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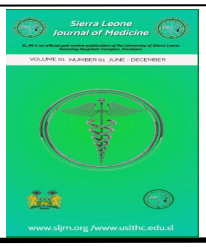

Hypoxaemia and Associated Factors among Children and Adolescents with Sickle Cell Anaemia in Steady State in a Tertiary Hospital in Nigeria.

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ABSTRACT

Background: Patients with sickle cell anaemia (SCA) develop complications as a result of repeated crises. Hypoxaemia has been observed in children with SCA in the absence of overt cardiopulmonary illness.

Objectives: To determine the prevalence of hypoxaemia and the clinical and laboratory features associated with hypoxaemia among SCA children in their steady state.

Methods: It is an observational cross-sectional study involving 102 SCA children aged 6-17 years in steady state. Their medical history was obtained, and oxygen saturation (SpO_2) was determined during the clinic visit. Echocardiography and spirometry were performed on the participants to investigate associated cardiopulmonary complications.

Results: The mean ± SD age of the children was 10.4 ± 3.49 years and the prevalence of hypoxaemia was 16.7%. Hypoxaemia was significantly associated with increasing age (p=0.003), repeated episodes of crisis of three or more times in the preceding year (p=0.030), type of crisis (haemolytic and vasoocclusive crisis) (p=0.038), non-usage of hydroxyurea (p=0.019) and tricuspid regurgitant velocity≥ 2.5 m/s (p=0.001). Previous history of acute chest syndrome, blood transfusion, haematocrit (PCV) and spirometry pattern had no significant relationship with hypoxaemia.

Conclusion: Hypoxaemia is common among children with sickle-cell anaemia in steady-state; hence, there is need to monitor the oxygen saturation of SCA patients, particularly adolescents and those with recurrent crisis.

Key words: Sickle-cell Anaemia, Haemolysis, Oxygen Saturation, Hypoxemia.

1. INTRODUCTION

Sickle cell anaemia (SCA) is a hereditary haematological disorder in which the individual's both β-globin subunit of haemoglobin has the sickle cell mutation (homozygous haemoglobin S- HbSS). This disorder impairs the oxygen carrying ability of the haemoglobin in the red blood cell. Appropriate delivery of oxygen to organs depends on efficient oxygen transport by the haemoglobin[1]. The lung being a highly vascularised organ is a notable organ that is distorted by SCA. The combination of chronic anaemia, repeated episodes of microvascular obstruction following vaso-occlusion, repeated pneumonia and/or acute chest syndrome (ACS) results in hypoxaemia[2-4]. These sickle cell events cause alteration of lung parenchyma, airways and pulmonary vasculature leading to reduced gas-exchange and ventilation-perfusion mismatch[5]. In addition, the inherent property of sickle cell haemoglobin-S causes a shift of the oxygen-haemoglobin dissociation curve to the right, resulting in abnormally low arterial oxygen saturation[6].

The peripheral oxygen saturation (SpO_2) reading below 90 per cent is low and considered hypoxaemia in low altitude settings[7], this value correlates with partial arterial oxygen pressure of lower than 60 mmHg and this is the point at which deterioration in clinical status manifests in ill patients. In a Nigerian study, hypoxaemia was observed to be present in SCA children both in the steady state and during crisis with a prevalence of 13% reported among those in steady state and 23.8% during crisis[3]. A

higher prevalence of 51.0% was reported by Ogah et al[8] among SCA children in steady state. Factors such as age, gender and reticulocyte count were observed to be associated with hypoxaemia in SCA patients.[3,4,8] Hypoxaemia was observed to be higher among individuals with haemoglobin less than 5 g/dl.[3] Quinn et al[5] reports that steady-state hypoxaemia is unrelated to previous episodes of acute chest syndrome, and it is not explained by chronic anaemia alone. Hypoxaemia in SCA patients may therefore be related to a subclinical or chronic cardiopulmonary disease due to irreversible remodelling of the pulmonary vasculature.[5] Gladwin et al,[9] observed that worsening steady-state hypoxaemia could be a marker of developing pulmonary hypertension or pulmonary dysfunction both of which are recognized complications of sickle cell anaemia.

Haemoglobin oxygen desaturation could be used to identify hypoxaemia in children with SCA who are at increased risk of developing pulmonary complications, particularly in settings where arterial blood gas measurement cannot be performed. The haemoglobin saturation can be determined non-invasively in a clinical setting through the use of pulse oximetry. Previous studies have shown a good correlation between SpO_2 measured by pulse oximetry and the value obtained from blood gas measurements.[6,10] The detection of hypoxaemia is important in SCA as hypoxaemia is a trigger for vaso-occlusive episodes. Hypoxaemia if left undetected and treated causes adverse effects on vital organs. This study aimed to find out the prevalence of hypoxaemia and to determine the clinical and laboratory features associated with hypoxaemia among SCA children in steady state.

