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Cardiovascular System Abnormalities in Sickle Cell Anaemia: Clinical Findings in Steady State Adult Nigerian Patients

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Abstract

Aim and objective: This study was aimed at examining the cardiovascular clinical features in steady state adult Nigerian sickle cell anaemia patients.

Method: The study subjects were drawn from adult patients (age ≥ 18 years), attending the adult sickle cell clinics who had haemoglobin genotype SS on haemoglobin electrophoresis and were in steady state. Age and sex matched normal subjects served as controls. All subjects were evaluated for symptomatology of cardiovascular disease with the aid of a questionnaire and then clinically examined to evaluate their cardiovascular status at rest.

Result: Significant increase in pulse rate was found in the study subjects (87.68 ± 8.91/minute) compared with the controls (72.13 ± 6.79/minute); {p < 0.05,}. The mean systolic blood pressure was comparable in the two groups. However the patients had significantly lower diastolic blood pressure, lower mean arterial blood pressure, as well as a higher pulse pressure than the control subjects. Abnormal physical findings found in the study group include loud pulmonary component of the second heart sound (83.3%), displaced cardiac apex (70.0%) and active precordium (43.3%) and radiologic evidence of cardiomegaly (cardiothoracic ratio {CTR} > 0.5) 86.67%.

Conclusion: The haemodynamic response to chronic anaemia in sickle cell anaemia results in significant cardiovascular dysfunction.

Keywords: Cardiovascular system abnormalities; Sickle cell anaemia; Clinical findings

Introduction

Cardiovascular system abnormalities are prominent features of sickle cell anaemia, and these have been thought to result from the cardiovascular effect of chronic anaemia seen in sickle cell disease [1] as well as vascular occlusion by sickled red blood cells and micro-vascular sludging [2]. The effect of chronic anaemia and intravascular sickling combine to present significant findings on examination of the cardiovascular system [3]. Sinus tachycardia occurred in 27% of steady state adult patients studied by Uzzoy [4]. Heart rates were significantly higher in patients with history of dyspnoea or fatigue than in asymptomatic patients [5]. In a study in Kenya of 52 sickle cell anaemia patients the mean heart rate was significantly lower in patients with haemoglobin level of 8.0 - 9.9 g/dl compared with patients with lower haemoglobin levels indicating that it is related to the cardiovascular response to anaemia [6]. The blood pressure is typically low in sickle cell anaemia and fails to show the age related rise common in normal population [7,8]. A thrill in the suprasternal notch was noted in 15 (45%) by Ng et al. [9] and was significantly more common in children with low haemoglobin levels. Accentuation of the pulmonary component of the second heart sound is common and does not seem to correlate with the presence of pulmonary hypertension [10]. These signs probably result from a pulmonary artery dilatation as a consequence of increased pulmonary blood flow, palpated more readily because of a thin chest wall [11]. Mid diastolic flow murmurs, particularly mitral were noted in 36% of children by Ng et al. and were significantly more frequent in patients with low haemoglobin levels9. Patients without audible murmurs tend to be those without cardiomegaly and with high haemoglobin levels.

Most of the previous studies on clinical features in sickle cell anaemia were carried out on children between the ages of 2-17 years. However, with the continual development of better supportive care for patients with sickle cell anaemia, and the resultant increase in life span there could be a change in the pattern of cardiac manifestation in sickle cell anaemia over the years.

This study was aimed at examining the cardiovascular clinical features in steady state adult Nigerian sickle cell anaemia patients.

Methodology

The study was carried out in the adult outpatient sickle cell clinics and the cardiac center of the University of Nigeria Teaching Hospital (UNTH) Enugu, Nigeria. The study subjects were drawn from adult patients (age ≥ 18 years) [12], attending the adult sickle cell clinics of the UNTH Enugu, who had haemoglobin genotype SS on

haemoglobin electrophoresis, were in steady state and consented to participate in the study.

Steady state is defined as absence of any crisis or blood transfusion in the preceding four weeks, absence of any symptoms or signs attributable to acute illness. A total of sixty two sickle cell anaemia patients and sixty two age and sex matched normal controls were studied. All subjects were evaluated for symptomatology of cardiovascular disease with the aid of a questionnaire and then clinically examined to evaluate their cardiovascular status at rest. The weight and height of each subject were recorded and the surface area determined from a standard formula [13]. All the patients had posterior – anterior chest X-ray examination.

