CARDIOVASCULAR ABNORMALITIES IN CHILDREN AND ADOLESCENTS WITH SICKLE CELL ANAEMIA AT MUHIMBILI NATIONAL HOSPITAL, DAR ES SALAAM, TANZANIA.

By

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A dissertation submitted (in partial) fulfilment of the requirements for the degree of Master of Medicine (Paediatrics and Child health)

University of Dar es Salaam.

2004



CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by the University of Dar Es Salaam a dissertation entitled **Cardiovascular abnormalities in children and adolescents with sickle cell anaemia at Muhimbili National Hospital, Dar es Salaam, Tanzani.** Submitted in partial fulfilment of the requirements for the degree of Master of Medicine (Paediatrics and Child Health) of the university of Dar es salaam.

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DECLARATION

I HELGA ELINEEMA DAVID NABURI declare that this dissertation is my own original work and that it has not been presented and will not be presented to any other university for a similar or any degree award.

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DEDICATION

To my loving parents Mr. and Mrs. E.D. Naburi.

To my loving sisters Grace and Edith

To my loving brothers Alfred, Cuthbert, Felix and Gareth.

To my dear niece Natasha on behalf of others

To my teachers

ABSTRACT

Objective: To determine the prevalence and pattern of cardiovascular abnormalities in children and adolescents with sickle cell anaemia attending sickle cell clinic at Muhimbili National Hospital.

Design: Cross –sectional hospital based descriptive study

Methodology: Children aged six months to seventeen years, attending sickle cell clinic were randomly selected. History was taken, physical examination was done and haemoglobin level was measured. Then chest radiography, electrocardiography and echocardiography were done.

Outcome: Magnitude and pattern of cardiovascular disorders among patients with sickle cell anaemia.

Results: Ninety-nine patients met the criteria for inclusion and were subject for final analysis. Males were 54 and females were 45, male to female ratio was 1:1.7. Mean haemoglobin level was 7.2g/dl (range 4.9-10)

The overall prevalence of cardiac abnormalities in this study was 28 %. Prevalence according to individual diagnostic parameters was ECG; 50.5%, CXR; 69.7%, cardiac signs 76.8% and ECHO; 83.3%.

Tachycardia was common in children aged 6 years or below (P=0.005), cardiomegaly, presence of cardiac murmurs and abnormal ST-T changes were significant in children above 6 years (p= 0.0009, 0.012 and 0.013 respectively).

Patients with haemoglobin of 8g/dl or less frequently had tachycardia (P=0.001), cardiac murmurs (P=0.00001), prominent pulmonary vasculature (P=0.04) and upper lobe blood redistribution (P=0.014).

Cardiac chamber dilatation and left ventricular hypertrophy were inversely related to haemoglobin level. Systolic dysfunction was significantly reduced in 23.3% of patients with haemoglobin of 8g/dl and below.

Diastolic dysfunction was found in 51 % of patients, this was about four times common in patients with haemoglobin of 8g/dl and below.

Conclusions and recommendations:

Cardiomegaly was the most common cardiovascular abnormality found in sickle cell anemia patients above six years, in particular those with chronic anemia and hemoglobin $\leq$ 8gm/dl. These patients need to have their hemoglobin maintained above 8gm/dl and those with hemoglobin below 8gm/dl plus cardiovascular signs would need cardiovascular evaluation.

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LIST OF ABBREVIATIONS AND ACRONYMS

AORD - Aortic root dimensions

BVH - Biventricular hypertrophy

BSA - Body surface area

BT - Blood transfusion

CFM - Colour flow mapping

CTR - Cardiothoracic ratio

CXR - Chest X-ray

2D - Two-dimensional

E/A - Ratio of flow velocity during early filling period, to flow velocity during late atrial contraction.

EF - Ejection fraction

ECG - Electrocardiography

ECHO - Echocardiography

HB - Haemoglobin

LAD - left atrial dimension

LA - Left atria

LBBB - left bundle branch block

LV - left ventricle

LVIDd - left ventricular dimensions during diastole

LVIDs - left ventricular dimensions during systole

LVH - left ventricular hypertrophy

MNH - Muhimbili National Hospital

M-mode - Motion mode echocardiogram

MUCHS - Muhimbili University College of Health sciences

PCV - Packed cell volume

PWD - Pulse Wave Doppler

RBC - Red blood cell

RVH - Right ventricular hypertrophy

FS - fraction shortening

VCF - Velocity of Circumferential fibre shortening

1.0 INTRODUCTION AND LITERATURE REVIEW

1.1 Background

Sickle cell disease is a group of inherited sickling disorders with abnormalities of haemoglobin synthesis. These disorders include sickle cell trait (AS), sickle cell anaemia (HbSS) compound heterozygous state of haemoglobin S and haemoglobin C, D, E and other structural variants. Sickle cell anaemia is the most severe form of these disorders characterized with sequelae of chronic haemolysis and repeated vaso occlusive episodes.[1, 2]

James B Herrick first described the disease in 1910 in a twenty-year-old West Indian dental student who had recurrent jaundice, fever and chronic ulceration of lower extremities. The patient was anaemic and striking morphologic abnormalities of the red blood cells were present. His circulating blood contained bizarre elongated, crescent shaped cells that were fancifully compared to the blade of the sickle. [3, 4]

1.2 Epidemiology

The sickle cell disorders are found very frequently in Afro Caribbean population and sporadically throughout the Mediterranean region, India and Middle East .[5] The highest gene concentration occurs in equatorial Africa where up to 40% of West African people posseses the HbS gene. The prevalence in African regions away from equator both north and south is considerably low. [3] In Oman sickle cell anaemia affects more than 0.2% of general population and there is a 6% sickle cell trait carrier rate.[6] In Dar es salaam, Tanzania approximately 17% of the children entering hospital for any reason are carriers of sickle cell gene, of these one in every four have

homozygous form (HbSS). In other areas like Karagwe, North West of Tanzania 13% of the population is carriers and one in every thirty patients has the homozygous sickle cell disease. [7] Sickle cell anaemia can be diagnosed at birth, but in 90% of the population clinical abnormalities do not occur before age of three to six months. This coincides with the replacement of much of the foetal haemoglobin by haemoglobin S. [2, 8] Infants are largely protected by high levels of foetal haemoglobin in the first six months of life, which represents 60% to 80% of the total haemoglobin. This provides a protective effect as it inhibits the polymerization of HbS in vitro. [2, 3] Thereafter foetal haemoglobin drops to about 10% to 20%, and HbS expression and the clinical condition becomes evident. [1, 3]

Cardiac disorders occur in more than 82% of patients with sickle cell anaemia, while only 2% of patients with sickle cell trait are affected [9]. Cardiomegaly, heart murmurs and echocardiographic anomalies are commonly found in patients with sickle cell anaemia. Wali et al [7] described the occurrence of murmur in 61% and cardiomegaly in 39% of their sickle cell study patients. Cardiomegaly develops in the first five years of life and it results from compensatory hypertrophy and dilatation from increased venous return due to anaemia.[10] Cardiomegaly in older children is partially caused by sickle related cardiomyopathy. [2] Left atria, left ventricular dimension in systole, end diastolic septal and left ventricular free wall thickness were increased in patients with sickle cell anaemia in relation to age but not to haemoglobin concentration .[11]

Among the adolescents and adults at Kenyatta National Hospital 64.1% had increased cardiothoracic ratio that was inversely related to haemoglobin concentration regardless of age. [12] Degree of cardiac dilatation in the cooperative

study was significantly associated with severity of anaemia and the relationship between left ventricular diastolic dimensions and haemoglobin was significantly dependent on age. [13]

Electrocardiographic abnormalities are found in 76.9%. Increased vagal tone compensating for prolonged hypoxia responsible for P-R interval prolongation is found in 11.3% of these patients. [12] Definite ischemic response occurs during exercise in 34% of patients who also have low haemoglobin concentration .[14]

Lippman et al [15] demonstrated ECG voltage changes consistent with left ventricular hypertrophy in 27% of patients with sickle cell anaemia.