2. MATERIALS AND METHODS

The Ethics and Research Committee of the Teaching Hospital gave approval for the study (protocol number: BUTH/ REC – 765).

2.1 Study Area:

This study was conducted at the Paediatrics sickle cell clinic of the Teaching Hospital. The hospital provides tertiary care to its patients and functions as a referral facility to primary as well as secondary healthcare centres within and outside the city, including neighbouring states.

2.2 Study Design:

This was an observational cross-sectional study. Children 6 - 17 years of age previously diagnosed with sickle cell anaemia in their steady state were studied. All the interested parents/ caregivers gave their written informed consent, while assent was also obtained from the older children. We excluded children whose parents/ caregivers did not give consent to participate in the study. All ethical principles guiding human research were adhered to.

2.3 Sample Size Determination:

The overall population of children with sickle cell anaemia is below 10,000; hence, the sample size for the study was calculated using the formula:[11]

nf (minimum sample size) = n/ 1+(n/ N)

$n = Z^2PQ/ D^2$

Where N is the estimated population sample size i.e., 195 sickle cell anaemic patients are seen at the Haematology clinic annually, Z is a constant usually set at 1.96, P is the proportion of SCA patients with hypoxaemia in steady state from a previous study and it is 13.0% per cent,[3] Q is 1-P; it is the proportion of the population not taking part in the study. D is the degree of desired accuracy usually put at 0.05. The sample size for the study was calculated as 102, with a 10% non-response rate allowance.

Participants: Children with sickle cell anaemia in their steady state[12] aged 6 - 17 years, who had no structural abnormality of the thoracic cage, with no previous diagnosis of asthma or heart disease were enrolled. The systematic sampling method was used to recruit participants for this study. We evaluated the interval of sampling (n) by dividing the calculated sample size of the study by the average number of children with SCA who attend the paediatric haematology clinic weekly. Using the average number of SCA children, every nth child with SCA who appears on the clinic register was chosen. The participants were chosen by balloting using the simple random sampling method. The process was done every week until the calculated sample size was achieved. When there was parental/ caregiver refusal of written consent, the next child with SCA on the clinic register was selected.

The study proforma was for data collection. Closed-ended questions were used in this study. The proforma was specifically developed for this study after a comprehensive literature review. The proforma was in English language and same was translated into the language the participants/caregivers understand. Information was obtained using the interviewer-administered method. The age, sex, parental education and occupation and the medical history such as frequency of crises, types of crises, number of transfusions in the preceding one-year, daily use of hydroxyurea in the last six months, and treatment histories were obtained and documented. Episodes of crisis, previous acute chest syndrome and treatment history were confirmed in their medical record. The parental socio-economic class was derived using the father's and mother's occupation and highest level of education according to the method described by Ibadin et al.[13]

A general and systemic examination was conducted for all participants in order to detect and exclude conditions, such as pneumonia and congenital or acquired heart disease. The haemoglobin oxygen saturation (SpO_2) of the SCA children was obtained using a pulse oximeter (Onyx II 9550™), two measurements were recorded during the ''steady state'' clinic visit (with an interval of 1-hour between each reading), the average of the two readings was recorded for each participant and was used to determine the prevalence of hypoxaemia. Hypoxaemia was defined as a haemoglobin oxygen saturation (SpO_2) value ≤ 90 per cent.[14] Three millilitres of blood were drawn from each participant for packed cell volume (haematocrit) estimation. Echocardiography and spirometry were done for the participants to investigate associated complications such as pulmonary hypertension and lung function abnormalities. Spirometry was done using the MIR Intermedical Spirolab spirometer which was standardized. Each child performed the test three times, the spirometer selected the best spirograms (of the three spirograms) that met acceptability and repeatability criteria. The measurement of FEV1; forced expiratory volume in the first second, FVC; forced vital capacity and ratio of FEV1/ FVC were recorded. The interpretation of spirometric measurements was done using the Global Lung Function Initiative - 2012 reference equation for African Americans.[15] Spirometry usually suggests one of the following types of ventilation patterns: normal, restrictive, obstructive or mixed pattern.[15] It is classified as: Normal values if FEV1/ FVC ≥ LLN; along with FVC ≥ LLN, Obstructive if FEV1/FVC < LLN; together with FVC ≥ LLN, Restrictive if FEV1/FVC ≥ LLN; with FVC < LLN and Mixed if FEV1/ FVC < LLN; together with FVC < LLN. The

echocardiography (transthoracic) was performed by a cardiologist. The Siemens Sonoline Omnia machine was used for echocardiography in line with standard guidelines.[16] Tricuspid regurgitant jet velocity (TRV) ≥ 2.5 m/s was considered suggestive of pulmonary hypertension.[9] The SCA children with hypoxaemia were further evaluated at the haematology clinic.