Data were presented as means ± standard deviation for continuous variables and as proportions for categorical variables. Comparison of continuous variables between groups was made with independent Student's t-test. For discrete variables distribution between groups were compared with Chi- square test and Fishers exact test as appropriate (where an expected cell is less than 5). In order to examine the effect of anaemia on the variables, the subjects were classified based on the hematocrit values into four classes in accordance with the World Health Organization classification of anaemia as follows: Class 1; normal (hematocrit ≥ 36%), Class 2; mild anaemia (hematocrit 30 - 35.9%), Class 3; moderate anaemia (hematocrit 21 - 29.9%), Class 4; severe anaemia (hematocrit 18 - 20.9%) [14]. Inter-class differences in clinical parameters in the patients were compared by one-way analysis of variance and post hoc multiple comparison of mean using the Tukey's honestly significant difference test. All statistical analyses were carried out using the Statistical Packages for Social Sciences (SPSS Inc. Chicago Illinois) software version 11.0. Statistical tests with probability values less than 0.05 were considered statistically significant.

Results

Age and gender distribution

A total of sixty two sickle cell anaemia patients (31 males, 31 females) and sixty two normal controls matched for age and sex were studied. All the patients were homozygous for the sickle cell gene on haemoglobin electrophoresis, while all the controls had haemoglobin genotype AA. The age and sex distribution of the subjects are shown in (Table 1). The mean ages for patients and controls were 28.27 ± 5.58 (range 18 - 44) and 28.37 ± 5.91 (range 18 – 45) years respectively. There were no statistically significant age and gender differences in patients and controls.

Parameters	SCA	Controls	T-test	P-value
	Mean (SD)	Mean (SD)		
Age (years)	28.27 (5.58)	28.37 (5.91)	0.987	0.924
Gender {frequency (%)}				
Male	31 (50)	31 (50)	0	1.00[a]
Female	31 (50)	31 (50)		
Total	62	62		
Weight (kg)	54.97 (10.61)	67.35 (8.37)	7.2	< 0.001*
Height (m)	1.62 (0.14)	1.72 (0.07)	4.96	< 0.001*
Body surface area (m^2)	1.62 (0.03)	1.78 (0.14)	3.723	< 0.001*
Body mass index (Kg/m^2)	20.47 (2.73)	23.87 (3.22)	6.181	< 0.001*
*Statistically significant, [a]Chi-square SCA-sickle cell anaemia				

Table 1: Age, gender and anthropometric data.

Anthropometric data and physiologic variables

The study subjects had statistically significant lower mean values than controls in the measurement of height, weight, body mass index, and body surface area {P < 0.001} (Table 1). Significant increase in pulse rate was found in the study subjects (87.68 ± 8.91) compared with the controls (72.13 ± 6.79); {p < 0.05,}. The mean systolic blood pressure was comparable in the two groups. However the patients had significantly lower diastolic blood pressure (64.87 ± 8.95; 76.88 ± 6.18 mm Hg), lower mean arterial blood pressure (81.18 ± 12.65; 91.71 ± 5.47 mm Hg), and a higher pulse pressure than the control subjects (54.63 ± 12.87; 44.31 ± 10.91 mm Hg), (Table 2).

Parameters	SCA	Controls Mean (SD)	T-Test	P-Value
	Mean (SD)			
Pulse rate (beat/min)	87.68 (8.91)	72.13 (6.79)	11.062	< 0.001*
Brachial systolic BP(mm Hg)	119.50 (11.70)	121.2 (8.97)	0.527	0.599
Brachial diastolic BP (mm Hg)	64.867 (8.95)	76.88 (6.18)	8.629	< 0.001*
Brachial pulse pressure (mm Hg)	54.63 (12.87)	44.31 (10.91)	4.735	0.001*
Mean brachial arterial BP (mm Hg)	81.18 (12.65)	91.71 (5.47)	5.85	< 0.001*
Haematocrit (%)	24.07 (3.10)	38.65 (1.97)	30.589	< 0.001*

Table 2: Physiologic data in patients and controls.

Hematocrit values in patients and controls

The mean hematocrit values were 24.07 ± 3.10%; (range 20 – 31.3%) for the patients and 38.65 ± 1.97%; (range 30 - 42%) for the controls. The mean hematocrit values was significantly lower in patients than controls (t = 30.589; P = 0.001).

