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Hematology Parameters and Clinical associations in Children with Steady-State Sickle Cell Anemia in Southwest Nigeria

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ABSTRACT

Background: Hematology parameters are essential for evaluating and managing sickle cell anemia patients and can be used to predict disease severity and outcomes.
Aim: To determine the mean values of hematology parameters of children with steady-state sickle cell anemia and relate the means to clinical parameters.
Methods: This study was a hospital–based cross-sectional descriptive study, with participants recruited through the nonprobability sampling method. The demographic characteristics, clinical findings and hydroxyurea usage of the study participants were recorded. A five milliliters blood sample was used to determine the full blood count and fetal hemoglobin level via a Sysmex kx-21 N (hematology auto analyzer) and a CEA996Hu enzyme-linked immunosorbent assay kit for fetal Hemoglobin (HbF), respectively.
Results: One hundred ten children, including 61 (55.5%) males and 49 (44.5%) females were studied. The mean PCV, WBC counts and HbF were 24.4±3.40%, 9806.91±4375.80×10°9c/l, and 4.29±2.72%, respectively. Males had significantly higher PCVs than females did (p=0.045), and the WBC count was significantly greater among those aged 6–10 years (p=0.043). A high WBC count was associated with disease severity (p=0.039), and hydroxyurea was associated with the frequency of blood transfusions (p=0.000).
Conclusion: The mean HbF level was low, and the mean PCV was within the normal range. A high mean WBC count was associated with disease severity, with individuals aged 6–10 years having significantly greater counts. Hydroxyurea had no effects on hematology parameters but was associated with the frequency of blood transfusions. Multicenter studies are desirable to further evaluate clinical benefits of hydroxyurea.

Keywords: Sickle cell anemia, children, hematology parameters, clinical associations

INTRODUCTION

Sickle cell anemia (SCA) is an increasing public health problem, and it affects more than 12 million people, mostly from sub-Saharan Africa, India, Saudi Arabia and Mediterranean countries [1]. In Nigeria, approximately 150,000 children are born

annually with the disorder [2]. The disease is regarded as a silent baby killer, with approximately 50 to 80% of infants born with the disorder dying before the age of 5 years [3]. SCA is inherited when the affected individual inherits two abnormal hemoglobin SSs (HbSSs) from both parents. The primary abnormality in SCA is the replacement of glutamic acid with valine at the sixth position on the β-globin chain [4]. The presence of valine, a fat-soluble amino acid, results in polymerization of hemoglobin (Hb) in red blood cells, with the cells assuming a sickle shape and becoming very fragile [5].

SCA (homozygous HbSS) is the most common and most severe form of sickle cell disease (SCD) [4]. This is because affected individuals suffer a range of complications. These complications stem from repeated sickling, inflammatory reactions, vascular blockages, ischemia, hypoxia, chronic hemolysis, anemia and organ damage [6,7]. Common complications found among sickle cell anemia patients include hyperhaemolysis, severe anemia, vaso-occlusive pain, splenic sequestration, infections, acute chest syndrome, and stroke [7,8].

One factor contributing to the highly variable natural history of SCA (homozygous HbSS) and its clinical severity appears to be the level of fetal hemoglobin (HbF) in an SCA patient [9]. Studies have evaluated the effects of HbF on the clinical manifestations and severity of SCA in affected patients and have suggested that the level of HbF is an important determining factor [10,11]. Additionally, HbF is the most powerful modulator of the clinical and hematological features of sickle cell anemia [10,11. Adeodu et al. [12] reported among 105 Nigerian SCA children, that patients with low HbF values (<10%) have a propensity to develop severe complications such as stroke. High HbF levels have also been found to reduce the frequecy of other severe complications including, severe priapism, osteonecrosis, acute chest syndrome and severe anaemia [10,13].

White blood cells have increasingly become important in the diagnosis and management of complications in SCA. A higher WBC count has been associated with complications in SCD patients and was found to be an accurate test for detecting acute chest syndrome [14]. Recently, there has been evidence that SCA patients with high WBCs have a high risk of frequent hospital visits and admissions [14-16]. The common causes of high WBC counts in the SCA population include infections, hyperactive bone marrow, vaso-occlusive pain and inflammation,[14,17] with males having a propensity to have higher WBC counts [14].