Typical angina and exercise induced ECG changes were described in a 7 year old boy and were relieved by transfusion program. A 17 years old patient developed cardiac ischemia during aplastic crises. [16]

M mode echocardiography demonstrated thickened interventricular septum in 40%, thickened posterior wall in 22% and increased left ventricular mass in 43%. [15]

In a clinical autopsy study of adult patients, myocardial infarction was found to be infrequent. Coronary artery in these patients did not have significant atherosclerosis.[14] However, a post-mortem study of 70 patients with HBSS disease revealed that 7 patients had myocardial infarction or fibrosis despite normal coronary arteries. This is thought to be due to coronary spasm as a secondary event of sickling. [16]

1.3 Pathophysiology:

The molecular basis of sickle cell anaemia arises from mutation substituting thymine for adenine in the sixth codon of the beta chain gene (GAG-GTG). Message transcribed from this segment of DNA is translated into valine rather than glutamic acid in sixth position. Charge at this site is altered and allows polymerization of haemoglobin during hypoxia which gives rise to sickling process. [2, 4] Haemoglobin S carries oxygen, but forms semisolid aggregate structures once oxygen is unloaded to the tissues. Intracellular polymerization of Hb S occurs when sickle erythrocytes are partially deoxygenated under hypoxia. The intracellular polymerization of Hb S causes the red cell to lose its flexibility. Repeated cycles of oxygenation and deoxygenation result in irreversible membrane damage and to the formation of irreversibly sickled cells. The increased mechanical fragility shortens RBC survival. Cell destruction occurs both in circulation and the reticuloendothelial system in patients with sickle cell anaemia. Red blood cell survival is only 10 to 20 days as compared to 120 days in normal persons.

Chronic haemolysis presents as chronic anaemia, with or without signs of heart failure. Jaundice, aplastic crisis, cholelithiasis, delayed growth and sexual maturation also occur. [1,4,5,7]

Relative rigidity of sickled cell, increased adhesiveness of sickle reticulocytes and increased leucocytes count causes aggregate formation in the microvasculature. This increases viscosity of blood leading to micro vascular occlusive disease and tissue ischemia. Patients may present with ischemic injury in multiple organs. [1, 2 3, 4]

1.3.1 Heart

Pathophysiologic derangements in the cardiovascular system of patients with sickle cell anaemia are mainly due to chronic anaemia and also intravascular sickling events as reported in different studies. [9,10,14,16]

1.3.1.1 Effects of chronic anaemia.

The heart in sickle cell patients is subjected to a long term stress. However anaemia is initially well tolerated by the cardiovascular system but like in chronic anaemia due to other causes, later cardiac functions are affected. The reduced oxygen carrying capacity increases demand on the heart, resulting in increased cardiac output. [1, 3, 17] This increase is achieved primarily by increase in stroke volume. Chronic volume overload initiates compensatory response primarily cardiac enlargement. [18] Children with haemoglobin levels in the range of 6 to 8 g/dl, increase cardiac output at rest by 50 percent to meet the need for oxygen delivery to the tissues. [8, 17, 19]

Lester et al [20] described high cardiac output in 53% of the patients, who also had increased ventricular mass progressive with age. Cardiac output was also reported to be high among 44 black children with haemoglobin between 5.8 to 12 g/dl. [21]

Functional and anatomical evidence of sickle cell cardiomyopathy evidenced by the presence of chamber dilatation, 2- dimensions and Doppler echocardiography have demonstrated eccentric hypertrophy of left ventricle and systolic dysfunction. [22]

Congestive cardiac failure and impaired myocardial function due to anaemia can be found in both children and adults independent of duration of disease. Congestive cardiac failure and significant depression of left ventricular muscle contractile performance have been reported in 85% of sickle cell anaemia patients. [23]

Additional features that may compromise cardiac functions or accelerate the appearance of left ventricular failure include distinct shift of oxygen dissociation curve causing a decrease in arterial oxygen saturation, increased peripheral oxygen extraction, and impaired capillary flow in systemic and possibly coronary circulation and contributions from shunting. [1, 3]

Clinically these patients presents with features reflecting hyperdynamic circulatory state including, dyspnoea, palpitations, and easy fatigability. The cardiac findings are rarely normal. The heart is usually enlarged and the precordium hyperactive. Patients have wide pulse pressure, loud heart sounds with wide split of second heart sound. Systolic murmurs are found in most patients and many patients carry the diagnosis of rheumatic heart disease. Flow murmurs with symptoms of sickle cell disease are mistaken for rheumatic fever in childhood especially if diagnostic facilities are limited. [18] Premature contractions are often present in adults. [1, 3, 17,24,25,26]

1.3.1.2 Intravascular sickling.

Small vessel disease may play a role in the pathogenesis of cardiac abnormalities in sickle cell anaemia. This is based on the fact that sickle cell crises are characterized by vascular occlusion, local hypoxic injury, tissue necrosis and infarction. Coronary spasm may also contribute to ischemic injury.[4, 26] There are numerous other contributing factors underlying the cardiac changes including platelets abnormalities, biochemical and morphological effects of sickle cell themselves. [5,7,27] Sickled erythrocytes are known to agglutinate within small arteries, capillaries and venules. They become immersed with circulating platelets to form obstructive masses. [4] In addition to direct effect of arresting the blood flow, they also cause endothelial

proliferation and fibro muscular dysplastic changes in many small coronary vessels. These additional vascular obstructive lesions also account for the focal degeneration and later focal fibrosis throughout the ventricular or atrial working myocardium as well as the conducting system. [4, 5]

Myocardium normally extracts a very high proportion of its oxygen supply. There fore any arterial desaturation might impair adequate oxygen delivery. This effect is more pronounced during exercise as myocardial oxygen demand increases greatly.

Alpert et al [11] demonstrated an ischemic response in 15% of sickle cell anaemia patients undergoing exercise testing, representing acute oxygen imbalance. Left ventricular end diastolic volumes in patients with sickle cell anaemia tend to fall on exercise due to impaired cardiac output response to exercise performance in these patients. [30]

Ursoy et al [31] observed ECG evidence of myocardial infarction in two out of 148 patients and autopsy confirmed presence of scar in one of these patients. In one study a significant inverse correlation was noted between ECG changes and hematocrit.

An adolescent with sickle cell disease and previous evidence of myocardial damage, presented with myocardial ischemia and necrosis at the age of 16 years. [32]

Sporadic autopsy findings in heart of patients who were not diagnosed as sicklers, showed capillaries and small arteries parked with sickled erythrocytes.[16] Also abundant foci of old and recent degeneration in sinus, atrioventricular node, bundle of His and coronary chemo receptors abnormalities were demonstrated. These findings may indicate that sudden death in sickle cell disease patient is due to lethal cardiac electrical instability. [2]

Hypoxia due to ischemia and oxygen free radicals as a result of reperfusion can trigger apoptosis leading to degeneration of cardiac structures. [4, 28, 29]

Mitral valve prolapse may occur as a result of ischemia of papillary muscles during episodes of aggravation of the disease. This is because they are terminally located in coronary circulation. Mitral valve prolapse has been reported in 25% of patients in one series, this was significant more than the 1-3% found in their general population.[30]

1.3.2 Central nervous system.

Generally Neurological complications are found in 26%, out of these stroke occurs in 7% to 8%, mainly in pre adolescent and older patients. Hemiparesis, monoparesis, aphasia or dysphasia and seizures are other common symptoms. Coma may also occur though is not common. Transient ischemic attack or complete stroke, subdural haematoma, meningitis and aneurysm resulting from vasoocclusion and infarction have also been reported. [2, 3, 7, 16, 31,]

1.3.3 Ocular manifestations.

Decreased blood flow and occlusion of small ocular blood vessel occurs in 90% of patients. Ischemic infarct of retinal vessel and retinal haemorrhage may progress to retinal detachment and blindness. [2, 3,7,16]

1.3.4 Abdominal involvement.

Infarction or haemorrhage can occur within abdominal structures such as the spleen liver or abdominal lymph nodes causing capsular stretching. Occasionally the pain may be severe and episodic signs of peritoneal irritation can occur. [2, 3,7,17]

1.3.5 Genitourinary tract

Renal pathology results from low oxygen tension. Acidosis and hyper tonicity favours sickling, vasoocclusion, tissue infarction and hence progressive loss of renal function. Anaemia causes reduced renal blood flow and reduced glomerular filtration rate contributing further to renal pathology. Hematuria, hyposthenuria, enuresis and nocturia are among the presenting symptoms. Nephrotic syndrome may also occur. Priapism occurs in 5% of male patients. This condition is extremely painful and can result in urine retention and impotence. [2, 3, 7, 14]

1.3.6 Hepatobiliary system

Hepatomegaly is observed by one year of age and persists to a moderate degree through childhood and adult life. Chronic haemolysis with hyperbilirubinemia associated with cholelithiasis is found in 30% of patients over 10years of age and less than 10% are symptomatic. Intrahepatic cholestasis can also be found as a result of Kupffer cell engorgement causing obstruction and hepatocellular necrosis. [1, 3,7,17]

1.3.7 Spleen

The spleen enlarges in the latter part of the first year of life and occasionally it undergoes acute splenic sequestration crisis.[1, 7, 14, 16] As a result of repeated infarction, over time spleen undergoes autosplenectomy. The non-functional spleen contributes to the immune deficiency that exists in these patients. [1, 2, 7, 16]

1.3.8 Chest

Pulmonary infarction in association with pneumonitis may produce a severe clinical picture of acute chest syndrome. It occurs in more than 50% of paediatric patients with Hb SS, probably beginning with infarction of ribs leading to chest splinting and atelactasis. Fat embolism resulting from bone marrow infarction plays an important etiological role in the pathogenesis of pulmonary infarction. [1, 7, 16, 17]

1.3.9 Skeletal

Skeletal abnormalities are found in over 50% of sickle cell patients. Dactilitis occurs during infancy. Avascular necrosis occurs in 12% of patients.