The patients and controls were categorized into four groups based on the hematocrit values (Table 3). Fifteen percent of the patients and 18.33% of the controls had hematocrit values between 30 and 35.9%. Sixty seven percent of the patients had hematocrit values between 21 and 29.9%, while 81.67% of the controls had haemotocrit values above 36%.

Hematocrit values (%)	Frequency (%)		X^2	P- value
	SCA	Controls		
> 36 (Normal)	0 (0)	49 (81.67)	79.47	< 0.001*

30 - 35.9 (Mild)	9 (15)	11 (18.33)	0.06	0.8065
21 - 29.9 (Moderate)	40 (66.67)	0 (0)	57.04	< 0.001*
18 - 20.9 (Severe)	11 (18.33)	0 (0)	10.01	0.0016*
*Statistically significant. (the degree of freedom = 1)				

Table 3: Hematocrit values in patients and controls.

Clinical findings

Clinical findings in patients and controls

Abnormal physical findings found in the subjects are summarized in table 4. Notable features in the study group include loud pulmonary component of the second heart sound (83.3%), displaced cardiac apex (70.0%) and active precordium {defined as visible precordial cardiac activity} (43.3%).

Parameters	**Frequency (%)**		**χ- Square**	**P-Value**
	SCA	**Controls**		
Leg ulcers	8 (13.33)	0 (0)	8.57	0.003*
Leg oedema	4 (6.67)	0 (0)	4.14	0.042*
Displaced cardiac Apex	42 (70.00)	0 (0)	64.62	< 0.001*
Raised JVP	13 (21.70)	0 (0)	14.58	< 0.001*
Left parasternal heave	5 (8.30)	0 (0)	5.22	0.022*
Active Precordium	26 (43.30)	0 (0)	33.19	< 0.001*
Loud P_2	50 (83.30)	0 (0)	85.71	< 0.001*
Expiratory splitting of S_2	10 (16.70)	0 (0)	10.91	< 0.001*
SCA- sickle cell anaemia, JVP- jugular venous pulsation, P_2- pulmonary component of second heart sound, S_2- second heart sound, CTR- cardiothoracic ratio.*Statistically significant (the degree of freedom = 1)				

Table 4: Clinical findings in patients and controls**Clinical findings in patients based on the hematocrit level.**

Comparison of the clinical findings in sickle cell anaemia patients with the degree of anaemia showed significant association of leg oedema, right ventricular heave and increased cardiothoracic ratio with the degree of anaemia, (Table 5).

Parameters	**Frequency (%)**			**χ^2**	**P-Value**
	Haematocrit Levels				
	Mild	**Moderate**	**Severe**		
Raised JVP	1 (11.11)	4 (10.00)	8 (72.73)	0.866	0.649
Displaced apex	6 (66.67)	28 (70.00)	8 (72.73)	2.044	0.36
Active precordium	5 (55.56)	15 (37.5)	6 (54.55)	3.922	0.141
Loud P_2	6 (66.67)	35 (87.50)	9 (81.81)	3.97	0.1373
Leg oedema	0 (0)	1 (2.50)	3 (27.27)	9.216	0.01*
RV heave	1 (11.11)	2 (5.00)	4 (36.36)	8.238	0.016*
↑CTR > 0.5	4 (44.44)	37 (92.5)	11 (100.00)	22.67	0.00001*
*Statistically significant (the degree of freedom = 2), RV heave = Right ventricular heave (Left parasternal heave). ↑CTR = increased cardiothoracic ratio.					

Table 5: Clinical parameters in sickle cell patients compared with the degree of anaemia.

Discussion

We observed significantly lower values of body surface area, body weight and body mass index in sickle cell anaemia patients. Body mass index is the body mass per unit per area and a measure of adiposity of an individual and a good indicator of nutritional status. Inadequacy of nutrients may result from inadequate diet, poor absorption or defective metabolic utilization. It is likely that the low anthropometric parameters in these patients are the product of the combined effect of chronic anaemia and chronic nutritional deficiencies resulting from inadequate food intake because of poor appetite especially during the vasoocclusive crisis.

Abnormal cardiovascular physical findings demonstrated by this study in sickle cell anaemia were increased pulse rate, increased pulse pressure, displaced cardiac apex (cardiomegaly), raised JVP, leg oedema, left parasternal heave, loud pulmonary component of second heart sound, and expiratory splitting of second heart sound.