2.4 Definition of Key Variables

A steady state is the absence of sickle cell crises or any other illnesses for more than four weeks and not being transfused with blood in the preceding four months.[12]

Hypoxaemia was defined as a haemoglobin oxygen saturation (SpO_2) value ≤ 90 per cent.[14]

Acute chest syndrome is the evidence of a new pulmonary infiltrate on the chest radiograph, often in addition to symptoms such as fever and/or respiratory symptoms.

Data analysis was done with the SPSS version 25.0. Means ± standard deviations (SD) were determined for continuous variables. The Chi-square test was used to assess the relationship between categorical variables, while Mann-Whitney U was used to determine the relationship between hypoxaemia and the packed cell volume. Statistical significance was set at p-value < 0.05

3. RESULT

One hundred and two (102) SCA children were enrolled. Forty-three (42.2 %) children belonged to the age group 6-9 years. The mean ± SD age of the studied children was 10.4 ± 3.49 years. Sixty -five (63.7%) were males, with M: F of 1:0.6. Sixty-three (61.8%) participants were from the lower socioeconomic class. Socio-demographic characteristics of the participants are shown in Table1.

Seventeen (16.7 %) of the SCA participants had hypoxaemia.

Forty-four (43.1%) of the SCA children had three (3) or more sickle cell crises in the preceding year, with vaso-occlusive crisis being the commonest type of crises experienced in 64 (62.7%) of them. Eleven (10.8%) of the participants had a previous diagnosis of acute chest syndrome. Sixty-five (63.7%) of the children had received blood transfusion three or more times in the last 1 year while fourteen participants (13.7%) used hydroxyurea daily in the preceding six months. Their mean ± SD PCV (%) was 24 ± 2.6. Three (2.9%) participants had tricuspid regurgitant jet velocity (TRV) ≥ 2.5 m/s suggestive of pulmonary hypertension, the mean ± SD TRV was 1.58 ± 0.75. Seventy-one (69.9%) participants had normal spirometry. Restrictive spirometric pattern was recorded in 23 (22.5%) while the obstructive pattern was observed in eight (7.8%) participants. These findings are depicted in Table 2.

Most of the hypoxaemic patients (10 of 17) were adolescents between the ages of 10 - 13 years. The relationship between hypoxaemia and age of participants was statistically significant (p = 0.003). No statistically significant relationship exists between the gender and socio-economic class and hypoxaemia. Details of the relationship between hypoxaemia and socio-demographic characteristics are shown in Table 3.

The frequency of crises in the preceding year, type of crises, daily use of hydroxyurea and pulmonary hypertension (TRV ≥ 2.5m/s) had a statistically significant association with the development of hypoxaemia p = 0.030, 0.038, 0.019 and 0.001 respectively. The details of the relationship between hypoxaemia and the participants' clinical characteristics are depicted in Table 4.

Table 1: Demographic and Basic Characteristics of the Study-Participants

Variables	Frequency (n=102)	Percentage (%)
Age (in years)		
6 – 9	43	42.2
10 – 13	34	33.3
14 – 17	25	24.5
Sex		
Male	65	63.7
Female	37	36.3
Socioeconomic Class		
Lower	63	61.8
Middle	28	27.5
Upper	11	10.8

4. DISCUSSION

A The study has shown that the prevalence of hypoxaemia among sickle cell anaemic children in steady state was 16.7%. This finding is comparable to previous studies.[3,17] Chinawa et al[3] observed a prevalence of 13.0% among SCA children in steady state in Enugu, Southeast, Nigeria, while Saad et al[17] reported 13.9% among SCA children in Sudan. Hypoxaemia can be attributed to the underlying chronic anaemic state and obstruction of small vessels within the pulmonary circulation by sickled haemoglobin which can result in defect in membrane diffusion and may result to impaired oxygenation of blood even in a steady state.[2,3,5] Hypoxaemia is however not a universal finding in all children with SCA; hence this raises the significance of hypoxaemia in SCA children in steady state. A higher prevalence of 51.0% was documented by Ogah et al[8] among SCA children in Jos, Nigeria. The difference in the prevalence can be explained by the varied cut-offs used in diagnosing hypoxaemia. The present study defined hypoxaemia as haemoglobin oxygen saturation (SpO2) ≤ 90% while the study by

