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Haematological and Clinical Assessment of Steady State Homozygous Hb Sand Homozygous Hb A

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Abstract
Introduction:*The abnormalities in patients with sickle cell anaemia (HbSS) result in multi- organ and systemic complications and clinical manifestations. The study aims at assessing and determining the correlates of the haematological and some clinical parameters in steady state adults with homozygous Hb S compared with adults with homogygous Hb A controls.*
Method: *It is a cross-sectional study involving 83 subjects (58 patients and age- and sex-matched 25 Hb A controls).Patients aged 16 – 52 years with confirmed HbSS using cellulose acetate electrophoresis at pH8.4 in steady state and age and sex- matched HbAA apparently healthy controls were recruited.*
Patients were physically examined and vital signs, height, weight, size of the liver and spleen, Karnofsky performance scale, KPS (0-100%) and visual analogue scale VAS for well-being were obtained. Venous blood (4.5mls) was collected into an EDTA bottle for a full blood count (WBC, RBC, Hb, PCV, MCV, MCH, MCHC, RDW and platelet count). Data was analyzed using Excel and SPSS version 20 statistical package.
Results*: Patients with Hb SS had a significantly lower mean ± SD for visual analogue scale out of 10 (VAS; 8.4 ± 1.1); Karnofsky (85.8 ± 7.8%); Pulse rate (83.8 ± 11.9 beats/mm) and diastolic BP (64 ± 9.4 mmHg) than the controls (P < 0.01), but systolic BP was not significantly different from Hb AA controls (102.9 ± 10 mmHg and 106.6 ± 10.8 mmHg respectively; P> 0.05). Hepatomegaly (15.2%), splenomegaly (6.8%) and both (17.2%) were observed in patients with sickle cell anaemia only. Out of the nine parameters measured with the use of automated cell counter seven parameters: RBC, Hb, PCV, WBC, platelets, MCHC, and red cell distribution width (RDW) were observed to be significantly lower in patients than controls but MCV and MCH were not significantly different (P > 0.05). Thirty six (62%) patients had elevated WBC (i.e. >10 ± 10/L) while 11 (19%) patients had elevated platelet counts (i.e. > 400 ± 10^9/L). Significant positive correlations were found between the red cell counts, Hb, haematocrit, SBP and DBP. While Hb and haematocrit correlated significantly with height and weight respectively. Weight and height also correlated significantly with SBP and DBP and furthermore WBC inversely correlated significantly with SBP and DBP (r = -0.314 and r = -0.303 respectively;P < 0.05).*
Conclusion:*Persistent splenomegaly was not as common as hepatomegaly in patientswith Hb SSin this study,who were observed to have a relatively lower diastolic blood pressure, pulse rate and state of well-being than the Hb AA controls. Patients had higher values of MCHC, platelets and white blood cell counts and the red cell count, haemoglobin, haematocrit, weight and height had a positive relationship with blood pressure indices in patients only.*

Keywords:*clinical assessment, haematological parameters, HbAA, HbSS, steady state.*

I. Introduction

Haemoglobin S is a mutant haemoglobin produced when a non-polar valine is substituted for polar glutamic acid at position six of the globin polypeptide chain. The solubility of Hb S in deoxygenated state is markedly reduced resulting to a tendency to polymerize into rigid aggregates that distort the cell membrane. Consequent to polymerization, the cells become sickled and appear like a crescent or holly leaf in shape. The sickled shape returns to normal during reoxygenation, however, repeated episodes of sickling and unsickling in circulation causes red cell membrane damage leading to the formation of irreversibly sickled red cells. The production of these abnormal sickle cells is the mainstay of crises and certain complications seen in these patients.Normal red blood cells life span is 90-120 days, but sickle cells have shortened life-span of about 10-20 days.[1] This accounts for low haemoglobin levels that range from 6 to 8g/dl and high reticulocyte counts even in the steady state. Haemolysis results from membrane fragmentation and loss as a result of sickling, increase red cell rigidityand destruction by reticuloendothelial cells (chronic extravascular haemolysis).[2-5]. Other

mechanisms by which haemolysis occurs includes the various aspects of the oxidative phenomenaand sickled haemoglobin instability.[6,7]

