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Hematology Case Reports and Reviews OPEN ACCESS JOURNAL

ISSN: 2640-7914 DOI: https://dx.doi.org/10.17352/ahcrr

Research Article

Evaluation of Haemoglobin F and Haemoglobin A2 among Sickle Cell Patients in Steady State at Selected Hospital in Ogun State, Nigeria

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Received: 11 October, 2024
Accepted: 21 October, 2024
Published: 22 October, 2024

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Keywords: Sickle cell anemia; Hemoglobin F; Hemoglobin A2; High-performance liquid chromatography; Steady-state

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Abstract

Background: Sickle cell anemia (SCA) is a genetic disorder characterized by abnormal hemoglobin variants, including hemoglobin F (Hb F) and hemoglobin A2 (Hb A2). Evaluating the levels of these hemoglobin variants in steady-state sickle cell patients can provide insights into disease prognosis and management. This study aimed to assess Hb F and Hb A2 levels among sickle cell patients in steady state at a selected hospital in Ogun State, Nigeria.

Objective: To evaluate the levels of hemoglobin F (Hb F) and hemoglobin A2 (Hb A2) in sickle cell anemia patients and determine their associations with demographic factors such as age and gender.

Materials and methods: A descriptive cross-sectional study was conducted at the Sickle Cell Center, Abeokuta, Ogun State, Nigeria, from September to October 2020. A total of 60 sickle cell patients in steady state were recruited using convenient sampling. Blood samples were collected, and Hb F and Hb A2 levels were measured using high-performance liquid chromatography (HPLC). Data were analyzed using SPSS version 26.0 with independent t-test and bivariate correlation.

Results: The mean levels of Hb F and Hb A2 varied across age groups and genders. Hb F levels were highest in patients over 35 years (10.4 ± 12.16%) and lowest in those aged 26-30 years (3.7 ± 1.3%). The majority of participants had Hb F levels between 2-10%, with a significant association between Hb F levels and age (p = 0.038). Hb A2 levels were consistently above 3.1% in 92.6% of the study population, with no significant association with age or gender.

Conclusion: There is a significant association between age and Hb F levels among steady-state sickle cell patients, while Hb A2 levels showed no significant demographic correlations. The findings suggest that Hb F may serve as a potential marker for clinical evaluation in SCA patients.

Introduction

Sickle cell disease (SCD) is one of the most prevalent genetic disorders globally, especially in sub-Saharan Africa, where the burden of the disease is significantly high. Sickle cell disease results from a mutation in the β-globin gene, leading to the production of abnormal hemoglobin S (HbS), which causes red blood cells to become rigid and sickle-shaped under deoxygenated conditions [1]. These distorted cells obstruct capillary blood flow, causing ischemic injury and leading to various complications such as pain crises, anemia, and organ damage. Despite advances in clinical care, patients with SCD continue to experience significant morbidity and mortality [2].

Hemoglobin F (HbF) and hemoglobin A2 (HbA2) have been identified as critical modulators of the clinical severity of SCD. Hemoglobin F is the primary hemoglobin in the fetal stage and is replaced by adult hemoglobin (HbA) after birth. However,

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certain individuals, especially those with SCD, may retain higher levels of HbF, which has been associated with a milder clinical course of the disease [3]. This is because HbF interferes with the polymerization of HbS, thereby reducing red blood cell sickling and improving clinical outcomes. Elevated HbA2 levels have also been observed in individuals with SCD, often in association with β-thalassemia traits [4]. Understanding the distribution of these hemoglobin variants in SCD patients, particularly in steady-state conditions, can provide insights into patient management and prognosis (Figure 1).

SCD is most prevalent in regions where malaria is endemic due to the evolutionary advantage conferred by the sickle cell trait [6]. It is estimated that over 300,000 infants are born annually with SCD worldwide, and Nigeria accounts for nearly 50% of this burden, with over 150,000 newborns affected yearly [7]. The condition remains a significant public health concern in Nigeria, contributing to high infant and under-five mortality rates, despite the availability of diagnostic and therapeutic interventions (Figure 2) [8].