Osteomyelitis caused by salmonella species occurs in the first 5 years of life and may be confused with vaso occlusive complications. [2, 3.7,17.] Erythroid bone marrow may also be damaged by Parvovirus like infection resulting in aplastic crisis. [2,3,16]

1.3.10 Skin

Chronic indolent skin ulcers around the ankles results from poor circulation and anaemia that impede healing of minor traumatic lesions. It may be associated with pain, secondary bacterial infection and loss of ankle movement. [2, 3, 16, 17]

2.0 RATIONALE OF THE STUDY.

Approximately 17% of children attending hospitals in Dar es Salaam have homozygous Hb SS disease. [9] Patients with sickle cell disease manifest with chronic organs damage from vasooclusive episodes. Myocardial dysfunction has been described as a result of chronic anaemia alone or with the combination of effects of recurrent intravascular sickling and thrombosis.

Few cardiovascular studies have been done in children. Among the studies done ventricular dilatation and hypertrophy together with left ventricular systolic and diastolic dysfunction were demonstrated. [11, 19, 20, 22] Sickle cell anaemia is common in Tanzania and the prevalence of cardiovascular abnormalities in children with sickle cell anaemia in Tanzania is not well known.

This study was done to determine the prevalence and pattern of cardiovascular abnormalities among stable children and adolescents with sickle cell anaemia, attending sickle cell clinic at Muhimbili National Hospital.

This study will help to identify hemodynamicaly at risk patients who requires more specific cardiovascular care. Also it will give a better understanding of the problem and thereby contributing to an improved management of patients with sickle cell anaemia who might have cardiac abnormalities.

3.0 OBJECTIVES

3.1 BROAD OBJECTIVE:

To determine the prevalence and pattern of cardiovascular abnormalities in children and adolescents with sickle cell anaemia attending sickle cell clinic at Muhimbili National Hospital.

3.2 SPECIFIC OBJECTIVES:

3.2.1 To determine the prevalence of cardiovascular abnormalities in children and adolescents with sickle cell anaemia.

3.2.2 To describe the patterns of cardiovascular abnormalities in children and adolescents with sickle cell anaemia according to age and sex.

3.2.3 To determine the effect of haemoglobin level in relation to cardiovascular abnormalities in children and adolescents with sickle cell anaemia.

4.0 METHODOLOGY

4.1 Study design: A Cross - sectional hospital based descriptive study

4.2 Study setting:

The study was done at Muhimbili National Hospital Sickle cell outpatient clinic. This is a university teaching and a referral tertiary level hospital in Tanzania. It is situated in Dar es Salaam, a big city with an estimated population of over 3million. [34]

The department of Paediatrics and Child Health runs a special sickle cell clinic weekly. Patients attending this clinic are confirmed by cellulose acetate electrophoresis to be HbSS. There is no age limit for attending this clinic. Patients are referred to this clinic from government and private clinics. The average clinic attendance is about 35 patients per week.

The hospital has capacity for doing sickling test, Hb electrophoresis, chest x-ray, electrocardiography and echocardiography.

4.3 Study Population:

Patients aged six months to seventeen years inclusive attending sickle cell follow up clinic of Muhimbili National Hospital were recruited for the study.

4.4 Duration of the study

Study was done from June 2003 to January 2004.

4.5 Sample size estimation:

The sample size was determined by the epiinfo version 6 using the following assumptions:

- The cardiac disorders occur in more than 82% of sickle cell disease patients. [9]
- Significance level = 5%
- The maximum likely error (d)=8%

Sample size was calculated by the following formula:

$$N = \frac{Z^2 P Q}{d^2}$$

Where:

N= sample size.

Z= confidence interval at 95% (1.96)

P= prevalence of cardiac abnormalities among sickle cell disease

Q= 100-P

d=maximum likely error

$$\text{Sample size (N)} = \frac{1.96^2 \times 82\ (100-82)}{8X8}$$

$$= 89.$$

The minimum sample size was 89 patients. The sample size was increased by 10% to allow for non-response, incomplete investigations and other factors that could decrease the yield of response there for the total sample size was 100 patients.

4.6 Sampling procedure and Recruitment of study subjects

All patients with sickle cell anaemia attending sickle cell clinic, aged six months to seventeen years were eligible for the study. Simple random sampling method was used to obtain study subjects. At every clinic day the names of eligible sickle cell anaemia patients were written on small pieces of paper, folded and mixed thoroughly in a box and the author picked up five pieces of paper randomly. These were the patients then studied.

Parents/guardians of the study participants were told the aim of the study and all the procedures involved. They were then requested to give an informed verbal consent for their children participation. Where consent was not obtained another patient was picked randomly from the box. To avoid re-recruitment patient's files were coded with a number.

4.7 Inclusion criteria

Patients were included in the study if:

- They had sickle cell anaemia HBSS.
- Aged 6 months to 17 years.
- Consent for participation was obtained.

4.8 Exclusion criteria

Patients were excluded from the study if they had:

- Co-existing congenital heart disease, rheumatic heart disease.
- Chronic respiratory problems eg. Bronchial asthma or chronic chest infection of more than one month duration.
- Clinical findings suspicious of Paediatrics AIDS.
- Clinical signs of acute infection at the time of investigation.
- Not given formal consent to participate in the study.

4.9 Definition of terms

Sickle cell disease: symptomatic disorders with common sickling properties but with variety of clinical manifestation. [24]

Sickle cell anaemia: Homozygous state of sickle cell disease (HBSS), documented by Haemoglobin electrophoresis (cellulose acetate paper).

Anaemia: Haemoglobin less than 11g/dl (WHO). [33]

Adolescents: Patients aged 10 years to 17 years.[7]

For the purpose of this study the following definitions were used:

I. Percentage of fractional shortening was calculated as:

$$FS = \frac{LVD-LVS}{LVD} \times 100\ \%$$

II. Left ventricular systolic dysfunction was detected if the percentage of fractional shortening was $\leq 28\%$.

III. Left ventricular diastolic dysfunction was defined by the presence of reversed transmitral E/A ratio >2

IV. Left ventricular hypertrophy was defined by increased intraventricular septum and left ventricular posterior wall thickness above normal during diastole.

V. Cardiac chamber dilatations were determined by the presence of increased left ventricular dimensions during diastole, increased left atrial dimensions.

VI. Endocardial disorders included the presence of abnormal flow across the heart valves and presence of prolapse, vegetations, regurgitation or stenosis.

4.10 Data collection

Once a week the author selected and interviewed at least five study subjects.

A structured questionnaire designed for the purpose of this study was used. Information on demographic data that included name, address, age, sex weight and height was obtained from parents/guardian and adolescents. History, clinical findings and investigations results were also filled in the questionnaire.

Length was measured using standard length board and height by standard height board to the nearest 10 mm. All study subjects were weighed to the nearest 10grams using solar cell SECA weighing machine.

Body surface area was calculated using The DuBois and DuBois Formula [35]

As follows:

$$\text{Body Surface Area} = 0.20247 \times \text{Height (m)}^{0.725} \times \text{Weight (kg)}^{0.425}$$

4.10.1. Physical examination

A detailed physical examination was carried out with specific reference to cardiovascular system examination. Cardiovascular assessment was done according to the principles of evaluating the cardiovascular system in pediatrics. Pulse rate, precordial abnormalities, heart sounds and cardiac murmurs were assessed and recorded in the questionnaire. Other findings included presence of edema, respiratory rate and basal crepitations.

4.10.2 Haemoglobin

Blood was taken from a finger using a capillary tube containing an anticoagulant. Blood sample was centrifuged for five seconds by automated centurion 8000 series machine. Then a column of packed red blood cells (PCV) was measured in millimetres and expressed as a percentage of the total blood volume. The haemoglobin was calculated by dividing packed cell volume value by three. This is based on the fact that there is normally a 3:1 ratio of PCV to haemoglobin value. [36]

4.10.3 Chest x-ray

The same radiographer took chest radiography view. Children below four years of age had an antero-posterior view taken in supine position. Mother or caretaker assisted the radiographer in positioning the child on the table while wearing protective lead apron and male patients were protected with gonadal shields. Patients above four years had a postero- anterior view taken in erect position during maximum inspiration phase.