Table 2: Clinical Characteristics of the Study Participants

Variables	Frequency n=102	Percentage
Frequency of Sickle Cell Crises		
None	0	0.0
1 Per Year	24	23.5
2 Per Year	34	33.3
≥ 3 Per Year	44	43.1
Type of Crises		
Vaso Occlusive Crisis	64	62.7
Haemolytic Crisis	22	21.6
Sequestration Crisis	0	0.0
Mixed Crisis*	16	15.7
Previous Acute Chest Syndrome		
Yes	11	10.8
No	91	89.2
Blood Transfusion History (in the Last One Year)		
None	23	22.5
1-2 times	14	13.7
≥ Three times	65	63.7
Daily Use of Hydroxyurea		
Yes	14	13.7
No	88	86.3
Pulmonary Hypertension (TRV ≥ 2.5 m/s)		
Yes	3	2.9
No	99	97.1
Spirometric Pattern		
Normal	71	69.6
Obstruction	8	7.8
Restriction	23	22.5

*Mixed crisis: combination of vaso-occlusive and haemolytic crisis. Mean Tricuspid Regurgitant Jet Velocity (TRV) is 1.58 ± 0.75SD

Table 3: Association Between Hypoxaemia and the Socio-Demographic Characteristics of the Participants

Variables	Hypoxaemia		χ^2	P-value
	Yes n(%)	No n(%)		
Age (in Years)				
6 – 9	1(2.3)	42 (97.7)	11.312	**0.003**
10 – 13	10 (29.4)	24 (70.6)		
14 – 17	6 (24.0)	19 (76.0)		
Sex				
Male	12 (18.5)	53 (81.5)	0.416	0.519
Female	5 (13.5)	32 (86.5)		
Socio-Economic Class				
Lower	13 (20.6)	50 (79.4)		
Middle	2 (7.1)	26 (92.9)	2.561	0.278
Upper	2 (18.2)	9 (81.8)		

Ogah et al 8 defined hypoxaemia using SpO2 ≤ 95%.

This study noted that hypoxaemia was associated with increasing age. The older the individuals with SCA live, the more likely they are to have developed complications of the disease. Pulmonary complications and poor alveolar wall compliance with alveolar hypoxia as a consequence of recurrent sickling are commoner with increasing age as seen by the higher frequency of hypoxaemia observed in the older age groups than in the younger ones. This finding is consistent with previous studies.[8,17] More males had a higher frequency of hypoxaemia, although this finding did not reach statistical significance, it is comparable to previous studies.[3,5] The biological explanation of this finding was not investigated in this study, however, a previous study reported that low oxygen saturation in males could be due to a transcription factor for haemoglobin-F and Endothelial-B receptors which have been connected to the X-chromosome.[18] The receptors are fewer in males compared to females.[3,18] Majority of the SCA children who were hypoxaemic belong to the lower socio-economic class, although, this was not statistically significant. Socio-economic status is known to be a determining factor of the severity of disease and the presence of complications in resource-poor settings.[19] Earlier study by Bello-Manga et al[20] reported that the prevalence of adverse events among children with SCA was higher in those from the low socio-economic class.

This study showed that repeated episodes of crisis of three or more times in the preceding year, haemolytic crisis, non-usage of hydroxyurea and tricuspid regurgitation velocity (TRV) ≥ 2.5 m/s were significantly associated with hypoxaemia. This finding is the same as Nouraie et al[21] who noted that haemolysis was lower with hydroxyurea therapy but increased haemolysis was associated with lower peripheral oxygen saturation and elevated measurements for tricuspid regurgitation velocity. Hydroxyurea reduces the frequency of crises and red cell haemolysis thus having a favourable effect on red blood cell volume and cellular deformability.[22] Haemolysis is a contributing factor to the development of pulmonary hypertension.[23,24] Haemolysis causes releases of free haemoglobin (Hb) into the blood circulation. The oxygenated haemoglobin (Fe2+) facilitates endothelial dysfunction by using up endothelial nitric oxide (NO) which is responsible for maintaining smooth muscle relaxation and vascular tone. During haemolysis, there is excessive production of reactive oxygen species which also reduces NO production. These processes contribute to the irreversible remodelling of the pulmonary vasculature.[23,24] Recurrent haemolysis results in chronic anaemia consequently leading to low oxygen saturation. A study also hypothesized that haemolysis causes abnormal regulation of blood flow to the lung, resulting in ventilation and perfusion match.[23] Similar to this study, Gladwin et al[9] observed that steady-state hypoxaemia could be a marker of developing pulmonary hypertension; a recognized complication of