SCA is a primarily red blood cell disorder resulting in early destruction of red blood cells. This destruction is caused by repeated sickling and fragility of the red blood resulting from the polymerization of HbS. Continuous destruction (hemolysis) leads to a reduction in the number of red blood cells and results in anemia (low packed cell volume) and chronic hypoxia. The packed cell volume (PCV) of SCA patients in the steady state ranges from 19.5–24.9% in Nigeria [18-20] and from 24–27% in Jamaica [21] and the USA [22].

Owing to the perceived importance and beneficial effects of high HbF levels, efforts have been made to identify agent(s) that can increase HBF production. Hydroxyurea (HU), known as hydroxycarbamide, is a myelosuppressive agent that can induce HbF production [23]. In addition, its cytotoxic effects reduce marrow production of neutrophils, reticulocytes and platelets, which are important mediators of inflammation that promote vaso-occlusion through vascular adhesions [24]. Hydroxyurea reduces adhesive ability and inflammatory properties of these blood cells [24]. It has been reported that hydroxyurea is strongly correlated with a reduction in the leukocyte count [24,25]. Hydroxyurea reduces the frequency of both painful episodes and acute chest syndrome [17].

Therefore, this study determined the fetal hemoglobin level, white blood cell count and packed cell volume of SCA children in the

steady state, aged 2–14 years, and related means to the hydroxyurea usage and the frequency of blood transfusion and crisis.

MATERIALS & METHODS

The study was conducted at the Pediatric Hematology Clinic at the Teaching Hospital where the study took place. The study had a cross-sectional descriptive design. At the time of the study, the pediatric hematology clinic had, among other patients, 200 sickle cell anemia patients. All stable SCA patients aged 2–14 years who attended the routine hematology clinic between January and July 2018 were eligible for recruitment. From the eligible study population, study participants were consecutively recruited. Patients who had any form of crisis within the last 4 weeks or any sickness or blood transfusion in the last 3 months to the time of data collection, patients on chronic transfusion, HbSC patients or other haemoglobinopathies were excluded from the study. Patients whose caregivers did not give consent or older patients (>7 years of age) who refused to give assent were also excluded.

Sample size

This study is a preliminary report of a research project that assessed hematology parameters and transcranial Doppler velocimetry in children with sickle cell anemia. The project minimum sample size was calculated using a 6.9% prevalence of abnormal high-risk brain blood flow velocity recorded by Oniyangi et al [26] among sickle cell disease (SCD) patients. The minimum number (n) of subjects needed was determined via the Leslie-Kish formula; [27] $n = z^2pq/d^2$, for cross sectional study. Where n is the calculated sample size, P = the prevalence at 6.9%, q = 1 − p, Z = standard deviation at the t 95% confidence level = 1.96, d = level of precision at 5%.

$$n = \frac{1.96^2 \text{ x } 0.069 \text{ x } 0.931}{0.05^2}$$

= 98.7

Therefore, the minimum sample size for this study was 99 steady state SCA children.

Ethical approval and consent

The Research Ethics Committee of the study institution approved the study protocol with approval reference number LTH/REC/2017/04/28/308. Ethical standards in conformity with the Helsinki Declaration 1975 (as amended) for conducting research were maintained during the study.

Before the data were collected from each of the study participants, written informed consent and assent were obtained from all the caregivers and older subjects who were old enough (>7 years of age), respectively. The caregivers and study participants were informed that their participation was voluntary and that they could withdraw from the study at any time without misgiving or being made to give any reason.

Data collection

Using purposively designed proforma, the data for this study were collected between January and July 2018. Each of the recruited subjects and his/her caregiver were informed about the scope and methods of the study. The study participants' demographic characteristics, physical examination findings and usage of hydroxyurea were entered into the proforma. Five (5) milliliters of blood samples were collected from each study participant via aseptic procedures at the hematology clinic.

Hematology data

The full blood count was determined by a Sysmex kx-21 N (hematology autoanalyzer). The levels of HbF in blood samples were determined via the CEA996Hu Enzyme-linked immunosorbent Assay Kit for Fetal Hemoglobin (HbF) by Cloud-Clone Corp, Wuhan, China.

