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An Estimation of Haemoglobin Variants Among Patients Attending A Tertiary Hospital In South West Nigeria

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A B S T R A C T

Background: Globally, hemoglobinopathies, which are genetic diseases of hemoglobin production, are a major cause of morbidity and mortality. African communities make up a sizable portion of the population that is susceptible to a variety of erythrocyte genetic and homological illnesses.

Aim: The aim of this study is to investigate the prevalence and spectrum of hemoglobin variants among patients attending a tertiary hospital in South West Nigeria.

Materials and Methods: The study research was conducted at the University of Medical Sciences Teaching Hospital, Ondo State Southwest Nigeria. Respondents were recruited from the hospital department clinics and tested at Department of Haematology, Faculty of basic medical science. Blood will be drawn via venipuncture into tubes that had been treated with the anticoagulant ethylene diamine tetracetic acid (EDTA)

Results: The study show the frequency and gender distribution of different forms of haemoglobin (Hb) among the subjects; Hb AA 264; HbAS 60; HbAC 6; HbSC 8 and HbSS 12. Of the 350 subjects studied, 106 were males, while 244 were females. Among the male subjects, 85 were HbAA, 12 were HbAS; 2 were HbAC; 3 were HbSC and 4 were HbSS. Among the female subjects, 179 were HbAA, 48 were HbAS; 4 were HbAC; 5 were HbSC and 8 were HbSS. The study shows the frequency of the fetal hemoglobin among the Hb SS patients in the study based on age range. 50% of the participants with fetal hemoglobin were between 10-15 years, 25% were between 16-20 years, 8.3% were between 21-25 years, 8.4% were between 31-35 years and 8.3 % were between 36-40 years

Conclusion: The study showed increased prevalence of various hemoglobin variants. Awareness should be created at religious centers, schools on the importance of genotype testing. As a preventative precaution. We advise the implementation of mutation identification and carrier screening.

Introduction

A major issue in global health is hemoglobinopathies. Approximately 80% of births with severe hereditary hemoglobin disorders take place in low- or middle-income countries, particularly in Africa, where it has been discovered that an estimated 300,000 number of such babies born each year [1]. Haemoglobin diseases known as hemoglobinopathies are hereditary. They are the most prevalent genetic illnesses, and 7% of people worldwide are carriers. Out of an estimated 25 million people worldwide, the sickle cell disease is most frequently found in sub-Saharan Africa (SSA), where 15 million people dwell [3,4]. But according to the 2019 Global Burden of Disease (GBD) study, the overall under-5 death rate in sub-Saharan Africa was just 0.66% (95% CI 041-094) attributable to sickle cell disease. The prevalence rate in Nigeria was 0.82% (95% CI 0.37-1.34). Disparities like this assist in explaining why child mortality from sickle cell disease in sub-Saharan Africa continues to receive little worldwide attention [5].

A mutation in the hemoglobin gene results in hemoglobin (Hb) S, a structural variant of normal adult hemoglobin (HbA) [6]. Any condition where there is more than 50% HbS and it has pathological effects is referred to as SCD. The homozygous inheritance of the beta-globin subunit mutation causes the most prevalent form (> 70%) of sickle cell disease (SCD), also known as sickle cell anemia, which is also the most severe form of the disease [7]. There are more than 700 structural haemoglobin variations, but only two are widespread in Africa (HbS and HbC) [7,8]. The carrier state, also known as the Sickle Cell Trait (SCT), is a heterozygous type distinguished by the presence of up to 40% HbS and the absence of anemia [8].

HbF is the most effective moderator of the clinical and hematologic features of sickle cell anemia, which is characterized by homozygosity for glu6val in the -globin gene or HBB. It was hypothesized that varied HbF concentrations were required to protect against distinct health outcomes, but any rise in HbF was thought to lower mortality [9]. Higher HbF

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levels were linked to lower rates of acute painful episodes, leg ulcers, osteonecrosis, acute chest symptoms, and disease severity [9].

