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Original Research Article

Assessment of Serum Homocysteine in Adult Sickle Cell Anaemia Patients in Steady State in Zaria, North West Nigeria

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Abstract: Sickle cell anaemia (SCA) is a lifelong condition; it has been recognised as a procoagulant state in which micro thrombi have influenced the evolution of many complications. Elevated homocysteine is linked to increased risk of vaso-occlusion crisis and hyperhaemolytic crisis. This was a cross sectional study conducted in adult with sickle cell anaemia (SCA) in steady state in Ahmadu Bello University Teaching Hospital (ABUTH), Zaria, Kaduna Nigeria. ***Aim***: To determine serum homocysteine levels in adult SCA patients in steady state and compare with those with HbAA phenotypes. ***Materials and Method***: This cross-sectional case control study was conducted in a tertiary hospital in Zaria, Nigeria among adult HbSS patients in steady state from January to May 2023. A total of 60 participants were enrolled, 30 subjects diagnosed with SCA and 30 HbAA controls. Serum homocysteine of all participants was performed with enzyme-linked immunosorbent assay and comparison made between the subjects and controls. The Statistical Package for Social Science software (SPSS) version 23.0 was used for data analysis. ***Results***: The mean value for homocysteine in the HbSS group was 9.72 ±0.96 µmol/L whilst that of the HbAA was 6.19 ±0.88 µmol/L. All the thirty (100%) SCA patients had homocysteine levels between 5-15 µmol/L whilst twenty-seven (90%) out of thirty participants in the HbAA group had homocysteine between 5-15 µmol/L. Three (10%) out of thirty in the HbAA group had homocysteine levels < 5 µmol/L. There was a statistically significant difference between the means of the two groups with p value of < 0.0001. ***Conclusion***: This study demonstrated higher mean serum homocysteine levels among the HbSS participants in comparison with the controls (HbAA).

Keywords: Homocysteine, Steady State, Sickle Cell Anaemia.

INTRODUCTION

Sickle cell disease (SCD) is a common haematological disorder affecting millions of people worldwide [1]. Each year in Africa, about 300, 000 infants are born with the disease contributing to 70% of the world's annual figure [2]. Nigeria has the largest population of people with sickle cell disease (SCD), with about 150,000 births annually [3]. Sickle cell disease is a genetic disorder that results from point mutation at the sixth codon of β globin gene, which leads to substitution of adenine by thymine [4]. Consequently, an abnormal haemoglobin that contains amino acid valine, in place of glutamic acid at position six of the β globin chain is formed [5].

Studies in US over a 26-year period revealed an 18.2% increase in mortality rate amongst sickle cell anaemia (SCA) patients, with a higher mortality rate recorded amongst adults [6]. Similar studies in Brazil revealed that 78.6% of deaths due to sickle cell anaemia occurred before the age of 29 years, with 37.5% concentrated among children under nine years old [7]. This high mortality mainly among children and young adults reflects the severity of the disease.

Most of the clinical manifestations of SCA are related to the two main pathophysiological mechanisms; these are vaso-occlusion and haemolytic anaemia [8].

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Sickle cell anaemia being a chronic hypercoagulable state caused by recurrent haemolysis, sterile inflammation, and endothelial dysfunction directly lead to vaso-occlusion [8]. Other factors that contribute to this vaso-occlusion may include elevated plasma levels of homocysteine, activated leukocytes/platelets that adhere to and activate endothelial cells, increased thrombin generation, and reduced natural anticoagulant like protein C and antithrombin [9].

Homocysteine is a sulfhydryl-containing, non-proeinogenic amino acid. Raised plasma levels of homocysteine in SCA may occur due to folate and vitamin B12 deficiency that is usually consequent to chronic haemolysis [10]. Therefore, increased plasma homocysteine levels could be used as an indicator of folate and B12 deficiency according to some studies [10, 11]. Studies have also revealed that increased serum homocysteine levels are associated with the development of cardiovascular and peripheral arterial disease [12, 13]. Homocysteine has been suggested as a potential haemolytic toxin [14]. Even though the actual process of the haemolytic effect has not yet been ascertained, its pro-oxidant feature has pointed to the latter.