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STATISTICAL ANALYSIS

All the information obtained was imputed into a personal computer and analyzed using the Statistical Package for Social Sciences software for Windows version 22 (IBM SPSS Inc. Chicago, IL, USA). The data are

presented in tables and prose. Continuous variables are expressed as the means and standard deviations, medians and modes. Means/medians were compared using Student's *t*-test, the Mann–Whitney U-test and analysis of covariance (ANOVA) where appropriate. Comparisons of categorical variables and tests for associations were performed via chi- square (x^2) tests. The level of statistical significance was set at $P < 0.05$.

RESULT

One hundred ten (110) steady state SCA children were studied between January and August 2018. Sixty-one (55.5%) were males, and 49 (44.5%) were females, resulting in male: female ratio of 1.2:1. The mean age of the patients studied was 7.20 ±3.82 years, while that of the males and females were 7.29 ±3.85 years and 7.17±3.81 years, respectively.

The overall means of the hematology parameters are as follows: HbF; 4.33±2.70% (range: 0.30–15), PCV; 24.44±3.40% (range: 18.0–32.0), and WBC; 9795.09±438.56x10^9c/l (range: 400.0–21000.0). For all the hematology parameters (HbF, PCV and WBC) assessed, males had higher mean values than females did. However, only the difference in PCV was statistically significant, as shown in Table 1. The means (SD) of PCV, WBC and HbF in relation to age group and sex are displayed in Table 2, and in all age groups, the WBC mean values were significantly greater in males than in females ($p = 0.043$). Compared with females, males in the 2–5 years age group presented significantly greater mean HbF ($t = 2.117$, $p = 0.04$) and mean PCV ($t = 6.047$, $p < 0.001$).

Table 1: Mean hematology parameters in relation to gender

Mean hematology parameters	Gender, n (%)		t-value	p-value
	Male 61 (55.5)	Female 49 (44.5)		
HbF (%)	4.41±2.60	4.23±2.84	2.033	0.723
PCV (%)	25.00±3.77	23.74±2.75	1.049	0.045
WBC x10^9 (c/l)	10192.79±4168.71	9300.00±4639.10	0.356	0.297

Table 2: Mean hematology parameters in relation to age groups and gender

Age groups (years) & Gender (n)		Hematology parameters: Mean ±SD		
		HbF (%)	PCV (%)	WBC x10^9c/l
2 - 5	Male (30)	5.13 ±2.64	25.90 ±3.90	10582 ±3783
	Female (20)	3.63 ±2.14	23.30 ±2.99	9900 ±5310
6 - 10	Male (16)	4.30 ±2.24	23.81 ±3.92	11062 ±4936
	Female (17)	4.89 ±3.81	23.77 ±2.49	9988 ±4246
11 - 14	Male (15)	3.11 ±2.49	24.47 ±3.04	8486 ±3796
	Female (12)	4.28 ±2.17	24.42 ±2.78	7325 ±3649
	F-value	1.228	0.989	3.245
	P-value	.297	.375	.043

The mean hematology parameters were related to the frequency of crises and blood transfusions

The mean values of the hematology parameters were related to the frequency of crises, as shown in Table 3. The mean WBC count of the study participants who had more than 6 crises was significantly greater than that of the study participants with fewer crises ($F = 2.878$, $p = 0.039$). Additionally, as shown in Table 3, the mean hematology parameters were related to the number of blood transfusions, with no statistically significant differences observed in any of the three parameters.

