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Assessment Of MicroRNA-451, P-Selectin, Haemoglobin Levels, And Platelet Counts In Steady-State Individuals With Haemoglobin-S Variants In Jalingo, Nigeria

[1]Amaechi, Rose A,, [1]Swem Collins A, [2]Akwiwu,Euphoria C [2]Akpotuzor, Josephine.O

[1]Haematology/ Blood Transfusion Science Department, Faculty of Medical Laboratory Science Ambrose Ali University Ekpoma, Edo State.

[2]Haematology/ Blood Transfusion Science Department, Faculty of Medical Laboratory Science University of Calabar, Cress-River State

ABBREVIATIONS
Hb, HbAA, HbAS, HbSS, HbAC, HBSC: Hemoglobin and its variants
miRNAs: Erythrocytic microRNAs-451 .
RBC: Red blood cell count
SCD : Sickle cell disease
SCA: Sickle cell anemia

Correspondence:
Akpotuzor,Josephine O,
Phone number:
+2348037134757
Email address:
j.o.akpotuzor@gmail.com

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ABSTRACT

BACKGROUND: Sickle cell disease (SCD) is a prevalent monogenic disorder characterized by abnormal hemoglobin and associated with various clinical complications. Homozygous sickle cell (HbSS) erythrocytes have differential expression of many erythrocytic microRNAs (miRNAs). Elevated levels of miR-451 and let-7i-5p have been reported in HbSS and HbAS erythrocytes. P-selectin, a member of a family of adhesive proteins, plays an essential role in the initial recruitment of leukocytes and in the recruitment and aggregation of platelets to the site of injury during inflammation. This interaction is thought to contribute to the inflammation of SCD.

AIM: This study aimed to assess the levels of microRNA-451, P-Selectin, hemoglobin concentration, and platelet counts in individuals with different hemoglobin-S variants in steady-state conditions in Jalingo, Nigeria.

METHODS: This cross-sectional study was conducted at Federal Medical Centre Jalingo in Taraba state, Northern Nigeria. Ethical approval was obtained from the Ethics Review Committee of Federal Medical Centre Jalingo, Taraba State. One hundred and twenty subjects were recruited for the study stratified as 40 HbSS on steady state, 40 HbAS and 40 HbAA. Blood samples were appropriately collected for the analysis of haemoglobin-S variants(alkaline cellulose acetate method),haemoglobin concentration (Hematology Auto-Analyzer), miRNA-451 (Real Time PCR) and P-selectin (ELISA technique). Statistical analysis was done using SPSS version 22 Software. A p-value of ≤ 0.05 was considered significant.

RESULTS: The study found that HbSS subjects had significantly higher levels of microRNA-451, P-selectin, and platelet counts compared to HbAS and HbAA subjects, with p-values <0.0001. Hemoglobin concentrations were significantly lower in HbSS individuals. HbAS subjects had elevated microRNA-451 and P-selectin levels compared to HbAA subjects, but with similar platelet counts. A moderate negative correlation ($r = -0.335$, $p < 0.035$) was observed between microRNA-451 and P-selectin levels

CONCLUSION: The results indicate that microRNA-451 and P-selectin are significantly elevated in HbSS individuals, which may contribute to the pathophysiology of sickle cell disease.

KEYWORDS: Sickle Cell Disease, MicroRNA-451, P-selectin, Hemoglobin Levels, Platelet Counts, Hemoglobin-S Variants