The distance between the x-ray tube to the patient's chest was 100cm to avoid the distortion of image. Ten to twelve-inch cassettes for paediatrics purposes were used. Voltage of between 48 to 53kv according to body size in 0.13 sec was applied to produce between 4Mas to 6.3Mas. Cardiothoracic ratio was calculated as a ratio between the transverse diameter of the heart to the maximal internal diameter of the chest. Transverse diameter of the heart was obtained as the sum of mid left and mid right diameters, these were measured by drawing a horizontal line from the midline to the farthest left and farthest right borders of the heart. A ratio of more than 0.6

right diameters, these were measured by drawing a horizontal line from the midline to the farthest left and farthest right borders of the heart. A ratio of more than 0.6 was defined as cardiomegaly.[2] The same radiologist reported Chest x-ray films. The report specified the presence or absence of cardiomegaly and other abnormalities.

4.10.4 Electrocardiography

Conventional twelve leads ECG were done to all the study subjects from 12 arbitrary viewpoints, taking six unipolar (standard) leads in the frontal plane and six chest leads in horizontal or transverse plane. Cardiovit AT-4 (Schiller) three channel ECG recorder was used with stamp electrodes. Pre-medication with rectal diazepam 0.5mg/kg was only given before ECG examination to very young patients who needed sedation. A recorded ECG paper was obtained and used for interpretation.

The investigator interpreted the ECG findings using guidelines for ECG interpretation for paediatric patients by Grauer .[37] Experienced cardiologist reviewed the findings.

4.10.5 Echocardiography

Standard echocardiographic views were done to all the study subjects, to assess anatomical orientation of the cardiac chambers, sizes, function and measure percentage of fraction shortening (FS). ECHO was also done to identify those with congenital and rheumatic heart disease for exclusion. Cardiac assessment was done using Toshiba (Model) using 5MHZ transducer. At Trans- thoracic echocardiography; parasternal long axis, short axis, apical four chambers and sub xiphoid views were done. Two-dimensional (2D), Pulsed wave Doppler (PWD) and



Colour Flow Mapping (CFM) were done and recorded on paper and videocassettes. M-Mode recordings were done to measure size of left atria, aortic root, left ventricular end diastolic and systolic dimensions. Left ventricular fractional shortening, septal and left ventricular free wall thickness and was also obtained.

Standard measurements were taken according to the recommendations of the American Society of Echocardiography. [38, 39, 40, 41]

The M-mode measurements were then compared to normal value for body surface area as described by Kampmann et al. [42] Doppler measurements were interpreted according to values for children described by Feigenbaum. [40]

Interpretations of the findings was done by the investigator and reviewed by experienced cardiologist before being recorded in the questionnaire for analysis.

4.11. Limitations of the study

- The lowest statistically acceptable sample size was used due to high investigation costs.
- Serology for HIV was not done so asymptomatic HIV patients might have been included in the study.
- This was a hospital based study hence prone to selection bias. However since all sickle cell patients in Dar es Salaam are referred to this clinic it reduces the chances of high selection bias.

4.12 Ethical clearance and patients benefit

In this study the participants were treated according to the usual sickle cell clinic management protocols. Ethical clearance was obtained from the MUCHS high degree ethical committee of the research and publication committee. During the study period patients were attending their usual follow up clinic and managed according to their presenting complaints.

At the end of the study all the children continued with the usual follow up in sickle cell clinic. Information about the detected cardiac findings were communicated to the patients and made available to the doctors attending the patients for close long-term follow up and management.

4.13 Data analysis

Data were entered in a computer using EPI INFO version 6 data entry program. Epiinfo version 6 was used for data analysis.

For the purpose of data analysis patients were subdivided according to age, those who were 6 years or below and those who were above 6 years. Haemoglobin level was grouped as 8g/dl or less and above 8g/dl. This was in consideration of the fact that cardiac abnormalities occur in sicklers by age of 5 years and cardiac changes starts when haemoglobin falls below 7g/dl.

Overal prevalence of cardiovascular abnormalities was defined if a patient had all of the following:

- At least one abnormal sign of cardiac abnormality (tachycardia, displaced apex beat and presence of cardiac murmurs)
- Chest X-ray abnormality (increased cardiothoracic ratio, vascular redistribution or prominent pulmonary vasculature)
- Abnormal ECG (ECG rate, P-R interval, QRS morphology and ST-T wave changes)
- Abnormality in at least one cardiac index as measured during 2D Echocardiography and pulse Doppler studies.

Unpaired student t-test was used to compare mean cardiothoracic ratio, fraction shortening. Mantel Hansel Chi-square test was used to compare proportions and 2-tailed fisher exact test was used where expected value was less than five. P- Values of less 0.05 were considered significant.

5. Results

During the study period a total of 1026 patients attended the sickle cell clinic of Muhimbili National Hospital. Out of these, 650 patients were eligible for the study but only 105 patients were randomly selected and recruited. Three patients did not give consent, one had congenital heart disease and two had incomplete investigations so they were excluded. Ninety nine patients met the inclusion criteria and had complete investigations which were interpreted and analysed.

Among the 99 patients, 54 (54.4%) patients had a history of blood transfusion and 45 (45.6%) had never had blood transfusion in their lifetime. The mean frequency of blood transfusion was 1.8 (0-12). The mean duration after blood transfusion was 19.4 (± 32.3) months.

Among the studied patients 54 (54.4%) were males and 45 (45.5%) were females. The male to female ratio was 1:1.7. Mean age was 90 (± 48) months and mean body surface area was 0.85 (0.25-1.49 m^2)

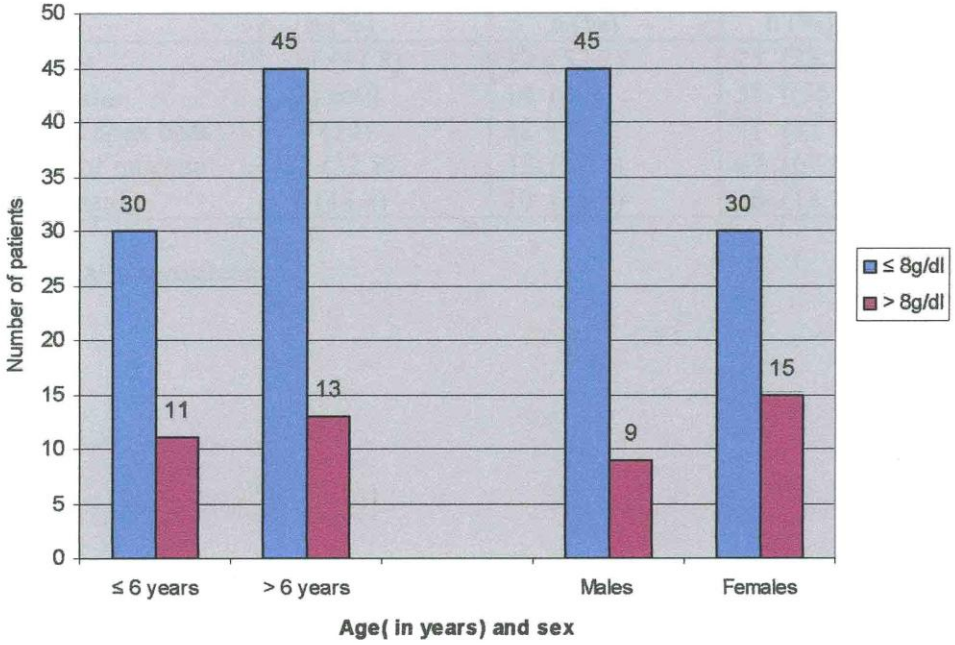
Table1. Demographic characteristics of the study patients

Demographic factor	Range	Mean (SD)
Age	8 – 192 months	90 (± 48)months
Weight	6.5 – 48 kg	20.73 (± 0.85) kg
Height	30 – 162 cm	112.7 (± 23) cm
Body surface area	0.25-1.49 m^2	0.84 (± 0.5) m^2
Age at diagnosis	4 – 108 months	34 (± 25.7) months

Males were (54.5%)

Patients aged 6 years or below were 41(41.4%) their mean age was 43.2, those above 6 years were 58 (58.6%) and their mean age was 123.2. Mean haemoglobin level was 7.2g/dl (range 4.9-10), 75 patients had haemoglobin level of 8g/dl or less and 24 had haemoglobin above 8g/dl (fig 1)

Fig 1.Distribution of patients according to age, sex and haemoglobin level



Displaced apex beat and presence of cardiac murmurs were the significant finding in children above 6 years of age. (P= 0.0009 and 0.012 respectively) Tachycardia was common in children aged 6 years or below and the difference was statistically significant (P=0.005) as a marker of presence of cardiac abnormality (table2).