There are several pathophysiologic processes by which homocysteine may cause endothelial damage: Generation of free radicals when it partakes in auto-oxidation which causes lipid peroxidation of the erythrocyte membrane. [14] Homocysteine's ability to inhibit the anti- oxidant, glutathione peroxidase; this compromises the red cells ability to detoxify reactive oxygen species (ROS) [15]. Additionally, homocysteine has the tendency to bind to the sulfhydryl group of proteins on the red cell membrane and cytoskeleton, forming mixed disulfides. This structural rearrangement could be responsible for the early destruction of red cells [16].

Considering the aforementioned factors therefore, raised plasma homocysteine levels is strongly linked with increased risk of development of hypercoagulability, vaso-occlusion and thrombosis in SCA patients.

The objective of this study is to determine the serum homocysteine levels in adult HbSS patients in steady state and compare it with those of HbAA controls.

MATERIALS AND METHODS

Study Area and Population

The research was performed in the Haematology Department, Ahmadu Bello University Teaching Hospital Zaria, Kaduna State Nigeria. Sixty (60) participants consisting of 30 individuals with HbSS in steady state (study group) and thirty (30) apparently healthy HbAA controls were enrolled into the study.

Study Period: The research was performed over a period of five months, from January 2023 to May 2023.

Study Design

It was a cross sectional case-control research comprising of two arms. The first arm consisted of adult individuals with SCA in steady state (study group). The second arm consisted of apparently healthy individuals with HbAA phenotype.

Inclusion Criteria

- Individuals who granted their written informed consent by signing the consent form.
- Age between 18-60.
- Confirmed HbSS patients in steady state (diagnosed by alkaline haemoglobin electrophoresis).
- HbAA controls (confirmed by alkaline haemoglobin electrophoresis).

Exclusion Criteria

- Individuals with electrophoresis of AS, AC
- Individuals with history of acute or chronic illness like asthma, febrile illness, diabetes and hypertension.
- HbAA patients in crisis.
- Intravenous drug abusers.
- Individuals who rejected a written consent

Participant's Informed Consent

An informed consent was obtained from the literate participants while the non-literate participants thumb printed the consent form after a detailed explanation of the nature and benefits of the study. The participatory need of the non-English speaking participants was addressed by the use of an interpreter.

Confidentiality: All information provided by participants were treated with utmost confidentiality.

Questionnaire Administration and History Taking

- Questionnaire was used to interview all the participants and as well to obtain clinical data.
- The questionnaire was administered to each participant by the researcher.

Sample Collection and Storage

In accordance with standard venipuncture procedure under aseptic condition, eight milliliters of venous blood were collected from all the participants. This was done using 21G needle attached to a 10mls disposable syringe, and the antecubital vein was used as an access. Five milliliters were dispensed into Tripotassium ethylene diamine Tetra-acetic acid (K3EDTA) sample bottle and mixed gently by inverting the sample bottle several times; this was used for the determination of FBC using automated Sysmex autoanalyzer machine, and was analyzed within 2 hours of collection. The remaining sample in the EDTA sample

bottle was used for haemoglobin electrophoresis in order to confirm the Hb phenotypes of all the participants.

Three milliliters of blood were dispensed into plain bottles and allowed to stand for 1-2hours, then spurned and obtained the serum, stored at -20◦C and subsequently used for serum homocysteine determination using enzyme linked immunosorbent assay (ELISA) kit from Elabscience with manufacturer's instructions strictly followed.

Ethical Consideration

Ethical approval for this study was obtained from the Health Research Ethics Committee (HREC) of ABUTH Zaria prior to the commencement of the research.
ABUTH/HREC/CL/05
Date of approval: 21st March 2022.

Statistical Analysis

Data analysis was done using the Statistical Package for Social Sciences (SPSS) version 23.0 which is a software package used for the analysis of statistical data. The results obtained were presented using tables and figures. Continuous variables were presented as mean and standard deviation (SD), or median with interquartile range (IQR) where appropriate, while categorical variables were presented as percentages. Comparison of means was carried out using the student's t-test.

RESULTS

Table 1 shows the socio demographic characteristics of subjects and controls. The median and interquartile age for the subjects and controls were 24(15) and 27(12) years respectively, with no significant difference. There was a significant sex difference between the subjects and controls. Subjects were predominantly females (80%) whilst majority of control participants were males (60%). The majority of the study group and controls were unmarried. Only 10 (33.3%) of the subjects and 7 (22.3%) of the control were married respectively. There was no ethnic difference between the subjects and the controls as Hausa was the predominant ethnic group among the subjects (80%) and controls (73.3%). The majority of the study subjects were students and traders while most of the controls were students.