In Nigeria, patients with SCD face numerous challenges, including late diagnosis, limited access to specialized care, and a lack of comprehensive public health strategies for disease management [10]. Consequently, SCD patients frequently experience severe complications such as stroke, acute chest syndrome, and renal impairment, which contribute to early mortality [1]. Furthermore, the stigma associated with the disease often leads to social isolation and poor mental health outcomes [7].

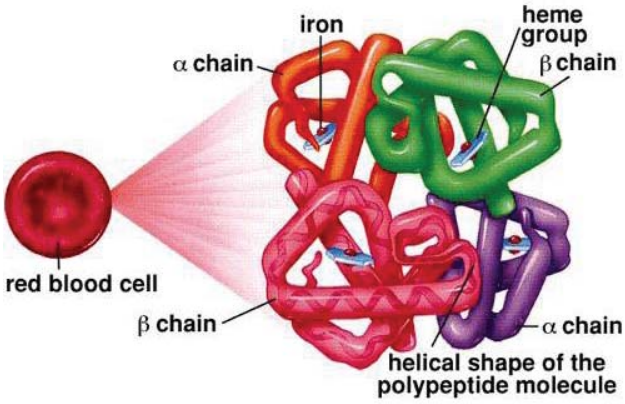

Figure 1: Haemoglobin molecule [5].

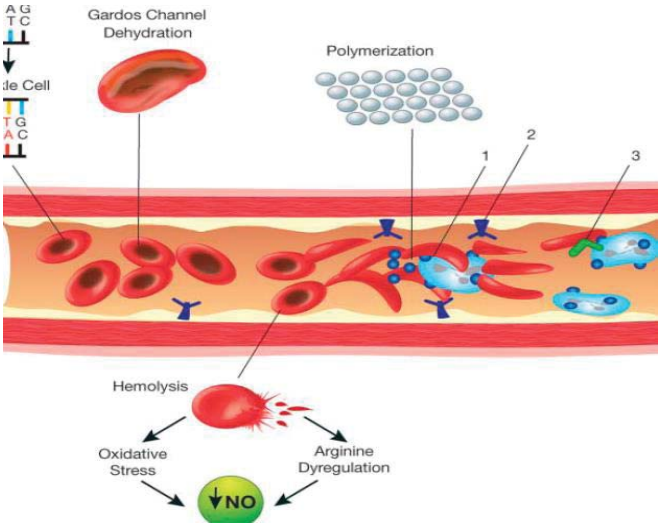

Figure 2: Schematic representation of the pathophysiology (in part) of sickle cell anemia [9].

The clinical heterogeneity observed among SCD patients has spurred extensive research into genetic and environmental modifiers of disease severity. Among these, the levels of HbF have been recognized as a key factor in modulating disease outcomes [3]. Higher HbF levels are associated with reduced sickling of red blood cells, fewer vaso-occlusive episodes, and improved survival [11]. In clinical practice, hydroxyurea, a drug that stimulates HbF production, is frequently used to manage SCD [2]. However, natural variations in HbF levels exist, with some patients demonstrating persistently high HbF without pharmacologic intervention, indicating a genetic predisposition [4].

The role of HbA2 in SCD is less well understood. HbA2 is typically elevated in individuals with β-thalassemia, a condition that can co-exist with SCD, complicating the clinical picture. The quantification of HbA2 is essential for the differential diagnosis of co-inherited hemoglobinopathies and can aid in predicting the clinical course of the disease [8].

