ABDOMINAL ULTRASONOGRAPHIC ABNORMALITIES IN PATIENTS WITH SICKLE CELL ANAEMIA AT MUHIMBILI NATIONAL HOSPITAL

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Hamim Abdul Rusheke

A Dissertation Submitted in Partial Fulfilment of the Requirements for the Degree of Master of Medicine (Radiology) of the Muhimbili University of Health and Allied Sciences

Muhimbili University of Health and Allied Sciences

October 2010

CERTIFICATION

The undersigned certify that he has read and hereby recommend for examination by Muhimbili University of Health and Allied Sciences a dissertation entitled ***"prevalence of abdominal ultrasonographic abnormalities in patient with sickle cell disease at MNH from October 2009 to January 2010"***, in partial fulfilment of the requirements for the Degree of Master of Medicine (Radiology) of Muhimbili University of Health and Allied Sciences.

Dr Kazema R.R.

(Supervisor)

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DEDICATION.

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ABSTRACT

Background

Sickle cell disease, particularly in homogeneous state, has significant contribution to the morbidity and mortality of this disorder during crisis. The various types of crises cause changes in different organs of the body, some of which may have long term complications to the sickle cell patient. Most of these changes occur in the abdominal organs, that is the liver, kidneys, spleen, gall bladder as well as the pancreas. Early detection of these changes which are mostly due to vaso-occlusion enables those involved in the care of sicklers to take preventive measures which may help reduce the degree of morbidity and mortality due to sickle cell anaemia. Ultrasound being the most simple, cheap and easily accessible imaging investigation modality, may play an important role in early detection of these changes so that appropriate intervention measures can be carried out. Determination of the pattern and prevalence of abnormal ultrasonographic findings in sickle cell patients in our set up was an important step to enable us decide whether or not there is importance of early ultrasonographic screening for all sickle cell patients.

Objective

The aim of this study was to evaluate the types and prevalence of abdominal ultrasonographic abnormalities in patients with sickle cell disease, attending sickle cell clinics of MNH.

Materials and Methods

A total of 152 patients with sickle cell anaemia at Muhimbili National Hospital were screened for intra-abdominal abnormalities in the liver, gall bladder, spleen and kidneys from October 2009 to January 2010. Their ages ranged from 3 to 46 years. 32% were below the age of 10 years and 79% below 20 years. 41.4% were males and 58.6 % were females. All patients were homozygous for HbSS. None of the patients had any clinical evidence of acute sickle cell crisis at the time of ultrasonographic examination. At the time of examination, 4 (2.6%) patients had undergone splenectomy and 2 (1.3%) patients had undergone cholecystectomy.

Results

The most frequent US findings were hepatomegaly (28.3%), splenomegally(22.4%) and cholelithiasis (17%). Bright liver was identified in 19(12.5%) patients, increased renal echogenicity in 15(10%) patients, shrunken spleen in 14(9%) patients, and renal enlargement in 6 (4%) patients. Biliary sludge was identified in 4(3%) patients, autosplenectomy in 10(6.6%) patients and renal cysts in 5(3%) patients.

Conclusion

In conclusion, abdominal US imaging of patients with sickle cell anaemia revealed a significant prevalence of abdominal abnormalities, in the liver, gall bladder, kidneys, and spleen.

Recommendations

There is a need to conduct further similar studies in order to establish the average prevalent rates for each of the abdominal pathologies in sickle cell patients

Also there is a need for correlation studies, to establish whether or not there is any association between US findings and biochemistry changes in these patients

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LIST OF ABBREVIATIONS

Hb……Hemaglobin

HV……..…....Hepatic Vein

MNH…….…... Muhimbili National Hospital

SC……..Sickle Cell

SCA……Sickle cell anaemia

SCD……....Sickle Cell Disease

TI……Thalassemia Intermedia

US …… …..Ultrasound/Ultrasonography

HbSC.....Example of heterozygous form of Sickle cell disease

.

HbSS.....Homozygous form of sickle cell disease.

HbSβ.....Another Haemoglobin sickle cell-*β* thalassemia (another example of heterozygous SCD)

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DEFINITION OF TERMS

- Gallstones: Highly reflective structures with or without acoustic shadowing, detected within the lumen of the gall bladder.
- Cholecystitis: biliary pain and tenderness in the right upper quadrant lasting more than 72 hours with associated fever.
- Cholestasis: Episodic jaundice with or without abdominal pain, dark urine, or pale stools, supported by raised liver enzyme activities.
- Hepatomegaly: For adult patients- the long axis of the right lobe of the liver is longer than 150 mm. For children- it will depend on the height or age of the child.
- Splenomegally: long axis of the spleen at the level of the hilum is greater than 130 mm. For children- it will depend on the height or age of the child.
- Renal enlargement: The right kidney- the long axis is greater than 128 mm.For the left kidney-long axis is greater than 130 mm.
- Diffusely increased renal echogenicity : An increase in reflectivity throughout the kidney and poor cortico-medullary differentiation.
- Medullary hyperechogenicity : A high reflective renal medulla with a normal renal cortex.
- Bright liver : A diffuse increase in liver echogenicity.
- Sickle cell disease(SCD): is an autosomal recessive genetic blood disorder characterized by red blood cells that assume an abnormal, rigid, sickle shape caused by mutation in the Hemoglobin gene.
- Homozygous sickle cell anaemia (HbSS): A specific form of sickle-cell disease in which there is homozygosity for the mutation that causes HbS
- Heterozygous sickle cell disease(HbAS): In this group, people have only one sickle gene and one normal adult haemoglobin gene.
- Non-paediatric patients: Patients above 12 years in this study were regarded as non-paediatric patients.

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

Sickle cell disease is an inherited haematological disorder characterized by banana, crescent-moon or sickle-shaped human red blood cells (1). This abnormality results in painful episodes, chronic anaemia, enlarged spleen, serious frequent infections, and damage to vital body organs (1). The normal human haemoglobin molecule is composed of four globin chains (two α and two s). SCD results from the inheritance of either two sickle S globin genes (HbSS, sickle cell anaemia) or one sickle S globin gene (heterozygote form of SCD). Sickle cell-ß thalassemia (HbAS/ßthal) is one of the heterozygote forms of SCD. Patients with S/ßthal have clinical features more similar to those of SCD than to those of thalassemia (2). Under normal circumstances, red blood cells are flexible and biconcave discs, and move easily through blood vessels to carry oxygen to all parts of the body for about 90-120 days. Sickled cells have relatively small oxygen contact area and they cause increased blood viscosity, which impedes normal circulation in small blood vessels, resulting in ischemia and infarction (1). In people with sickle cell anaemia, these irregular-shaped red cells become rigid and sticky, and die prematurely, resulting in a chronic shortage of haemoglobin in the body. While travelling through small blood vessels, they can get stuck and slow down or block blood flow and thus oxygen to certain parts of the body. This blockage produces pain and serious complications (1). Repeated vaso-occlusion accounts for the majority of the clinical manifestations of the disease (2,3) These effects can, however, vary from person to person depending on the type of sickle cell disease, nutritional status, and other concomitant factors.

Elongated sickle cells are fragile. They break apart easily and die, leaving a chronic shortage of red blood cells to carry oxygen to tissues — a condition known as anaemia. Without enough red blood cells in circulation, the body cannot get the oxygen to energize the tissues, and this accounts for the main cause of fatigue in anaemia (1). Periodic episodes of pain, called painful crises, are a major symptom of sickle cell anaemia. Pain develops when sickle-shaped red blood cells block blood flow through tiny blood vessels to any part of the body. Pain can also occur in bones, varying in intensity and last for a few hours to a few weeks. Some people experience only a few episodes of pain, whereas, others experience a dozen or more crises in a year. If a painful crisis is severe enough, painkillers are to be injected intravenously, and the patient may need hospitalization (1).

Swollen hands and feet are often the first signs of sickle cell anaemia in babies and present what is known as 'Hand-Foot' syndrome. The swelling is caused by sickle-shaped red blood cells blocking blood flow out of the hands and feet, accompanied by pain and fever (1).

Often, people who have sickle cell anaemia have some degree of jaundice because the liver, which filters harmful substances from the blood, is overwhelmed by the rapid breakdown of red blood cells. Even in whites jaundice is visible as the eye sclera becomes yellowish (1).

Sickle cells damage the spleen, an organ that fights infections, making sickle cell patients more vulnerable to infections. Doctors commonly prescribe antibiotics to infants and children to prevent potential life-threatening infections, such as pneumonia (1). Red blood cells provide oxygen and nutrients needed for the growth. A shortage of healthy red blood cells can slow down growth in infants and children and delay puberty in teenagers (1), causing stunted growth.

Some people with sickle cell anaemia experience vision problems. Tiny blood vessels that feed eyes become plugged with sickle cells. This damages the retina — the portion in each eye that processes visual images (1).

Vaso-occlusive crisis is caused by sickled red blood cells that obstruct capillaries and restrict blood flow to an organ, resulting in ischemia, pain, and organ damage. Because of its narrow vessels and function in clearing defective red blood cells, the spleen is frequently affected. It is usually infarcted before the end of childhood in individuals suffering from sickle-cell anemia. This auto-splenectomy increases the risk of infection from encapsulated organisms; preventive antibiotics and vaccinations are recommended for those with such asplenia. Bone is also a common target of vaso-occlusive damage, especially when the bone is particularly weight-bearing. Such damage may result in avacular necrosis (especially of the femur) and bone deterioration. The pain experienced by sickle-cell patients is also due to bone ischemia (1).

