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Hemoglobin F and the Clinical Trajectory among Eastern Sudanese Patients with Sickle Cell Anemia

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Abstract: ***Background:*** The intensity of sickle cell anemia (SCA) is significantly modified by fetal hemoglobin (HbF). However, in eastern Sudan, HbF estimation is not a common trend. Additionally, scarcity is known to be the connection between HbF and the intensity of SCA in afflicted patients. This study aimed to identify the impact of fetal hemoglobin on disease severity in eastern Sudanese sickle cell patients. ***Materials and Methods*:** A cross-sectional descriptive study was implemented from January 2013 to December 2015. Twenty-six patients were enrolled in the trial. The hematological outcomes and HbF were consecutively verified using a hematology analyzer and capillary electrophoresis. ***Results:*** The average HbF level across the 26 SCA patients was 9.8±6.3%. Males showed considerably lower mean levels of HbF than females, 7.7±5.8% vs. 10.6±6.7%, respectively (P = 0.222). The mean fetal hemoglobin levels of 18 patients (69.2%) with severe disease were significantly above those of 8 patients (30.8%) with moderate disease (7.1±10.4% vs. 4.7±6.0%, respectively). A statistically insignificant link existed between the average HbF levels for patients with complications (7.4±10.3) and those without complications (4.7±6.3) (P= 0.371). ***Conclusion*:** It is found that the scale of HbF dramatically inversely correlates with the clinical course of the disease in eastern Sudanese patients with sickle cell anemia. To lessen the morbidity and mortality among these patients, it is advised that tools for early determination of fetal hemoglobin and HbF induction be made accessible.

Keywords: Sickle cell anemia, Fetal hemoglobin, Clinical course, Eastern Sudanese.

Research Paper

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INTRODUCTION

One of the more prominent hemoglobin disorders in Africa is sickle cell anemia, which affects about 67% of the population on the continent. Sickle anemia is a genetic blood condition brought on by a point mutation that changes adenine (A) to thymine (T), prompting valine to change to glutamic acid at the 6th position of the β-chain of hemoglobin. The generation of hemoglobin S (HbS) is triggered by this mutation [1]. Patients with this illness experience high rates of morbidity and mortality. According to reports, Africa's under-5 death rate ranges from 50% to 80%. In Sudan, there is a substantial correlation between high consanguinity rates and sickle cell anemia. Fetal hemoglobin (HbF) level is yet another factor that affects the intensity of SCA. Fetal hemoglobin prohibits HbS from polymerizing, which tends to happen when there is less oxygen concentration. SCA patients who have erythrocytes with higher Hb-F levels may survive better [1, 2]. The intensity and kinks of SCA, such as vaso-occlusive crisis, acute painful episodes, acute chest syndrome, and osteonecrosis, may be brought about by the extremely low level of HbF. Patients with SCA have variable HbF levels, and these levels are affected by genetic predisposition, environmental factors, and haplotypes. So, the β-S globin haplotypes and HbF levels affect how sickle cell disease manifests clinically [3]. Those who have SCA might use their beta S-globin haplotypes to learn more about their ancestry. The haplotypes encompass Senegal (SEN), Benin (BEN), Bantu or Central African Republic (CAR), Cameroon (CAM), and Arab-Indian (ARAB). Cameroon and Benin were the two haplotypes that were most prevalent in Sudan [4]. There is a dearth of information in Sudan about the impact of fetal hemoglobin levels on the clinical course of the disease in SCA-affected patients. Therefore, the main intention of this work was to identify the association between fetal hemoglobin levels and illness severity in SCA.

MATERIALS AND METHODS

In the Port Sudan teaching hospital, descriptive cross-sectional research was achieved between January 2013 and December 2015. Twenty-six SCA patients between the ages of 1 and 65 years who had not experienced a crisis, an infection, or fever for at least four weeks, and who had not received a blood transfusion and hydroxyurea in the three months prior, were sequentially included. Ministry of Health Research Board gave its approval for this study (Red Sea State). Before collecting samples, each participant gave their informed consent. Parents were asked for permission on behalf of their kids. Parents' medical records and demographic information were mined for clinical history and clinical information (age, gender, number of transfusions, hospitalizations, pain crisis in the previous year, complications). Information from participants in the investigation was kept confidential. Each participant who took part in the study received a copy of the laboratory results. Port Sudan Teaching Hospital granted permission for the specimen collection.