The clinical course of SCD is influenced by numerous factors, including hemoglobin genotype, baseline hemoglobin levels, and the presence of other hemoglobin variants like HbF and HbA2 [2]. Given the high prevalence of SCD in Ogun State and the lack of comprehensive data on the distribution of hemoglobin variants in this population, it is critical to evaluate the levels of HbF and HbA2 among SCD patients in steady-state conditions. This study aims to provide a better understanding of the correlation between these hemoglobin variants and the clinical manifestations of SCD, with a view toward improving patient management and outcomes.

The findings from this study are expected to contribute to the growing body of literature on SCD in Nigeria and provide evidence for the implementation of tailored therapeutic strategies aimed at increasing HbF levels in patients with severe disease manifestations. Furthermore, the study will explore the potential role of HbA2 as a diagnostic marker in SCD patients, particularly those with concomitant β-thalassemia traits.

Materials and methods

Research design

This study was a descriptive cross-sectional study to evaluate hemoglobin A2 and hemoglobin F among sickle cell anaemia patients between September and October 2020

Study area

This study was carried out in Sickle Cell Center, Abeokuta, Ogun state located at latitude 6.322 °N and longitude 5.6176 °E in the South-Western region of Nigeria.

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Study subjects and population

The convenient sampling method was used for this study. Adults and children who have sickle cell anaemia in steady state (study subjects) in Sickle Cell Center in Abeokuta, Ogun state, Nigeria (study population), willing to participate in the study were recruited after informed consent was obtained from each of them. Their participation was highly voluntary.

Sample size determination

The sample size was determined using the Cochran formula for estimating proportions in a population outlined by Onyemereze, et al. [12]:

$$n = \frac{Z^2(Pq)}{e^2}$$

Where n = minimum sample size

Z = 1.96 at 95% confidence level,

P = known/expected prevalence

e = error margin tolerated at 5% = 0.05

q = 1 - p

The existing prevalence is 3.5%.

P = 3.5% = 0.035

q = 1 – p

= 1 – 0.035

= 0.965

$$n = \frac{(1.96)^2 (0.035 \times 0.965)}{(0.05)^2}$$

$$n = \frac{3.8416 \times (0.033775)}{0.0025}$$

$$n = \frac{0.12975}{0.0025} = 51.9$$

The minimum sample size was 52. However, for uniformity and accuracy, the value was scaled up to a higher value of 60 (comprising 60 test samples and 60 control samples).

Eligibility of subjects

Inclusion criteria

- ✓ Children and adults diagnosed with sickle cell anaemia in steady state
- ✓ HIV-negative sickle cell anaemic patients

Exclusion criteria

- ✓ Subjects who are unwilling to provide consent for the collection of data
- ✓ HIV-positive sickle cell anaemic patient

Consent

Informed consent was obtained from participants before beginning the study. The aim, purpose, objective, nature, and benefits of the study as well as the method of sample collection were properly explained to each of the participants. They were assured of confidentiality, voluntariness, and protection. They were well informed of their option to withdraw from the study at any time. The intending participants were requested to complete a consent form which was properly endorsed by a signature indicating that they were willing to partake without any form of pressure. The investigation was carried out at no cost to the participants.

Ethical consideration

Ethical clearance was obtained from Babcock University Health Research Ethics Committee (BUHREC) with reference number BUHREC 165/20b before the study commenced.

Sample collection

Five millilitres (5 ml) of venous blood were obtained from each participant via vein puncture. The collected blood sample was transferred into EDTAk_2 bottles, the container was inverted to mix the anticoagulant with the blood.

Evaluation of hemoglobin F and hemoglobin A2

For this study, high-performance liquid chromatography (HPLC) was used to estimate the level of hemoglobin F and Hemoglobin A2.

High-performance liquid chromatography (HPLC) is an important analytical method commonly used to separate and quantify components of liquid samples. In this technique, a solution (first phase) is pumped through a column that contains a packing of small porous particles with a second phase bound to the surface. The different solubilities of the sample components in the two phases cause the components to move through the column with different average velocities of these components.

The pumped solution is called the mobile phase, while the phase in the column is called the stationary phase.

