Odunlade et al. [20]. reported that 33.3% of SCA children had ferritin levels above 300 ng / ml, 6 (37.5%) of whom had no history of blood transfusion. Oluboyede [21] in south western Nigeria documented mean ferritin levels of 296.3 ± 61.9 ng/mL in older children and young adult SCA patients in steady state with much higher mean of 1,470 ng/mL in those with complications of chronic osteomyelitis. Noteworthy is the fact that none of these patients had had a blood transfusion for any known cause in the two years prior to their study. Neither Odunlade [20] nor Oluboyede [21] documented the number of children with iron overload or requiring iron chelation therapy.

1.1 Aim/Objectives

The general aim of this study was to identify the serum ferritin levels of SCA children in steady state. The specific objectives were to ascertain the prevalence of elevated serum ferritin and identify the risk factors associated with elevated serum ferritin in this set of South-East Nigerian, steady state, SCA children.

2. METHODS

This was a cross-sectional, descriptive study. The study regarded elevated iron stores as serum ferritin level ≥ 200 ng/ml which was classified as mild (200 to 500ng/ml), moderate (500 to 1000ng/ml) and severe(>1000ng/ml). Normal were values between 10 and 150 ng/ml. Steady state SCA children were those crisis free, with no recent drop in the haemoglobin level and no symptoms or signs of acute illness in the previous 4 weeks [22]. Included in the study were 10 months to 17 years old subjects confirmed to be sickle cell patients by haemoglobin electrophoresis, on regular follow-up at the Paediatric haematology clinic of Enugu state university teaching hospital, Enugu, southeast Nigeria and in steady state. Demographic and socio-economic data were obtained from the parent/guardian and the participant where appropriate and entered into a study proforma. Using the scheme proposed by Oyedeji [23] the occupation and educational attainment of parents were used to classify participants into one of five social classes (I–V) in descending order. Further stratification into upper (classes I and II), middle (class II), and lower (classes IV and V) socioeconomic groups was done [24]. History of blood transfusions and frequency of VOC of ≥3 in the previous 12 months were confirmed by checking through their case notes. SCA children who were hospitalized or had a major vaso-occlusive crisis within the last 4 weeks before the study, patients on iron containing haematinics or erythropoiesis stimulating agents such as vitamin C were excluded. Excluded also were patients with history of recent overt blood loss, concurrent medical or surgical conditions like peptic ulcer disease, renal failure, liver disease, malignancy, or chronic inflammatory disease. The aim and study procedures were explained to the participants' primary care-givers and written consent obtained from them before any of the subjects were included. Serum ferritin was assayed by the enzyme immunoassay using a Mini vidas® device (BioMérieux, France). Quality control measures were observed in the tests by adhering to reagent manufacturers' guidelines and standard specimen handling/laboratory operating procedures to ensure the validity of results. The Chi Square test or Fisher Exact test was used to comparing the categorical variables, while the Student's t-tests were used for the numerical variables. The associated risk factors were identified using univariate analysis at a 5% level of significance ($p < 0.05$).

3. RESULTS

Sixty-two SCA patients who were in a steady state were studied. There were 27 males (43.5%) and 35 females (56.5%). The mean age of these subjects was 9.06±4.97 years, with the youngest being 10 months and the oldest 17 years. The majority of them were in the middle socioeconomic class (50.0%). These are represented in Table 1 as the demographic characteristics of the children under study.

Table 2 depicts serum ferritin with a the range of 7.5-4634.7, mean and standard deviation of 517.53±696.78. Majority 27(43.5%)of our study subjects had mildly elevated ferritin levels, while 7(11.3%) had significantly elevated levels, 17(27.4%) had normal levels and none of them had lower than normal levels. HbF of the patients ranged from 2.9-29.0 with mean and standard deviation, 10.48±5.89 and the majority had HbF below 10 (50.0%). For HbS, majority of them were above 80% (67.7%); the range was 48.4-93.7 and the mean and standard deviation was 81.64±8.08.