All patients' venous blood samples were taken and placed in potassium ethylene diamine tetra acetic acid (K_3EDTA) blood tubes. The automated capillary electrophoresis machine (Sebia Minicap, France) and the semi- automated hematology analyzer (Sysmex KX21N, Japan) were used to assess the Hb F level and the complete blood count (CBC), respectively.

Data Analysis

The Statistical Package for Social Sciences (SPSS), version 25.0, was used to evaluate all demographic, clinical, and laboratory data. The application of means (with standard deviation, SD), proportions, and percentages was determined. For continuous variables, averages and standard deviations (SD) were calculated, whereas, for categorical variables, proportions and percentages were computed. As stated, continuous data were compared with an independent sample t-test while categorical variables were compared with chi-squared or Fisher's exact tests. Pearson's correlation analysis was employed to assess the degree of correlation of continuous data. The p-value was used to determine statistical significance when it was less than 0.05.

RESULTS

In total, 26 patients with SCA participated in this study. Male patients made up 9 (34.6%) while female patients made up 17(65.4%). The age range of the patients was 1 to 65 years (mean±SD: 24.4±19.4). Anemia was extreme in 18 (69.2%) of the patients and moderate in 8 (30.8%). 16 (61.5%) patients exhibited sequelae, while 10 (38.5%) patients did not. Pain episodes, delayed growth, pneumonia, hand-foot syndrome, hepatosplenomegaly, infection, cerebrovascular accidents, vision issues, jaundice, constipation, epistaxis, difficulty speaking, hearing problems, headaches, skin infection, and auto-splenectomy were all HbF sequelae.

The values of HbF varied from 0.00% to 17.3% (mean±SD 9.8%±6.3). Male participants had mean lower HbF levels (7.7±5.3) than those of female patients (10.6±6.7). This difference was statistically insignificant (P= 0.222). As a result, the average HbF level declined with age throughout all age groups, and the correlation between these two variables was statistically significant (r = -0.475, P= 0.023). Unexpectedly, HbF levels were observed to be much greater in patients with complications compared to those without issues (mean±SD: 7.4±10.3 and 4.7±6.3, respectively; P= 0.371). The majority of the individuals under investigation (69%) experienced pain episodes as a complication. HbF levels were lower in patients with pain episodes than in those without pain episodes (9.3±6.1 and 11.0±7.2, respectively; P= 0.013). When patients with and without complications were examined, statistically meaningful variations were found in mean Hb concentration, hematocrit, and erythrocyte cell count (Table 1). According to Table 2, 18 (69.2%) of the patients had severe anemia, while 8 (30.8%) had moderate anemia. No patient had even a slight case of anemia. It was discovered that patients with severe anemia had higher HbF levels than those with moderate anemia. This difference's correlation was statistically insignificant (P= 0.443; mean±SD: 7.1±10.4 and 4.5±6.0, respectively).

Table 1: Association of anemia markers in participants with and without HbF complications

Variables	With Complication (n=16)	Without complication (n=10)	P. value
HbF %	7.4±10.3	4.7±6.3	0.371
Hb g/dl	7.0±1.3	11.6±1.4	0.000
Hct %	21.8±4.1	33.3±3.1	0.000
MCV fl	81.9±11.3	76.3±9.5	0.210
MCH pg	26.8±5.1	26.6±4.2	0.849
RBCs µl	2.72±0.76	4.35±0.65	0.000

HbF; hemoglobin F, Hb; hemoglobin, Hct; hematocrit, MCV; mean corpuscular volume, MCH; mean corpuscular hemoglobin, RBCs; red cell counts

Table 2: Anemia parameters in sickle cell patients versus the World Health Organization normative ranges

Variables	Severe anemia (n=18)	Moderate anemia (n=8)	P. value
HbF %	7.1±10.4	4.5±6.0	0.442
Hb g/dl	7.3±1.4	12.2±0.8	0.000
Hct %	22.5±4.5	34.6±1.7	0.000
MCV fl	80.1±11.9	78.3±8.4	0.664
MCH pg	26.2±5.2	27.6±3.5	0.520
RBCs µl	2.87±0.91	4.42±0.44	0.000