Principle of high-performance liquid chromatography

The separation principle of HPLC is based on the distribution of the analyte (sample) between a mobile phase (eluent) and a stationary phase (packing material of the column). Depending on the chemical structure of the analyte, the molecules are retarded while passing the stationary phase. The specific intermolecular interactions between the molecules of a sample and the packing material define their time "on-column". Hence, different constituents of a sample are eluted at different times. Thereby, the separation of the sample ingredients is achieved. A detection unit (e.g. UV detector) recognizes the analytes after leaving the column. The signals are converted and recorded by a data management system

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(computer software) and then shown in a chromatogram. After passing the detector unit, the mobile phase can be subjected to additional detector units, a fraction collection unit, or to waste. In general, an HPLC system contains the following modules: a solvent reservoir, a pump, an injection valve, a column, a detector unit, and a data processing unit. The solvent (eluent) is delivered by the pump at high pressure and constant speed through the system. To keep the drift and noise of the detector signal as low as possible, a constant and pulseless flow from the pump is crucial. The analyte (sample) is provided to the eluent by the injection valve.

Procedure

The system was set up, the pump was primed, the column was prepared, and the software for sample run was set up. About 5 to 8 µl whole blood was diluted with 1 ml Hemolysis Reagent, it was mixed well (vortex). The injection port plug was released by turning the bottom lever down. The round silver port plug was removed and placed in the hole in the valve handle. About 10 ul of the sample was drawn into the Hamilton syringe. The syringe was inserted fully into the sample port. The sample was injected. The round silver port plug was replaced into the port. The bottom lever was turned up until the lever was tight. The upper switch was turned to the "Inject" position. This automatically started data acquisition. The upper switch was turned to the "Load" position after 30 seconds. This should start the data acquisition. The display changed from "Waiting for Injection" to "running". The syringe was rinsed thoroughly with deionized water until clean. Chromatograph data was obtained after the test had been carried out.

Statistical analysis

The collected data was entered into Microsoft Excel. Statistical analysis was then carried out using the SPSS (Statistical Package for Social Sciences) software package (version 26.0), independent t-test, and bivariate correlation. Statistical analysis outputs were presented using tables and graphs. Data were considered significantly different at a 95% confidence level ($p < 0.05$).

Results

The socio-demographic data in Table 1 shows that the majority of the study subjects were aged between 18-25 years (48.1%) and identified as Christians (88.9%). Most participants were single (85.2%) and predominantly of Yoruba ethnicity (66.7%). The gender distribution was fairly balanced, with 55.6% male and 44.4% female participants.

Regarding hemoglobin levels, Table 2 illustrates the mean ± SD values for Hb F and Hb A2 across different age groups and gender. Although no significant difference was observed in Hb F ($p = 0.073$) or Hb A2 ($p = 0.078$) based on age, participants under 18 years had the highest mean Hb F levels (9.74 ± 4.14), while those aged 26 - 30 had the highest Hb A2 levels (4.1 ± 0.14). There were no significant differences in Hb F ($p = 0.630$) or Hb A2 ($p = 0.608$) levels between males and females.

Table 3 reveals that age significantly impacted Hb F levels ($\chi 2 = 13.37$, $p = 0.038$), with the highest percentage of participants (66.7%) having Hb F levels between 2% - 10%.

Table 1: Socio-demographic variations of study subjects.

Variable	Frequency	Percentage
Age (years)		
<18	10	37%
18-25	13	48.1%
26-30	2	7.4%
>35	2	7.4%
Religion		
Christianity	24	88.9%
Islam	3	11.1%
Marital status		
Married	4	14.8%
Single	23	85.2%
Tribe		
Hausa	1	3.7%
Igbo	3	11.1%
Yoruba	18	66.7%
Others	5	18.5%
Gender		
Male	15	55.6%
Female	12	44.4%

Table 2: Comparison of Mean±SD of Hb F and Hb A2 of study subjects.