Table 3: The mean values of the hematology parameters in relation to number of crises and blood transfusions per year			
Severity (n)	**Hematology parameters Mean ±SD**		
	HbF (%)	**PCV (%)**	**WBC (x 10^9)**
Number of crises within the last one year			
Nil (16)	4.78 ±2.25	24.38 ±3.05	8968.75 ±4029.51
1-2 [Mild] (46)	4.11 ±2.37	24.39 ±3.54	9586.96 ±4450.45
3-5 [Moderate] (38)	4.01 ±2.71	24.53 ±3.43	9412.10 ±4451.09
≥6 [Severe] (10)	5.85 ±4.18	24.40 ±3.66	13530.00 ±2818.21
F-value	1.151	0.130	2.878
p-value	0.216	0.998	0.039
Number of blood transfusions within the last one year			
Nil (89)	4.50 ±2.73	24.63 ±3.29	9362.47 ±4191.67
1-2 times (17)	3.79 ±2.42	23.71 ±4.20	11594.12 ±5275.12
3-5 times (3)	3.33 ±3.46	22.67 ±1.43	12566.67 ±2354.43
≥6 times (1)	1.40	25.00	9400.00
F-value	0.871	0.631	1.674
p-value	0.459	0.597	0.177

The HbF concentration is typically classified as low or high when a 10% cut-off is used [28,29]. Among the 110 study participants assessed in the present study, only one subject (0.91%) had a HbF concentration ≥10%. The HbF levels were then further classified using a 5% cut-off for low or high levels;[11] 63 (57.3%) of the participants had relatively high HbF levels, and 47 (42.7%) had relatively low HbF levels. The levels of HbF (5% cut-off) were related to the number of crises and blood transfusions, as shown in Table 4, and no statistically significant difference was detected.

Table 4: Fetal hemoglobin levels in relation to the number of crises and blood transfusions per year				
Severity	**HbF levels, n (%)**			
	<5%	**≥5%**	**Total**	**χ^2 (p-value)**
Number of crises within the last one year				
Nil	8 (50)	8 (50)	16 (100)	1.251 (0.741)
1-2 (Mild)	29 (63.0)	17 (37.0)	46 (100)	
3-5 (Moderate)	21 (53.3)	17 (46.7)	38 (100)	
≥6 (Severe)	5 (50.0)	5 (50.)	10 (100)	
Total	63 (57.3)	47 (42.7)	110 (100)	
Number of blood transfusions within the last one year				
Nil	48 (53.9)	41 (46.7)	89 (100)	2.492 (0.477)
1-2 times	12 (70.6)	5 (29.4)	17 (100)	
3-5 times	2 (66.7)	1 (33.3)	3 (100)	
≥6 times	1 (100)	0 (0.0)	1 (100)	
Total	63 (57.3)	47 (42.7)	110 (100)	

Relationship between hydroxyurea use and hematology parameters, number of crises and blood transfusions

Most of the study participants, 94 (85.5%), were not on hydroxyurea, while 2 (1.8%) and 14 (12.7%) were on it for <6 months and >6 months, respectively. Table 5 shows the hydroxyurea usage and the means of hematology parameters. Table 6 displays hydroxyurea usage in relation to the number of crises and blood transfusions. A statistically significant p- value (0.000) was recorded for the frequency of blood transfusion.

Observations/Results of your study should be written in this section along with tables/charts/figures etc. write serial numbers and appropriate heading/title of tables and legend/caption of figures.

Table 5: Duration of the hydroxyurea usage in relation to the hematology parameters mean values					
Hematology parameters mean values	**Duration hydroxyurea usage n (%)**				
	None 94 (85.5)	**<6 months 2 (1.8)**	**>6 months 14 (12.7)**	**F-value**	**P-value**
	Mean (SD)				
HbF (%)	4.44±2.64	4.25±4.46	3.59±2.96	0.604	0.549
PCV (%)	24.57±3.43	20.50±2.12	24.07±3.15	1.514	0.225
WBC (x 10^9 c/L	9503.83±4369.24	11600.00±3676.96	11492.86±4416.83	1.437	0.242

Table 6: Duration of the hydroxyurea usage in relation to the number of crises and blood transfusions					
Severity	**Duration of hydroxyurea usage, n (%)**				
	None	**<6 months**	**>6 months**	**Total**	**χ^2 (p-value)**
Number of crises within the last one year					
Nil	12 (75.0)	0 (0)	4 (25.0)	16 (100)	3.114 (0.794)
1-2 (Mild)	40 (87.0)	1 (2.2)	5 (10.8)	46 (100)	
3-5 (Moderate)	33 (86.9)	1 (2.6)	4 (10.5)	38 (100)	
≥6 (Severe)	9 (90.0)	0 (0.0)	1 (10.0)	10 (100)	
Total	94 (85.5)	2 (1.8)	14 (112.7)	110 (100)	
Number of blood transfusions within the last one year					
Nil	83 (93.3)	1 (1.1)	5 (5.6)	89 (100)	34.904 (0.000)
1-2 times	10 (58.8)	1 (5.9)	6 (35.3)	17 (100)	
3-5 times	0 (0.0)	0 (0.0)	3 (100)	3 (100)	
≥6 times	1 (100)	0 (0.0)	0 (0.0)	1 (100)	
Total	94 (85.5)	2 (1.8)	14 (12.7)	110 (100)	