Table2 Distribution of abnormal cardiac signs according to age.

	Age in years			
signs	≤6years; N=41 n (%)	>6years;N=58 n (%)	Total; N=99 n (%)	p-value
Tachypnea	11 (47.8)	12 (52.2)	23 (23.2)	0.47
Tachycardia	21 (60)	14 (40)	35 ((35.3)	0.005 *
Displaced apex beat	9 (22)	32 (78)	41 (41.1)	0.0009 *
Presence of murmur	22 (32.8)	45 (67.2)	67 (67.6)	0.012 *
Hepatomegaly	8 (44.4)	10 (55.6)	18 (18.1)	0.77

* Statistically significant

The signs of cardiac abnormalities were detected more frequently in males than females, except for the presence of cardiomegaly; however the difference was not statistically significant (table 3).

Table 3. Distribution of abnormal cardiac signs according to sex

	Sex			
Signs	Male; N=54 n (%)	Female; N=45 n (%)	Total; N=99 n (%)	P-value
Tachypnea	10(43.5)	13 (56.5)	23 (23.2)	0.22
Tachycardia	23 (65.7)	12 (34.3)	35 (35.3)	0.09
Displaced apex beat	23 (56)	18 (44)	41 (41.1)	0.79
Cardiac murmur	39 (58.2)	28 (41.8)	67 (67.6)	0.90
Hepatomegaly	11 (61.1)	7 (38.9)	18 (18.1)	0.53

ECG and chest X-ray findings were compared between those below and above 6 years. Radiological findings did not show a statistical significant difference between the two age groups. All the patients were noted to have normal sinus rhythm. ST-T segment abnormalities were significant ECG finding in patients above 6 years of age (P=0.013). Axis deviation was noted in 12 (12.1%), left axis deviation in 7 (7.07%) and right axis deviation in 5 (5.05%). Axis deviation was common in patients above 6 years of age and the difference was statistically significant. (P=0.01). First degree heart block was found in 9 (9.1%) of the study subjects and out of these 2 (22.2%) had complete heart block. There was no significant difference in the two age groups (table 4).

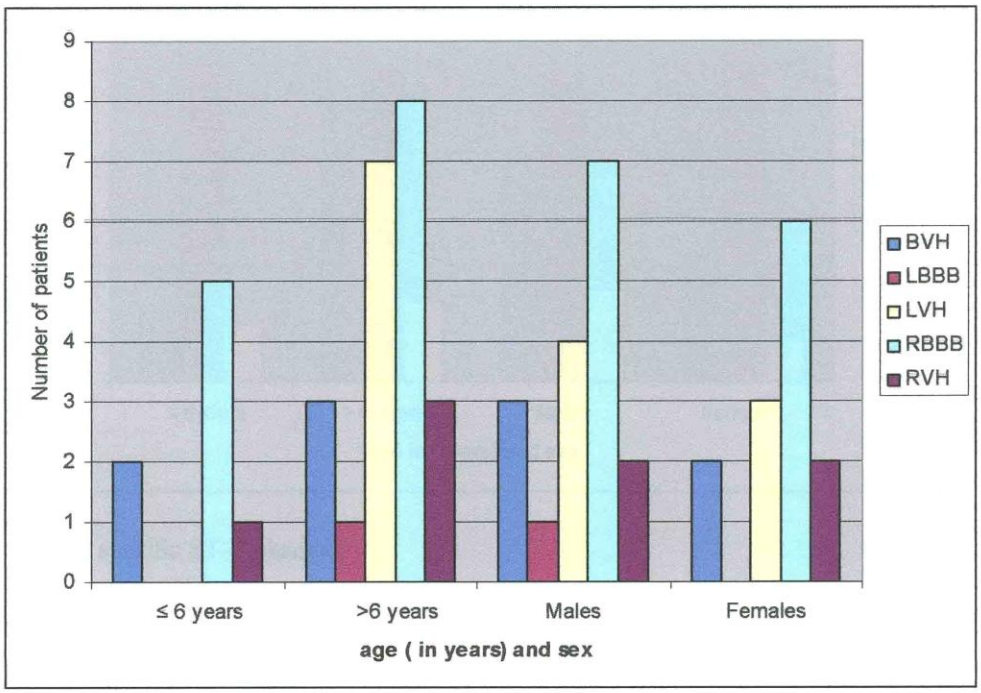
Table 4 . Distribution of radiological and ECG abnormalities according to age

	Age			
Radiological changes	≤ 6 years; N=41 n (%)	> 6years; N=58 n (%)	Total; N=99 n (%)	P value
Increased cardiothoracic ratio	30 (45.4)	36 (54.6)	66 (66.6)	0.25
Upperlobe blood redistribution	5 (29.4)	12 (70.6)	17 (17.1)	0.19
Prominent pulmonary vasculature	9 (40.9)	13 (59.1)	22 (22.2)	0.95
ECG changes				
Axis deviation	1 (8.3)	11 (91.7)	12 (12.2)	0.01*
Prolonged PR interval	3 (33.3)	6 (66.7)	9 (9.0)	0.60
Abnormal QRS morphology	12 (41.4)	17 (58.6)	29 (29.2)	0.99
Abnormal ST-T changes	11 (26.2)	31(73.8)	42 (42.4)	0.01*

* statistically significant

Among the 30 patients with QRS abnormalities 13 (43.3%) had right bundle branch block (RBBB). Other findings were BVH in 5 (5.1%) patients, LVH in 7 (7.1%) patients and RVH in 4(4%) patients LBBB was detected in only 1(1%) patient. All these were common findings in males and patients above 6years of age (Fig 2).

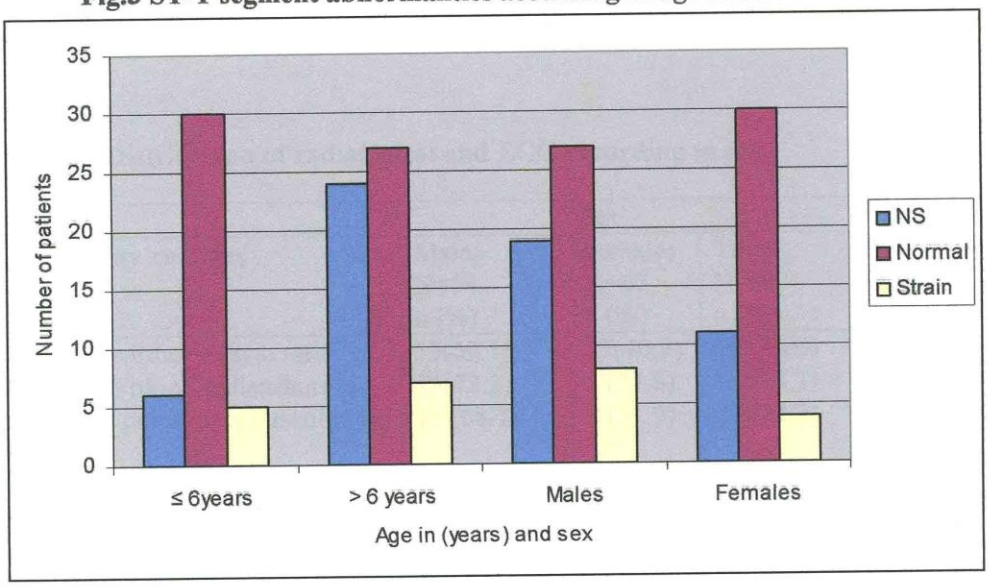
Fig 2. Abnormal QRS morphology according to age and sex



BVH; biventricular hypertrophy: LBBB left bundle branch block: LVH left ventricular hypertrophy RBBB; right bundle branch block: RVH; Right ventricular hypertrophy.

Among the 42 patients with ST-T segment abnormalities, non-specific changes occurred in 30.3% (30) and strain pattern in 12.1% (12) of the study patients. These findings were slightly prevalent in male patients and I patients above 6 years of age (Fig 3).

Fig.3 ST-T segment abnormalities according to age and sex



NS; non specific ST-T changes

The mean cardiothoracic ratio was 62.6 ± 47 (range 50-77). There was no difference in mean cardiothoracic ratio between males and females (63 ±4.8 males, 61 ± 4.8 females). Increased cardiothoracic ratio, pulmonary vascular redistribution and prominent pulmonary vessels were found more commonly among males than females, but the difference was not statistically significant. ECG changes were evenly distributed between male and female patients. (Table 5)

Table 5. Distribution of radiological and ECG according to sex.