	Hb F		Hb A2	
Age (years)		p - value = 0.073		p - value = 0.078
<18	9.74 ± 4.14		3.5 ± 0.4	
18 - 25	5.36 ± 3.4		3.9 ± 0.39	
26 - 30	3.7 ± 1.3		4.1 ± 0.14	
>35	10.4 ± 12.16		3.8 ± 0.00	
Gender		p - value = 0.630		p - value = 0.608
Male	6.85 ± 5.2		3.7 ± 0.5	
Female	7.7 ± 4.4		3.8 ± 0.3	

Table 3: Distribution and association analysis between Hb F Levels with respect to age and gender among study subjects.

	Hb F Level (%)			Total	χ2	p - value
	<2	2-10	>10			
Age (years)					13.37	0.038*
<18	0(0%)	5 (18.5%)	5 (18.5%)	10 (37%)		
18-25	1(3.7%)	11 (40.7%)	1(3.7%)	13(48.1%)		
26-30	0(0%)	2 (7.4%)	0(0%)	2 (7.4%)		
>35	1(3.7%)	0(0%)	1(3.7%)	2 (7.4%)		
Total	2 (7.4%)	18(66.7%)	7(25.9%)	27(100%)		
Gender					0.707	0.702
Male	1(3.7%)	11 (40.7%)	3(11.1%)	15(55.6%)		
Female	1(3.7%)	7(25.9%)	4(14.8%)	12(44.4%)		
Total	2 (7.4%)	18(66.7%)	7(25.9%)	27(100%)		

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Gender, however, did not significantly influence Hb F levels ($\chi 2 = 0.707$, $p = 0.702$).

In Table 4, Hb A2 levels were mostly above 3.1% (92.6%) across age groups and genders, with no significant associations between Hb A2 levels and age ($\chi 2 = 0.420$, $p = 0.936$) or gender ($\chi 2 = 1.728$, $p = 0.189$). Furthermore, Table 5 shows no significant association between Hb A2 and Hb F levels ($\chi 2 = 1.080$, $p = 0.583$).

Figures 3 and 4 reinforce these findings, showing that 92.6% of participants had Hb A2 levels above 3.1%, and 66.7% had Hb F levels between 2% - 10%. The correlational analysis in Figure 5 highlights a negative correlation between Hb A2 and Hb F levels (R = -0.252), though the relationship was not statistically significant (p = 0.205).

Table 4: Distribution and association analysis between Hb A2 Levels with respect to age and gender among study subjects.

	Hb A2 Level (%)		Total	χ2	p - value
	1.5 - 3.1	>3.1			
Age (years)				0.420	0.936
<18	1(3.7%)	9(33.3%)	10 (37%)		
18-25	1(3.7%)	12(44.4%)	13(48.1%)		
26-30	0(0%)	2 (7.4%)	2 (7.4%)		
>35	0(0%)	2 (7.4%)	2 (7.4%)		
Total	2 (7.4%)	25(92.6%)	27(100%)		
Gender				1.728	0.189
Male	2 (7.4%)	13(48.1%)	15(55.6%)		
Female	0(0%)	12(44.4%)	12(44.4%)		
Total	2 (7.4%)	25(92.6%)	27(100%)		

Table 5: Distribution and association analysis between Hb A2 Hb F among study subjects.

