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Comparative analysis of Sonographic evaluation of the Spleen between subjects with Hemoglobin SS and AA at the University College Hospital, Ibadan, Nigeria

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Abstract

Introduction: Sickle Cell Anaemia is the most common genetic disease globally and is due to replacement of glutamic acid with valine at position 6 of the Beta haemoglobin chain. This study aims to describe the sonographic findings in the spleen of patients with sickle cell anaemia and compare same with those of the controls.

Methodology: A prospective, case-control study conducted in University College Hospital Ibadan. One hundred and twenty-eight consenting patients with HbSS ages 2 to 60 years attending the adult and children Haematology clinics were recruited while 128 HbAA healthy controls were recruited from the general outpatient department. Patient's demographics, clinical history and ultrasound of the spleen was performed and documented into the study proforma.

Results: The mean splenic length in the cases and controls were statistically significant (5.41 ± 4.28cm vs 8.96 ± 1.51cm; p = 0.000). The mean splenic length of SCA patients in the paediatrics age group was 4.43cm and adults was 4.38cm. Normal splenic size (44.5%) was the most common in this study with autosplenectomy seen only in 34.4% of all the SCA patients studied. Abnormal splenic parenchymal findings were observed in 22 (17.2%) of the cases with only 4 (3.1%) seen in the control group and this was statistically significant (p= 0.000).

Conclusion: This study demonstrated the use of sonography as an invaluable imaging tool in the assessment of the splenic size as well as its parenchymal pattern and therefore recommends its use for sickle cell anaemia patients in crises and / or follow up.

Keywords: Sickle cell anaemia, splenic size, Ultrasonography

Abstrait

Introduction: L'anémie falciforme est la maladie génétique la plus répandue dans le monde et est due au remplacement de l'acide glutamique par la valine en position 6 de la chaîne de l'hémoglobine bêta. Cette étude vise à décrire les résultats échographiques de la rate des patients drépanocytaires et à les comparer avec ceux des témoins.

Méthodologie: Une étude prospective cas-témoins menée à l'hôpital universitaire d'Ibadan. Cent vingt-huit patients consentants atteints d'HbSS âgés de 2 à 60 ans fréquentant les cliniques d'hématologie pour adultes et enfants ont été recrutés tandis que 128 témoins sains HbAA ont été recrutés dans le service ambulatoire général. Les données démographiques, les antécédents cliniques et l'échographie de la rate du patient ont été réalisés et documentés dans le formulaire d'étude.

Résultats: La longueur moyenne de la rate chez les cas et les témoins était statistiquement significative (5.41 ± 4.28 cm vs 8.96 ± 1.51cm ; p = 0.000). La longueur moyenne de la rate des patients atteints d'ACS dans le groupe d'âge pédiatrique était de 4.43cm et celle des adultes de 4.38cm. La taille normale de la rate (44.5%) était la plus courante dans cette étude, l'autosplénectomie étant observée seulement chez 34.4% de tous les patients atteints d'ACS étudiés. Des anomalies parenchymateuses spléniques ont été observées dans 22(17.2%) des cas, dont seulement 4(3.1%) dans le groupe témoin, ce

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qui était statistiquement significatif (p = 0.000).
Conclusion: Cette étude a démontré l'utilisation de l'échographie comme outil d'imagerie précieux dans l'évaluation de la taille de la rate ainsi que de son aspect parenchymateux et recommande donc son utilisation chez les patients drépanocytaires en crise et/ou en suivi.

Mots clés: Drépanocytose, taille de la rate, échographie

Introduction

Sickle cell disease (SCD) is a group of inherited red blood cell disorders with sickle cell anaemia (SCA), the homozygous being the most common type.[1] Pauling with his colleagues in 1949 discovered that sickle cell anaemia occurs as a result of a disorder in the haemoglobin molecule which is a point mutation in both Beta chains (â) of hemoglobin- the replacement of glutamic acid with valine at position 6 of the Beta chain (â) which results into sickling of the red blood cell.[2–6] This change in the Beta haemoglobin chain results in deformity of the red blood cells (sickling) especially when the oxygen saturation in the body is lowered with resultant occlusion of the micro-vessels.[2]