Red blood cell (RBC) membrane distortion caused by HbS deoxygenation results in the distinctive sickle-shaped cell [10]. As a result of these aberrant RBCs occluding tiny capillaries and venules, tissue ischemia, acute discomfort, and progressive end organ damage are caused [11]. As a chronic condition, SCD is characterized by quiet intervals punctuated by acute crises that prompt patients to seek medical attention and frequently check themselves into hospitals [12]. In Africa, death rates for children under the age of five range from 50 to 90% [13]. This is because there aren't many facilities that can save lives, like prenatal diagnostic services, organized follow-up, and a wide range of life-saving interventions like routine penicillin prophylaxis, vaccination against common bacterial diseases, and the availability of hydroxyurea-based disease-modifying therapy [14]. Another contributing factor may be the lack of availability of the only potentially curative treatment, hematopoietic stem cell transplantation (HSCT) [14].

In order to properly counsel couples and families who may be at risk of serious haematological repercussions, it is crucial to identify and characterize haemoglobinopathies early [15]. Doctors, nurses, and social workers generally have poor knowledge of the fundamental diagnosis, counseling, and therapy of hemoglobinopathies, especially in Africa where the illness burden is highest [16]. Identification of mutations and carrier screening frequently fall short of ideal. In the industrialized world, carrier screening and mutation detection form the core of the preventative strategy for hemoglobinopathies [16]. Many populations and ethnic groups in Nigeria have had their frequencies of these hereditary traits published [17]. The distribution pattern and frequency of frequent haemoglobin variations from South West have not yet been reported in any known published data, nevertheless.

Therefore, the purpose of this study is to investigate the prevalence and spectrum of hemoglobin variants among patients attending a tertiary hospital in Ondo state, South West Nigeria.

METHODOLOGY

Study Area

The study was conducted in Ondo State southwest Nigeria. Ondo state lies between 4 degree 30 and East of the Greenwich Meridian 5 degree 45 and 8 degree 15 north of the equator. The temperature throughout the year ranges from21 degree to 39 degree Celsius while humidity is relatively high. According to the Nigeria population census of 2006, Ondo state is populated with 3,460,024 people, has 3 Senatorial Districts, 18 Local Governments and 203 Electoral wards. 60% of the population lives in the rural areas. The state is bounded in the North by Ekiti and Kogi state, in the East by Edo state, in the West by Osun and Ogun states and in the south by the Atlantic Ocean.

The study was conducted at the University of Medical Sciences Teaching Hospital, Ondo state. The teaching hospital comprises of four hospitals in Ondo town namely; Mother and Child Hospital, Trauma and Surgical Centre, Kidney Care center and the state specialist hospital in the ancient town. It also comprises of the State Specialist Hospital in Akure, the Millenium Eye center, Akure

Study Design

The study was an experimental study of patients on routine haematologic test in the tertiary hospital where the concern patient's blood was obtained by clean venipuncture drawn into plastic tubes containing EDTA

Sample Size Determination

The sample size was determined by using Fisher's approach on patients attending at the tertiary hospital.'

$$n = \frac{Z^2 pq}{d^2}$$

Where, N = Minimum sample size for a statistically significant survey, Z = Standard Normal deviant set at 1.96 (approx. 2.0), p= proportion in the target population usually 50% (0.5) , q = 1- p= 1 – (14.3/100) = 1-0.143= 0.857, d = degree of accuracy of 0.05

Therefore,

$$n = \frac{(1.96)^2 \times 0.3 \times 0.857}{(0.05)^2} = 350$$

Study Population

The respondents or participants were berecruited from the hospital department clinics and tested at Department of Hematology, Faculty of basic medical science with the presumptive diagnosis of normal and variant Haemoglobin (hemoglobinopathy). Three hundred and fifty patient's blood samples were collected and analyzed for identification of their unique genotype which involve screening for hemoglobinopathy by standard methods

Sample Collection and Methods

Blood was drawn via venipuncture into tubes that had been treated with the anticoagulant ethylene diamine tetracetic acid (EDTA) in order to identify any aberrant Haemoglobin variations and foetal hemoglobin which will be determined using BIO-RAD D10 high-performance liquid chromatography (HPLC) at the Pose specialist diagnostic center, Akure, Ondo state. As checks, haemolysate from blood samples containing known amounts of hemoglobin (AA, AS, and AC) will be used.

Inclusion Criteria

Subjects were eligible for enrolment if;

1. Patients that are between ages of 10-60 years of age and are normal and stable in health with no episodes
2. Patients who had voluntarily given written informed consent to participate in the study
3. Patients who were enrolled for routine laboratory test

Exclusion criteria

1. Patients above the age of 60 years
2. Patients not enrolled for laboratory test

Method of Data Analysis

Data will be managed using SPSS software version 23.0 (IBM Corp., New York, NY, USA). Consistency of data will be checked by double entry and checking for outliers. Descriptive analysis was done with derivation of proportions, 95% confidence interval (CI), mean and standard deviations. Test of significance was done using bivariate analysis and Chi square test, and $P < 0.05$ will be considered statistically significant.