	Hb A2 Level (%)		Total	χ2	p - value
	1.5 - 3.1	>3.1			
Hb F Level (%)				1.080	0.583
<2	0(0%)	2 (7.4%)	2 (7.4%)		
2-10	2 (7.4%)	16(59.3%)	18(66.7%)		
>10	0(0%)	7 (25.9%)	7 (25.9%)		
Total	2 (7.4%)	25(92.6%)	27(100%)		

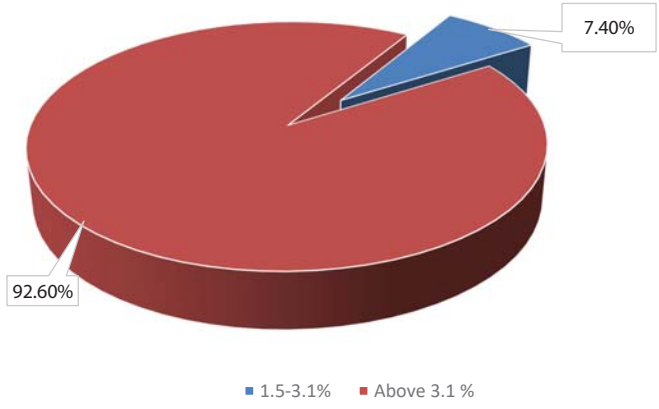

Figure 3: Distribution of Hb A2 Level among study.

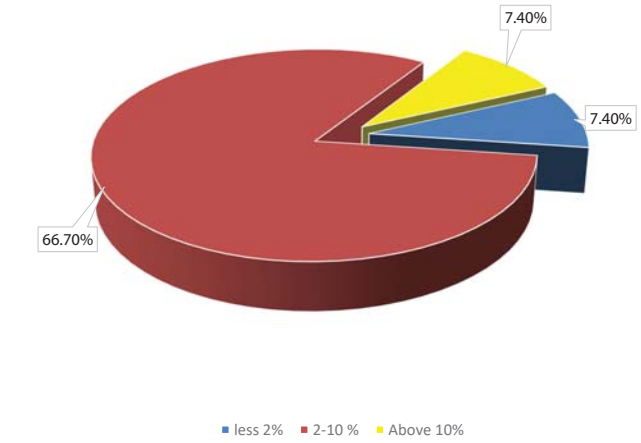

Figure 4: Distribution of Hb F Level among study.

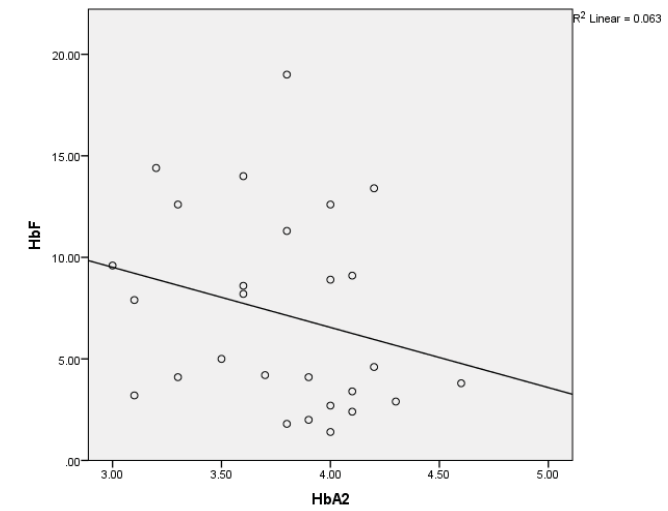

Figure 5: Correlational Analysis between HbA2 and Hb F among study subject.

Discussion

The current study evaluated the levels of Hemoglobin F (Hb F) and Hemoglobin A2 (Hb A2) among sickle cell patients in a steady state at a selected hospital in Ogun State, Nigeria. The findings revealed several important demographic and clinical insights about Hb F and Hb A2 distribution, with significant implications for the management of sickle cell disease (SCD).

The study population had a higher representation of individuals between the ages of 18 and 25 (48.1%), while the proportion of participants under 18 years was 37%. These results are consistent with the demographic trends observed in similar studies, where young adults and adolescents with sickle cell anemia (SCA) constituted a large proportion of study populations due to their frequent need for healthcare interventions during the transition from pediatric to adult care.

In terms of gender distribution, males accounted for 55.6% of the study subjects, while females made up 44.4%.

