Correlation between Transabdominal Sonographic and Clinical Findings in Children with Sickle Cell Disease

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Abstract. *Background:* Sickle cell disease (SCD) is a major cause of morbidity and mortality in Sub-Saharan Africa where intraabdominal manifestations of the disease are common. *Objective:* To correlate transabdominal sonographic and clinical findings in children with sickle cell disease. *Materials and Methods:* A cross-sectional study of 400 SCD patients aged 1-15 years, conducted in the Radiology department of Jos University Teaching Hospital. Patients were scanned using Aloka 3500 Ultrasound machine with frequency transducer range 2-10MHz. The patient lies supine and a hypoallergic gel is applied over the abdomen and the intra-abdominal organs are then scanned and their measurement/morphology are then documented. *Results:* Normal sonographic findings were seen in 192 (48.0%) patients while 208 (52.0%) had various abnormal findings. Two hundred and ninety-seven (74.2%) patients had various clinical abdominal presentations while 103 (25.8%) had none. The commonest abnormal transabdominal ultrasonographic (TAUS) finding was hepatomegaly seen in 120 (25.2%) patients, autosplenectomy seen in 77 (16.2%) and hyposplenism seen in 5 (1.1%). Higher abnormal TAUS findings were noted in the older age groups 11-15 years with 69 (85.2%). Patients who had a history of blood transfusion had significant abnormal TAUS findings (p-0.001). *Conclusion:* Abdominal ultrasonographic imaging of patients with sickle cell disease revealed various abdominal abnormalities.

Keywords: Sickle Cell Disease, Ultrasonographic, Transabdominal

Introduction

Sickle cell disease (SCD) is an autosomal recessive genetic blood disorder that is characterized by red blood cells assuming an abnormal, rigid, and sickle shape. Sickling occurs due to a mutation in the hemoglobin gene which decreases the cells' flexibility and results in a risk of various complications commonly from vascular occlusion and ischemia in multiple organs (Azubuike & Nkanginieme, 2007; Dahnert, 1994).

Altered shape plus plasticity of red blood cells (RBCs) occurs under lowered oxygen tension which leads to increased blood viscosity, stasis, log jam occlusion of small blood vessels, infarction, necrosis, and super-infection.

Sickling occurs in areas of slow blood flow (spleen, liver, renal medulla) and rapid metabolism. Repeated vaso-occlusion accounts for most of the clinical manifestations of the disease (Azubuike & Nkanginieme, 2007; Dahnert, 1994).

The global prevalence of sickle cell disease (SCD) and other data estimated that around 20-25 million individuals worldwide have homozygous SCD: 12-15 million in sub-Saharan Africa.

Sickle-cell disease (SCD) is particularly common among people whose ancestors come from Sub-Saharan Africa, India, Saudi Arabia, and Mediterranean countries.

Abnormal hemoglobin includes HbS (i.e DNA mutation substituting glutamic acid in position 6 on β-chain with valine) and HbC (DNA mutation substituting glutamic acid in position 6 on β-chain with lysine) (Dahnert, 1994). Homozygous state (HbSS) results in

sickle cell anemia while the heterozygous state (HbAS) gives the sickling trait but no anemia. Heterozygous variants include HbSC (less severe form) and HbS β-thalassemia (seen occasionally). Other abnormal hemoglobin includes Hbs (Azubuike & Nkanginieme, 2007; Dahnert, 1994).

In Nigeria, more than 150,000 children are born with the disease annually and 4 million people are afflicted generally. It is the most common genetic disease and affects approximately 2% of the Nigerian population (Bakhieta, 2010).

In West Africa, the incidence of the trait of the disease is about 25% and the homozygous state accounts for about 3%.

In the United States, 8-13% of American Blacks carry sickling factor (HbS); 1:40 with sickle cell trait will manifest sickle cell anemia (HbSS); 1:120 with sickle cell trait will manifest HbSC disease (Dahnert, 1994).