Ethical approval with number NHREC/TR/UNIMED-HREC-Ondo St/22/06/21 was obtained from the Health Research and Ethics committee of the University of Medical Science Teaching Hospital, Ondo state.

RESULTS

In this study, we estimated the hemoglobin variants of 350 residents in a tertiary hospital in Ondo state. The prevalence of hemoglobin were estimated in this study by using age groups and it was observed in our study that Hb AA as well as Hb AC and Hv SC prevalence was the highest among the age group of 21-30 years whereas the Hb AS and Hb SS were among the age group 10-20 years.

Table 1 show the distribution of the various haemoglobins based on age groups of subjects. **Table 2** show the frequency and gender distribution of different forms of haemoglobin (Hb) among the subjects; Hb AA 264; HbAS 60; HbAC 6; HbSC 8 and HbSS 12. Of the 350 subjects studied, 106 were males, while 244 were females. Among the male subjects, 85 were HbAA, 12 were HbAS; 2 were HbAC; 3 were HbSC and 4 were HbSS. Among the female subjects, 179 were HbAA, 48 were HbAS; 4were HbAC; 5 were HbSC and 8 were HbSS.

Table 3 shows the frequency of the fetal hemoglobin among the Hb SS patients in the study based on age range. 50% of the participants with fetal hemoglobin were between 10-15 years, 25% were between 16-20 years, 8.3% were between 21-25 years, 8.4% were between 31-35 years and 8.3 % were between 36-40 years.

Figure 1 shows the distribution of hemoglobin variants among the study population. 75.5% has Hb AA, 17.1% has Hb AS, 1.7% has Hb AC, 2.3% has Hb SC and 3.4 % has Hb SS. Figure 2 shows the distribution of fetal hemoglobin among the study population. 6 study participants with fetal hemoglobin are within age range of 10-15 years, 3 study participants are within age range of 16-20 years, 1 study participant is within 21-25 years, none of the study participant is within 26-30 years, 1 study participant is within 31-35 years and 1 study participant is within 36-40 years

Age range	Hb AA	Hb AS	Hb AC	Hb SC	Hb SS
10-20	75	25	0	1	9
21-30	120	11	3	3	1
31-40	38	4	3	2	2
41-50	10	20	0	2	0
51-60	21	0	0	0	0
Total	264	60	6	8	12

Table 1: Distribution of hemoglobin types among participants based on age groups.

Genotype	Frequency	Percentage	Male	Female
AA	264	75.5%	85(32.2%)	179(67.8%)
AS	60	17.1%	12(20%)	48(80%)
AC	6	1.7%	2(33.3%)	4(66.7%)
SC	8	2.3%	3(37.5%)	5(62.5%)
SS	12	3.4%	4(33.3%)	8(66.7%)

Table 2: Frequency and gender distribution of different haemoglobin (Hb) electrophoretic pattern among the study population.

Age	Hb SS	Mean Hb F
10-15	6 (50%)	4.81±1.08
16-20	3(25%)	3.15 ± 2.26
21-25	1(8.3%)	2.97±1.45
26-30	0(0%)	0.00±0.00
31-35	1(8.4%)	2.48±1.22
36-40	1(8.3%)	2.12±0.73

Table 3: Distribution of fetal hemoglobin among sickle cell participants in the study population.

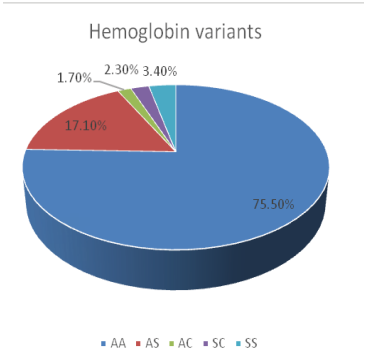

Figure 1: Distribution of hemoglobin variants among study population.