DISCUSSION

The overall mean HbF (4.29±2.72%) in this study was lower than the values obtained by Adeodu (9.9±6.0%), [12] Akinlosotu (9.6±5.9%), [29] Tsilolo (7.2±5.0%) [30] and Kotila (7.40±3.60%) [31]. However, Uko [32] in Calabar, Isah [11] in Sokoto and Omoti [33] in Benin city, all in Nigeria, reported lower values of 3.05±1.61%, 2.99±1.56% and 2.17±1.81%, respectively. The different methods used by the authors to estimate fetal hemoglobin could explain the varying values. For example, Akinlosotu [29] used high-performance liquid chromatography (HPLC), and Tsilolo [30] used flow cytometry, and an ELISA kit was used in this study. Lower values are usually observed in studies that employed the alkali denaturation method (Betke's) [11,31].

In contrast to Tsilolo in Congo [30] and Isah [11] in Sokoto, Nigeria, the 6–10-year age bracket had the highest HbF mean value, with ages 11–14 years having the lowest HbF mean value in this study. Additionally, in one study, individuals aged 1–10 years were observed to have higher HbF values than those aged 11–20 years [34]. Considering these findings, lower HbF values are more common in children above 10 years than in children below 10 years of age. This finding is consistent with the assertion that the level of HbF decreases with increasing age, as adult hemoglobin predominates.

In addition, inconsistency exists with respect to which sex has the highest HbF value on average. Kotila et al [31] and Akinsheye et al., [10] as well as the present study, reported the highest mean HbF values among males, whereas Tsilolo [30] and Fatunde [28] reported the highest values among females. On the other hand, Akanni et al [34] reported that males had the highest mean HbF value at ages ranging from 1–9 years, whereas females the highest mean HbF value at ages 10–20 years. The authors posited that the effect of female sex hormones at puberty could have been responsible for the higher values in the female adolescent age group.[34] The semblance of this claim is demonstrated in Table 2 in this study, whereas females had the highest values from preadolescent to adolescent age.

Sickle cell anemia patients usually live with chronic anemia because of ongoing chronic hemolysis with episodic hyperhaemolysis crisis that can be triggered by many factors,

including infections, stress and changes in body homeostasis. The mean PCV of 24.44% among the steady-state SCA children studied is low compared with what is expected among HbAA children. However, the mean PCV in this study is comparable to the reported normal range of 19.5–24.9% in Nigeria [18-20] and elsewhere in Africa [35] for steady–state SCA children. Compared with the values (24–27%) reported in Jamaica[21] and the USA, [22] these values are lower. The likely explanations for this lower value in the study participants could be the prevailing poor socioeconomic conditions, chronic malnutrition and recurrent malaria infection common in the study environment. These factors are common causes of anemia in childhood, especially in children suffering from sickle cell disease, because more resources are needed to provide quality care and adequate food.

In contrast to the findings of West et al., [36] the mean PCV in males this study was statistically greater than that in females ($p = 0.045$) and across all the age groups (Table 2). Akinbami et al. [19] attributed this observation to increased erythropoiesis due to androgens in males and low iron due to blood loss in females during the menstrual period. However, these suggestions could not be supported in this study, as differences run through all the ages in favor of males, with the 2–5-year age groups showing statistically significant differences ($t = 6.047$, $p < 0.001$). In this age group (2–5years), however, there is not much difference in sex hormones circulating in the children's bloodstream and no menstrual loss. The more likely explanation could be the preferential care that is usually accorded to male children in the study environment [37].