Studies have shown that the most common documented abdominal manifestations of the disease include abdominal pain (mesenteric crisis), hepatomegaly, splenomegaly, autosplenectomy, cholelithiasis, renal enlargement, and increased renal echogenicity (Azubuike & Nkanginieme, 2007; Dahnert, 1994; Babadoko *et al.*, 2012).

There is a paucity of information on the correlation between transabdominal ultrasonographic and clinical findings in children with sickle cell disease which could be used for predicting clinical outcome and management options in this environment, hence the need to embark on this study.

Justification for the Study

Ultrasonography is the most commonly used imaging technique for the evaluation of abdominal abnormalities in sickle cell disease patients in Nigeria. It is cheap, reproducible, and readily available and does not use ionizing radiation. Its high specificity makes it very helpful for ruling out abdominal abnormalities, even where abdominal Computerized Tomography (CT) is available.

The role of transabdominal ultrasonography as an integral and vital method for identifying abdominal abnormalities affecting children with SCD, especially in resource-limited settings such as ours is unquantifiable and has not diminished in modern practice.

Material and Methods

Study Size and Population

The study population comprised 400 children aged 1 to 15 years who are on follow up visits at the pediatrics Sickle cell clinic of the Jos University Teaching Hospital.

Sampling Technique

Eligible participants were recruited consecutively until the sample size of 400 was reached.

Data Collection

The procedure was explained to all subjects and their parents/guardians and written consent was obtained from each of them before carrying out the procedure.

A structured questionnaire was used to obtain relevant data such as age at diagnosis and duration of the disease, history of abdominal pains, anemia, and other symptoms.

Inclusion Criteria

1. Children with Sickle cell disease aged 1 to 15 years.

Exclusion Criteria

1. Patients below 1 or above 15 years
2. Patients/Parents/Guardian's refusal
3. Patients with other forms of Haemoglobinopathies
4. Patients who were positive for hepatitis B & C

Procedure

All the patients were scanned using Aloka 3500 Ultrasound diagnostic equipment with a variable frequency transducer at 2-5MHz or 5-10MHz. After the patient had fasted overnight, the examination was performed with the patient in the supine, right or left side position to obtain an optimal view of the abdominal viscera.

Measurement of the visceral organs and their morphology was then documented.

Data Analysis

The data obtained from the structured questionnaire was entered into a computer to generate a computerized database for subsequent analysis and processing using SPSS version 16.

Statistical parameters such as chi-square, student's test, and frequency tables were used for the association between different variables. A P-value of 0.05 or less was considered statistically significant. The results were presented in the form of tables as appropriate.

Results

A total of 400 sickle cell disease patients aged 1-15 comprising of 227 (56.8%) males and 173 (43.3%) females were recruited (Table 1). The mean age of the study population was 6.85years SD 3.98.

Normal sonographic findings were seen in 192(48.0%) of the patients. This was highest in age group 1-5years consisting of 145 (75.5%) patients, while abnormal findings were noted in the older age groups of 6-10 & 11-15 years comprising 92 (72.4%) and 69 (85.2%) patients respectively (Table 2).

The commonest abnormal sonographic finding in this study was hepatomegaly seen in 120 (25.2%) patients, followed distantly by autosplenectomy seen in 77 (19.3%) patients, while hyposplenism was the least finding seen in 5 (1.1%) (Table 3).

The commonest clinical abdominal presentations were abdominal pain and jaundice seen in 152 (40.7%) and 145 (38.9%) patients respectively, while blood in urine was the least clinical finding seen in 12 (3.2%) patients (Table 4).

Normal sonographic and clinical findings were seen in 192 (40.3%) and 103 (21.6%) patients respectively. Only about a tenth (46) of the patients (9.7%) had both normal sonograms and normal clinical findings.

A third of the 152 (31.9%) patients with abdominal pain had a normal sonogram, while 44 (9.2%) patients of the 120 (25.2%) patients with hepatomegaly had abdominal pain. This was statistically significant p-0.000 (Table 5).

One hundred and twenty-five (31.25%) patients who had blood transfusion had abnormal sonographic findings while 83 (20.75%) patients who had no history of blood transfusion also had abnormal findings. This was statistically significant (p-0.001, Table 6).