INTRODUCTION

Sickle cell disorder (SCD), a condition characterized by the production of abnormal hemoglobin, is among the most prevalent severe monogenic disorders globally, often leading to significant clinical complications. It is a genetic condition resulting from a mutation in the beta-globin chain of hemoglobin (Hb) on both alleles, causing red blood cells (RBCs) to alter their shape under low-oxygen conditions (1). The hemoglobin variant S (HbS) is responsible for sickle cell anemia (SCA (2,3). Both HbS and HbC variants can lead to SCA when inherited together (HbSS or HbSC). In contrast, sickle cell trait (SCT) occurs when one HbS or HbC allele is inherited from one parent, and a normal allele (HbA) is inherited from the other (HbAS or HbAC). Individuals with SCT (AS or AC) generally do not experience complications from carrying the HbS or HbC allele (4,5). However, those with HbSS can exhibit a wide range of clinical symptoms, from severe anemia and vascular complications to growth delays and multiple organ damage due to recurrent vascular occlusions (6,7). These patients are often hospitalized due to delayed growth, hand-foot syndrome, fatigue, chronic pain episodes, frequent infections, and vision problems (4,8). Globally,SCD is the most common hemoglobin disorder, with approximately 7% of the world's population carrying hemoglobinopathies (2). Research has revealed that HbSS erythrocytes display differential expression of several erythrocytic microRNAs (miRNAs) (9,10). Of the hundreds of miRNAs, two—miR-451 and let-7i-5p—have been identified as associated with HbSS and HbAS, as well as with inhibiting parasite growth in vitro (11). MiRNA-451, a small, non-coding RNA, regulates gene expression at the post-transcriptional level and is abundantly expressed in RBCs, where it functions alongside miRNA-144 (11). This miRNA cluster is crucial for regulating the expression of genes essential for erythropoiesis (12,13). During the differentiation of erythroid cells, the expression of miRNA-144/-451 increases significantly, playing a vital role in maintaining erythroid homeostasis (14). The miRNA-144/-451 locus, a key downstream target of GATA-1, is critical for the full maturation of hematopoietic cells, and its dysregulation can lead to mild anemia (14). Although the severity of anemia in SCD is primarily linked to miRNA-144, miRNA-451 plays a significant role in modulating α and β globin levels and has a lesser impact on γ globin (13,14).

P-selectin is part of a family of adhesive proteins, which includes E-selectin and L-selectin, that regulate the transient interactions between endothelial cells and leukocytes, a process known as cell rolling. This single-chain glycoprotein is produced by activated platelets and endothelial cells, acting as a cell adhesion molecule on the surface of endothelial cells that line blood vessels, with a plasma concentration of approximately 100 ng/ml in healthy individuals (16,17). P-selectin is crucial in the early stages of leukocyte recruitment and the aggregation of platelets at injury sites during inflammation. It specifically mediates the initial capture, rolling, and recruitment of leukocytes on activated vascular endothelium, as well as the interactions between activated platelets and leukocytes. These interactions, triggered by molecules like histamine and thrombin, activate neutrophils and monocytes, contributing to inflammation in individuals with sickle cell disorder (SCD) (16,17). P-selectin also plays a significant role in atherosclerosis and circulates in plasma as a soluble form (sP-selectin), promoting the formation of procoagulant microparticles and leading to vascular occlusive tendencies. At the molecular level, these vaso-occlusive tendencies may result from hypoxia-induced polymerization of hemoglobin SS (HbSS), which decreases red blood cell survival in peripheral circulation (16,18). The tendency of sickle red blood cells to adhere to the vascular endothelium is believed to be a major, if not the primary, cause of the vaso-occlusive process in HbSS patients (19,20). Inhibitors of P-selectin have been shown to alleviate blood flow obstructions associated with sickle cell disease. Studies have demonstrated that P-selectin antibody therapy has been approved for preventing vaso-occlusive pain episodes (VOE) in sickle cell disease patients, making it a promising new target for pharmacological treatment of sickle cell disease complications (21, 22). This study aims to assess the levels and relationship of miRNA-451 and P-selectin in individuals with hemoglobin-S variants in steady-state conditions in Jalingo, northern Nigeria.