An acute worsening of the patient's baseline anaemia producing pallor, tachycardia, and fatigue is termed as aplastic crisis. Reticulocyte counts drop dramatically during the illness and the rapid destruction of red cells leads to the drop in hemoglobin. Most patients can be managed supportively; some need blood transfusion (1).

The most common abdominal manifestations include hepatomegaly, splenomegaly, autosplenectomy, cholelithiasis, renal enlargement, and increased renal echogenicity(3,4). The liver can be affected by a number of complications due to the disease itself and its treatment (5,6). In addition to the vascular complications from the sickling process, patients with sickle cell disease have often received multiple transfusions placing them at risk for viral hepatitis, iron overload, and, combined with the effects of chronic haemolysis, the development of pigment gallstones, all of which may contribute to the development of liver disease. The term "sickle cell hepatopathy" has sometimes been used to reflect the overlapping causes of liver dysfunction in these patients(5,6). Sickle cell hepatopathy occurs predominantly in patients with homozygous sickle cell anemia, and to a lesser extent in patients with HbSC disease and HbSß-thalassemia(5,6).

Gall stones are common in sickle cell anaemia owing to the chronic haemolysis, but the importance of this complication has not been established. In the first two reports of sickle cell disease in 1910 (7) both patients had recurrent "bilious" attacks, and one had a cholecystectomy. The prevalence of gall stones reported in homozygous sickle cell disease (Hb SS) has varied widely, being from 34% to 70% in the United States (8), 29% in Jamaica(9) from 4% to 25% in Africa(7), and 8% in Saudi Arabia(7). This variability may reflect differences in the patients studied, age, and the sensitivity of diagnostic methods (plain radiography or oral cholecystography). Recently, ultrasonography has become a reliable non-invasive method for investigating the biliary tract. Prospective studies restricted to children have shown that the prevalence of gall stones is from 17% to 29% and increases with age (7-9) but studies in adults are lacking. Symptomatic biliary tract disease is difficult to diagnose in a patient with sickle cell disease who has acute abdominal pain, fever, and jaundice because such symptoms can occur in a vaso-occlusive crisis. In one study five out of seven patients who had emergency laparotomy for presumed acute cholecystitis had a normal gall bladder (10). US remains the method of choice for the diagnosis of gallstones and is generally accepted as an initial imaging technique in gallstone complications, such as acute cholecystitis. US is still considered the first diagnostic procedure when stones are suspected in the common bile duct.

There are no previous reports concerning the frequency and spectrum of abdominal US findings in patients with SCD in Tanzania. According to the reviewed literature, this study will be the first to be conducted in Tanzania.

Various studies have been done in various parts of the world to establish the types and prevalence of different abdominal ultrasound abnormalities in sickle cell patients.

In 1979, Massawe ME(11), carried out a study to determine the phenotypic expression of sickle cell anaemia(SS) in non-paediatric patients attending medical care at the Muhimbili Medical Centre. In his study, 70 sickle cell anaemia patients were seen during a period of five months. Although no US examination was done in this study, he had the following physical findings: splenomegally (18%), hepatomegaly (28.3%) (11).

Another study (10) was carried out in UK in 1985 at King's College Hospital, London, by Bond R.L et al, to determine the prevalence of gall stones in sickle cell patients. In this study, all patients aged 10 years or more attending sickle cell clinics from March to December 1985 were asked to attend for an abdominal ultrasound examination unless they had had a cholecystectomy. For adult patients a standard questionnaire was used to elicit relevant symptoms and the clinical notes were reviewed for evidence of previous symptoms, admissions for abdominal crises, and possible biliary complications. Results of the following investigations were recorded: haemoglobin electrophoresis, steady state haemoglobin concentration, reticulocyte count, fetal haemoglobin (Hb-F) concentration, and serial liver function tests. The patients who had had a cholecystectomy were asked about recurrent symptoms or complications in the same questionnaire, and their notes were reviewed. All scans were performed using a real time mechanical sector scanner with a transducer frequency of 3.5 MHz for adults and 5 MHz for children. All patients were asked to fast for eight hours before the examination. Of 95 patients with homozygous sickle cell disease, 55 (58%) had gall stones or had had a cholecystectomy. Gall stones were present in four out of 24 (17%) patients with haemoglobin S+C disease and two out of 12 (17%) with haemoglobin Sβ thalassaemia. The presence of gall stones was not related to sex, geographical origin, or haematological variables and was not associated with abnormal results of liver function tests. Symptoms typical of biliary colic were reported by 32 out of 47 adult patients with gall stones, and cholecystitis or cholestasis was diagnosed in 18. Cholecystectomy was performed in 29 patients with good relief of symptoms in most cases. Postoperative complications were common, occurring in 10 of the 28 patients who could be evaluated, but not generally serious; they were considerably lessened by a

preoperative exchange blood transfusion that reduced the haemoglobin S concentration to below 40%. The study recommended that all patients with sickle cell disease should be screened routinely for gall stones and that elective cholecystectomy should be performed in those with symptoms or complications.

In 2003, Marina G.P et al, in Greece, conducted a study to investigate the spectrum and prevalence of abdominal ultrasonographic findings in patients with sickle-cell anaemia and thalassaemia intermedia(12). This study included 105 patients, 13 homozygous for sickle-cell anaemia (HbSS) and 92 with Thalassemia Intermedia syndromes. The patients' ages ranged from 1 to 54 years, with 49 males and 56 females. At the time of the examination, 41% of the patients had undergone splenectomy and 23.8% had undergone cholecystectomy. The most frequent US findings were: hepatomegaly (70.5%), splenomegaly (48.6%) and cholelithiasis (20%). The prevalence of hepatomegaly and splenomegaly in this study was much higher compared to the findings in a study by Massawe M.E (11), cited above, in which the prevalence of hepatomegaly and splenomegaly were 28.3% and 18% respectively. Nevertheless, the prevalence of gallstones in this study was much lower when compared to the findings in a previous study by Bond R.L et al cited above, in which gallstones were detected in 58% of cases. A bright liver was identified in 3.8% and focal hepatic lesions were present in two patients of the TI group. Functional disorders of the gallbladder concerned mainly patients with sickle-cell syndromes. Of those with S/S, 30.8% had a shrunken spleen. An echogenic pancreas was identified in one patient in each group. Increased renal echogenicity was observed in 17.6% of patients with sickle-cell syndromes. One case of polycystic kidney disease was diagnosed and coexisted with S/S[8].

Another study (13) was carried out in 2004 by Ali Balci et al in Eastern Turkey, to determine the prevalence of intra-abdominal abnormalities in sickle cell patients by abdominal ultrasonography. A total of 102 patients with SCD at the centre of Hemoglobinopathy of the Antakya State Hospital were screened for any intra-abdominal abnormalities by abdominal ultrasonography (US). Their ages ranged from 3 to 46 years (mean age, 19.7 ± 8.5). Eighty-four patients were homozygous for sickle cell disease (HbSS), and 18 patients had sickle cell-β thalassemia (S/β^{thal}). None of the patients had any

clinical evidence of acute sickle crisis at the time of ultrasonographic examination. At the time of examination, 15.7% of patients (16/102) had undergone splenectomy and 18.6% of patients (19/102) had undergone cholecystectomy. Informed consent was obtained from all patients (or parents of minor patients), and the study protocol was approved by the ethics committee of their institution. All patients were examined by B-mode US scanner with a variable frequency probe at 1–4 MHz or 4–9 MHz. After the patient fasted overnight, the examination was performed with the patient in the supine, right side, or left side position to obtain an optimal view of the abdominal viscera. Measurements of the liver, spleen, and kidneys were performed in all patients and the organ sizes were compared to published data obtained from a healthy Turkish population of normal distribution for age and height for infants and children. B-mode parameters such as frequency, focus, gain, and tissue harmonics application were optimized by the radiologist on a case-by-case basis.
Image analysis was performed visually and qualitatively. All patients were also evaluated for biliary tract and pancreatic abnormalities, intra-abdominal fluid collections, masses, and enlarged lymph nodes. In this study, the most frequent US findings were hepatomegaly (71.6%), renal enlargement (30.4%), autosplenectomy (33.3%), cholelithiasis (30.4%), and splenomegaly (17.4%). Bright liver was identified in 6 (5.9%) patients. One case in the HbSS group had the ultrasonographic findings of cirrhotic liver. A hepatic hemangioma was observed in 1 patient of the S/βthal group. Echogenic pancreas was identified in 4 patients (3.9%), and pancreatic punctuate echogenic foci were identified in 5 patients (4.9%). Medullary or diffusely increased renal echogenicity was observed in 16 (15.7%) patients. Sonographic findings typical of renal papillary necrosis, multiple round or triangular cystic spaces communicating with the collecting system in the medullary region without dilated renal pelvis were observed in one patient with HbS/S. Periportal lymphadenopathy was detected in 10 (11.9%) of 84 patients of the HbS/S group and 2 (11.1%) of 18 patients of HbS/βthal group. Some of the findings in this study concurs with those in the previous two studies cited above (10,12), and these includes the prevalence of hepatomegally (71.6%) and colelithiasis (30.4%). However, when comparing the prevalence of splenomegally it was found to be lower in this study (17.4%) as compared to 48.6% found in the study by Marina G.P et al (12). Another striking finding in this study was the relatively high prevalence of renal enlargement (30.4%), which was never reported in the previous studies.