Sickle cell anemia (HbSS) is wide spread and the most common genetic disease worldwide.[3,7] The global prevalence is estimated at around 20-25 million individuals worldwide of which 12-15 million are in sub-Saharan Africa.[7] In the West African country of Nigeria, more than 150,000 children are born with the disease annually and over 4 million people are afflicted.[7–9] It accounts for about 5% of all under-five deaths in the African continent with more than 9% in West Africa and 16% in Nigeria.[6,10]

The spleen is the most common and earliest organ affected in sickle cell anaemia patients.[11] Other organs affected by SCA include the liver, kidneys and gall bladder.[10,12]

The spleen can increase in size (splenomegaly) which is usually seen in children, decrease in size (shrunken spleen) or even be absent (autosplenectomy) which usually occurs in adult sickle cell disease due to splenic infarction from repeated vaso-occlusion with resultant atrophy- the spleen in this instance may not be demonstrable on ultrasound or may be seen as a non-functional small irregular nodule in the splenic bed. [2,7]

Radiologically the spleen can be evaluated with several imaging modalities and the advent of ultrasonography has revolutionized imaging of organs in the body and becoming a workhorsein clinical imaging of especially intrabdominal organs. It is a cross sectional imaging modality that does not utilize ionizing radiation like conventional radiography and can be repeated frequently.

The normal sonographic length of the spleen in adult is between 6 - 12.9cm, enlarged when the ultrasound measurement is greater than or equals to 13cm, reduced in size (shrunken spleen) when visualized but less than 6cm and when not visualized it's termed anatomical splenectomy (autosplenectomy). [11,13] However, in children a nomogram chart is usually used which shows the normal range of splenic size in relation to their height.[14]

Apart from assessing the splenic size, ultrasonography can be used to assess the parenchymal echogenicity of the spleen in HbSS patients. Studies have shown different splenic parenchymal echogenicities that can occur in them which ranges from coarse hyperechoic, fine hyperechoic, fibrotic, infarction/abscess, calcification and it can even be normal parenchyma.[3,10] Early monitoring as well as detection of these abnormalities can be made by ultrasound examination of the spleen.

This study therefore aims at determining splenic changes in terms of the size and parenchymal echogenicity between ages 2 to 60 years of HbSS patients and compare same with those of the healthy controls, as well as determining the prevalence of autosplenectomy in HbSS patients using abdominal ultrasonography at the University College Hospital, Ibadan.

Materials and Method

This is a prospective study carried out at the ultrasound suite of the Department of Radiology, University College Hospital, Ibadan (UCH) among a total of 128 consenting consecutive HbSS patients aged 2-60years recruited from adult and children hematology outpatient clinics of the hospital and were matched with 128 healthy controls (HbAA) recruited from consenting members of staff of the hospital and their children.

Haemoglobin SS with age ranging between 2 years to 60 years attending Haematology outpatient clinic of University College Hospital within the study period with a steady state PCV and no crises such as vaso-occlusive, visceral sequestration, hyper-haemolytic and aplastic crises in the 4weeks prior to the study were included, while those with known infections like HIV and Hepatitis as well as pregnant

sickle cell anaemia women and individuals with history of surgical splenectomy were excluded.

Ethical approval was obtained from the Joint University of Ibadan/University College Hospital Ethics Committee. Convenience sampling technique of eligible consenting individuals was used to recruit the cases and controls. Informed consent was obtained from the adults and the care givers of the children as well as assent from children 8 years and above. The study abided by the tenents of the declaration of Helsinki for studies on human subjects.

Information about subject's age, any previous history of surgical splenectomy, steady state Packed Cell Volume (PCV), last period of any crisis related to sickle cell anaemia in the past one year and the frequency of blood transfusions in the past one year were sought directly from the adult patients and from the parents / care givers of the children. The steady state PCV and infections like HIV and Hepatitis were cross-checked from patient's hospital records.

Grey scale transabdominal ultrasound of the spleen was carried out for both the cases and control using 3– 5 MHz, curvilinear array transducer of Mindray Diagnostic Ultrasound System, model DC-30, 2019® (China).