Table 1. Age and sex distribution of the patients

Age (yrs)	Sex		
	Male Freq. (%)	Female Freq. (%)	Total Freq(%)
1 – 5	102(53.1)	90(46.9)	192(100.0)

6 – 10	84(66.1)	43(33.9)	127(100.0)
11 – 15	41(50.6)	40(49.4)	81(100.0)
Total (%)	227(56.8)	173(43.2)	400(100.0)

Table 2. Relationship between the age of patients and transabdominal ultrasonographic findings

Age group	Findings		
	Normal Freq. (%)	Abnormal Freq. (%)	Total Freq. (%)
1-5 6-10 11-15	145(75.5) 35(27.6) 12(14.8)	47(24.5) 92(72.4) 69(85.2)	192(48.0) 127(31.8) 81(20.2)
Total (%)	192(48.0)	208(52.0)	400(100.0)

Note: χ^2-115.259 df – 2 P - 0.001

Table 3. Frequency distribution of ultrasound findings

Ultrasound findings	Frequency	Percentage (%)
Normal	192	40.3
Hepatomegaly	120	25.2
Autosplenectomy	77	16.2
Splenomegaly	37	7.8
Renal parenchymal disease	26	5.4
Cholelithiasis (Thickened GB walls+sludge)	19	4.0
Hyposplenism	5	1.1

Note: N > 400 because some patients had multiple findings

Table 4. Distribution of clinical findings in children with SCD

Clinical findings	Frequency	Percentage (%)
Pain	152	40.7
Jaundice	145	38.9
Distension/swelling	64	17.2
Blood in urine	12	3.2
Total	373	100

Table 5. Relationship between abdominal ultrasonographic findings with clinical symptoms among the patients

Ultrasound findings	Clinical findings					
	Normal Freq. (%)	Pain Freq. (%)	Jaundice Freq. (%)	Abdominal distension Freq. (%)	Blood in urine Freq. (%)	**Total (%)**
Normal	46(9.7)	55(11.5)	59(12.4)	30(6.3)	2(0.4)	**192(40.3)**
Hepatomegaly	22(4.6)	44(9.2)	42(8.8)	10(2.1)	2(0.4)	**120(25.2**
Autosplenectomy	12(2.5)	30(6.3)	28(5.9)	7(1.5)	0(0.0)	**77(16.2)**
Splenomegaly	13(2.7)	8(1.7)	5(1.0)	11(2.3)	0(0.0)	**37(7.8)**
Renal parenchymal disease	3(0.6)	11(2.3)	4(0.8)	3(0.6)	5(1.0)	**26(5.4)**
Cholelithiasis	7(1.5)	0(0.0)	6(1.3)	3(0.6)	3(0.6)	**19(4.0)**
Hyposplenism	0(0.0)	4(0.8)	1(0.2)	0(0.0)	0(0.0)	**5(1.1)**
Total (%)	**103(21.6)**	**152(31.9)**	**145(30.5)**	**64(13.4)**	**12(2.5)**	**476(100.0)**

Note: X^2 – 90.922 df – 24 p-0.000

Table 6. Relationship between the history of blood transfusion and transabdominal ultrasonographic findings

History of blood transfusion	Findings		
	Normal Freq. (%)	Abnormal Freq. (%)	Total (%)
Yes	67(16.75)	125(31.25)	192(48.0)
No	125(31.25)	83(20.75)	208(52.0)
Total (%)	192(48.0)	208(52.0)	400(100.0)

Note: χ^2 - 25.402 Df – 1 P - 0.001

Discussion

Sickle cell disease is an inherited autosomal recessive disorder characterized primarily by chronic anemia and periodic episodes of pain. In Nigeria, sickle cell disease is common and manifests in a variety of abdominal problems, including hepatomegaly, autosplenectomy, splenomegaly, abdominal pain and distension, biliary tract abnormalities, increased renal and pancreatic echogenicity (Babadoko *et al.*, 2012; Ali *et al.*, 2008). Transabdominal ultrasonography (TAUS) has advantages over other imaging modalities in assessing the abdominal manifestations of sickle cell disease because it is a simple, rapid, non-invasive, and non-ionizing tool for assessing the abdominal manifestations of SCD.