Blood pressure and pulse pressure

The brachial systolic blood pressure in sickle cell anaemia patients from this study was not significantly different from that of the controls but the diastolic blood pressure was found to be significantly lower in the patients than in the controls. The significantly lower diastolic blood pressure and increased pulse pressure noted in the patients in this study could be as a result of the haemodynamic effect of chronic anemia. However, increased pulse pressure has been shown to predict cardiac morbidity in studies carried out in diabetic and hypertensive

patients [15,16]. Its relevance in patients with sickle cell anaemia is yet to be explored.

Leg oedema and jugular venous pulsations

The finding of leg oedema and raised jugular venous pulsation in 6.67% and 21.7 percent respectively of the patients and none in the controls can be so striking as to suggest congestive heart failure. In many of the cases these signs represent systemic effects of chronic anaemia rather than true congestive heart failure.

In one study, clinical evidence of congestive heart failure was found before death in 17 patients (33%) out of 52 adult sickle cell patients. At autopsy, 7 had moderate to severe left ventricular hypertrophy associated with chronic renal failure and hypertension, 2 had right ventricular hypertrophy with organized pulmonary thrombosis, 2 had rheumatic mitral valve disease and only 2 patients had congestive cardiac failure [17].

It has been suggested that patients with congestive cardiac failure usually have severe coexisting disease secondarily affecting myocardial function rather than a cardiomyopathy specific for sickle cell anaemia [17]. Although the patients in this study did not have any clinical or biochemical finding suggestive of renal impairment, the possibility of background sickle cell nephropathy cannot be ruled out.

Leg edema has been shown to precede leg ulcers in sickle cell anaemia [18]. The occurrence of leg ulcers in 13.33% of the patients in this study may contribute to the significant finding of leg edema in these patients.

Heart sounds

Pulmonary hypertension is an increasingly recognized complication of sickle-cell anaemia and a risk factor for early death [19,20]. We have previously reported electrocardiographic and echocardiographic data consistent with pulmonary hypertension in 41.9% of this cohort of patients [21,22].

Besides the presence of pulmonary hypertension in some patients, the loud pulmonary component of the second heart heard in 83.3% of the patients may reflect increased flow in the pulmonary vascular bed which is readily auscultated because of their thin chest wall. Tress et al. [23], in Rio de Janeiro, Brazil noted loud pulmonary component of the second heart sound in 75% of patients aged between 6 to 48 years. The slight difference compared with the present finding could be accounted for by the large numbers of relatively younger patients included in the latter study. Increased hemodynamic load in the patients would also explain the widely spit second heart sound heard in the patients.

Cardiomegaly

Cardiomegaly was found in 70% of patients by clinical assessment (displaced cardiac apex; defined as location of the cardiac apex below the left 5^{th} intercostals space or at the 5^{th} left intercostals space lateral to the mid clavicular line) and in 86.67% of patients by radiology (increased cardiothoracic ratio > 0.5). Uzsoy found clinical evidence of cardiomegaly in 80% of patients while Ng et al. found radiological evidence of cardiomegaly in 85% of patients aged 2 – 17 years [9]. Cardiomegaly is largely due to sustained increase in hemodynamic circulation with increased cardiac output. A clinicopathological study in sickle cell patients reported finding of right and left ventricular dilatation in 64% and 44% of patients respectively and biventricular hypertrophy in 36% of patients [17].

The impact of anaemia

The effect of chronic anaemia and the resultant increased volume load and increased cardiac output could, at least in part, explain some of the clinical findings in sickle cell anaemia in this study. Increased pulse pressure, raised jugular venous pulsation, leg oedema, left parasternal heave and cardiomegaly were significantly found in sickle cell patients in this study. Subdivision of the patients into three groups based on their hematocrit values identified significant differences in some of these parameters that would suggest progressive deterioration in heart function with increasing degree of anaemia. Although, increased cardiothoracic ratio on chest X-ray showed significant variation with the degree of anaemia, the clinical measurement cardiac apex did demonstrate any such discrimination. This underscores the greater value of chest radiography in evaluation of cardiomegaly.

It is recognized that the degree of chronic anaemia in these patients cannot be adequately quantified by single hematocrit measurement as was used in this study. Further studies are therefore recommended using patients with chronic anaemia from other causes other than sickle cell anaemia as controls in order to evaluate the role of anaemia and/or sickling in the pathogenesis of the cardiac changes seen in sickle cell anaemia.