In the same year 2004, another study(14) was conducted in the western belt of Orissa in India, by Mohanty et al, to evaluate the various spectrum of abdominal sonographic findings involving the liver, spleen, gall bladder and kidneys. Their study included fifty patients of SCD presented with acute symptoms of sickle cell crisis. In this study, hepatomegaly had the highest prevalence (72 %), similar to findings in the other 2 previous studies (12). However, the prevalence of splenomegaly (64 %) was much higher compared to the findings in all the other previous studies. The prevalence of cholelithiasis was (22 %) and this was within the same range as found in other studies cited before(12,13). Furthermore 22% of patients presented with splenic infarction, 10% of patients showed splenic calcification. Increased bilateral renal echogenicity was observed in 16 % of patients. It was then concluded that ultrasonography is a readily accessible and non invasive method for the evaluation of different abdominal organs in sickle cell patients (14).

Another study (15) was carried out in 2007 in Brazil by Fabiola T et al, to evaluate the incidence and etiology of chronic liver abnormalities in 70 living patients with sickle cell disease from the Hematology and Hemotherapy Center of the State University of Campinas. Sixty-seven (96%) patients had some liver abnormalities; these included abnormal liver function tests, viral hepatitis, liver ultrasonographic changes or cholelithiasis. The sickling process was the only explanation for the abnormal liver function tests or liver ultrasonographic changes in 24% of these patients. One or more defined reasons, including viral hepatitis, cholelithiasis, clinical hemosiderosis, alcoholism or diabetes, justified the liver abnormalities in 76% of the patients (15).

In yet another study (16) by Namjosh SP, increased renal echogenicity was noted in 13.8% of patients with SCD (16) . Medullary hyperechogenicity has also been reported in many other conditions including hypercalciuria, medullary sponge kidney, hyperparathyroidism, and papillary necrosis (17).

SCA is associated with many structural and functional abnormalities of the kidney (22) which may progress to chronic renal failure and end-stage renal disease (23). Several studies have reported focal (medullary) or diffuse (Image 4.2) increase in reflectivity on renal sonography in patients with SCD(22,23) . The cause and significance of this entity is

unknown; however, renal papillary necrosis, high concentrations of iron deposits within tubular epithelial cells, focal scarring and interstitial fibrosis in vasa recta system, glomerular hypertrophy, and renal sclerosis have been suggested as factors that may cause increased renal echogenicity (22).

If we take the findings in the above mentioned studies, hepatomegaly appeared to have a consistently high prevalence in all the studies, compared to other abnormalities, followed by splenomegaly. The Prevalence of other abnormalities had a wide fluctuation among different studies, which makes it important that a similar study is done in order to establish the prevalence of similar abnormalities in sickle cell patients in our geographical settings.Many more studies have been done to establish the value of US imaging in detecting complications of sickle-cell diseases, but none has been carried out in our set up, and this leaves a gap of knowledge that needs to be filled.

CHAPTER 2

STATEMENT OF THE PROBLEM

In Tanzania and other parts of Africa, Sickle cell anaemia is common, and constitutes a major challenge in ultrasonographic examinations. Sickle cell anaemia manifests in a variety of abdominal problems, including hepatomegaly, splenomegaly, autosplenectomy, biliary tract abnormalities, renal enlargement, and increased renal and pancreatic echogenicity (2, 3). US is a simple, rapid, non-invasive, and non-ionizing tool for assessing the abdominal manifestations of sickle cell anaemia. Vascular occlusion, viral hepatitis, iron overload, and drug reactions may contribute to sickle cell anaemia-related liver disease (3).

Despite high prevalence of Sickle cell anaemia in our country, no study has been carried out to determine the prevalence of abdominal ultrasonographic pathologies in sicklers in Tanzania. The findings from this study, will help clinicians involved with management of sickle cell patients, to set up guidelines for proper examinations of sickle cell patients in order to detect complications of sickle cell anaemia at early stages and where necessary to carry out intervention measures before it is too late.

CHAPTER 3

RATIONALE

Sickle cell anaemia has a significant contribution to the morbidity and mortality of this disorder during crisis. The various types of crisis cause changes in different organs of the body including the liver, kidneys and spleen (18). Real time ultrasonography is now becoming a standard screening procedure in all cases of sickle cell disease patients for the assessment of the pathological changes occurring in the abdominal organs, especially liver, gall bladder, spleen and kidneys (18). The extent and changes in the various organs can accurately be observed and thereby help the clinicians to modulate their mode of treatment. In acute crisis, the patients can be divided as to whether needing surgical or medical intervention. Therefore, abdominal sonography is an easy, cheap, and accurate method for diagnosis, management and follow up of patients suffering from sickle cell disease and can be carried out as an outpatient diagnostic procedure (18). Unfortunately, no studies have been carried out in our set up to establish the prevalence of abdominal ultrasonographic abnormalities in our country, as well as to establish the usefulness of ultrasonography in the assessment of such abdominal pathologies. Information obtained from this study will be used to initiate intervention measures with regard to abdominal complications of sickle cell disease.

CHAPTER 4
OBJECTIVES

4.1.BROAD OBJECTIVE

To determine the prevalence of abdominal ultrasonographic findings in various abdominal organs of patients with Sickle cell anaemia at Muhimbili National Hospital from October 2009 to January 2010

4.2. SPECIFIC OBJECTIVES

1. To determine age and sex of patients with SCA at MNH
2. To determine the prevalence and distribution of abnormal US findings in the livers of patients with SCD at MNH.
3. To determine the prevalence and distribution of abnormal US findings in the biliary tracts of patients with SCA at MNH.
4. To determine the prevalence and distribution of abnormal US findings in the spleens of patients with SCA at MNH.
5. To determine the prevalence and distribution of abnormal US findings in the kidneys of patients with SCA at MNH .

CHAPTER 5
MATERIALS AND METHODS

5.1. Study Design

It was a cross-sectional study

5.2. Study Area

Muhimbili National Hospital

5.3. Study Population and Subjects

All patients attending the SCD clinic at MNH

5.4. Sampling Methods

Simple random sampling procedures were used. Patients were selected from the attendance list of each particular day. Those with Odd numbers were selected, and among them, those who concented to the study were recruited. Patients were given appointment dates for US examination depending on their convenience.

5.5 Sample size

The minimum sample size was calculated using the formula:

$$N = \frac{Z^2P(1-P)}{D^2}$$

Where:

N = Sample size

Z = Standard normal deviation of 1.96 corresponding to 95% confidence interval

P= expected prevalence rate of abnormal abdominal ultrasonographic findings 70%

D = Is a degree of accuracy of the results(marginal error), set at 8%

Thus: $N = \frac{1.96 \times 1.96 \times 0.7 (1-0.7)}{(0.08 \times 0.08)} = 126.053$

Thus the minimum sample size required was 127 patients. In my study 152 patients were enrolled.

5.6. Inclusion Criteria

All patients aged 3 years and above, attending sickle cell clinics at MNH, and who consented to the study or whose parents consented, were enrolled.

I used the cut off age of 3 years because of poor compliance we usually experience from 1 to 2 years old children during US examination, and this can significantly affect examination results.

5.7.Exclusion criteria

Patients who refused to give consent to participate in the study.

5.8. Research tools

Ultrasound machines and probes

Height measuring tool

Calculators, plain papers, pencils and pens.

Statistical computer software package for data analysis and processing (EPI info) was used.

5.9.Data Collection Procedures

Informed consent was obtained from all patients (or parents of minor patients), and the study protocol was approved by the ethics committee of MUHAS.

The Haematology Department of MNH runs clinics for sickle cell patients every Thursday and Friday, from 8 am.The average attendance per day is about 40 to 50 patients.

All patients attending sickle cell clinics from October 2009 to January 2010, who consented to the study, were asked to attend for an abdominal ultrasound examination. A standard questionnaire was used to record all the relevant findings. Patient's records/files were reviewed for evidence of previous investigations done especially Hb electrophoresis, operations (cholesystectomy or splenectomy) and recent height measured. Results of above parameters were recorded in the questionnaire.

All patients were examined by B-mode US with Philips HDI 4000 US scanner (Medison Co.Ltd ,Gangnam-Gu, Seoul, Korea) with a variable frequency probe at 2–5 MHz or 5-12MHz.