Figure 1 shows the age distribution of subjects and controls.

Table 1: Sociodemographic characteristics of subjects and controls

Variables	**SS, n =30**	**AA, n= 30**
	Freq. (%)	**Freq. (%)**
Age (years)	24.0(15.0)*	27.0(12.0)*
Min., Max. (age range)	18, 50	20, 47
Sex		
Male	6(20.0)	18(60.0)
Female	24(80.0)	12(40.0)
Marital Status		
Single	20(66.7)	23(76.7)
Married	10(33.3)	7(23.3)
Ethnic Group		
Hausa	24(80.0)	22(73.3)
Fulani	0	3(10.0)
Yoruba	4(13.3)	3(10.0)
Nupe	2(6.7)	2(6.7)
Occupational Status		
Student	12(40.0	17(56.7)
Trader	12(40.0)	5(16.7)
civil servant	3(10.0)	8(26.7)
house wife	3(10.0)	0

*Median (Interquartile range)

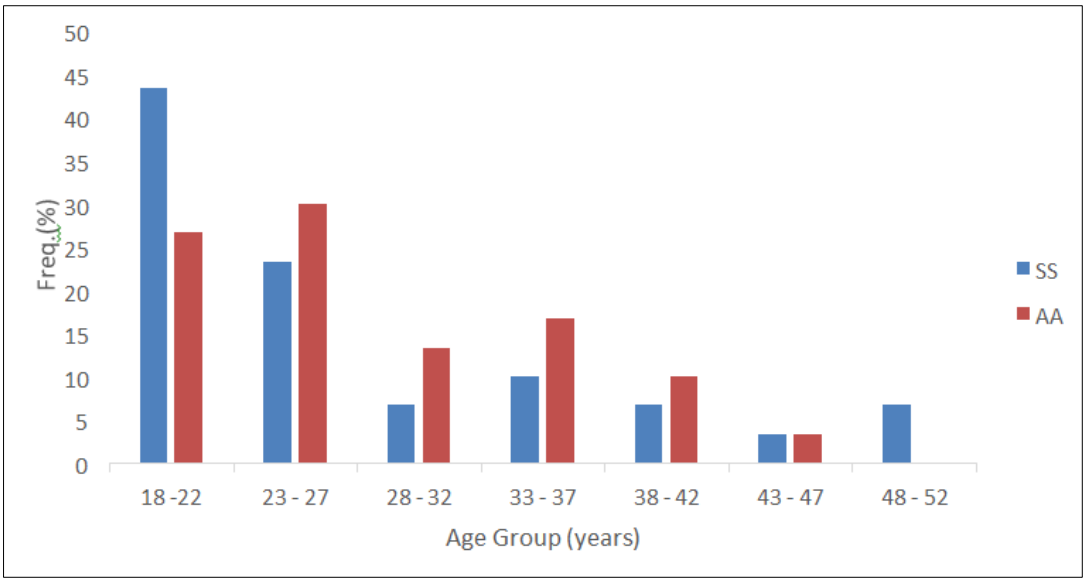

Figure 1: Age distribution of subjects and controls

Table 2 shows the mean value of haemoglobin (Hb), haematocrit (HCT), white blood cell (WBC) and Platelet (PLT) count.

The mean Hb and HCT were significantly lower in the SCA group, ($p < 0.001$).

The mean ±SD WBC count was significantly higher in the SCA group; SCA-(12.93 ±3.14x109/L), controls- (5.57 ±1.73x109/L); ($P< 0.001$).

There was also a significantly higher mean platelet count in the SCA group; ($P< 0.001$).