MATERIALS AND METHODS

The research was conducted at the Federal Medical Centre in Jalingo, the capital of Taraba State in Northern Nigeria. This facility serves as a referral center for the state's fifteen local government areas, as well as for neighboring states and countries, including Nasarawa and Benue to the west, Plateau to the northwest, Bauchi and Gombe to the north, and Cameroon to the east and south. This study was cross-sectional in design, with participants selected based on specific criteria. A preliminary hemoglobin genotype test was conducted, and individuals with hemoglobin SS were recruited from the hospital. The control group, comprising individuals with hemoglobin AA and AS, was drawn from the general population in the Jalingo area. Ethical approval for the study was granted by the Ethics Review Committee of the Federal Medical Centre, Jalingo, Taraba State. Informed consent was obtained from participants aged 18 years and older, while consent for participants under 18 years of age was provided by their parents or guardians. Exclusion criteria included individuals with abnormal fetal hemoglobin (HbF), HbSS patients in crisis (due to the small sample size), pregnant women, those who were ill or had any form of complications, and those who tested positive for HIV. The inclusion criteria required participants to be confirmed as having hemoglobin SS, AS, or AA . The sample size was calculated based on the prevalence of sickle cell disease in Nigeria and using the sample size formula of $n=Z^2 Pq/d^2$ with prevalence rate of 2.4% (23), $[(1.96)^2 x2.4/100(1-(2.4/100)]/(0.05)^2$ n = 36 (which is approximated to 40 for better statistical inference). Therefore, a total of one hundred and twenty (120) subjects were recruited for the study stratified as 40 HbSS on steady state after removal of those on crisis due to small size number encountered, 40 HbAS and 40 HbAA. Their ages ranged between 1 – 50 years. During the entire recruitment individuals with HbSC or HbAC, genotype,were not found.

Laboratory Evaluation of Blood Samples

Five(5) milliners of blood sample was collected into 2mg/ml EDTA sample bottle for the analysis of haemoglobin-S variants, haemoglobin concentration, miRNA-451 and P-selectine.The genotype of subjects for sickle cell status was conducted at first using alkaline cellulose acetate membrane electrophoresis method using HbAA, HbSS,and HbCC controls to determine participants' hemoglobin status. Questionnaire was used for enrollment where all subjects biodata including the clinical data of the HbSS were obtained. Haemoglobin concentration was determined by automation using Abacus -5part Auto Hematology Analyzer. Plasma was separated from red blood cells (RBCs) within hours of collection and HIV status was determined with RDTs HIV-1–2 kits).

Taqman MicroRNA451 Assays was used to detect and accurately quantify mature miRNA-451 using Applied Biosystems Real Time PCR instruments. The miRNA is first, extracted by lysing the sample in homogenized lysate buffer, which contains guanidine thiocyanate, a chaotropic salt capable of protecting RNA from endogenous RNases. The lysate is then mixed with ethanol and loaded on a purification column. The chaotropic salt and ethanol cause RNA to bind to the silica membrane while the lysate is spun through the column. Subsequently, impurities are effectively removed from the membrane by washing the column with wash buffers. Then, using nuclease-free water and low ionic strength, pure RNA is eluted and stored at −80 °C until further analysis.

Real-Time Quantitative PCR (RT-qPCR)

RNA was reverse transcribed using TaqMan MicroRNA Assay (Applied Biosystems, Waltham, MA, USA) and the TaqMan MicroRNA Reverse Transcription Kit (Applied Biosystems). RT-qPCR was performed using the Roche LightCycler 480 (Roche Applied Science) and the Bio-Rad CFX96 Real-Time PCR System using TaqMan MicroRNA Assay and TaqMan Universal Master Mix II, no UNG (Applied Biosystems). The manufactures instruction was used to complete the process with the focus on miR-451 expression.

A Human ELISA (Bioassay) kit was utilized to determine the levels of P-selectin. The assay operates on the principle that when a sample is added to a well plate coated with an antibody specific to human P-Selectin, the antibody in the well binds to the P-Selectin in the sample, forming a biotinylated anti-human P-Selectin complex. Upon the addition of a substrate solution containing streptavidin-HRP, followed by incubation, any unbound streptavidin-HRP is washed away. The reaction is then stopped by adding an acidic solution, which changes the color of the solution from blue to yellow. The absorbance is measured at 450 nm, with the intensity of the color being directly proportional to the concentration of P-selectin in the sample. The procedure was carried out according to the manufacturer's instructions. Statistical analysis was done using SPSS version 22 Software. ANOVA and Tukey's multiple comparison tests were used to assess within and between group's significance among variables. MiR-451 was correlated with P-selectin using Pearson correlation A p-value of $p \leq 0.05$ was considered significant for all tests.

RESULTS

Table 1 presents the distribution of participants by age and gender. The majority of HbSS subjects were in the 1-10 year age group, accounting for 11.7% of this category, with an equal distribution between genders. Participants aged 11-20, 21-30, and 31-40 years were more prevalent across all three genotype (HbSS, HbAS, HbAA), with a higher number of males in these age ranges 25, 18, and 21, respectively. Those aged 41 years and older comprised 13 individuals (10.8%), and were also represented across all genotype.