All patients were asked to fast for 6 hours before the examination. The examination was performed with the patient in the supine, right side, or left side position to obtain an optimal view of the abdominal viscera. Measurements of the liver, spleen, and kidneys were performed in all patients as follows: long axis of the right lobe of the liver; long axis of the spleen at the level of the hilum; and long axis of each kidney. The organ sizes were compared to sizes from standard reference values (19-21). For children aged 3 to 12 years, reference values for each age group were used, based on height of each individual. In children above 12 years and all adults, hepatomegaly and splenomegaly were defined as the long axis of the organs longer than 150 mm and 130 mm, respectively (19-21). The upper limits for normal right and left kidneys were accepted as 120mm (19-21). The parenchyma of the kidneys and liver were also evaluated. An increase in reflectivity throughout the kidney and poor cortico-medullary differentiation was defined as diffusely increased renal echogenicity. A high reflective renal medulla with a normal renal cortex was defined as medullary hyperechogenicity. A diffuse increase in liver echogenicity was defined as "bright liver". Gall bladder calculi were diagnosed if highly reflective structures, with or without acoustic shadowing, were detected within the lumen of the gall bladder.

5.10. Data Analysis

This was done using Epi info software program as well as by using appropriate statistical formulas for calculating the required parameters.

5.11. Ethical consideration and clearance

Ethical clearance was sought and guaranteed from the ethical committee of MUHAS. Detailed explanation about the purpose of the study and how it was to be carried out were explained to all participants before accepting to participate in the study. Informed and written consent forms were given to all participants.

For the minors, explanations about the research was done to parents/guardians and asked to give their informed written consent.
Those who agreed and signed the written consent forms were included in the study, whereas those who refused to sign the consent papers were not included in the study . .
Report for the ultrasonographic fingings for all patients were written and kept in the patients files. All significant findings were also communicated to the phyisician/paediatrician taking care of the patients.
No ethical problems were encountered during the study.

5.12. LIMITATIONS

About 20 (13%) patients did not comply with the request of fasting for 6 hours before the examination, which might have made it more convenient, the examination of the gall bladder to rule out the presence of gall stones. Because of this failure of some patients to comply, there is a possibility of having missed small gall bladder stones, and this might have contributed to the relatively low prevalence of cholelithiasis in this study, as compared to other studies.

Another limitation of this study is that several abdominal ultrasonographic findings including hepatomegaly, splenomegaly and increased renal echogenicity are non-specific. I did not perform biopsy or any other imaging methods to confirm the ultrasonographic findings in my study patients

CHAPTER 6

RESULTS

A total of 152 patients with SCA at Muhimbili National Hospital were involved in the study from October 2009 to January 2010. Their ages ranged from 3 to 46 years. 32% were below the age of 10 years and 79% below 20 years. 41.4% were males and 58.6 % were females (Table 1).

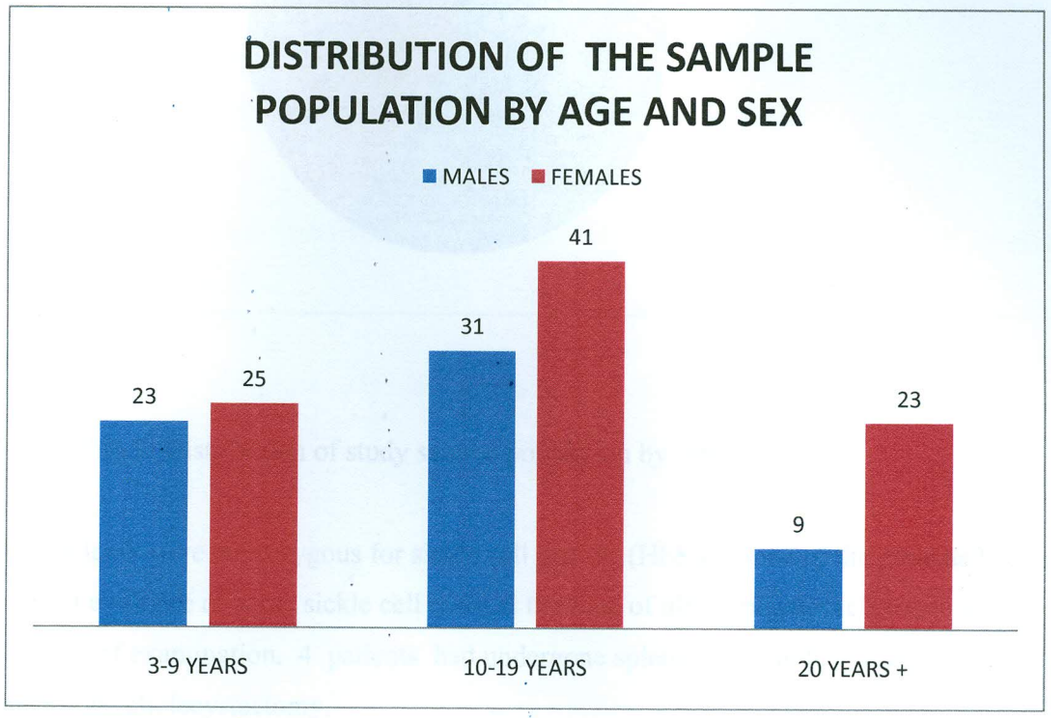


Illustration 1: Distribution of study sample by sex and age group.

Table1. Distribution of participants by age and sex

AGE(yrs)	Sex		TOTAL
	Male	Female	
3-9	23(37%)	25(28%)	48(32%)
10-19	31(49%)	41(46%)	72(47%)
20+	9(14%)	23(26%)	32(21%)
TOTAL	63(41.4%)	89(58.6%)	152(100%)

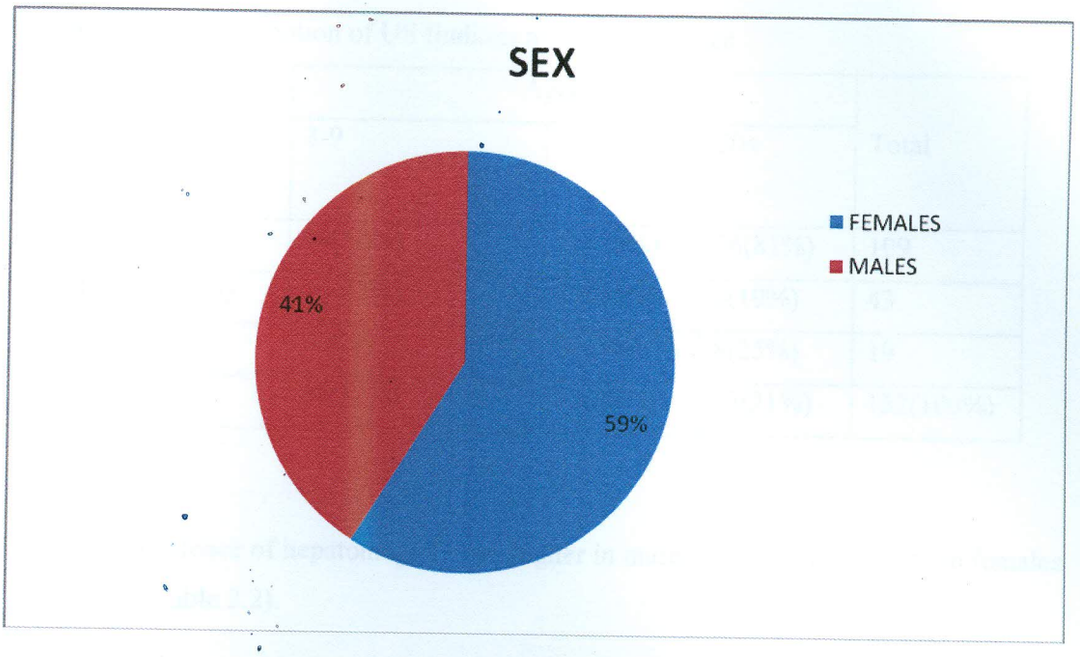


Illustration 2: Distribution of study sample population by sex.

All patients were homozygous for sickle cell disease (HbSS). None of the patients had any clinical evidence of acute sickle cell crisis at the time of ultrasonographic examination. At the time of examination, 4 patients had undergone splenectomy and 2 patients had undergone cholecystectomy.

The most frequent US findings were hepatomegaly (28.3%), splenomegaly (22.4%) and cholelithiasis (17%). Bright liver was identified in 19 (12.5%) patients, increased renal echogenicity in 15 (9.9%) patients, shrunken spleen in 14 (9.3%) patients, and renal enlargement in 6 (4%) patients.
Biliary sludge was identified in 4 (3%) patients, autosplenectomy in 10 (7%) patients and renal cysts in 5(3.3%) patients.
One patient had a thickened gall bladder wall and gallstones.

Of 43 patients with hepatomegally, 20 (46.6%) were below 10 years of age and 17 (39.6%) between 10 and 20 years, whereas only 6 (14%) were above 20 years.(Table 2.1)

Table 2.1: Distribution of US findings in the liver by age

US findings	Age(yrs)			Total
	3-9	10-19	20+	
Normal liver	28(58%)	55(76%)	26(81%)	109
Hepatomegaly	20(42%)	17(24%)	6(19%)	43
Bright liver	2(4%)	9(13%)	8(25%)	19
Total	48(32%)	72(47%)	32(21%)	152(100%)

The prevalence of hepatomegally was higher in males (32%) as compaired to females (26%) (Table 2.2).

Table 2.2: Distribution of US findings in the liver by sex

US findings	Sex		Total
	Male	Female	
Normal liver	43(68%)	66(74%)	109
Hepatomegaly	20(32%)	23(26%)	43
Bright liver	11(17%)	8(9%)	19
Total	63(41%)	89(59%)	152(100%)

The prevalence of cholelithiasis was found to be higher in those above 20 years (34%) and lowest in those below 10 years (8%). With regard to sex, males had the higher incidence of cholelithiasisi (17%) as compared to females (15%) (Table 3.2).

