Nigerian Journal of Paediatrics 1992; 19(2): 37 - 43

Cardiovascular findings in children with sickle-cell disease

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Summary

Ogunkunle OO and Jaiyesimi F. Cardiovascular findings in children with sickle-cell disease. *Nigerian Journal of Paediatrics 1992;* **19:37.** The physical findings in 96 children with sickle-cell disease (SCD) and in 52 age - and sex - natched controls, were compared with a view to defining the cardiovascular sequelae of SCD. The pulse rates of the sicklers were faster than those of the controls ($P<0.01$). The systolic blood pressures were higher and the diastolic, lower in the subjects than in the controls making the pulse pressures of the sicklers significantly wider than those of the controls ($P<0.001$). The apex distance from the midline was further in the sicklers than in the controls ($P = 0.02$) and was related to the severity and duration of anaemia. Murmurs occurred more commonly among the subjects than the controls ($P<0.01$), the commonest murmurs being soft, ejection systolic in timing and located most often at the left upper sternal edge. Prevalence of murmurs was related to severity, but not duration of anaemia.

Introduction

THE cardiovascular features of chronic anaemia have been recognized for many years.[1-5] Similarly, the added effects on the heart, of the sickled erythrocytes in sickle-cell disease (SCD) have been studied extensively, particularly in the United States of America.[6-12] By contrast, relatively little is known about the cardiovascular sequelae of SCD in Africa, where, owing largely to the adverse socio-economic milieu (poverty, malnutrition, frequent infections, etc) the disease tends to run a more severe course.[13] The present study was, therefore, undertaken in order to document the cardiovascular complications of SCD among our children.

Subjects and Methods

The study group comprised 96 children (57 males and 39 females) with SCD, aged between one year and 16 years, who were selected randomly from the Anaemia Clinic, Children's Outpatient department, University College Hospital (UCH), Ibadan. Eighty-four (87.5 percent) of the subjects were homozygous for HbS, while the remaining 12 (12.5 percent) had HbSC haemoglobinopathy. They were all in steady state. Patients in crisis or those with evidence of respiratory or other

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acute infections, were excluded from the study, as were those with clinical or other evidence of congenital or acquired heart defects and those who had received blood transfusion within the preceding three months. Fifty-two healthy non-sicklers (29 males and 23 females) with haematocrit levels of 30% or more, formed the control group. They were aged between one year and 15 years and the same exclusion criteria applied to them.

The sex, weight, height, haemoglobin genotype and haematocrit (Hct) value of each subject and control were determined and recorded. The cardiovascular system in each subject and control was assessed by the first author and the findings were confirmed by the second author. Particular attention was paid to the pulse rate and character, blood pressure (BP), apex beat (AB), heart sounds and murmurs as well as the position of any abnormal impulses or thrills. BP was measured with a standard mercury sphygmomanometer, using one of three sizes of cuff (4, 9 or 13 cm wide) selected so that at least 2/3 of the right upper arm was covered. Measurements were taken with the patient seated and calm, with the right arm extended. The systolic BP was taken as the point at which Korotkoff sound became audible (Phase I) and the diastolic as that at which the sounds became muffled (Phase IV). Readings were recorded to the nearest 5mm gradation. The AB was measured from the midline (ML) and the distance recorded to the nearest 5mm gradation.

The data obtained were subjected to statistical analysis, using Pearson's Correlation Coefficient (r) for evaluating the association between 2 quantitative variables, while the Chi squared (X^2) test was used for determining the association between two qualitative variables. Student's 't' test was used to compare two mean values and where there were more than two mean values, the one-way analysis of variance technique was used for the comparison. The level of significance was taken to be <0.05.