Other blood constituents are also affected in the pathophysiology of this disease condition as vascular lumen obstruction in sickle cell anaemia is as a result of interaction of erythrocyte, platelets, leucocyte, plasma protein and blood vessels. High level of leukocytes correlate positively with clinical severity of sickle cell anaemia.[8] Leucocytosis in the absence of infection is common in patients with sickle cell anaemia (SCA) and it is a predictive feature for stroke, acute chest syndrome and overall mortality. Neutrophils and monocytes have been shown to be activated in these individuals.[9]A study conducted by TetWun (2001) to determine the neutrophil activity in sickle cell disease (SCD), showed significant differences in the activated state of neutrophils in non-symptomatic patients with SCD when compared to healthy HbAA controls as shown by the significant decrease in L-selectin expression, enhanced expression of CD64, and increased levels of soluble markers like sL-selectin, elastase, and sCD16[10]. It was also observed that during vaso-occlusive crisis the differences were even more pronounced. These results show that neutrophils are activated in SCD, thus suggesting their importance in the pathophysiology of the disease.[11]

There are evidences suggesting that circulating platelets in patients with SCD are chronically activated and may contribute to the observed hypercoagulable state in these indivduals.[12] A recent study suggests that haemolysis, with decreased bio-availability of nitric oxide, may contribute at least in part, to the pathogenesis of platelet activation in SCD.[13]Lower arterial blood pressure has been reported, but another study showed a comparable systolic blood pressure in patients and controls while the diastolic blood pressure was lower and pulse pressure was significantly higher in patients than in controls.[14,15] Factors contributing to the lowered arterial blood pressure include: salt losing sickle cell nephropathy, a lowered peripheral resistance, alteration in circulating levels of catecholamine, renin, aldosterone, and prostaglandin, or changes in the sensitivity of receptors to these agents.[16-18]Splenomegaly is a usual feature in patients with sickle cell anaemic (SCA)in the first decade of life, but thereafter, atrophy sets in due to repeated infarction leading to autosplenectomy. Some may have persistent splenomegaly even into adult life.[19-21]Patients with hepatomegaly had significantly higher clinical severity scores.[22] The impact of organomegaly on the haematological parameters in patients with SCA in the steady state is yet to be fully elucidated in this environment. The study aims at assessing and determining the correlation of the haematological and clinical parameters of steady state adults with homozygous Hb S compared to adults with homogygous HbA only controls.

II. Methods

It is a cross-sectional study involving 58 patients and 25age- and sex-matched HbA only controls. Informed consent was obtained from all the participants, and ethical approval for the study obtained from the Ethical and Research Committee of OAUTHC, Ile- Ife, Nigeria. Patients aged 16 – 52 years with confirmed Hb S only using cellulose acetate electrophoresis at pH8.4 in the steady state, which is defined as a period of stable clinical condition that occurs at least one week before or three weeks after a vaso – occlusive crisis (VOC) or three months after a haemolytic crisis requiring blood transfusion.[23]Those who had received blood transfusion in previous three months, or had hypertension, diabetes mellitus, smoked cigarettes, or took excessive amounts of alcohol were excluded from the study. Age and sex- matched Hb A only as confirmed by cellulose acetate electrophoresis who were apparently healthy individuals were recruited as controls.