Table 2: The mean haematological parameters of subjects and controls

Haematological Parameters	SS	AA		
	Mean ±SD	Mean ±SD	t-test	P-value
Hb (g/dL)	8.37 ±1.77	16.03 ±2.71	-12.981	<0.0001
HCT (%)	23.57 ±5.60	41.93 ±5.36	-12.971	<0.0001
WBC ($x10^9$/L)	12.93 ±3.14	5.57 ±1.73	11.240	<0.0001
MCV (fl)	86.73 ±10.19	82.60 ±8.11	1.735	0.088
MCH (pg)	31.16 ±4.68	31.89 ±3.88	-0.658	0.513
MCHC (g/dL)	35.05(1.57)	41.55(10.35)	550.000	0.139*α
Reticulocyte (%)	8.11 ±3.16	2.00 ±0.46	10.499	<0.0001
PLT ($x10^9$/L)	406.33 ±139.48	268.00 ±85.18	4.636	<0.0001

A: Independent Sample t-test, *Mann-Whitney test, Median (Interquartile Range)
MCV: Mean Corpuscular Volume; **MCH**: Mean Corpuscular Haemoglobin; **MCHC**: Mean Corpuscular Haemoglobin Concentration

Table 3 shows the mean serum homocysteine levels of subjects and controls. There was significant difference between the mean serum homocysteine levels of the study group and control group when compared, with p value < 0.0001.

Table 3: Mean serum homocysteine levels of subjects and controls

Homocysteine (µmol/L)	Min., Max.	Mean ±SD	t-test	P-value
HbSS	7.01, 11.39	9.72 ±0.96	14.872	<0.0001
HbAA	4.06, 7.58	6.19 ±0.88		

Independent Sample t-test

DISCUSSIONS

This is a study done in patients with sickle cell anaemia visiting the Haematology Department of Ahmadu Bello University Teaching Hospital Zaria, Kaduna, Nigeria. 60 participants were studied, 30 sickle cell and 30 healthy controls. The median age of the subjects was comparable to that obtained by Ebele *et al*., [17], and Ugwu *et al*., [18], who worked independently in Lagos and Ebonyi States of Nigeria respectively. This indicates that the subjects were older than the presumed age (paediatric age group) of death. This may be due to introduction of public health measures such as penicillin prophylaxis, vaccinations and hydroxyurea that

contributed to an impressive decline in SCD-related childhood mortality [19].

SCA is an inherited autosomal recessive disorder characterized by a hypercoagulable state, and multiple factors contribute to it pathophysiology. Increased serum homocysteine levels have been linked with thrombo-embolic phenomena in these group of patients and some previously published studies have reported the abnormal homocysteine [20]. This study reported statistically significantly higher serum homocysteine levels among HbSS subjects (9.72 ±0.96 µmol/L) when compared with that of HbAA controls (6.19 ±0.88 µmol/L) with a p-value of $p < 0.0001$, even though all were with in normal range. This is similar to a study conducted in India by Kamble *et al*., [21], which also revealed a significantly higher mean serum homocysteine in the HbSS arm. Additionally, studies by Raouf *et al*., [22], in Egypt, Ebele *et al*., in Nigeria [17], which were performed independently found significantly higher mean serum homocysteine in the sickle cell subjects.

These studies however, contrast with a survey in Ibadan by Olaniyi *et al*., [23], in which 60 HbSS subjects were studied (30 in VOC and 30 in steady state); the mean plasma homocysteine level was significantly lower in HbSS subjects when compared with the HbAA control group. The mean value of homocysteine levels in VOC was 6.34±0.72 as compared to those in steady state, 5.24±0.59. Olaniyi argued that this finding could be as a result of a high compliance rate among HbSS subjects with folic acid intake as folate supplementation has been shown to reduce serum homocysteine levels even in the presence of folate deficiency [23]. It is also possible that the higher mean serum homocysteine in the HbSS arm of this study could be due to poor compliance with folic acid. This is because 70% of the subjects had history of skipping doses in their last six months before enrolment.

Another possibility is that the concentration of folate required to normalize homocysteine levels in individuals with HbSS may be higher than in HbAA individuals since they have a higher nutritional requirement for folic acid than the general population.

Furthermore, it is a known fact that the kidneys play a vital role in homocysteine metabolism [24], therefore, an impaired renal function which is not unexpected in HbSS patients could be a cause of increased homocysteine levels reported in some of the SCA patients in this study.

Taking into consideration the relationship between elevated serum homocysteine and hypercoagulability/thrombosis in SCA in previous studies, and the finding in the current study of increased plasma homocysteine, it is of paramount importance that patients with elevated homocysteine be evaluated more often and treatment with combination B-vitamin therapy instituted as soon as possible in order to prevent the various complications associated with hyperhomocysteinaemia.

CONCLUSION

Subjects with HbSS had significantly higher mean serum homocysteine when compared with HbAA controls. Studies incorporating HbSS patients in crisis and relating serum homocysteine with disease severity are recommended.

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