References

1. Varat MA, Adolph RJ, Fowler NO (1972) Cardiovascular effects of anaemia. Am Heart J 83: 415-426.
2. Francis RB, Johnson CS (1991) Vascular occlusion in sickle cell disease: current concepts and unanswered questions. Blood 77: 1405-1414.
3. Karayalcin G, Rosner F, Kim KY, Chandra P, Aballi AJ (1975) Sickle cell anaemia: clinical manifestation in 100 patients and review of literature. Am J Med Sci 269: 51-68.
4. Uzsoy NK (1964) Cardiovascular findings in patients with sickle cell anaemia. Am J Cardiology 13: 320-328.
5. Rees AH, Stefadouros MA, Strong WB, Miller MD, Gilman P, et al. (1978) Left ventricular performance in children with homozygous sickle cell anaemia. Br Heart J 40: 690-696.
6. Ayuo PO, Abinya NA, Joshi MD, Lore W (1993) Cardiovascular features of adolescents and adults with sickle cell anaemia. East Afr Med J. 70: 270 -276.
7. Johnson CS, Giorgio AJ (1981) Arterial blood pressure in adults with sickle cell anaemia. Arch Intern Med 141: 891-893.
8. De Jong PE, Landman H, Status Van Eps LW (1982) Blood pressure in sickle cell disease. Arch Intern Med 142: 1239-1240.
9. Ng ML, Leibman J, Anslovar J, Cross S (1967) Cardiovascular findings in children with sickle cell anaemia. Dis Chest 52: 788-799.
10. Shubin H, Kaufman R, Shapiro M, Levinson DC (1960) Cardiovascular findings in children with sickle cell anaemia. Am J Cardiol 6: 875-885.
11. Sergeant GR (1992) Sickle cell disease. Second edition Oxford University press Ltd. New York 170-183.
12. (1989) United Nations Organization. United Nations Convention on the right of the child. General Assembly resolution 44/24. Geneva 2.
13. Ganong WF (1989) Review of medical physiology. (14th edn) Appleton and Lange. California, USA.
14. De Mayer EM, Dallman P, Michael GJ, Hallberg L, Sood SK, et al. (1989) Preventing and controlling iron deficiency anaemia through primary health care. World Health Organization 58.
15. Schram MT, Kostense PJ, Van Dijk RA, Dekker JM, Nijpels G, et al. (2002) Diabetes, pulse pressure and cardiovascular mortality: the Hoorn study. J Hypertension 20: 1743 -1751.
16. Benetos A, Safar M, Rudnichi A, Smulyan H, Richard JL, et al. (1997) Pulse pressure: a predictor of long-term cardiovascular mortality in a French male population. Hypertension 30: 1410 - 1415.

17. Gerry JL, Bulkly BH, Bulchins GM (1978) Clinicopathologic analysis of cardiac dysfunction in 52 patients with sickle cell anaemia. Am J Cardiol 42: 211-216.
18. Phillips G, Eckman JR, Hebbel RP (1994) Leg ulcers and myofascial syndromes. Sickle cell disease: Basic principles and clinical practice 1994, Raven press Ltd New York 681-688.
19. Machado RF, Gladwin MT (2005) Chronic sickle cell lung disease: new insights into the diagnosis, pathogenesis and treatment of pulmonary hypertension. Br J Haematol 129: 449-464.
20. Anthi A, Machado RF, Jison ML, Taveria-Dasilva AM, Rubin LJ, et al. (2007) Hemodynamic and functional assessment of patients with sickle cell disease and pulmonary hypertension. Am J Respir Crit Care Med 175: 1272-1279.
21. Oguanobi NI, Ejim EC, Onwubere BJC, Ike SO, Anisiuba BC, et al. (2012) Clinical and electrocardiographic evaluation of sickle cell anaemia patients with pulmonary hypertension. ISRN Hematol: 1-9.
22. Oguanobi NI, Ejim EC, Anisiuba BC, Onwubere, BJC, Ike SO, et al. (2015) Echocardiographic assessment of adult Nigerian sickle cell patients with pulmonary hypertension. European Journal of Cardiovascular Medicine 3: 430-434.
23. Tress JC, Oliveira MA, Costa LS, Nelo CD, Matta K (2005) Cardiovascular complications in sickle cell disease; clinical and echocardiographic features. Am J Hypertension 18: 155A -156A.