The correlation between serum ferritin (elevated and normal) with Haemoglobin variants (HbF and HbS), PCV/Haemoglobin levels (Hb) in Table 3 showed there was a significant negative relationship between ferritin and HbF (r = -.272, p = .034). There was no significant relationship between ferritin and age (r = -.010, p = .938) and between ferritin and HbS (r = .017, p = .899). There was also no significant relationship between ferritin and PCV (r = -.197, p = .180) and ferritin and Hb (r = -.173, p = .239).

However, in the correlation of the same variables with elevated serum ferritin as depicted in Table 4 found no significant relationship between ferritin and age (r = .201, p = .186), ferritin and HbF (r = -.290, p = .053), ferritin and HbS (r = .124, p = .417). There was also no significant relationship between ferritin and PCV (r = -.271, p = .121) and ferritin and Hb (r = -.163, p = .356).

From Table 5, there was no significant difference in the ferritin level between the sex (p = .166) and SEC groups (p = .955). There was likewise no significant difference between those that have had 3 or more crises in past year and those who had not(p = 1.000), those that have had up to 3 or more blood transfusion in the past year and those who had not(p = .214).

Table 6 shows that the serum ferritin levels were more markedly elevated in females, among the lower SEC and among those with frequent crises and blood transfusion. However, there was no statistically significant difference in the ferritin level between the sexes (p = .725) and SEC (p = .950). There was likewise no significant difference between those that have had 3 or more crises in past year and those who had not (p = .918), those that have had up to 3 or more blood transfusions in the past year and those who had not(p = .097). Although these all had elevated serum ferritin.

4. DISCUSSION

Several investigators have documented high SF levels of SCA patients on hospital management as indicating an increase in body iron stores. The mean SF value of 517.53±696.78 found in this study is higher than 367 g/L reported by Hussain et al. [25] in London among steady-state SCA children of the same age bracket but much higher than 220 g/L by Akodu and co-workers [24] among younger (six months to five years) steady state SCA children in southwest Nigeria. The observed differences have been attributed to possible modification of SF by age, being higher in adults [20] and older children [26] as in our study but lower in younger children [24]. Also a possible influence of genetic factors on SF has earlier been implied [27], evidenced by the obvious difference in the mean SF values of the black children recruited in the current study and the white children recruited by Hussain et al. [25] in spite of the similar age bracket of the recruited children.

In the present study, 45(62.5%) of SCA children in steady state had elevated SF although most (43.5%) had mildly elevated SF with only 7(11.3%) having very high SF more than 1000ng/ml. Seventeen(27.4%) of our study population had SF within the normal range and none had low SF. Oyiro et al. [28] observed that comparable to our study fifty-six (70.5%) of SCA patients in their study population had elevated SF, (28.8%) had SF within the normal range and none had low SF even among those who had never been transfused. Their study differed from ours in that a larger proportion than ours (31.3% versus 11.3%) had SF levels >1000ng/ml, these they identified as those on chronic blood transfusion as well as being older chidren and young adults.These finding are also replicated by Makulo and co workers [29] who classified this group of participants having very high SF more than 1000ng/mlas requiring iron chelation therapy. Similar to our study, Stettler et al. [30] also demonstrated normal to high SF in non-transfused SCA children and adolescents in Philadelphia. High levels of SF in non or periodically transfused SCA patients is clinically significant considering that the impact of inflammation and hemolytic crises on measured ferritin levels should be markedly reduced in the steady state. This suggests the role of additional factors in such instances.

An earlier study in the our setting compared the SF of 1 to 18 year old periodically transfused SCA children and age, sex matched normal haemoglobin type controls [31]. That study [31] identified that irrespective of gender, the mean SF was significantly higher among subjects than the controls (p = 0.000). Similarly our study did not find any correlation between SF and sex nor SEC.

High levels of SF have also been reported in studies conducted among SCA patients in other geo-political zones of Nigeria such as North-Central Nigeria [32] [(mean SF of 589.33 ± 427.61 ng/ml which was significantly higher than

the mean SF of the 'AA' controls (184.53 ± 119.74 ng/mL)], south west [21], south-south [16] as well as other parts of West Africa such as Kenyatta [28].