Results

There was no difference (P>0.05) between the two groups in relation to the sex ratios. Table 1 shows that whereas the two groups did

Table 1

Ranges, means and standard deviations of parameters in subjects and controls

Parameter	Subjects			Controls			t	p
	No of cases	Range	Mean±1SD	No of cases	Range	Mean±1SD		
Age (years)	96	1.0-16.0	6.2±3.9	52	1.0-15.0	7.0±3.8	1.21	>0.2
Weight (kg)	96	7.5-39.9	18.2±7.6	50	9.0-39.8	20.4±8.1	1.61	>0.1
Height (cm)	96	73-159	108.1±22.0	48	76-159	111.5±22.6	1.82	>0.05
Haematocrit (%)	96	15-34	24±4.0	52	30-42	35±3	16.30	<0.001***
Pulse rate (beats/min)	96	64-148	104±17	52	60-132	95±16	2.85	<0.01**
Systolic blood pressure (mm Hg)	71	70-120	98±10	49	80-125	96±12	1.02	>0.3
Diastolic blood pressure (mm Hg)	71	30-80	58±12	49	35-80	61±10	1.89	>0.05
Pulse pressure (mm Hg)	71	20-60	41±10	49	20-55	35±9	3.51	<0.001**
Apex distance from midline (cm)	93	4.0-12.0	6.7±1.5	52	4.0-9.0	6.1±1.5	2.33	=0.02*

t = Student's 't' test
* = degree of significance

not differ significantly in age, weight or height, the mean Hct (24 ± 4 percent) of the subjects was significantly lower ($P<0.001$) than that of the controls (35 ± 3 percent).

Pulse Rate

The pulse rates of the subjects were significantly ($P<0.01$) faster than those of the controls (Table 1).

The pulse was regular in all the controls, but irregular in one subject, a 10-year old girl, who had frequent ectopic beats. The younger patients in each group tended to have faster rates (Table 11). Conversely, there was no significant correlation between pulse rate and Hct in either group of patients (Table II).

Blood Pressure

The systolic, or diastolic BP in the two groups did not differ significantly ($P>0.3$ and $P>0.05$ respectively); the pulse pressure was however, significantly wider ($P<0.001$) in the subjects than the controls (Table 1).

Figure and Table II show that in both subjects and controls systolic and diastolic BP increased with age. However, whereas correlation between systolic BP and age was significant among the sicklers ($P<0.05$), this was not the case in the control group (Table II). Similarly, among the sicklers, there was no correlation between pulse pressure and age, but the

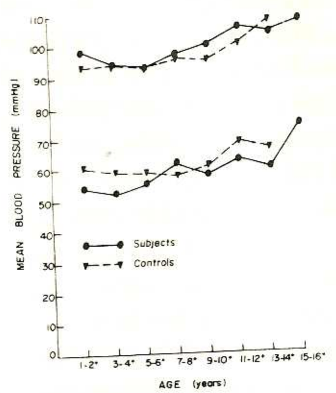

Figure: *Mean Systolic and Diastolic Blood Pressures in Subjects and Controls.*

Table II

Correlation coefficient between some evaluated parameters with respect to age and haematocrit level

Parameter	Age		Haematocrit	
	Subjects	Controls	Subjects	Controls
Pulse rate	-0.61***	-0.63***	0.14	-0.05
Systolic BP	0.29*	0.24	-0.21	0.38**
Diastolic BP	0.27	0.26	0.03	0.36**
Pulse Pressure	-0.04	0.04	-0.25*	0.11
Apex distance from midline	0.80***	0.81***	-0.32**	0.14

Figures refer to Pearson's correlation coefficient.

* = $P<0.05$
** = $p<0.01$
*** = $p<0.001$

subjects with lower Hct levels were found to have significantly wider pulse pressures. There was no correlation between Hct and pulse pressure in the control group.

Location of the Apex Beat

The AB was evaluated in 93 subjects and 52 controls; it was significantly further away from the ML in the subjects (mean 6.7 ± 1.5cm) than in the controls (mean 6.1 ± 1.5cm), P = 0.02 (Table I). In both groups of children, there was highly significant correlation (P<0.001) with age (Table II). However, the more anaemic subjects had clinically larger hearts (P<0.01), but there was no correlation between Hct and heart size in the controls (Table II).