The mean age of the study population was 6.85 years SD 3.98. Normal sonographic findings were seen in almost half (48.0%) of the patients. This was highest in age group 1-5 years consisting of 145 (75.5%) patients, while abnormal findings were noted commonly in the older age groups of 6-10 & 11-15 years comprising 92 (72.4%) and 69 (85.2%) patients respectively. This pattern may be due to HbF levels. Co-polymerization is usually low in HbS and SS patients with elevated HbF levels which usually have a milder course and that is the case in the younger age group.

Hepatomegaly was the commonest abnormal TAUS finding in this study seen in 25.2% of subjects. This is at variance with those of Ma'aji *et al.* (2012) in Sokoto and Ali *et al.* (2008) in Turkey who found hepatomegaly in 70.5% and 98.6% of the patients respectively. Hepatitis is a common cause of hepatomegaly especially in SCD patients who had repeated blood transfusions. The lower percentage of hepatomegaly (25.2%) in this study may be because patients with hepatitis were excluded from the study.

However, hepatomegaly is a common clinical finding with various causes. Infectious, infiltrative, and granulomatous disease, malignancy, and other hematologic diseases may cause hepatomegaly.

Repetitive sickling of red cells in the splenic microcirculation leads to splenic infarction, which progresses over time to autosplenectomy. The necrotic tissue is replaced by fibrosis, with the deposition of calcium and hemosiderin. Finally, the spleen becomes small, shrunken, and calcified.

Autosplenectomy was observed to follow distantly in this study seen in 77 (16.2%). This varied slightly but laid in the middle when compared to similar studies by Ma'aji *et al.* (2012) in Sokoto, Bakhieta (2010) in Sudan, and Babadoko *et al.* (2012) in Zaria who documented 4.2%, 4.8%, and 55.4% of patients respectively. This may be due to the larger sample size in this study.

Splenomegaly was another common finding, seen in 37(7.8%) patients which is similar to that reported by Bakhieta (2010) (6.6%) working in Sudan. Higher values were seen in other studies by Ma'aji *et al.* (2012) in Sokoto and Ali *et al.* (2008) in Turkey of 21.1% and 17.9% and 16.7% in SS and S β thalassemia, respectively. In Ibadan, Lagundoye (1970) ascribes the high percentage of splenomegaly in their study to high malarial endemicity in the west African subregion.

Other diseases that cause splenomegaly include infectious or granulomatous disease, malignancy, congestive conditions, and other hematologic diseases. A common cause of splenomegaly in SCD is acute splenic sequestration.

In a report by Babadoko *et al.* (2012) working in Zaria observed that although in 31% of patients, the spleen was present; it was however shrunken. Shrunken spleen was seen in 5 (1.1%) of patients in this study.

The prevalence of cholelithiasis is usually secondary to chronic hemolysis seen in SCD. The study among the pediatric age group in Ilorin by Nzeh and Adedoyin (1989) showed a prevalence of 4.2% which was similar to the study done in Sokoto by Ma'aji *et al.* (2012) with a 4.2% prevalence of cholelithiasis and also consistent with the finding in the current study of 4.0% (Ma'aji *et al.*, 2012; Nzeh & Adedoyin, 1989).

SCD is associated with many structural and functional abnormalities of the kidney, which may progress to chronic renal failure and end-stage renal disease. Several studies have reported a medullary or diffuse increase in reflectivity on renal sonography in patients with SCD. The cause and significance of this entity are unknown; however, renal papillary necrosis, high concentrations of iron deposits within tubular epithelial cells, focal scarring and interstitial fibrosis in the vasa recta system, glomerular hypertrophy, and renal sclerosis have been suggested as factors that may cause increased renal echogenicity (Ma'aji *et al.*, 2012).