	Sex			
Chest X-ray changes	Male; N=54 n (%)	Female; N=45 n (%)	Total; N=99 n (%)	P-value
Increased cardiothoracic ratio	39(59.1)	27(40.9)	66 (66.6)	0.20
Upper lobe blood redistribution	13(72.2)	5 (27.8)	18 (18.1)	0.14
Prominent pulmonary vasculature	15 (68.1)	7 (31.9)	22 (22.2)	0.09
ECG changes				
Axis deviation	6 (50.0)	6 (50.0)	12 (12.1)	0.70
Increased P-R interval	6 (66.7)	3 (33.3)	9 (9.0)	0.52
QRS changes	17 (56.7)	13 43.3)	30 (30.3)	0.93
ST-T changes	27 (64.3)	15(35.7)	42 (42.4)	0.09

The M –mode echocardiographic indices and Doppler flow indices were increased in patients who were above 6 years than those aged 6 years or below. The difference was not statistically significant (table 6). Other echocardiographic abnormalities were mitral valve prolapse observed in 19 (19.1%), mitral regurgitation in 6 (6.1%) and pulmonary regurgitation in 7 (7.1%) patients, and were not related to age, sex or haemoglobin level.

Table 6. Echocardiographic changes according to age

Echocardiographic findings	≤ 6years: N=41 n (%)	> 6years; N=58 n (%)	Total; N=99 n (%)	P-value
Increased LAD	19 (40.4)	28 (59.6)	47 (47.5)	0.84
Increased AORD	6 (42.9)	8 (57.1)	14 (14.1)	0.90
Increased LVDd	8 (36.4)	14 (63.6)	22 (22.2)	0.58
Reduced FS	12 (46.2)	14 (53.8)	26 (26.3)	0.53
Increased IVSd	31 (46.3)	36 (53.7)	67 (67.7)	0.15
Increased LVPWd	12 (40)	18 (60)	30 (30.3)	0.85
Increased Mitral A flow velocity	17 (50)	17 (50)	34 (34.4)	0.20
Increased Pulmonary flow velocity	26 (44.8)	32 (55.2)	58 (58.6)	0.41
Increased Tricuspid A flow velocity	7 (46.7)	8 (53.3)	15 (15.2)	0.65
Reversed Mitral E/A ratio >2	20 (39.2)	31 (60.8)	51 (51.5)	0.84

LAD=left atrial dimensions, AORD=aortic root dimensions, LVDs left ventricular dimensions during diastole, LVDs = left ventricular dimensions during systole, FS= fractional shortening, IVSd interventricular septum thickness in diastole, LVPWd left ventricular posterior wall thickness in diastole.

Echocardiographic indices were slightly increased among male patients however the differences were not statistically significant. (Table 7)

Table 7. Echocardiographic abnormalities according to sex.

	Sex			
Echocardiographic findings	Male; N=54 n (%)	Female; N=45 n (%)	Total; N=99 n (%)	P-value
Increased LAD	25 (53.2)	22 (46.8)	47 (47.5)	0.79
Increased AORD	8 (57.1)	6 (42.9)	14 (14.1)	0.83
Increased LVDd	14 (63.6)	8 (36.4)	22 (22.2)	0.33
Reduced FS	13 (50)	13 (50)	26 (26.3)	1.0[1]
Increased IVSd	39 (58.2)	28 (41.8)	67 (67.7)	0.28
Increased LVPWd	15 (50)	15 (50)	30 (30.3)	0.54
Increased Mitral A flow velocity	18 (52.9)	16 (47.1)	34 (34.4)	0.81
Increased Pulmonary flow velocity	34 (58.6)	24 (41.4)	58 (58.6)	0.33
Increased Tricuspid A flow velocity	9 (60)	6 (40)	15 (15.2)	0.64
Reversed Mitral E/A ratio >2	27 (52.9)	24 (47.1)	51 (51.5)	0.75[1]

1=**Unpaired student t- test**;

LAD=left atrial dimensions, AORD=aortic root dimensions, LVDs left ventricular dimensions during diastole, LVDs = left ventricular dimensions during systole, FS= fractional shortening, IVSd interventricular septum thickness in diastole, LVPWd left ventricular posterior wall thickness in diastole.

The signs of cardiac abnormalities were frequently found in patients who had haemoglobin of 8g/dl or less. Tachycardia and murmurs showed a statistically significant difference in patients with haemoglobin of 8g/dl or less (P= 0.0001 and 0.00001 respectively) table 8.

Table 8 Signs of cardiac abnormalities in relation to haemoglobin level.

	Haemoglobin level in g/dl			
Signs	≤ 8; N=75 n (%)	>8;N=24 n (%)	Total;N=99 n (%)	P value
Tachypnea	20 (87)	3 (13)	23 (23.2)	0.15
Tachycardia	33 (94.3)	2 (5.7)	35 ((35.3)	0.001 *
Displaced apex beat	35 (85.4)	6 (4.6)	41 (41.1)	0.25
Presence Murmur	58 (86.6)	9 (13.4)	67 (67.6)	0.00001*
Hepatomegaly	16 (88.9)	2 (11.1)	18 (18.1)	0.12

* Statistically significant

Increased cardiothoracic ratio was more than 3 times common in patients with haemoglobin of 8 g/dl or less than those with haemoglobin above 8g/dl. Prominent pulmonary vasculature and upper lobe blood redistribution were also frequently found in patients with haemoglobin of 8g/dl or less. ECG findings were common in patients with haemoglobin of 8g/dl or less, but the difference was not statistically significant (Table 9).

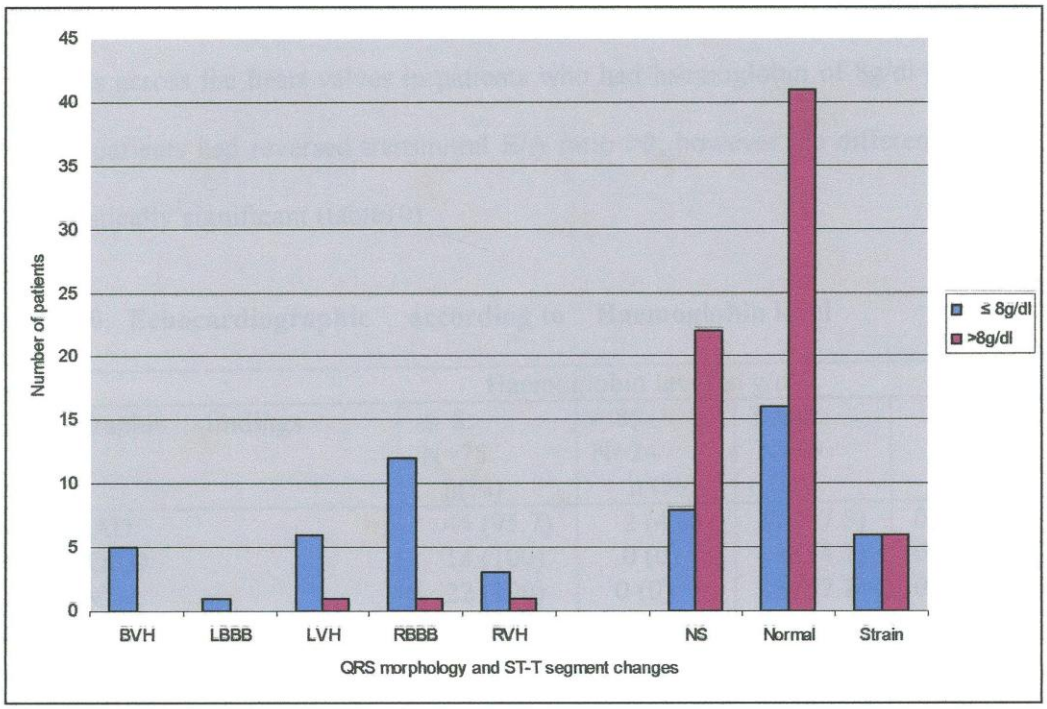
Table 9. Radiological and ECG abnormalities in relation to Haemoglobin level

	Haemoglobin level in g/dl			
Radiological abnormalities	≤ 8 ; N=75 n (%)	>8; N=24 n (%)	Total; N=99 n (%)	P-Value
Increased Cardiothoracic ratio	50 (75.7)	16 (24.3)	66 (66.6)	1.00
Upper lobe blood redistribution	16 (88.8)	1 (17.2)	18 (18.1)	0.04 *
Prominent pulmonary vasculature	21 (95.4)	1 (16.6)	22 (22.2)	0.014*
ECG abnormalities				
Axis deviation	10 (83.3)	2 (16.7)	12 (12.1)	0.39
Prolonged PR interval	9 (100)	0 (0)	9 (9.0)	0.10
QRS changes	26 (86.7)	4 (13.3)	30 (30.3)	0.09
ST-T changes	35 (83.3)	7 16.7)	42 (42.4)	0.31

*Statistically significant

Normal ST-T segment was found in 41 (41.1%) patients. Non specific changes were common in patients with haemoglobin of 8g/dl or below. Strain pattern showed no relationship to haemoglobin level. QRS abnormalities were common in patients with haemoglobin of 8g/dl or less (Fig4).