Patients were physically examined for vital signs, height, weight, size of the liver and spleen, Karnofsky performance scale, KPS (0-100%) and visual analogue scale VAS for well-being (1 representing the worst state of well-being (a near death experience), while 10 represented the best feeling of well-being ever experienced) were determined. Venous blood (4.5mls) was collected into an EDTA bottle for full blood count (WBC, RBC, Hb, PCV, MCV, MCH, MCHC, RDW and platelet count). Data was analyzed using Excel and SPSS version 20 statistical package. Continuous variables were presented using descriptive [means, standard deviation (SD)] and compared using inferential statistics (e.g. Student T-test, chi- square and Fisher's exact test) appropriately. A P-value ≤ 0.05 was considered to be statistically significant.

III. Results

Patients with SCA had a significantly lower mean ± SD for VAS (8.4 ± 1.1); Karnofsky (85.8 ± 7.8%); Pulse rate (83.8 ± 11.9 beats/mm); diastolic BP (64 ± 9.4 mmHg) and pulse pressure (38 ± 2.9) than the controls (Table 1), but the systolic BP was not significantly different from that of controls (102.9 ± 10 mmHg and the 106.6 ± 10.8 mmHg respectively; P> 0.05). Organomegaly (hepatomegaly and splenomegaly) was observed in the patients only (17.2%). The mean ± SD of liver size in nine (15.2%) patients with hepatomegaly was 5.9 ±3.2 cm and the mean spleen size of four(6.8%) patients with splenomegaly was 5.5 ± 2.5cm.

Out of the nine parameters obtained from the automated cell counter, four parameters; WBC, Platelets, MCHC, and red cell distribution width (RDW) were observed to be significantly higher in patients (11.1 ± 3.3, 309 ± 121.8, 31.3 ± 1.4, 19.5 ± 5.3 respectively) than the controls (4.8 ± 1.4, 210 ± 44.9, 29.5 ± 1.7, 15.7 ± 3.4

respectively;Table 2), but MCV and MCH were not significantly different (P > 0.05). Thirty six (62%) patients had elevated WBC (i.e. >10 ± 10x 10^9/L), while 11 (19%) patients had elevated platelet count (i.e. > 400 ± 10 x 10^9/L). None of the controls had either leukocytosis or thrombocytosis. There was no significant difference in WBC differential for both patients and controls (Table 3).

Table 1: Clinical assessment of patients and controls

Parameter	**Patients Mean± SD (n = 58)**	**Controls Mean± SD (n = 25)**	**P-value**
VAS (well-being)	8.4 ± 1.1	10.0 ± 0.2	<0.0001
KARNOFSKY (%)	85.8 ± 7.8	99.2 ± 2.8	<0.0001
PR (beats/min)	83.8 ± 11.9	74.7 ± 11	<0.01
SBP (mmHg)	102.9 ± 10.8	106.6 ± 10.8	NS
DBP (mmHg)	64 ± 9.4	74 ± 7.9	<0.0001
Pulse Pressure	38.5 ±2.9	32.3 ± 1.4	<0.0001
Hepatomegaly(cm) (below costal margin)	5.9 ± 3.2 (15.2%) n = 9	0	
Splenomegaly (cm)	5.5 ± 2.5 (6.8%) n = 4	0	

VAS- visual analogue scale, SBP- systolic blood pressure, DBP- Diastolic blood pressure, PP- pulse pressure.

Table 2: Haematological parameters of patients and controls

Parameter	**Patients Mean± SD n = 58**	**Control Mean± SD n = 25**	**P-value**
WBC (10^9/L)	**11.1 ± 3.3**	**4.8 ± 1.4**	**<0.0001**
RBC (10^6/L)	**3 ± 0.6**	**4.8 ± 0.6**	**<0.0001**
Hb (g/dl)	**8.1 ± 1.3**	**12.5 ± 1.5**	**<0.0001**
PCV (%)	**26.2 ± 4.3**	**42.1 ± 4.7**	**<0.0001**
MCV (fl)	**87.7 ± 8.3**	**88.5 ± 7**	**NS**
MCH (pg)	**27.5 ± 3.1**	**26.2 ± 2.4**	**NS**
MCHC(mg/dl)	**31.3 ± 1.4**	**29.5 ± 1.7**	**0.0001**
Plt (10^9/L)	**309.2 ± 121.8**	**210 ± 44.9**	**<0.001**
RDW (%)	**19.5 ± 5.3**	**15.7 ± 3.4**	**<0.01**