Table 3.1: Distribution of US findings in the biliary tracts by age

US findings	Age(yrs)			Total
	3-9	10-19	20+	
Normal gall bladder	42(88%)	61(85%)	20(63%)	123(81%)
Cholelithiasis	4(8%)	10(14%)	9(28%)	23(15%)
Cholecystectomy*	0(0%)	0(0%)	2(6%)	2(1%)
Biliary sludge	2(4%)	1(1%)	1(3%)	4(3%)
Total	48(32%)	72(47%)	32(21%)	152(%)

* All patients who underwent cholecystectomy due to gallstones

Table 3.2: Distribution of US findings in the biliary tracts by sex

US findings	SEX		Total
	Male	Female	
Normal Gall bladder	49(78%)	74(83%)	123(81%)
Cholelithiasis	11(17%)	12(13%)	15(10%)
Cholecystectomy*	0(0%)	2(2%)	2(1%)
Biliary sludge	3(5%)	1(1%)	4(3%)
Total	63(42%)	89(58%)	152(100%)

* All patients who underwent cholecystectomy due to gallstones

Concerning splenomegaly, the prevalence was higher in those below 10 years (43.8%) followed by 10-19 years(13.9%).There was no significant difference in the incidence of splenomegaly between males (23.8%) and females (21.4%).(Table 4.1 and 4.2)

Table 4.1: Distribution of US findings in the spleen by age

US findings	Age(yrs)			Total
	3-9	10-19	20+	
Normal spleen	47(98%)	61(85%)	0(0%)	108(71%)
Splenomegaly	18(38%)	9(13%)	3(9%)	30(20%)
Splenectomy*	3(6%)	1(1%)	0(0%)	4(3%)
Autosplenectomy	0(0%)	4(6%)	6(9%)	10(7%)
Shrunken spleen	0(0%)	0(0%)	13(41%)	13(9%)
Hypoechic parenchymal lesions	0(0%)	4(6%)	2(6%)	6(4%)
Total	48(32%)	72(47%)	32(21%)	152(100%)

*patients who underwent splenectomy as a treatment for splenomegally.

Table 4.2: Distribution of US findings in the spleen by sex

US findings	Sex		Total
	Male	female	
Normal spleen	47(75%)	61(69%)	108(71%)
Splenomegaly	12(19%)	18(20%)	30(20%)
Splenectomy*	3(5%)	1(1%)	4(3%)
Autosplenectomy	1(2%)	9(10%)	10(7%)
Shrunken Spleen	5(%)	8(9%)	13(9%)
Hypoechic parenchymal lesions	3(8%)	3(3%)	6(4%)
Total	63(41%)	89(59%)	152(100%)

*patients who underwent splenectomy as a treatment for splenomegally.

The prevalence of increased renal echogenicity was 10%. Only 6 (4%) patients were found to have renal enlargement . Simple renal cysts were observed in 5 (3%) patients with SCD (Tables 5.1 and 5.2)

Table 5.1: Distribution of US findings in the kidneys by age

US findings	Age(yrs)			Total
	3-9	10-19	20+	
Normal kidney	48(100%)	57(79%)	19(59%)	124(82%)
Increased renal echogenicity	0(0%)	6(8%)	9(28%)	15(10%)
Renal enlargement	0(0%)	3(4%)	3(9%)	6(4%)
Renal cyst	0(0%)	5(7%)	0(0%)	5(3%)
Renal stones	0(0%)	1(1%)	1(3%)	2(1%)
Total	48(32%)	72(47%)	32(21%)	152(100%)

Table 5.2: Distribution of US findings in the kidneys by sex

US finding	sex		Total
	Male	female	
Normal	49(78%)	75(83%)	15(82%)
Increased renal echogenicity	8(13%)	7(47%)	15(10%)
Renal enlargement	2(3%)	4(67%)	6(4%)
Renal cysts	3(5%)	2(40%)	5(3%)
Renal stones	1(2%)	1(50%)	2(1%)
Total	63(41%)	89(59%)	152(100%)

CHAPTER 7

DISCUSION

SCA is one of the most common inherited hemoglobinopathies worldwide (1). In Tanzania, SCA is common, and constitutes a major challenge in ultrasonographic examinations. Currently no formal studies have been carried out to determine the prevalence of SCA in Tanzania. However, hospital based surveys have revealed the prevalence of SCA (HbSS) to be between 6%-7%, and that of heterozygous disease (HbAS) between 15% - 20% (Personal communication). SCA manifests in a variety of abdominal problems, including hepatomegaly, splenomegaly, autosplenectomy, biliary tract abnormalities, renal enlargement, and increased renal and pancreatic echogenicity (3,4). US is a simple, rapid, non-invasive, and non-ionizing tool for assessing the abdominal manifestations of SCA.

Vascular occlusion, viral hepatitis, iron overload, and drug reactions may contribute to SCD-related liver disease(3) . Hepatomegaly (Images 1.2-1.3) was the most common pathologic finding in this study, its prevalence being 28.3%. This results concurs with the findings by Massawe ME (11) cited before, whereby the prevalence of hepatomegally was found to be 28.3%. However, this frequency is much lower compared to other 5 different studies (5,12,13,15), where by the prevalence of hepatomegally was in the range of 70% to 72%. Some reasons could be attributed to such a wide variation in the prevalence of hepatomegally, including genetic factors as all the above cited studies were conducted in non-African origin patients. But also hepatomegally is a common clinical finding with various other causes. Infectious, infiltrative, and granulomatous disease, malignancy, and other hematologic diseases may cause hepatomegaly (3) . Blood-transfusion-related viral infections such as hepatitis B and C may also cause hepatomegaly in SCD.

The prevalence of bright liver in this study was 12.5% .This finding is higher compared to previous studies (13) where the prevalence of bright liver ranged from 3% to 6%. Several features of liver histology in patients with SCD may contribute to the bright liver. These include hemosiderin pigment, periportal fibrosis, and distension of sinusoids with sickle cells (3).

In this study, cholelithiasis was observed in 16.7% patients and 2 among these had already undergone cholecystectomy due to complications of cholelithiasis.This finding does not differ much from previous 2 studies(12,14) where the prevalence of colelithiasis was found to be between 20% and 22% . However this prevalence is much lower compared to findings in other 2 previous studies (10,13) where the prevalence of cholelithiasis ranged from 30.4% to 55% . The chronic hemolysis of SCA predisposes patients to cholelithiasis,(Images 2.2-2.4) the prevalence of which by ultrasonographic examination has been reported to be 11–55% in patients with SCD(30,32) . Prevalence varies with age, gender, and method of examination (1).

The prevalence of biliary sludge (Image 2.1) was 3%. This observation is in accordance with other studies (4). It is well known that majority of SCD patients with biliary sludge eventually develops gall stones (4). At the time of examination, only 2 patients (1.4%) had undergone cholecystectomy for gallstones. This differs from previous studies(10,13) where cholecystectomy was recorded in as high as 18.6%.The reason for such difference could be due to the different in the Social economic status between developing and developed countries and this has a big implication on availability and utilization of health services particulary advanced surgical procedures such as cholesystectomy.

The prevalence of splenomegaly was found to be 22.4%. This findings concurs with the findings in a study by Ali Balci et al (13), where splenomegally was found in 17.4% of patients. However, this prevalence is much lower than found in other two studies (12,14) where the prevalence had been found to be between 48.6% and 64%. A common cause of splenomegaly in SCD is acute splenic sequestration (3). However, none of the study patients had any clinical evidence of splenic sequestration at the time of examination. Other diseases that cause splenomegaly include infectious or granulomatous disease malignancy, congestive conditions, and other hematologic diseases(3).

Shrunken spleen was observed in 8.8% of patients. At the time of examination, 6.6% of patients were noted to have autosplenectomy. Hypoechoic focal parenchymal splenic lesions were observed in 4.1% of patients, and these represented splenic infarction.This finding is lower compaired to findings in a previous study (14) in which the prevalence of

splenic infarction has been reported to be 22%. At the time of examination, 4 (2.7%) patients had undergone splenectomy because of splenomegaly.

In this study, the prevalence of increased renal echogenicity was 9.9%.This frequency is lower compared to the findings in previous studies (13,14) where the prevalence of increased renal echogenicity was found to be 16%.

The prevalence of renal enlargement in this study was found to be be 3.9%.This prevalence is quite lower compared to findings in previous studies (13) in which the prevalence of renal enlargement was found to be 30.4%. The aetiology of renal enlargement in SCA is unknown. However, glomerular hypertrophy and increased renal blood volume have been suggested as likely contributors (22,23).

Simple renal cysts (Images 4.1, 4.3) were observed in 5 (3.3%) patients with SCA.

CHAPTER 8

CONCLUSIONS

In conclusion, abdominal US imaging of patients with SCA revealed a significant prevalence of abdominal abnormalities, in the liver, kidney, and spleen.