In terms of the biomarkers measured, HbSS individuals in steady state showed significant increases in microRNA-451, platelet-selectin, and platelet count ($p < 0.0001$), while their hemoglobin concentration was notably lower compared to HbAS and HbAA individuals. Additionally, microRNA-451 and P-selectin levels were significantly higher in HbAS subjects compared to HbAA subjects, although HbAS individuals had a significantly lower hemoglobin concentration. Platelet counts in HbAS subjects were similar to those in HbAA subjects. A scatter plot of miRNA-451 versus P-selectin is illustrated in Fig 1, showing a moderate negative correlation with an r-value of -0.335 and a p-value <0.035

DISCUSSION

A single amino acid mutation in the normal globin gene causes the qualitative defect known as sickle cell disease, which leads to faulty haemoglobin polymerization and haemolysis (6,24,25). MicRNA-451 is markedly over expressed in chronic haemolytic anaemia, inefficient haematopoiesis, reduced levels of α chain, glycophorin-A, and GATA1 transcripts. The miRNA-451 (cp/5µl Cdna) was much more over expressed in HbSS subjects (32.97±3.48 cp/5µl Cdna)) with 1.4 times (32.97/23.35) more than that of HbAS (23.35±3.60 cp/5µl Cdna)) and 1.6 times (32.97/20.71)more in HbAA subjects(20.71±3.84 cp/5µl Cdna) $p<0.0001$) however,the rate between HbAS and HbAA is 1.2 times (23.35/20.71) ($p<0.0045$). The possible reasons for the differential expressions are due to inefficient haematopoiesis and dysregulation of the miRNA-451.This finding is supported by earlier works that reported similar findings between HbSS subjects and HbAA subjects as well as HbAS and HbAA respectively (9-11). This work therefore concludes, that the presence of S-gene inherited either as homozygous HbSS or Carrier state HbAS is likely to drive the overexpression of miRNA-451

The level of P-selectin followed a similar trend to that of microRNA-451 but with considerably higher ratios. P-selectin is a cell adhesion molecule located on the surface of endothelial cells lining blood vessels, with a normal plasma concentration of 100 ng/ml T (15,16). In HbSS subjects at steady state, P-selectin levels were significantly higher compared to those in HbAA and HbAS individuals ($p < 0.0001$), although all values remained within the reference range. One of the roles of P-selectin is in promoting the formation of procoagulant microparticles, which can lead to vascular occlusion. The high level of P-selectin which is 10.7 times (46.38/4.35) greater in HbSS subjects is likely a major factor contributing to the vaso-occlusive processes observed in HbSS patients(.17,18). In HbAS subjects, P-selectin level was elevated 5.9 times (25.77/4.35) more than those of normal adult haemoglobin thus suggesting that, even in carrier state, there is vascular occlusive tendencies.

The hemoglobin concentration in HbSS subjects was significantly lower compared to HbAS and HbAA individuals. This is expected due to the chronic hemolysis associated with sickle cell disease. HbAS subjects had a slightly lower hemoglobin level than HbAA subjects, suggesting that the presence of the S gene adversely affects hemoglobin production. Thrombocytosis, a common feature of sickle cell anemia, is known to significantly contribute to vascular occlusion (19). Our results showed that HbSS subjects had a mean platelet count of 381.78±91.23 x10^9/L, which was significantly higher than that of HbAS (295.68±81.35 x10^9/L) and HbAA (299.33±79.61 x10^9/L) subjects ($p < 0.0001$), with similar platelet counts observed between HbAS and HbAA groups. This finding is consistent with studies by Ahmed & Onwukeme (20,21). The moderate thrombocytosis observed in steady-state homozygous sickle cell disease is attributed to the loss of splenic platelet sequestration due to functional asplenia, a characteristic of the disease.