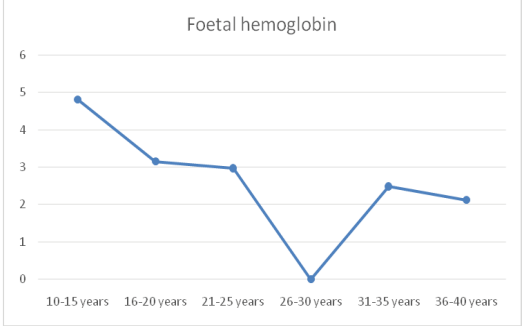

Figure 2: Distribution of fetal hemoglobin among study population.

DISCUSSION

Hundreds of hemoglobin variations have been described, and they are likely rather widespread in Africa [18]. Control and management of Hb problems have experienced significant organizational and financial challenges over time [18]. A wide variety of phenotypic consequences can result from hemoglobin mutations, including anemia brought on by red cell lysis and protein instability [19] as well as tissue ischemia, infarction, and chronic hemolytic anemia from blockage of the microvascular circulation [18]. To reduce the likelihood of catastrophic illnesses like sickle cell anemia in future generations and to directly benefit carriers, reproductive decision-making requires knowledge of hemoglobin variations and carrier status [19].

This study as shown in **Table 1** shows the prevalence of hemoglobin variants among residents attending a tertiary hospital in Ondo state. In this study, the prevalence of Hb AA was 75.5%. This finding is in correlation with study done by Abdulrahman et al., [20] in Sokoto, Akogu et al., [21] among students in River's state university with a prevalence of 66.5%. Also, our study correlates with study done by Mondal et al., [22] which shows prevalence rate of 72.5% of Hb AA among residents in India. The fact that these characteristics actually offer malaria protection is supported by a substantial body of evidence [23]. There is evidence that the treatment of clinical Plasmodium falciparum malaria serves as a protective measure. However, the study done in Ghana by Awaitey et al., [24] showed a high prevalence of Hb AS which is in contrast with our study. Hb AS is the second commonest hemoglobin variant seen in our study with a prevalence rate of 17.1%. Our finding is slightly above the prevalence rate of Hb AS among resident in India in a study done by Mondal et al., [22].

The prevalence of Hb SS in our study is 3.4%. This finding is in agreement with the study conducted by Akogu et al., [21] among students in River's state south south Nigeria, and with study conducted in Bayelsa State, both in the South-South of Nigeria [25]. But our results are not in agreement with other studies in Kenya, East Africa [26] and in Port Harcourt, Nigeria [27], both of which found no frequency of HbSS. The zero rates seen in these studies may indicate that premarital counseling and improved awareness in the environment has caused the sickling gene pool in some African groups to gradually decline. Increased public awareness of the disease, better socioeconomic conditions, enhanced premarital counseling, environmental and genetic factors that have an overall impact on the sickling gene pool, and others may be responsible for the low prevalence of HbSS seen in this research. The absence of prevalence may also be due to Nigeria's intensive prenatal diagnosis program for expectant mothers.

In comparison to study done in United States by Richard et al., [28], 9% of black Americans and 30–40% of African Americans overall are said to have HbSS. This is a low prevalence rate as compared to our study. Inadequate premarital counseling and awareness in our study may be the cause of this high prevalence. In addition, cultural and religious belief play a major role in the high prevalence of Hb SS seen in our study. This can be traced by fear of premarital testing among the couples as seen in the study done by Musaddad et al., [29] on premarital testing among Muslims in Nasarawa state which shows that level of marriages conducted without premarital testing is alarming. This could be due to inadequate awareness as well as fear of unfavorable result which could affect their marriages.

In line with the prevalence of Hb SS in our study as seen in **Table 3,** the average range of fetal hemoglobin was done among the sickle cell patient in this study. The highest mean foetal hemoglobin was (4.81%) was seen among the participants within the age group of 10-15 years. This is in correlation with study done by Olaniyi et al., [30] in Ibadan with mean Hb F of 5.4%, Omoti et al, [31]. Furthermore, our study was similar with the study done in Uganda by Mpalampa *et al.* [32] where the sickle cell patients had Hb F <10%. Also, in comparison of our findings with the study carried out in Saudi Arabia, their patients' mean HbF levels substantially greater [33]. The pathogenesis of sickle cell disease is fueled by the polymerization of sickle hemoglobin (HbS, 2S2), which can be inhibited by fetal hemoglobin (HbF, 22). Since neither HbF nor its mixed hybrid tetramer (2S) may reach the deoxyHbS polymer phase, the effect of HbF is caused by a decrease in mean cell HbS concentration, a key factor in polymerization propensity [34].