Table 1. Distribution of Age, Sex and SEC of Participants

	Frequency	Percent	Range	M±SD
Age(years)			10mths -17yrs	9.06±4.97
- < = 4	13	21.0		
- 5-8	15	24.2		
- 9-12	15	24.2		
- > 13	19	30.6		
Sex				
- Male	27	43.5		
- Female	35	56.5		
SEC				
- Upper	19	30.6		
- Middle	31	50.0		
- Lower	11	17.7		
- *No response*	1	1.6		

Table 2. Distribution of HbF, HbS and SF levels of participants

	Frequency	Percent	Range	M±SD
HbF			2.9-29.0	10.48±5.89
- < 10%	31	50.0		
- 10-19.9%	26	41.9		
- > 20%	4	6.5		
- *No response*	1	1.6		
HbS			48.4-93.7	81.64±8.08
- < 50%	1	1.6		
- 50-80%	18	29.0		
- > 80%	42	67.7		
- *No response*	1	1.6		
Ferritin			7.5-4634.7	517.53±696.78
- Not elevated	17	27.4		
- Mildly elevated(200-500ng/ml)	27	43.5		
- Moderately elevated (<500-1000ng/ml)	11	17.7		
- Severely elevated(<1000ng/ml)	7	11.3		

Table 3. Correlation between SF levels and Age, HbF, HbS, PCV and [Hb]

	Age (years)	HbF(%)	HbS(%)	PCV(%)	[Hb] (g/dl)
Ferritin					
- Spearman's Correlation Coefficient	-.010	-.272	.017	-.197	-.173
- p-value	.938	.034	.899	.180	.239
- N	62	61	61	48	48

Table 4. Correlation between elevated SF levels and Age, HbF, HbS, PCV and [Hb]

	Age(years)	HbF(%)	HbS(%)	PCV(%)	Hb(g/dl
Ferritin(ng/ml)					
- Spearman's Correlation Coefficient	.201	-.290	.124	-.271	-.163
- p-value	.186	.053	.417	.121	.356
- N	45	45	45	34	34

Table 5. Comparing mean SF of subjects by sex, SEC, past 12 months-crises and blood transfusions frequencies

	N	M±SD	Statistic	p-value
Sex			-1.384*	.166
- Male	27	433.04±534.70		
- Female	35	582.71±801.49		
SEC			.093**	.955
- Upper	19	479.62±511.72		
- Middle	31	439.78±440.13		
- Lower	11	800.88±1341.38		
Crises frequency(≥3/year)			.000*	1.000
- No	19	428.22±452.56		
- Yes	11	485.93±637.63		
Blood Transfusion(≥3/year)			-1.242*	.214
- No	24	379.20±409.92		
- Yes	5	774.14±902.99		

Statistic used: indicates Mann-Whitney test (Z was reported) & ** indicates Kruskal-Wallis test*

Table 6. Comparing mean elevated SF levels of participants by sex, SEC, past 12 months-crises and blood transfusions frequencies.

	N	M±SD	Statistic	p-value
SEX			-.351	.725
- Male	17	628.65±594.15		
- Female	28	701.49±857.57		
SEC			.104	.950
- Upper	14	611.34±539.71		
- Middle	22	578.98±453.24		
- Lower	8	1062.65±1510.82		
Crises frequency(≥3/year)			-.102	.918
- No	14	535.82±485.34		
- Yes	8	625.04±706.28		
Blood Transfusion(≥3/year)			-1.658	.097
- No	17	481.25±450.50		
- Yes	4	952.66±935.26		

Statistic used: indicates Mann-Whitney test (Z was reported) & ** indicates Kruskal-Wallis test*

None of our study patients had lower than norma SF values, this was also the case in the study by Oyiro et al. [28] in Kenyatta and Mohany et al. [33] in India. Ukoha [31] also reported that the prevalence of iron deficiency anaemia (IDA) was not significantly higher in her SCA subjects. Although a low SF would be highly suggestive of IDA the chronic hemolysis with the subsequent recycling of iron makes iron deficiency a rare complication of SCA patients.