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Previous studies have shown varying gender distributions in SCD populations; however, many have reported no significant differences in the clinical presentation or progression of SCD between genders. The higher representation of males in this study might be incidental rather than indicative of any gender-based predisposition.

In this study, the mean levels of Hb F were found to vary significantly across age groups (p = 0.038), with younger participants (under 18 years) displaying higher mean Hb F levels (9.74 ± 4.14%) compared to older age groups. Interestingly, participants aged above 35 years also demonstrated elevated Hb F levels (10.4 ± 12.16%), though the small sample size in this category could have contributed to the wide standard deviation. These findings are in line with established literature, which suggests that Hb F levels are higher in younger individuals due to residual fetal hemoglobin, which gradually declines with age.

Higher Hb F levels have been associated with milder disease symptoms in SCD, as Hb F inhibits the sickling of red blood cells by preventing the polymerization of hemoglobin S. The variation of Hb F levels across age groups highlights the importance of early diagnosis and possible therapeutic interventions aimed at increasing Hb F to mitigate the complications of SCD.

For Hb A2, the age-related variations were not statistically significant (p = 0.936), with mean Hb A2 levels ranging from 3.5% to 4.1% across the different age groups. These values align with previous reports, which have found that Hb A2 levels remain relatively stable across different ages in sickle cell patients.

The distribution of Hb F and Hb A2 levels between males and females did not show significant gender-based differences. The mean Hb F levels for males (6.85 ± 5.2%) and females (7.7 ± 4.4%) were not statistically different (p = 0.630). Similarly, no significant difference in Hb A2 levels between males (3.7 ± 0.5%) and females (3.8 ± 0.3%) was observed (p = 0.608). These findings are consistent with previous studies that have shown no significant gender-based variations in Hb F or Hb A2 levels among SCD patients.

A significant association was found between Hb F levels and age ($\chi 2$ = 13.37, p = 0.038), with younger participants predominantly exhibiting Hb F levels between 2% - 10%. A similar observation has been reported in previous studies, where elevated Hb F levels were noted in younger individuals with SCD. The protective effect of Hb F in reducing the severity of SCD symptoms is well documented, as higher Hb F levels are associated with fewer pain crises and reduced need for transfusions.

Regarding Hb A2, no significant associations with age ($\chi 2$ = 0.420, p = 0.936) or gender ($\chi 2$ = 1.728, p = 0.189) were found. This is consistent with literature that suggests Hb A2 levels are relatively stable in SCD patients and are not influenced by demographic factors.

The study found a weak, negative correlation (R = -0.252) between Hb A2 and Hb F levels, although this correlation was not statistically significant (p = 0.205). Previous research has demonstrated that while Hb F levels tend to vary widely in SCD patients, Hb A2 levels generally remain within the normal range, suggesting that the two hemoglobin fractions do not directly influence each other. This weak correlation may indicate independent regulatory mechanisms for Hb F and Hb A2 synthesis in sickle cell patients.

The findings from this study emphasize the clinical importance of monitoring Hb F levels in SCD patients. Elevated Hb F levels have been associated with better disease outcomes, including fewer vaso-occlusive crises, improved hemolysis markers, and enhanced overall quality of life. Thus, therapeutic approaches such as hydroxyurea, which stimulates Hb F production, could be further explored in this population to manage SCD effectively.

While Hb A2 levels are generally not elevated in SCD patients, the slight increase observed in some participants could be indicative of β-thalassemia traits, which can coexist with SCD. This warrants further genetic studies to explore possible co-inheritance of hemoglobinopathies among this population.

Conclusion

This study provided important insights into the distribution of Hb F and Hb A2 among sickle cell patients in Ogun State, Nigeria. Age-related variations in Hb F levels underscore the potential for targeted therapies aimed at increasing Hb F, especially in younger patients. Further research with larger sample sizes is recommended to validate these findings and explore additional factors influencing hemoglobin variants in SCD patients.

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