Fig.4 QRS morphology and ST-T segment changes according to haemoglobin level



BVH; biventricular hypertrophy: LBBB left bundle branch block: LVH; left ventricular hypertrophy RBBB; right bundle branch block: RVH; Right ventricular hypertrophy .NS; non specific ST-T wave changes.

M-mode echocardiographic measurements were compared to those with haemoglobin of 8g/dl or less and those with haemoglobin above 8g/dl. Left atrial diameter and interventricular septum thickness during diastole was significantly increased in patients with haemoglobin below 8g/dl or less (P=0.00001 and 0.017 respectively). None of the patients with haemoglobin above 8g/dl had increased aortic root dimensions or left ventricular dimensions during diastole (P=0.014 and 0.006 respectively). Fractional shortening was reduced below 28% in patients with haemoglobin of 8g/dl or less (P=0.01). Doppler flow showed abnormal flow velocities across the heart valves in patients who had haemoglobin of 8g/dl or less. Many patients had reversed transmitral E/A ratio >2; however the difference was not statistically significant (table10).

Table 10. Echocardiographic according to Haemoglobin level

	Haemoglobin level in g/dl			
Echocardiographic findings	≤ 8; N=75 n(%)	> 8; N=24 n (%)	Total; N=99 n (%)	P-Value
Increased LAD	45 (95.7)	2 (4.3)	47 (47.5)	0.0001 [2]*
Increased AORD	14 (100)	0 (0)	14 (14.1)	0.014 [2] *
Increased LVDd	22 (100)	0 (0)	22 (22.2)	0.006 [2] *
Reduced FS	15(57.7)	11(42.3)	26 (26.3)	0.01[1] *
Increased IVSd	57 (85)	10 (15)	67 (67.7)	0.017 *
Increased LVPWd	26 (86.7)	4 (13.3)	30 (30.3)	0.09 [2]
Increased Mitral A flow velocity	28 (82.4)	6 (17.6)	34 (34.4)	0.26
Increased Pulmonary flow velocity	47 (81)	11(190	58 (58.6)	0.14
Increased Tricuspid A flow velocity	14 (93.3)	1(6.7)	15 (15.2)	0.10 [2]
Reversed Mitral E/A ratio >2	41 (80.4)	10(19.6)	51 (51.5)	0.26[1]

1=**Unpaired student t- test**; **2**=fishers exact test; * = statistically significant
LAD;left atrial dimensions, AORD=aortic root dimensions, LVDs; left ventricular dimensions during diastole, LVDs ; left ventricular dimensions during systole, FS; fractional shortening, IVSd; interventricular septum thickness in diastole, LVPWd; left ventricular posterior wall thickness in diastole.

Prevalence of cardiac abnormalities in this study was found to be 28 %. This included the abnormalities detected by combination of cardiac signs, radiological changes, ECG changes and echocardiographic changes. Clinical signs of cardiac abnormalities and echocardiographic indices revealed many patients who had at least one abnormal parameter reflecting cardiac abnormalities (table11).

Table11. Prevalence of cardiac abnormalities by different diagnostic methods (N=99)

Diagnostic methods	Abnormal: n (%)	Normal n (%)
Physical signs	76 (76.8)	23 (23.2)
CXR	69 (69.7)	30 (30.3)
ECG	50 (50.5)	49 (49.5)
ECHO	82 (83)	27 (27)
Overall	28 (28.3)	71 (71.7)

CXR; chest x-ray .ECG; Electrocardiography. ECHO; Echocardiography

DISCUSSION

Cardiac disorders in sickle cell anaemia patients have been reported in previous studies to be more than 82%, according to a review done by Gacon et al. [8] These included heart murmurs, radiological cardiomegaly and eletrocardiographic anomalies. In this study the overall prevalence of cardiac abnormalities detected by a combination of cardiac signs, radiological, ECG and echocardiographic changes was 28%. However by using echocardiography alone (the gold standard method) the prevalence was 83%. Cardiac signs, radiological and ECG methods alone detected prevalence of 76.6%, 69.7% and 50.5% respectively. The overall prevalence appears small, when an overall prevalence is determined using a combination of diagnostic methods. The overall prevalence in this study represents a group of asymptomatic patients with significant cardiovascular abnormalities who need regular monitoring of cardiac functions so as to detect risks that can cause further deterioration of their cardiac function.

The difference in prevalence rates in different studies could be partially explained by the differences in investigation methods and pattern of cardiovascular changes used to define cardiac abnormalities. The prevalence of cardiomegaly varies between 33% to 86% by radiological criteria, 50% to 76% by electrocardiographic criteria and has been reported to be as high as 83% by echocardiography similar to the present study. A prevalence of 39% was reported when clinical signs alone were used.[9, 10, 12, 21] Sample size and age differences in the various studies could also account for the variation in prevalence rates.

In normal children the heart rate varies with age, the younger the child the higher is the rate. Anaemia fever and anxiety also cause an increased heart rate due to catecholamine release and as a compensation for the decreased stroke volume.[43] In this study the mean heart rate was 103. All the patients were afebrile, in a relaxed state and the heart rate was counted over one full minute. Tachycardia was detected in 35.5% of the patients. Patients below 6 years were found to have significantly elevated heart rates compared to normal values for their ages. This is a reflection of an early adaptation to chronic anaemia.

Patients with sickle cell anaemia presents with signs of adaptation to hyper dynamic state as a result of increased cardiac output. However, successful adaptation to chronic sickle cell anemia results in only minimal increases in heart rate. [24] Increased heart rate in acute anaemic state and increased stroke volume in chronic anemic state is responsible for increased cardiac output. Ayou et al [12] found only 7% of patients aged 13 to 27 years to have tachycardia at rest. Their patients were older than the patients in the present study hence they might have already adapted to the state of chronic anaemia. The lower mean haemoglobin of (7.4 ±0.12 g/dl) in this study compared to (8.5 ±1.4 g/dl) in Ayou's study is a further explanation for the differences in tachycardia in the two studies.

Changes in cardiac structure are age dependent and most children with sickle cell anaemia develop cardiomegaly in the first five years of age. [10]

In this study cardiomegaly as detected by displaced apex beat was found in 41% of patients. This was significantly more common in patients aged above 6 years than

patients aged below 6 years and was about eight times more prevalent in patients with haemoglobin less than 8 g/dl than those with haemoglobin levels above 8g /dl. Wali et al [9] found clinical evidence of cardiomegaly in 39% of his patients aged 8 to 14 years. High mean haemoglobin level (8.1±1.3g/dl) and the mean age (112 months) of their patients can partially explain the slight difference in the prevalence rate of cardiomegaly. This finding implies that, both the severity of anaemia and its chronicity are responsible for development of cardiomegaly.

In this study increased cardiothoracic ratio was detected in 66% of patients. This was about three times more in patients with haemoglobin of 8g/dl or less and a slight increase with age was noted. Ayou et al [12] found increased cardiothoracic ratio in 64.1% of patients studied and this was inversely related to haemoglobin level regardless of age. The present study also shows similar results although Ayou's patients were older and had higher haemoglobin levels. However, Uzsoy reported radiological cardiomegaly in 79% of patients with a mean haemoglobin of 7.8 g/dl similar to present study and as in Ayou's study patients were much older (Range 2 - 65 years, mean age 18.6 years). These results shows that cardiothoracic ratio in patients with sickle cell anaemia is almost always increased as a compensatory mechanism to the increased cardiac output and both the age and severity of anaemia are the important factors.