Cardiac Impulse

The apical impulse was hyperactive in 17 (18.3 percent) of the 93 subjects and in only one (1.9 percent) of the 52 controls, the difference being significant ($x^2 = 6.4$; P<0.02). Similarly, there was a significantly higher frequency of increased RV impulse among 12 (12.9 percent) of the 93 subjects than the controls, none of whom had any such abnormality ($x^2 = 4.51$; P<0.02). Thrills were not encountered in any of the subjects or controls.

Heart Sounds

Abnormal heart sounds were heard in 13 (13.5 percent) of the 96 subjects and in 2 (3.8 percent) of the 52 controls. The difference in frequency was not significant ($x^2 = 2.50$; P>0.10).

Among the subjects, the abnormal heart sounds comprised nine instances of loud pulmonary closure sound (P_2), two cases of soft apical ejection click, and one each of a loud first heart sound (S_1) and an apical 3rd heart sound (S_3). Two controls had soft apical ejection clicks. Table III shows the relationship between abnormal heart sound and Hct level in the subjects. The Hct of the nine subjects with loud P_2), ranged from 16 to 28 percent with a mean of 21 ± 3 percent, which was significantly lower than the Hct of the subjects with normal heart sounds (range = 18 to 34 percent, mean 25 ± 4 percent) t = 2.78, P<0.01. Conversely, there was no difference (P>0.05) in age between those subjects who had abnormal heart sounds and those who had normal heart sounds (Table III).

Table III

Relationship between heart sounds, haematocrit level and age in subjects

Heart Sound	No of Cases (n=96)	Haematocrit (percent) Mean±1SD	P Value	Age (Years) Mean±1SD	P Value
Normal	83	25±4)		5.8±3.7)	
Loud pulmonary closure	9	21±3)		7.9±3.5)	
Apical ejection click	2	29±5)	<0.05*	7.0±5.0)	>.05
Loud first heart sound	1	25±0)		5.0±0.0)	
Apical third heart sound	1	27±0)		16.0±0.0)	

P = probability

* = degree of significance

Murmurs

Cardiac murmurs were audible in 61 (63.5 percent) of the 96 subjects, compared with seven (13.5 percent) of the 52 controls (x^2 = 28.9; P<0.001). The various types of murmurs encountered are depicted in Table IV. The majority of murmurs were ejection systolic in timing, occurring in 57 (93.4 percent) of the 61 subjects with murmurs. In 48 (84.2 percent) of these 57 patients, the murmurs were soft (grades 1 or 2/6), the remaining nine (15.8 percent) being grade 3/6. Of the 57 patients with ejection systolic murmurs (ESMs), 30 had murmurs audible equally loudly in more than one auscultatory area; in the remaining 27, the murmurs was restricted to a single auscultatory area. The upper sternal edge (LUSE) was the commonest site for ESMs to be detected, occurring in 36 (59.0 percent) of the 61 patients. This site was following in descending order of frequency by the apex (29 patients), left lower sternal edge (LLSE), 18 patients and right upper sternal edge (RUSE), 15 patients. A diastolic murmur was detected in one sickler. This was a grade 2/6 apical diastolic murmur, which was also associated with grade 2/6 ESMs at the apex and LUSE. Venous hums were heard in seven patients with SCD, three of whom also had ESMs either at the LLSE or at the apex. All seven controls who had murmurs had ESMs either at the LUSE or LLSE.