WBC- white blood cell, RBC- red blood cell, Hb- haemoglobin, PCV- pack cell volume, MCV- mean cell volume, MCH- mean cell haemoglobin, MCHC- mean cell haemoglobin concentration, Plt-platelet, RDW- red cell distribution width

Table 3: WBC differentials in both patients and controls

	Patients	**Controls**	**T-test**	**P-value**
Neutrophils (%)	47.1±14.3	43.2±15.6	25	NS
Lymphocytes (%)	50.6±14.2	53.9±16	25	NS
Eosinophils (%)	2.0±1.2	1.7±1.2	18	NS
Basophils (%)	1.9±0.8	1.7±0.8	10	NS
Monocytes (%)	1.3±0.5	1.4±0.5	5	NS

Effect of organomegaly on haematological parameters: haematological parameters of patients with organomegaly mild (<5cm below the subcoastal margin) to moderate organomegaly (<8cm below the subcoastal margin) had lower values of RBC, Hb, PCV, and platelets when compared to patients without organomegaly that were not statistically different (P > 0.05). The reduction was found to be more in severe organomegaly(>8cm below the subcoastal margin), but it was also not significance statististically, however,the WBC values were higher in patients with organomegaly than those without organomegaly though not significant statistically.

Table 4:Correlation between haematological parameters, blood pressure indices and anthropometric variables

Haematological Parameters	SBP	DBP	PP	PR	Height	Weight	BMI
Red blood cell							
r	0.312*	0.328*	-0.064	-0.206	0.097	0.203	0.140
P	0.023	0.017	0.632	0.138	0.476	0.134	0.305
Haemoglobin							
r	0.434**	0.415**	-0.051	-0.049	0.281*	0.310*	0.117
P	0.001	0.002	0.701	0.728	0.036	0.020	0.389
Haematocrit							
r	0.341*	0.343*	-0.127	-0.081	0.172	0.281*	0.173
P	0.013	0.012	0.341	0.565	0.205	0.036	0.201
Platelets							
r	-0.146	-0.129	-0.084		-0.096	-0.236	-0.206
P	0.296	0.358	0.533		0.484	0.080	0.128
WBC							
r	-0.314*	-0.303*	0.146	0.198	0.098	-0.121	-0.169
P	0.022	0.028	0.275	0.155	0.474	0.373	0.214
Height							
r	0.289*	0.387**	0.186	0.146			
p	0.036	0.004	0.166	0.308			
Weight							
r	0.373**	0.317*	0.161	0.185			
p	0.006	0.021	0.232	0.193			
BMI							
r	0.164	0.013	0.037	0.088			
p	0.240	0.928	0.784	0.537			

Key:**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).

Table 4 shows a significant correlation between red cell count and systolic blood pressure, (r = 0.312;p= 0.023), diastolic blood pressure (r =0.328; p =0.017). Haemoglobin correlated significantly with systolic blood pressure (r = 0.434, p = 0.001), diastolic blood pressure (r = 0.415; p = 0.002) and also with height (r = 0.281, p = 0.036) and weight (r = 0.310, p = 0.020). Haematocrit correlated with systolic blood pressure (r = 0.341; p = 0.013), diastolic blood pressure (r = 0.343, p = 0.012)and weight (r = 0.281; p = 0.036). White blood cell inversely correlated with the systolic blood pressure (r = -0. 314, p = 0.022), and diastolic blood pressure (r = -0.303; p =0.028). Height (r = 0.289; p = 0.036) and weight (r = 0.373, p = 0.006) correlated significantly with SBP, but BMI did not correlate with any blood pressure measurement or haematological parameter.