The overall mean WBC count of 9795.09 ±438.56 $x10^9$cl (range: 400.0 - 21000.0) in the present study is comparable to the 10.27 ±3.94 $\times 10^9$/L [20] and 10.7 ±6.3 $\times 10^9$/L [14] reported in previous studies. The range of 400–21000 counts observed in this study revealed that SCA in the steady state could present with leucopenia or leukocytosis, which is in agreement with the findings of Ahmed et al [14]. The mean WBC count was significantly greater in males than in females across all the age groups. Additionally, Ahmed et al. [14] alluded to this observation; however, the reason for this is not well understood. The causes of leukocytosis in SCA include a genetic predisposition [22] and hyperactive bone marrow, which inadvertently produces more WBCs while producing more red blood cells due to the hypoxic drive [17]. Other causes of leukocytosis include infections, pain, autosplenectomy, vaso-occlusive crisis, [17,20] and inflammation [6].

Furthermore, leukocytosis has been associated with vaso-occlusive crisis pain, acute chest syndrome, silent cerebral infarction, and overt stroke [20]. It is also a risk factor for frequent hospital admissions [15] and early sickle cell disease related death [9]. White blood cells obstruct blood vessels more effectively than sickled red blood cells because of their size (RBCs; 7.2 μm versus WBCs; 10–20 μm), [20] adhering to the endothelium lining of blood vessels and stimulating the vascular endothelium to increase the expression of ligands for the adhesion of molecules on other blood cells [6]. Vascular obstruction slows blood flow through the microvasculature, prolonging the transit time of sickle red blood cells (SS-RBCs) and thus increasing the likelihood of HbS polymerization within the microvasculature.[38]

Using the number of blood transfusions and crises per year to evaluate SCA severity in this study and relating their frequency to the hematology parameters, it was observed that only the WBC count could predict severity (Table 3). Consistent with what has been reported in the literature, elevated WBC counts are associated with severe complications such as acute chest syndrome, overt stroke and increased mortality [9,14,20,39]. In addition, the WBC count has been found to be an accurate test for detecting acute chest syndrome in SCD patients [14]. Despite the use of a 5% cut-off to classify HbF levels as high or low, there were no significant effects on the number of

blood transfusions or crises. The generally low HbF levels observed in this study could be an explanation. This observation agreed with the claim that significant effects of HbF on painful crises or clinical severity would only be evident if the HbF level is 20% and above, and 10% and above to prevent stroke [12].

Studies have shown that patients placed on hydroxyurea for varying durations had fewer pain episodes than did placebo-treated patients [24,40] and had significantly higher hematocrits and lower white blood cell (WBC) counts [41]. However, the present study could not establish any beneficial effects of hydroxyurea on the HbF level, WBC count, PCV or number of episodes of crisis. These observations could be explained by the fact that a large proportion, 94/110 (85.5%) of the study participants were not on hydroxyurea, and only 2 (1.8%) and 14 (12.7%) were on it for <6 months and >6 months, respectively. Therefore, the relatively small number of study participants on hydroxyurea and the short duration of its use might have prevented a clear or true picture of the effects of hydroxyurea from being observed in the present study. It has been documented that it takes several months to years of hydroxyurea use to be able to record meaningful effects [40,41]. Table 6 shows that the frequency of blood transfusions was significantly associated with hydroxyurea usage. This could be explained by the fact that HU is usually offered to SCA patients to ameliorate disease severity, and repeated blood transfusions are inclusive.

Limitations

The HbF values in this study were generally low, probably because of the method used for HbF determination. Additionally, only a few study participants were on hydroxyurea for a shorter duration, and which could explain its lack of effect on hematology and clinical parameters.

CONCLUSION

The mean HbF level was low, the mean PCV was within the normal range for the steady state, and the mean WBC count was high. Males had significantly greater PCVs, and those aged 6–10 years had significantly greater WBC counts. A high WBC count was associated with disease severity, and hydroxyurea use was associated with the frequency of blood transfusions. Multicenter studies with larger sample sizes are recommended to further evaluate the beneficial effects of hydroxyurea usage in the management of SCA.

Declaration by Authors

Ethical Approval: Approved, with approval reference number LTH/REC/2017/04/28/308.

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