Rees et al reported increased cardiothoracic ratio in 33% of asymptomatic and 97% in symptomatic patients with sickle cell anaemia aged 2 to 14 years (mean age 100.8 months), their mean haemoglobin was 7.8 ± 0.2 and 6.5 ± 0.8 respectively. [21]

In the present study patients were young and had low haemoglobin level compared with the other studies. These findings support that cardiomegaly is secondary to

anaemia and represents compensatory cardiac dilatation and hypertrophy from increased venous return. [18]

Systolic murmurs are common in patients with sickle cell anaemia and reflects a hyperdynamic event resulting in increased blood flow across the normal valves.[24] Patients without audible murmur tends to be those without cardiomegaly and with high haemoglobin levels.[10]

Systolic murmurs were found in 67.6% of the patients. This was more prevalent in patients above 6 years of age and was inversely related to haemoglobin level.

Wali et al [9] reported systolic murmurs in 61% of patients, and the relationship of haemoglobin level to presence of systolic murmur was not reported. The difference can be explained by the presence of low haemoglobin and high prevalence of cardiomegaly in this study compared to Wali's study.

Hepatomegaly occurs in children with heart failure as an expression of increased venous pressure. In this study hepatomegaly was found in 18% of patients regardless of haemoglobin level, age or sex. Patients in this study noted to have hepatomegaly had no other clinical findings suggestive of heart failure. Therefore the occurrence of hepatomegaly might be due to a co existence of intrahepatic cholestasis known to occur in patients with sickle cell anaemia. [17, 18]

The study has also shown that a significant number of sickle cell anaemia patients have prominent pulmonary vasculature and increased upper lobe blood redistribution that was inversely related to haemoglobin level ($p=0.04$ and 0.014 respectively). The increased pulmonary blood flow is primarily due to anaemia as previously described by Ng et al in 36 % of the study patients as quoted by Serjeant. [10]

The characteristically prominent pulmonary vascular structure results from an increased blood flow across the pulmonary vessels and may occasionally be confused with left to right shunt on radiological appearance. [18, 24]

In a normal ECG the QRS axes in the frontal plane swings from an almost horizontal position on the right in the newborn period to somehow inferior position in the infancy, becoming more leftward in childhood and swings back inferiorly with linear growth in puberty.

ECG abnormalities though commonly reported in patients with sickle cell anemia they are non-specific. [10,24] The prevalence rate of 50 to 78% have been reported in previous studies. [9, 10, 11,12,21,31] In this study a conventional 12 leads ECG was used and the prevalence was 50%. Uzsoy reported 69.7% of his patients having ECG abnormalities using a 14 leads ECG with addition of two right precordial leads (V3R and V4R) for children. The prevalence of ECG abnormalities was higher than in present study because pediatric norms for mean QRS axis are often more rightwards than adults. [37] The occurrence of abnormal ST-T wave changes in sickle cell anaemia patients have been related to myocardial injury resulting from chronic hypoxia or from occlusion of small coronary vessels causing subendocardial ischemia. [24] The prevalence of ST-T segment abnormalities ranged from 19.4% to 58% in previous studies, [12. 15, 31] and 42.4% in the current study.

ST-T segment abnormalities were significantly common in patients above 6 years of age than those aged 6 years or less and fairly prominent in patients with haemoglobin of 8g/dl or below. The differences in prevalence rates can be explained by variation of haemoglobin level and age between these studies. Prolonged P-R interval was

found in 9.09% of the patients with haemoglobin level less than 8g/dl. Similarly Ayou et al, Lippman and Uzsoy et al found prolonged P-R interval in 11.3% 5%, and 10.6% of patients respectively. [12, 15, 24] Prolonged P-R interval is caused by increased vagal tone as a compensation for hypoxia resulting from anaemia.

Echocardiographic changes in this study showed a significant increase in Left ventricular diastolic dimensional indices, left atrial dimensions, aortic root dimensions and interventricular septum thickness during diastole. These abnormalities were inversely related to haemoglobin level. These findings were also common in patients above 6 years and no sex difference was noted. Several studies have also reported dilatation of left cardiac chambers in relation to low haemoglobin levels. [11, 13, 15, 25] This is a reflection of the compensatory dilatation in response to the increased stroke volume and left heart diastolic overload. [18, 24]

Left ventricular posterior wall thickness during diastole was increased in 30% of sickle cell anaemia patients. Patients above 6 years with haemoglobin level below 8g/dl were more likely to have thickened left ventricular posterior wall and no sex difference was noted. Thickened interventricular septum showed a significant inverse relationship to haemoglobin level, regardless of age or sex. Lippman et al found increased Left ventricular posterior wall thickness during diastole in 22% and thickened interventricular septum in 40% of the patients. Wali et al [9] also found sickle cell patients to have more increased left posterior wall and interventricular thickness than the controls. This is a result of the compensatory changes in response to the volumetric overload due to chronic anaemia. Septal and myocardial hypertrophy occurs in an attempt to normalize the wall stress. [18, 24]

Pulmonary artery pressure rises minimally with age, exercise, and high output states such as anaemia. This is an attempt to maintain arterial oxygen tension and delivery and to eliminate carbon dioxide. [43] In this study increased flow velocities across the heart valves was found in 58.6%. Increased pulmonary flow velocity was common and found more in patients aged more than 6 years with haemoglobin of 8g/dl or less. This may be a result of sub clinical hypoxic events that goes unchecked. The pulmonary vascular dilatation and inhibition of endothelial damage caused by nitric oxide are absent in patients with sickle cell anaemia, due to increased production of arginase and the nitric oxide scavenger effect of plasma haemoglobin. This also explains the high rate of pulmonary hypertension that have been reported in patients who do not have repeated episodes of acute chest syndrome.[46] According to the review done by Falk et al [18] pulmonary artery pressure ($P= 4 \times velocity^{2}$) was found to be increased in 30% of patients after exercise. However since the characteristics of that study population and their sample size were not reported it is difficult to make comparison with the findings in this study.

The ratio of blood flow velocity during early filling period (E) to flow velocity during atrial contraction (A) is a sensitive index of left ventricular diastolic dysfunction. In this study E/A ratio of more than two was found in 51% of the study patients. Transmitral E/A ratio >2 was four times more common in patients with haemoglobin of 8g/dl or less and was common in patients above 6 years of age. These findings are almost similar to those of 57% asymptomatic sickle cell anaemia patients aged 19 to 39 years studied by pulsed Doppler echocardiography. [44] Abnormal diastolic dysfunction has been reported in 80% of North African patients with sickle cell anaemia. [45] This suggests that high atrial pressure at rest found in

these patients due to volume overload is likely because of rapid early diastolic left ventricular filling.

This pattern is also found in restrictive filling disorders in patients with ischemic cardiomyopathy causing severe decrease in left ventricular compliance. [41] This Pattern of altered left ventricular diastolic filling in absence of symptomatic heart failure may be the early indicators of cardiac disease in these patients before alteration of systolic function.

The reduced percentage fractional shortening as an index of ejection phase, reflects left ventricular systolic dysfunction. [37] This was detected in 26% of patients with sickle cell anaemia. A significant direct relationship between reduced percentage fractional shortening and haemoglobin level was also found. Rees et al also found significant depressed left ventricular performance indices (ejection fraction, mean fibres shortening velocity, and percentage fraction shortening) especially in symptomatic patients with mean haemoglobin 6.5 ± 0.8 g/dl, indicating the presence of left ventricular dysfunction in sickle cell anaemia patients with low haemoglobin level. [21] Other studies showed normal ejection phase indices. [11,13,15,22] Martins et al [22] and Denenberg et al [23] found altered systolic dysfunction in patients with sickle cell anaemia. The difference was statistically significant when they compared their study subjects to normal control. By using end systolic parietal stress/volume ratio, as an addition index, considered independent from loading conditions, they explained the occurrence of normal systolic functions to be affected by load alterations. Compensatory hypertrophy decreases wall stress and there is a tendency for pseudo normalization of Left ventricular functions as preload increases while the after load is normal or decreased causing indices of ejection phase to be normal. [22, 23]

This was a hospital based cross section study and was prone to selection bias like any other hospital study, however sickle cell clinic receives patients from almost all over Dar es Salaam, and therefore this minimized the chances of a high selection bias.

CONCLUSION

- The most common cardiovascular abnormality found in sickle cell anaemia patients above six years, in particular those with chronic anaemia and haemoglobin $\leq$ 8gm/dl was cardiomegaly. The prevalence is likely to be much higher as patient survival improves.
- There is left ventricular systolic and diastolic dysfunction with no clinical evidence of congestive cardiac failure in patients with sickle cell anaemia.

RECOMMENDATIONS

- Patients with sickle cell anaemia need to have their haemoglobin maintained above 8gm/dl.
- Patients with sickle cell anaemia, haemoglobin below 8gm/dl plus cardiovascular signs would need echocardiographic evaluation and those with significant cardiac abnormalities should have close follow up.

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