The prevalence of Hb AC and Hb SC in our studies are 1.7% and 2.3% respectively. This is in correlation with studies done in South-West Nigeria with a prevalence of SC of 2.0% [35]. Our research is in line with a recent study's finding that HbC prevalence in Ecuador, a tropical Latin American nation with a sizable afro-descendant population, was 1% [36]. One of the most prevalent structural haemoglobin variants in human populations is hemoglobin C (HbC). Despite the fact that HbC only has minor clinical side effects, early detection and genetic counseling are crucial to preventing inheritance of other hemoglobinopathies. HbC has clinical significance

primarily when it is co-inherited with HbS (sickle-haemoglobin C disease), resulting in chronic hemolytic anemia and sporadic sickle cell crises that are slightly less severe or common than in homozygous HbS patients (SS), and when it is co-inherited with -thalassaemia (haemoglobin C- thalassaemia), resulting in moderate hemolytic anemia with splenomegaly [36].

Sickle cell disease is usually ignored even though it is the most common genetic disease in Africa and is linked to major health and socioeconomic consequences [37]. SCD, which usually affects young children and adolescents, ultimately leads to multiple organ failure and untimely death [38]. When compared to the general population, sickle cell disease is associated with a higher overall mortality rate and a lower life expectancy [39]. The most typical complication of sickle cell disease in both children and adults is painful vaso-occlusive episodes.

In comparison to their counterparts in western countries, a sizable number of sickle cell disease patients live in developing nations. In Africa, the survival rate for people with sickle cell anemia to maturity was estimated to be between 10 and 15 percent in the first decade of life and around 5 percent in the following decades [40]. The majority of those who passed away did not exhibit overt chronic organ failure; instead, they passed away from sudden episodes of discomfort, infections, acute chest syndrome, strokes, and anemia crises [40].

Patients with HBSS and SC have a higher mortality rate than patients in developed economies for a variety of reasons, including the cost of disease-modifying drugs like hydroxycarbamide (hydroxyurea) or Sailin HbS, antibiotics like phenoxymethylpenicillin and cefotaxime, pneumococcal vaccination, inadequate access to adequate and safe red cell transfusion support, lack of availability of iron chelating drugs like deferoxamine, and the presence of other diseases [40].

The most typical complication of sickle cell disease in both children and adults is painful vaso-occlusive episodes. Hydroxyurea is frequently used to alter the disease etiology in evidence-based care for sickle cell disease patients, especially in the industrialized world. Vaccination against pneumococcal disease, antibiotics, steroids, effective pain management with opioids and non-steroidal anti-inflammatory medications (NSAIDS), as well as fluid replacement, are additional supportive therapy [40].

LIMITATIONS

There are several limitations faced in conducting this study. Firstly, the study is a cross-sectional study conducted in a single location. Recall, investigator, and survivor biases are all potential problems with this kind of study design. Despite the study of pertinent medical charts and clinical histories to collect that information, information on the lifetime incidence of complications and frequency of significant pain episodes may have been vulnerable to recall bias. Second, the limited sample size of the patients studied might possibly limit the generalizability of our conclusions. Future research ought to include a longitudinal design, involve a broader population, and be multi-centered.

CONCLUSION

Hemoglobinopathies has been a challenging condition in Nigeria and has brought various changes to the public health response to this condition in Nigeria and throughout the globe. Little or no awareness have been made available on the genotype testing among the people in various environment most especially in the religious centers.

Our study showed increased prevalence of hemoglobin variants among the patients attending a tertiary hospital in South West, Nigeria. Hb AA was the most prevalent hemoglobin variants seen in our study, Hb AS was the second most prevalent. Also, Hb SS was seen in this study among the children with all of them in steady state. Fetal hemoglobin was assessed among the sickle cell patients in this study.

RECOMMENDATIONS

i. Awareness should be created at religious centers, schools on the importance of genotype testing

ii. In order to lower morbidity and death, facilities for early and routine testing of genotype should be made available, and access to HbF inducing drugs, notably hydroxyurea, should be encouraged.

iii. As a preventative precaution, we advise the implementation of mutation identification and carrier screening.

iv. It is necessary to create genetic counseling policies that offer evidence-based information to help prospective couples make decisions with the goal of lowering the occurrence of hemoglobinopathies in Ondo state, South West Nigeria

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