Medullary-increased renal echogenicity was seen in 5.4% of patients in this study which is higher than 1.4% reported by Ma'aji *et al.* (2012) researching in Sokoto. However, this finding is at variance with that recorded by Ali *et al.* (2008) working in Turkey which reported a prevalence of 10% in SS and 11% in S beta thalassemia groups (Ma'aji *et al.*, 2012). Mild to moderate enlargement of the kidneys together with caliectasis in some American studies by Plunket, Leiken, and LoPresti (1996) and papillary necrosis was noted, which is claimed to be more common in HbSC patients. Papillary necrosis has also been seen in the sickle cell trait (Nzeh & Adedoyin, 1989; Plunket, Leiken, & LoPresti, 1996).

The etiology of renal enlargement in SCD is unknown, however, glomerular hypertrophy and increased renal blood volume have been suggested as likely contributors.

Incidental findings of unilateral ectopic kidney and intra-abdominal mass were observed in 0.4% and 0.6% of patients respectively in this study. The incidence of ectopic kidney in the general population is 1 in 900.

Few reports have described pancreatic hemosiderosis in patients with SCA or thalassemia syndromes. No abnormal pancreatic findings were noted.

Normal sonographic and clinical findings were seen in 192 (40.3%) and 103 (21.6%) patients, respectively. Only about a tenth (46) of the patients (9.7%) had both normal sonograms and normal clinical findings.

About a third (55) of the 152 patients with abdominal pain had a normal sonogram, while 44 patients of the 120 patients with hepatomegaly had abdominal pain. This was statistically significant (p-0.000) and may be due to mesenteric blood vessel occlusion when sickling occurs in areas of slow flow (including the liver) plus superinfections.

More male patients than females were observed in the current study, however, a higher percentage of the female patients had abnormal TAUS findings (56.1%) compared to the percentage in the male patients (48.9%). The disease condition is not a sex-linked inherited disorder; hence, it may be a chance finding.

The educational levels of the patients together with that of their parents i.e fathers and mothers, showed a statistically significant relationship with abnormal sonographic findings (p-0.001, p-0.012 & p-0.005 respectively). One could infer that the more educated the parents are, the more enlightened they would be in taking care of their children with SCD.

However, the relationship between the occupation of the father and abnormal sonographic findings was not statistically significant (p-0.057).

This study also showed that a slightly higher percentage i.e. 12.0% of abnormal TAUS findings are noted in the patients who had none or only one other sibling with the disease compared to the lower percentage seen in those who had more than one other siblings with the disease i.e 9.0%. This further goes to buttress the fact that the more enlightened (by experience), the more care is taken to manage these patients with the condition within the family setting.

A high percentage of patients with severe wasting (using the expected weight for age classification by WHO) were noted to have abnormal TAUS findings (80%). This is consistent with the fact that it is a chronic condition characterized by chronic anemia, repeated vaso-occlusion, and superinfections.

However, the data from this study shows that TAUS examination has a high diagnostic yield for abdominal abnormalities in SCD children. This underscores the need for TAUS to remain an integral part of pediatric SCD management.

Conclusion

Abdominal ultrasound imaging of patients with sickle cell disease showed several abnormal abdominal manifestations, especially in the liver, gallbladder, and spleen. Trans-abdominal ultrasonographic findings of these patients and clinical abdominal findings agree.

Recommendations

1. Transabdominal Ultrasonography (TAUS) has advantages over other imaging modalities in assessing the abdominal manifestations of sickle cell disease because it is a simple, readily available, non-invasive, inexpensive, reproducible, and non-ionizing tool for assessing the abdominal manifestations of SCD, hence it should be employed routinely in all health care establishments.
2. Prevention via pre-marital counseling and testing should be made mandatory to all intending couples to mitigate against increasing the prevalence of this condition.
3. National Health insurance scheme to cover treatment to reduce economic burden.
4. Genetic counseling/chorionic villi sampling should be encouraged.

Limitations of the Study

1. The procedure is grossly operator-dependent; hence findings could be subjective (Intra/inter-observer variability).
2. Some of the patients were uncooperative especially younger children, thereby making optimal image acquisition difficult.
3. Some of the findings detected on trans-abdominal ultrasonography could be because of undiagnosed diseases/co-morbidities.

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