IV. Discussion

The visual analogue scale and Karnofsky performance scale though significantly lower in patients than in the controls revealed a good quality of life for the patients in this series since adequate performance status is associated with Karnofsky score > 70%and normal VAS ≥ 8.[24]Blood pressure in these patients showed a comparable systolic blood pressure to that of the controls while the diastolic blood pressure and pulse pressure were found to be significantly lower (Table1; P< 0.001) than the controls. These findings are similar to that of

the study conducted in UNTH, Enugu and that by Ayo *et al* while another studies reported a significantly lower systolic and diastolic blood pressure. [15,25-26]The relatively lower blood pressures were partly explained in these patients by anaemia.[26] Splenomegaly with hepatomegally was observed in 17.2% of these patients. This is in keeping with findings that some patients have persistence splenomegaly even into adult life.[19,20]

This study also tried to elucidate the effect of organomegaly (splenomegaly with or without hepatomegaly) on haematological parameter. There was a reduction in red cell parameters and platelet counts with increasing organomegaly that was however not statistically significant. Significant positive correlations were observed between the red cell counts, Hb, haematocrit, SBP and DBP. While Hb and Haematocrit correlated significantly with height and weight respectively. Weight and height also correlated significantly with SBP and DBP and furthermore, WBC inversely correlated significantly with SBP and DBP. These findings are in keeping with previous studies where haemotocrit correlated significantly with blood pressure indices.[14,15,]These studies also showed a positive correlation between BMI, renal function, age and sex.[14,15]However, our study did not demonstrate significant correlation between blood pressure and BMI and did not correlate with age and sex. Sickle cell anaemia is characterized by a state of chronic haemolysis even in the steady state and this accounts for the clinical and laboratory features seen in this disorder. In this study, the values of the haematocrit, haemoglobin, were found to be significantly lower in patients with SCA than in controls as expected (Table2). This is similar to the results of previous studies conducted in this country and these features are part of the characteristic features of this chronic haemolytic disorder.[27-30] The mean total white blood cell count seen in the patients compared to the controls was significantly higher (Table 2; $P < 0.0001$) as reported in previous studies.[26-29]Leucocytosis above 15 x 10^9/l in the absence of infection is common in SCA and this predicts the risk of stroke, acute chest syndrome, mortality and overall survival.[9] Neutrophil and monocytes have been found to be activated in patients with SCD.[9] Activated leucocytes further promote vascular inflammation and vessel damage. There is no significant difference between the WBC differentials in both patients and controls, confirming that the patients were in the steady state (Table 3).

The mean platelet count in these patients was significantly higher than in the controls (Table 2; $P < 0.001$) and this agrees with other reports.[27,28,30] Thrombocytosis in SCA has been associated with the background haemolytic anaemia and loss of splenic platelet pool function resulting from autosplenectomy/functional asplenia.The mean cell haemoglobin concentration (MCHC) in this study was significantly higher in patients compared with controls (Table 2; $P < 0.0001$), while there is no significant difference in the mean of MCV for both patients and controls; these findings are in agreement with previous studies.[28,29] Although the mean MCH of patients was not significantly higher than that of controls and this is not in agreement with reports from elsewhere.[27,31] The high MCHC result from an increase in the concentration of haemoglobin in solution and cellular dehydration and this can predispose the cell to sickle when subsequently deoxygenated. Furthermore, a high MCHC is associated with an increase in cytoplasmic viscosity and a decrease in deformity thus leading to obstruction of small vessels and ultimately vaso-occlusive crisis.

V. Conclusion

Patients with homogygous Hb S have relatively lower diastolic blood pressure than the homozygous Hb A controls. Hepatomegaly is more common than splenomegaly in patients. Red cell count, haemoglobin, haematocrit, weight and height have a positive relationship with blood pressure indices in patients with HbS. Patients with homozygous HbSS have higher values of MCHC, platelets and white blood cell counts when compared to controls.

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