It has been documented that high levels of HbF ameliorate the severity and incidence of sickle cell crisis and other complications of the disease [34]. This it does by inhibiting deoxy sickle hemoglobin (HbS) polymerization. Also the HbF/F-cell and the proportion of F-cell (HbF containing red cells) as well as the protective levels of HbF (approximately 10pg) within each F-cell are the most critical factors for ameliorating disease severity [35]. The number of protected F-cells approach 70% when the total HbF concentration is near 30% [35]. However patients with sickle cell anemia have individual characteristic distributions of HbF/F-cell regardless of their total HbF level [36]. Thus our study participants whose HbF levels were mostly <20% may or may not be protected from elevated SF due to haemolysis. Thus one wonders if the negative correlation found between SF and HbF levels is an indicator that low HbF is associated with high SF. Could these participants have less quantity and protection of F-cells, resultant increased polymerization and haemolysis. The answers to these questions are beyond the scope of the present study. Similar to our study, Usang [37] and Odunlade [20] and their respective co-investigators observed no

significant correlation between SF and [Hb]/PCV and attributed this to increased utilization of iron in growing children in correcting for anaemia.

Several authors have documented an association between volume, nature of blood product, method of blood transfusion and SF [10,29]. Ikusemoro [16] observed that the mean SF concentration was elevated in the sickle cell anaemia patients whose multiple transfusions (MT) were more than those who were rarely transfused (RT) as compared with the control groups ($p < 0.001$). There was found also a positive correlation between the serum ferritin and the number of units of blood transfused ($r = 0.719$, $p = 0.000$) [16]. A high level of SF, percentage transferrin saturation and a reduction in total iron binding capacity were observed by Ikusemoro et al. [16] in sickle cell anaemia patients who received 3≥ units of packed cells per year, suggesting an increase in iron stores and a risk of developing iron overload. They [16] concluded that serum ferritin should be routinely assayed for patients with SCA requiring frequent blood transfusions for early detection of iron overload and advocated the need for iron chelating agent to be incorporated into the management of sickle cell anaemia patients, particularly those requiring multiple blood transfusions. A study at the University of California also supports that SF should be interpreted in combination with parameters such as transferrin saturation, serum iron, total iron binding capacity in the estimation of transfusional iron overload having found SF a poor marker for accurately assessing serum iron overload [38].

Contrary to these authors, neither frequency of crises 3≥ times nor transfusions 3≥ units of blood over the last 12 months was identified as risk of elevated iron stores in our study. In addition, the other variables regarding blood transfusion as well as the additional parameters for evaluating serum iron were not accounted for in the present study. Moreso very few participants in the present study had 3 or more blood transfusions per year and none was on chronic transfusion therapy. Although these factors limit the ability of the study to test the influence of blood transfusion on serum ferritin, sporadic blood transfusion is probably less likely to lead to iron overload. This has been noted by previous studies on non-chronically transfused subjects [25,39,40]. In the absence of significant difference between the mean SF value of those with blood transfusion and those without, the observed mild to moderate elevation of SF may then be attributed to intravascular and extravascular hemolysis present in steady-state [41] as well as increased iron absorption from the gastro-intestinal tract [20]. Furthermore, some other studies from developing countries have even suggested that individuals with sickle cell disease who have never been transfused, are more likely to be iron deficient rather than have iron overload [42], especially in men [43].

5. CONCLUSIONS

In steady state SCA children on periodic blood transfusion, serum ferritin is mostly mildly elevated despite age, gender, socioeconomic class and HbS levels while low HbF levels may be a risk for elevated serum ferritin.

6. RECOMMENDATION

Management measures which optimize HbF levels are encouraged in SCA children.

7. LIMITATION OF THE STUDY

Inability to evaluate those with markedly elevated srum ferritin for possible iron overload using MRI.

CONSENT

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

Ethical approval for the study was given by the institution’s Research ethics review board.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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