RECOMMENDATIONS

There is a need to conduct further similar studies in order to establish the average prevalent rates for each of the abdominal pathologies in sickle cell anaemia patients

There is a need for correlation studies, to establish whether or not there is any association between US findings and biochemistry changes in those patients

Physicians should be trained well in Ultrasound, so that they are able to perform proper scanning of sickle cell patients for early diagnosis of sickle cell related complications.

From the district hospital level (level II hospital services in Tanzania) ultrasound services should be available for early diagnosis of SCA complications, thus providing management plan well ahead.

IMAGES

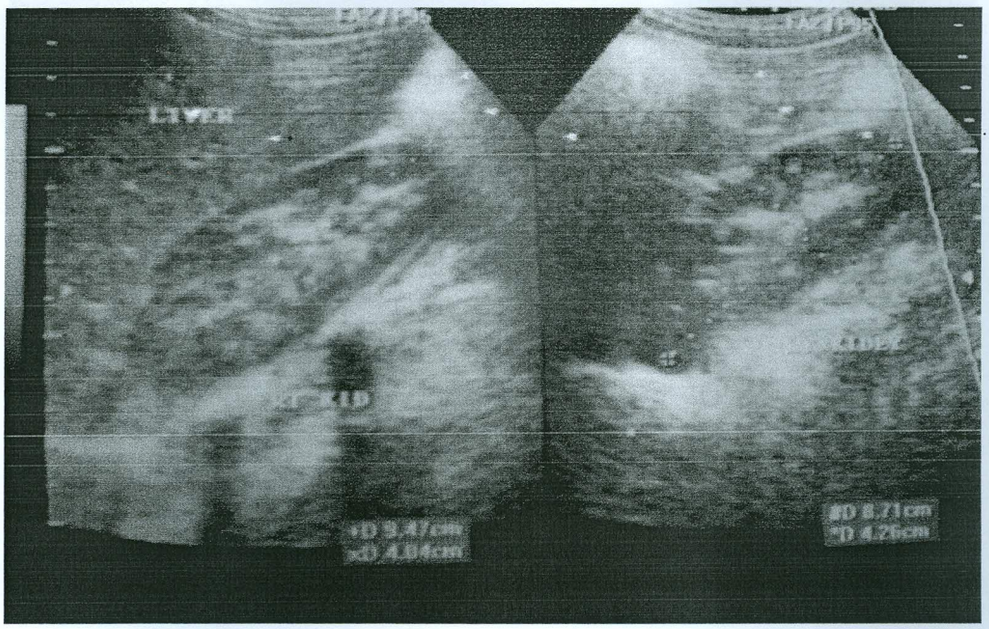


Image 1.1: US image from a 14 year old boy with sickle cell disease showing normal liver, kidneys and spleen.

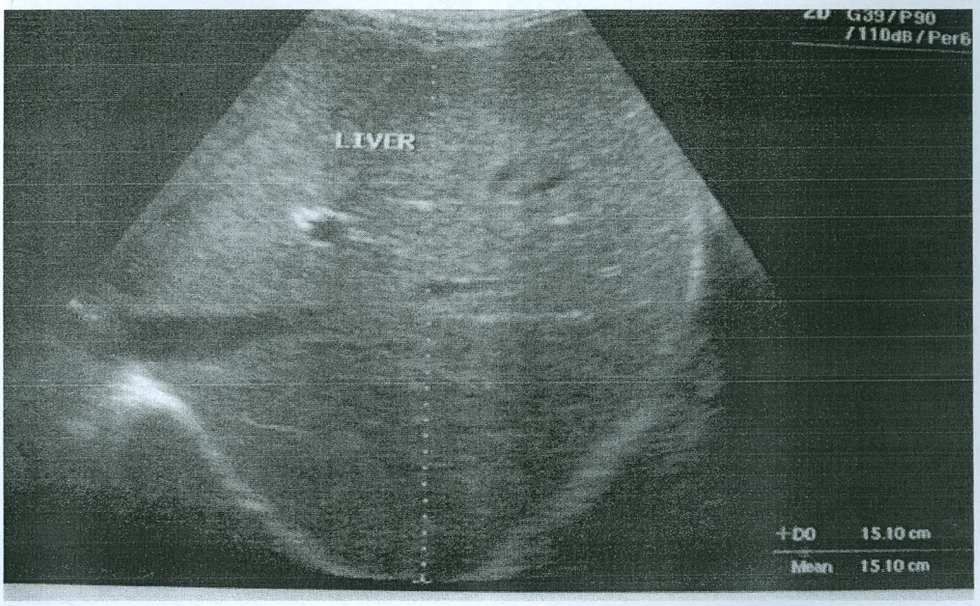


Image1.2: US image from a 9 year old boy with SCD showing enlarged liver

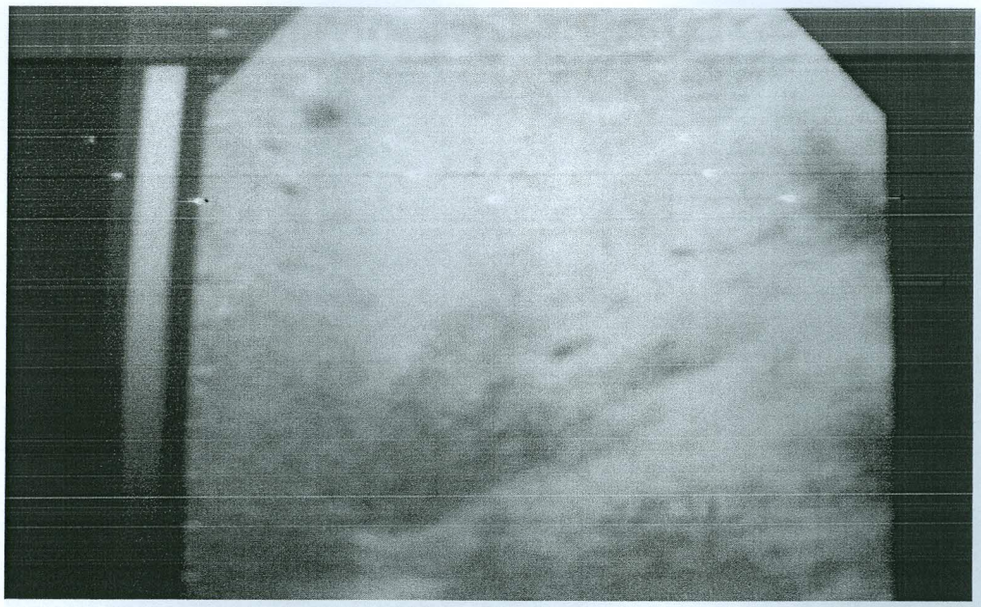


Image 1.3: US image from a 30 year old sickle cell patient showing a bright liver.

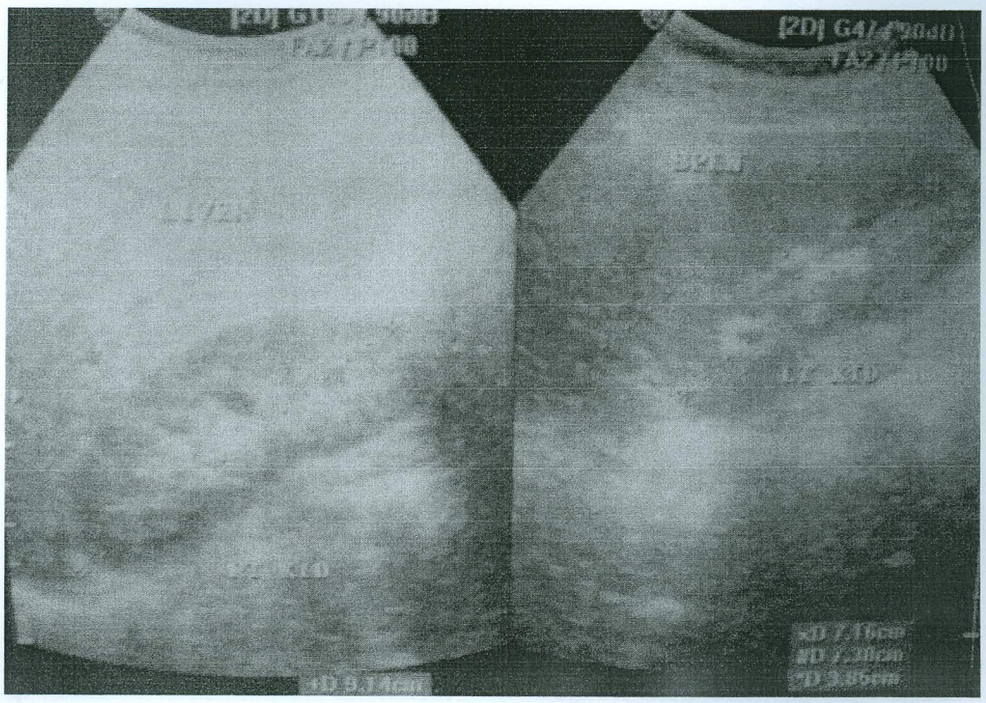


Image1.4: US image of a sickle cell patient with a bright liver.