Table 4: Association Between Hypoxaemia and the Participants' Clinical Characteristics

Variables	Hypoxaemia		Test Statistics	P-value
	Yes n(%)	No n(%)		
Crisis in Preceding Year				
Once	0 (0.0)	24 (100.0)		
Twice	6 (17.6)	28 (82.4)	χ^2=7.024	**0.030**
≥ Three Times	11 (25.0)	33 (75.0)		
Type of Crisis				
Vasoocclusive Crisis	12 (18.8)	52 (81.3)	LRχ^2=6.562	**0.038**
Haemolytic	5 (22.7)	17 (77.3)		
Sequestration	0 (0.0)	0 (0.0)		
Mixed	0 (0.0)	16 (100.0)		
History of Acute Chest Syndrome				
Yes	2 (18.2)	9 (81.8)	χ^2=0.020	0.886
No	15 (16.5)	76 (83.5)		
History of Blood Transfusion				
None	2 (8.7)	21 (91.3)		
1-2 times	2 (14.3)	12 (85.7)	χ^2=1.629	0.443
≥ Three times	13 (20.0)	52 (80.0)		
Daily Use of Hydroxyurea				
Yes	0 (0.0)	14 (100.0)	LRχ^2=5.533	**0.019**
No	17 (19.3)	71 (80.7)		
Median PCV	23.0	24.0	U = 590.0	0.231
Pulmonary Hypertension				
Yes	3 (100.0)	0 (0.0)		
No	14 (14.1)	85 (85.9)	LRχ^2=11.225	**0.001**
Spirometry Pattern				
Normal	13 (18.3)	58 (81.7)	χ^2=0.455	0.796
Restrictive	3 (13.0)	20 (87.0)		
Obstructive	1 (12.5)	7 (87.5)		

LRχ^2 = Likelihood Ratio Chi-square

sickle cell anaemia. Odeyemi et al[25] also reported an association between pulmonary hypertension and decreasing oxygen saturation and haematocrit.

The present study shows that there was no association between the pattern of spirometry and hypoxaemia. The majority; 13 of 17 children who had hypoxaemia had normal spirometry, this may explain why the SCA subjects had no apparent respiratory symptoms. The predominant abnormal spirometry observed was a restrictive pattern, with 13% of them having hypoxaemia. Earlier study has shown that spirometric lung function abnormalities increase with increasing age.[26] In this study, the older adolescents who were likely to have spirometric abnormalities were the minority, this may explain why the pattern of spirometry and hypoxaemia was not significantly different. Similar finding was reported by Dei-Adomakoh et al[27] who observed that the mean oxygen saturation of Hb-SS subjects with normal or abnormal spirometry outcomes was not significantly different. Previous history of acute chest syndrome, blood transfusion history and PCV had no significant effect on the development of hypoxaemia. Similar to this finding, Saad et al[17] noted that hypoxaemia did not correlate with the patient's haematocrit level. In this study, majority of the SCA children received repeated blood transfusions, this may be the reason why there was no association with hypoxaemia; as blood transfusion is one of the treatment modality of treating severe hypoxaemia. The total number of participants with a history of acute chest syndrome (ACS) in this study were few, this might have contributed to why it did not reach statistical significance. Previous study reported that acute chest syndrome is associated with the development of hypoxaemia.[3] Longstanding hypoxaemia in steady state may contribute to the development of sickle cell vasculopathy resulting in chronic organ damage. This highlights the need for monitoring oxygen saturation in children with sickle cell anaemia.

4.1 Conclusion:

Hypoxaemia is prevalent among children with SCA who are in steady state; hence, there is need to monitor the haemoglobin oxygen saturation of children with SCA; particularly adolescents and those with repeated haemolytic crises. Echocardiography is valuable in screening children with SCA with hypoxaemia for the development of pulmonary hypertension.

Limitation: An important limitation of this study is the inability to perform cardiac catheterization, which is considered the gold standard for the diagnosis of pulmonary hypertension; this was due to its unavailability at the study center. Nonetheless, the use of spirometry and echocardiography represents a methodological strength, as these non-invasive tools enabled the detection of cardiopulmonary abnormalities in the study participants.

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Authors' Contribution:

OAO; conceptualization, data acquisition, data analysis, validation and writing of initial draft

OYT and OOO; data acquisition, validation, reviewing and editing the content of the manuscript.

OAO; data acquisition, data analysis, validation, reviewing and editing the content of the manuscript.

IOJ and OAT; data acquisition, validation and reviewing of the manuscript.

Availability of Data

The data for the study are available on request from the corresponding author.

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