HbF; hemoglobin F, Hb; hemoglobin, Hct; hematocrit, MCV; mean corpuscular volume, MCH; mean corpuscular hemoglobin, RBCs; red cell counts

DISCUSSION

Hemoglobin F level impacts the hematological markers and clinical course of sickle cell anemia. This study's goal was to look into the correlation between fetal Hb levels and the clinical severity of the illness in eastern Sudanese sickle cell anemia patients. In this study, the mean HbF values were (9.8%±6.3), which is comparable to studies in Uganda (9.9%), Sudan (9.7%), and Nigeria (9.0%) [2, 5, 6]. It was higher than HbF mean levels recorded in Northern Brazil (5.2%), Congo (7.2%), and reduced than in Southern Iraq (19.7%), and Saudi Arabia (15.7%) [7-10]. This conflict may be caused by the age incidence, hydroxyurea treatment, which is documented to stimulate HbF synthesis, as well as our extremely smaller sample size.

In our study, the mean HbF values of male participants were lower (7.7±5.8) than those of female patients (10.6±6.7). This difference's correlation was statistically negligible (p = 0.222). The HbF levels were negatively correlated with age in both males and females (r= -0.195, P= 0.340) in this study, even though the mean age was (24.4±19.4 years). The results of this study relatively correlate with those published in Nigeria and Uganda [6, 11].

In the present research, patients with HbF complications had substantially higher HbF levels (7.4±10.3) than patients without troubles (4.7±6.3; P=0.371). In this study, sequelae were evident in 16 (61.5%) patients while they were absent in 10 (38.5%). The most frequent consequence in the current study (69%) was a painful episode. In Nigeria, over 85% of patients had at least one episode of extreme pain [6]. The most likely reason for admission (73.8%) in Iraq was an acute painful crisis [9]. In certain nations, including Saudi Arabia, the frequency rate of hospitalizations and pain has been limited [10]. These variations could result from the interaction of several variables that affect fetal hemoglobin synthesis in SCA patients. One of the contributing causes is the disease's beta gene haplotype (β^S haplotypes), whereas the haplotypes most consistently found in Sudan are those from Cameroon and Benin, which are related to those from Nigeria and Iraq. The intensity of sickle cell anemia is attributed to the Benin and Cameroon haplotypes. All of the patients chosen for this study did not receive hydroxyurea medication, which is often used in developed nations to lessen the likelihood of occurrence of pain and hospital turnover. This is a further important element that may impact HbF levels [12].

In this study, 69.2% of patients had extreme anemia, while 30.8% of patients had moderate anemia. Consistently, in Khartoum, 59% of patients were reported to have severe anemia, and 41% of patients had moderate anemia [5]. In opposition to this, in Morocco, 50% of patients were said to have severe anemia, 24% had moderate anemia, and 26% had mild anemia [13]. The disparity between the results of our analysis and the Moroccan work may be due to variations in environmental and genetic factors, age incidence, and the proportion of female patients in the two experiments.

Our research has several restrictions. It is a cross-sectional study from a single institution. Despite the review of pertinent medical documents as well as clinical histories to collect such information, recall bias may have affected data on the lifetime incidence of sequelae and frequency of significant pain episodes. Furthermore, the limited number of patients studied could have an impact on how generalizable our results are. Future research should have a multi-center design and include a bigger population. It may be suggested based on the results of this study that attempts be made to assess HbF levels in patients with SCA at an early age and to research genetic polymorphisms in patients with SCA to keep track of the illness complications. Additionally, it is advisable to treat SCA patients with disease-modifying medications such as hydroxyurea and genetic treatment.

CONCLUSION

It is determined that among patients with sickle cell anemia, the level of HbF significantly inversely correlates with the clinical course and burden of the disease. Inadequate HbF levels in these patients were also substantially correlated with advanced age and male gender.

Authorship Contributions

Concept: B.A.; Design: B.A.; Data Collection or Processing: M.O.G; Analysis or Interpretation: B.A.;

Literature Search: B.A, M.O.G.; Writing: B.A. and M.O.G.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

FINANCIAL DISCLOSURE

No sources of funding for the research to report.

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