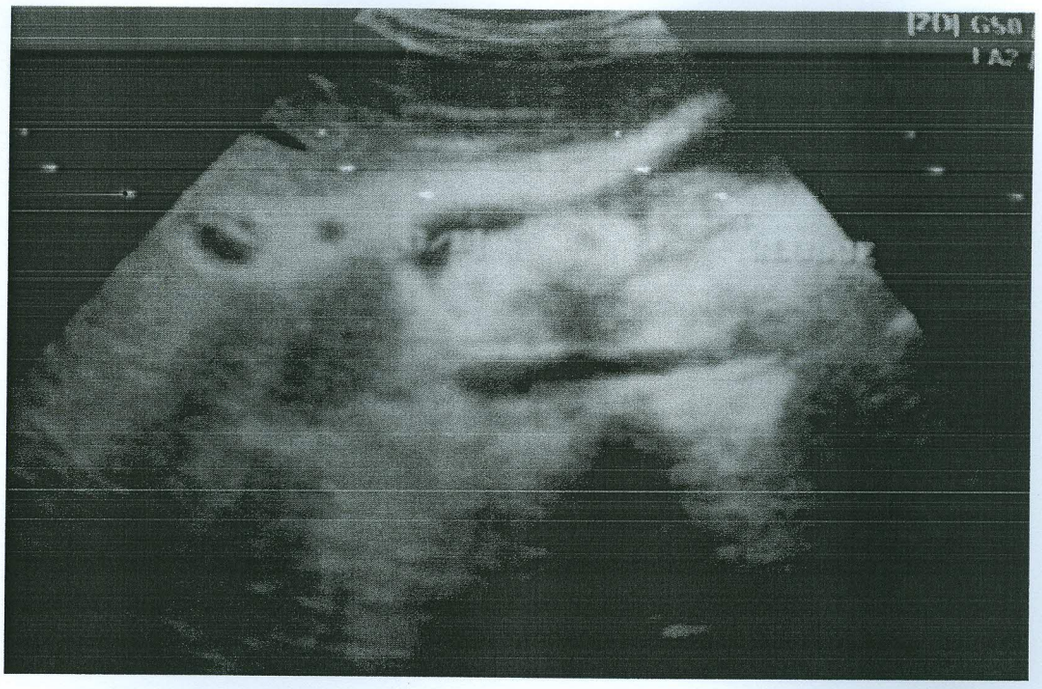


Image 2.1: US image from a sickle cell patient with biliary sludge.

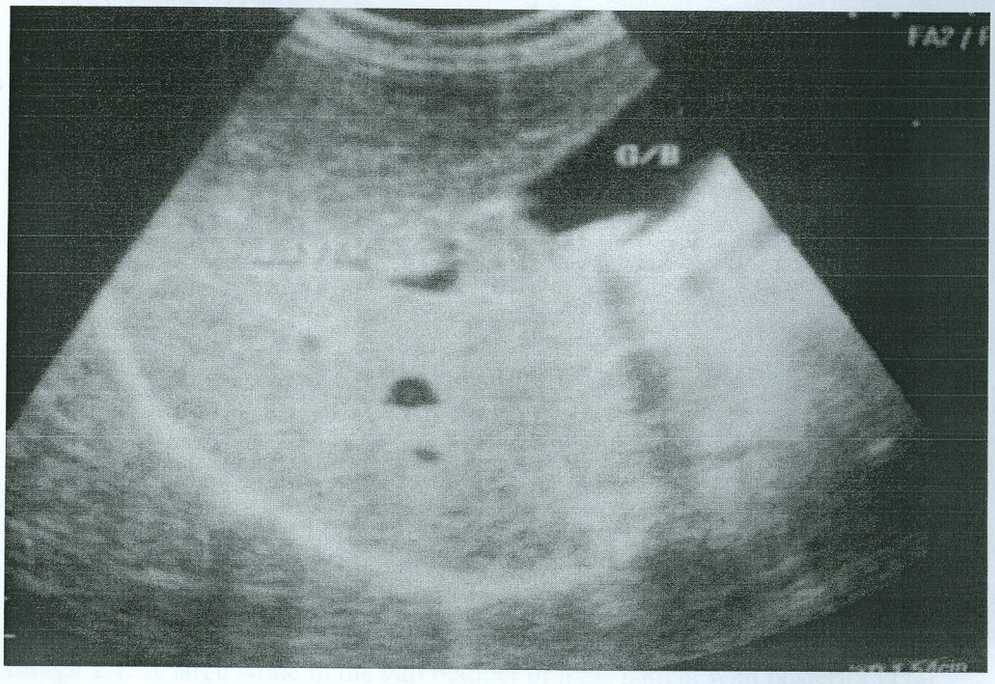


Image2.2: US image from a 12 year old girl with SCA showing a gallstone with posterior echo attenuation.



Image 2.3: US image from a 15 year old girl with SCD showing multiple gallstones

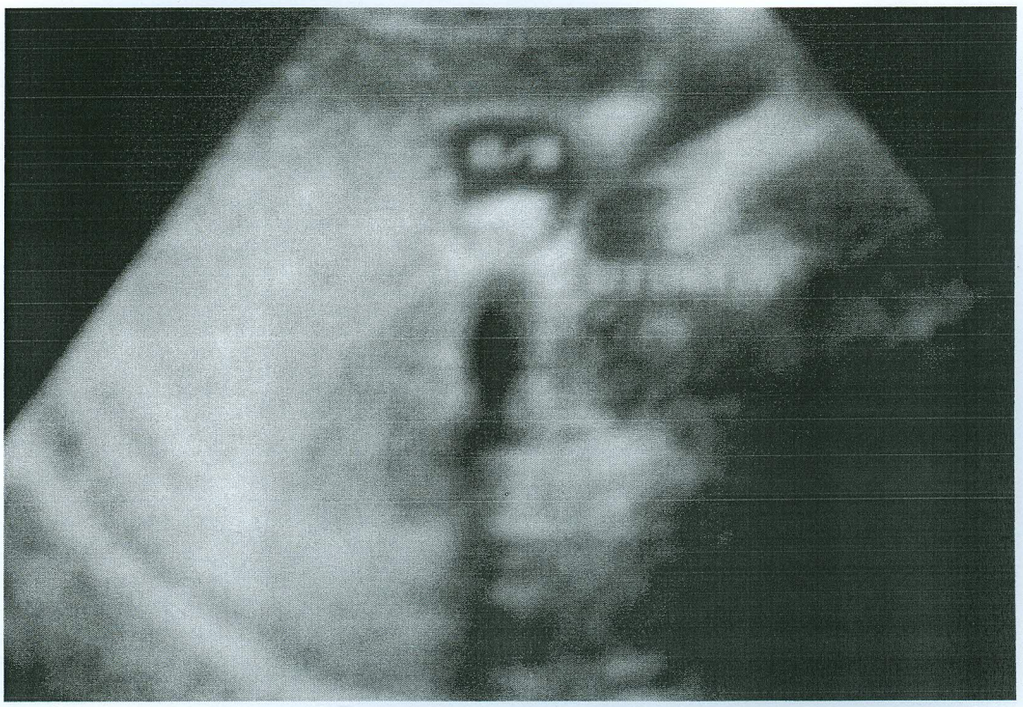


Image 2.4: A large stone in the gall bladder of a SC patient with posterior echo attenuation.

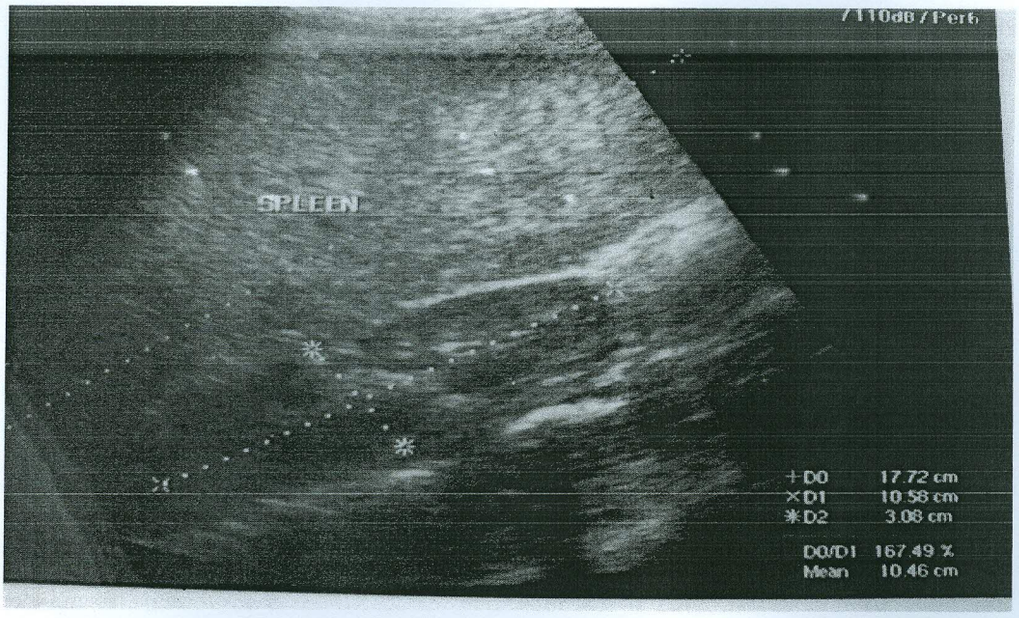


Image 3.1: US image from a sikcle cell patient showing enlarged spleen.