We also found a moderate, negative significant correlation ($r = -0.335$, $n = 40$, $p < 0.035$) between miRNA-451 and P-selectin. MicroRNAs (miRNAs) are small, non-coding RNAs that regulate the expression of over 60% of protein-coding genes by binding to the 3′ untranslated region (3′UTR) of target gene mRNA, thus inhibiting protein translation either through degradation or translational repression (10,11,20,26). Our results indicate that miR-451 directly reduces P-selectin levels, suggesting that miR-451 may inhibit platelet adhesion by lowering P-selectin levels and could potentially serve as a therapeutic target for managing sickle cell anemia. There is limited information on the relationship between microRNAs and adhesion molecules in sickle cell anemia.

In conclusion, our study demonstrated significant increases in miRNA-451, P-selectin, and platelet count, alongside a decrease in hemoglobin levels in steady-state sickle cell subjects. The overexpression of miRNA-451 appears to downregulate platelet adhesion, potentially offering a new therapeutic approach for sickle cell management.This study contributes to understanding the molecular and hematological changes associated with different hemoglobin-S variants and highlights the need for further research into targeted therapies for sickle cell disease.

Table 4.1: Age and Gender related Distribution Participants.

Gender	HbSS		HbAS		HbAA			
	Female	Male	Female	Male	Female	Male	Total	Frequency
Age (years)								
1-10	7	7	0	0	0	0	14	11.7
11-20	6	10	10	3	7	6	42	35.0
21-30	0	5	6	5	8	8	32	26.7
31-40	1	2	5	2	2	7	19	15.8
41-50	1	1	1	8	2	0	13	10.8
Total	15	25	22	18	19	21	120	100

Table 4.2: Comparison between Parameters of HbSS, HbAS, HbAA Subjects

Parameters	HbSS	HbAS	HbAA	F	P-value
miRNA451(cp/5µl Cdna)	32.97±3.48^{a}	23.35±3.60^{ab}	20.71±3.84^{abc}	125.21	0.0001*
P selectin(ng/ml)	46.38±12.16^{a}	25.77±5.84^{ab}	4.35±1.16^{abc}	289.17	0.0001*
Hb (g/l)	81.35± 10.6^{a}	121.15± 12.66^{ab}	133.35± 14.36^{abc}	185.29	0.0001*
PLT (x10^{9}/l)	381.78±91.32^{a}	295.68±81.35^{ab}	299.33±79.61^{ac}	13.36	0.0001*

Key: P- value*statistically significant (P=0.0001), Hb=Haemoglobin, PLT=platelets, microRNA451, P selectin = Platelet Selectin.

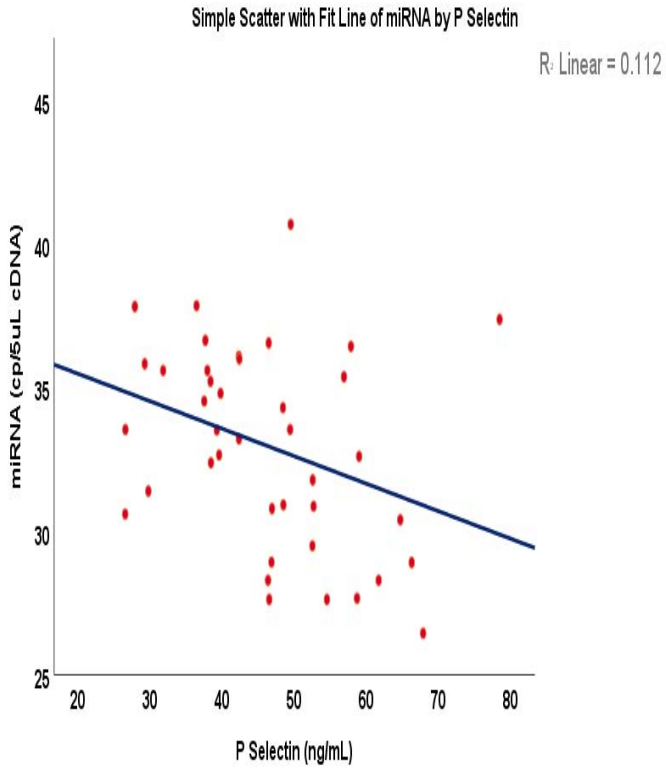

Figure1. Scatter plot of miRNA451 and P- Selectin (r=0.335, p<0.035).

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