Table IV also shows the relationship between the frequency of murmurs and the Hct level in the subjects. The mean Hct (23 ± 4 percent) of the subjects with grade 2/6 ESMs was significantly lower than the mean value (26 ± 4 percent) of those subjects in whom no murmur was audible (t = 3.86, P<0.001). Similarly, the mean Hct of subjects with venous hums (21 ± 3 percent) was significantly lower than in subjects without murmurs (t = 2.54,

Table IV

Relationship between cardiac murmurs, haematocrit level and age in subjects

Heart murmur	No of Cases (n=96)	Haematocrit (percent) Mean±1SD	P Value	Age (Years) Mean±1SD	P Value
Absent	35	26±4)		5.1±3.9)	
ESM_1	2	26±1)		7.7±5.2)	
ESM_2	43	23±4)		7.0±3.9)	
ESM_3	8	23±4)	<0.05*	4.8±2.2)	>.05
DM + ESM_3	1	25±0)		5.0±0.0)	
ESM_2 + VH	3	25±2)		7.7±4.5)	
VH	4	21±3)		7.2±2.3)	

ESM_1 = Grade 1/6 ejection systolic murmur
ESM_2 = Grade 2/6 ejection systolic murmur
ESM_3 = Grade 3/6 ejection systolic murmur
DM = Grade 2/6 diastolic murmur
VH = Venous hum
P = Probability
* = degree of significance

P<0.02). Although the mean Hct of subjects with grade 3/6 ESMs was the same as that of subjects with grade 2/6 ESMs, the difference from subjects with no murmurs did not reach statistical significance ($t = 1.95$, $P>0.05$), probably because of the small number of the subjects involved. There was no significant difference in age between subjects with murmurs and those without (Table IV).

Discussion

The cardiovascular sequelae of chronic anaemia [1-6] that have been previously documented were present to a large extent in the present series. The faster pulse rates, wider pulse pressures, larger hearts, and increased frequency of cardiac murmurs found among the sicklers were expected findings that are consistent with the hyperdynamic state induced by chronic anaemia.[5] The more anaemic subjects were shown to have the larger hearts.

Studies on BP in adult patients with SCD[14-16] have shown that both systolic and diastolic BP are consistently lower in such patients than in controls and that expected positive correlation with age does not occur. In the present study, although diastolic BP was lower in the subjects, systolic BP was actually higher in the subjects than in the controls and tended to increase with age as it did in the controls. It is known that renal abnormalities do occur in children with SCD,[17] but it is possible that the various renal and humoral mechanisms suggested for the findings in adults, have not yet had time to affect the BP in children.

Although the prevalence of abnormal heart sounds did not differ significantly between the two groups of children, it would appear from the results of the present study that the degree of anaemia was important in determining those subjects who had a loud P_2 and also those who had murmurs, both findings which can be explained on the basis of a hyperdynamic circulation. A loud P_2 has also been reported in patients with sickling, pulmonary infarction, pulmonary hypertension and cor pulmonale,[18] but these phenomena were not present in the nine patients in the present series, all of whom were in steady state, with no symptoms or signs of lung pathology. The finding of an apical S_3 in only one out of the 96 subjects of the present study is contrary to previous reports that an apical S_3 or even S_4 are commonly encountered in patients with chronic anaemia.[1,6]

The commonest type of murmur found in our study was a soft ejection systolic murmur, most often located at the left upper sternal edge, followed by the apex. By contrast, Wintrobe [7] and Winsor and Burch [8] cited the apex as the most common site for murmurs to be heard. While some workers[19] have suggested an association between SCD and mitral valve prolapse (which might account for the apical murmur), others[12] have disproved such an association. Venous hums were found in seven patients. This murmur may be present in healthy children, but is more common in patients with severe anaemia. The significantly low mean Hct of subjects in the present study with venous hums would support this assertion. The frequency of abnormal heart sounds and murmurs was not age - related; it is, therefore, unlikely that duration of anaemia affected their development.

The present study has shown that Nigerian children with SCD do manifest cardiovascular anomalies which are a physiological consequence of chronic anaemia. Both the degree and duration of anaemia influenced the abnormalities encountered on simple clinical examination. However, more accurate evaluation of the effects of SCD on the heart, using chest radiography, electrocardiography and echocardiography will form the basis of further study into this topic.

Acknowledgement

Appreciation is expressed to Miss Funmi Murana and Mr Richard Ezeah for typing the manuscript.

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