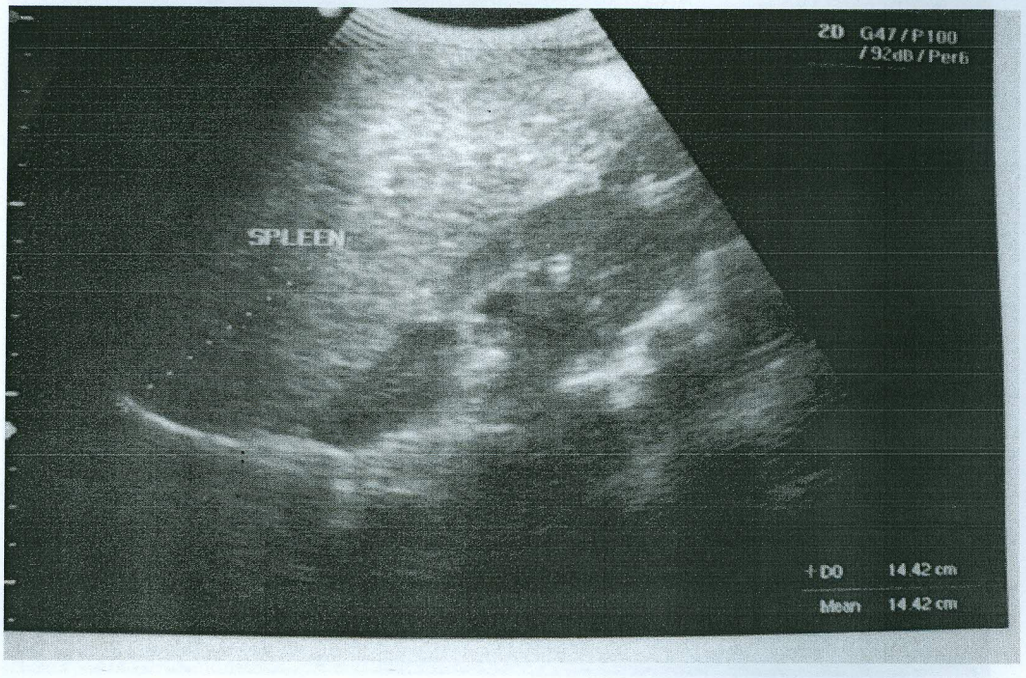


Image 3.2: US image from a sickle cell patient showing the enlarged spleen.

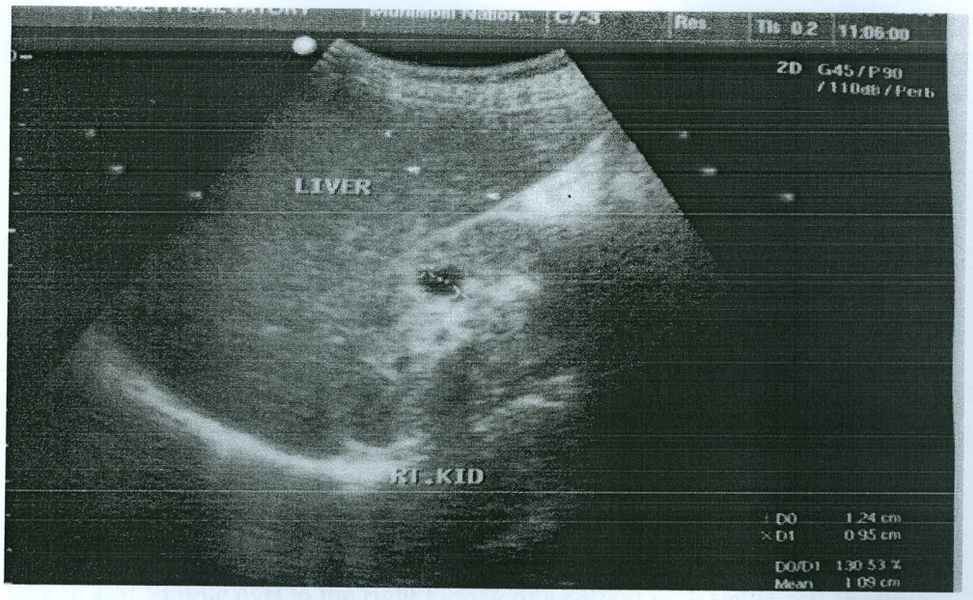


Image 4.1: US image showing a simple cyst in the right kidney of a patient with SCA.

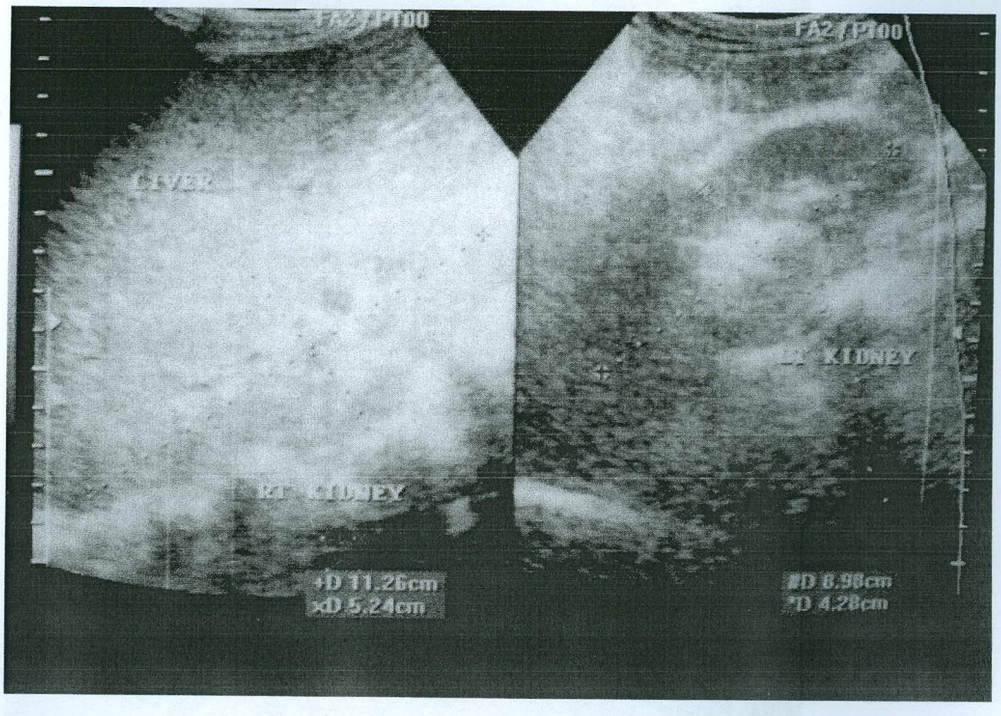


Image 4.2: US images from a 28 year old sickle cell patient showing diffuse increase in echogenicity of the right kidney.

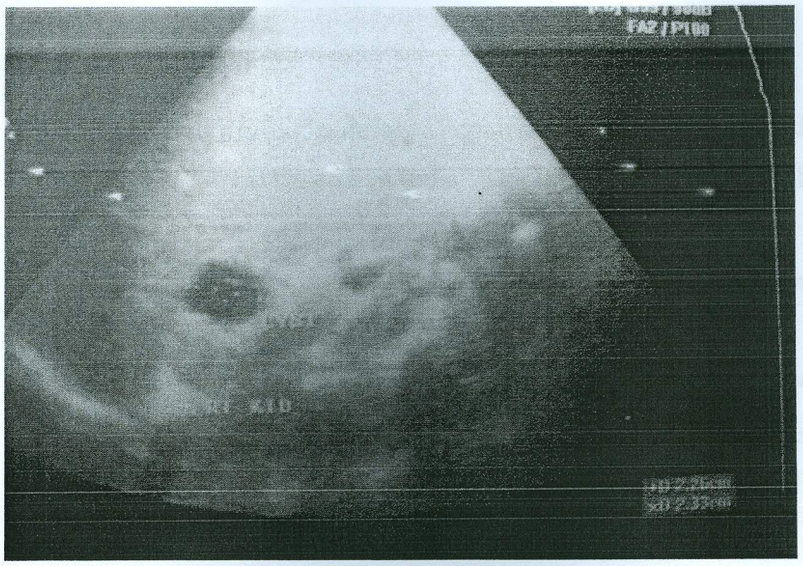


Image 4.3: Simple cyst in the right kidney of a patient with sickle cell anaemia.



Image 5: Philips HDI 4000 Ultrasound machine

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APPENDICES

APPENDIX I

QUESTIONNAIRE

1. Date of interview……/……/……..

2. Serial Number…… [ ]

3. SCD Number..... [XX]

4. Age……. [ ]

5. Height.....cm

6. SEX (a) male
   (b) female [ ]

7. SCD Genotype ..... a)HbSA b)HbSS C) unknown [ ]

8. US findings in the liver:
   Size……
   a. Hepatomegally i)Absent
      ii)Present [ ]

   b. Bright liver i) present ii) absent [ ]

9. US findings in the biliary tract
   a. Colelithiasis i) present ii) Absent [ ]
      ii) colecystectomy
   b. Biliary sludge i) present ii) absent iii)NA [ ]