The participants were examined in the supine position and adequately exposed from the xiphisternum superiorly to the pubic symphysis inferiorly.[15] The ultrasound coupling gel was applied on to the left hypochondrial region of the patient to remove trapped air and facilitate better transmission of the ultrasound beam. The transducer was placed directly on the skin with the left 9th and 11th intercostal spaces serving as acoustic window for imaging the spleen.[16] Images were obtained in both transverse and longitudinal planes.

The splenic Length (LS) which is the maximum distance from the dome of the spleen to the splenic tip was measured in the region of the ninth to eleventh intercostal spaces at the anterior axillary, mid-axillary and posterior axillary lines with the subjects in the right lateral decubitus position and supine position whenever there was need for it. [17,18] These measurements were added together and averaged as the splenic length to minimize intra-observer error. The splenic width was obtained by measuring from the most supero-medial aspect of the spleen to the most supero-lateral margin of the spleen perpendicular to the splenic length.

The transverse dimension (TS) was obtained by rotating the transducer through 90 degrees from the plane of maximal splenic length to obtain the anteroposterior dimension of the spleen.[19]

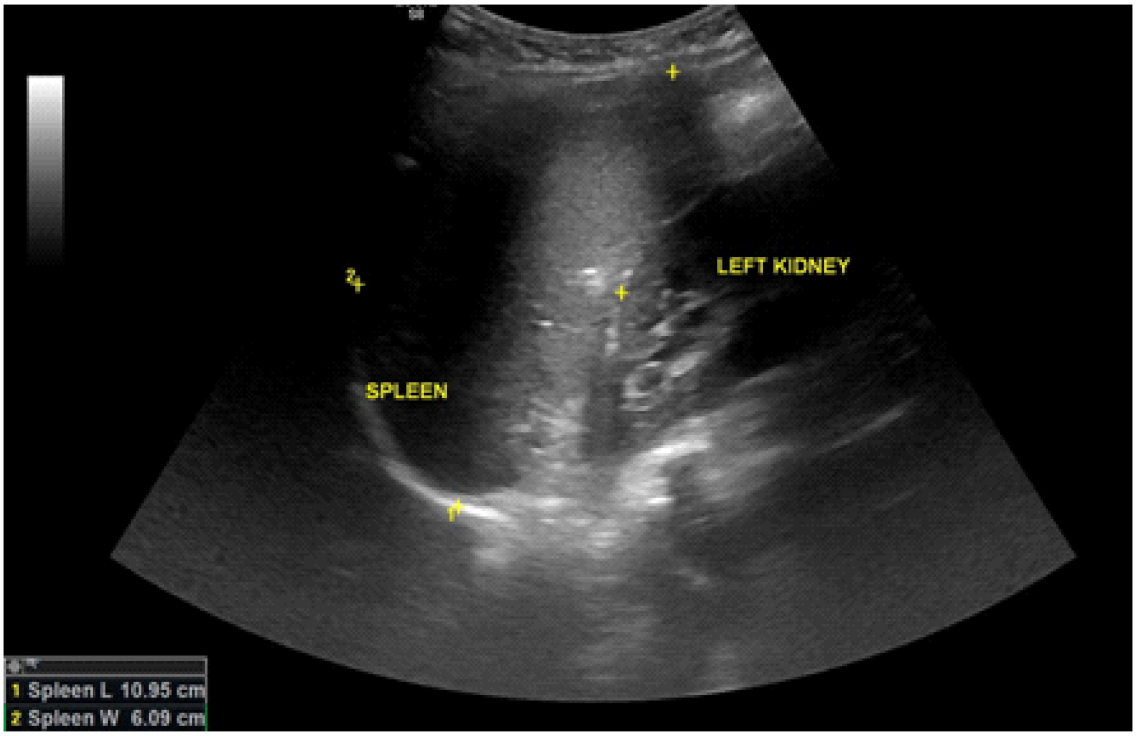

Figure 1: B-mode abdominal ultrasound of the spleen showing the measurement of

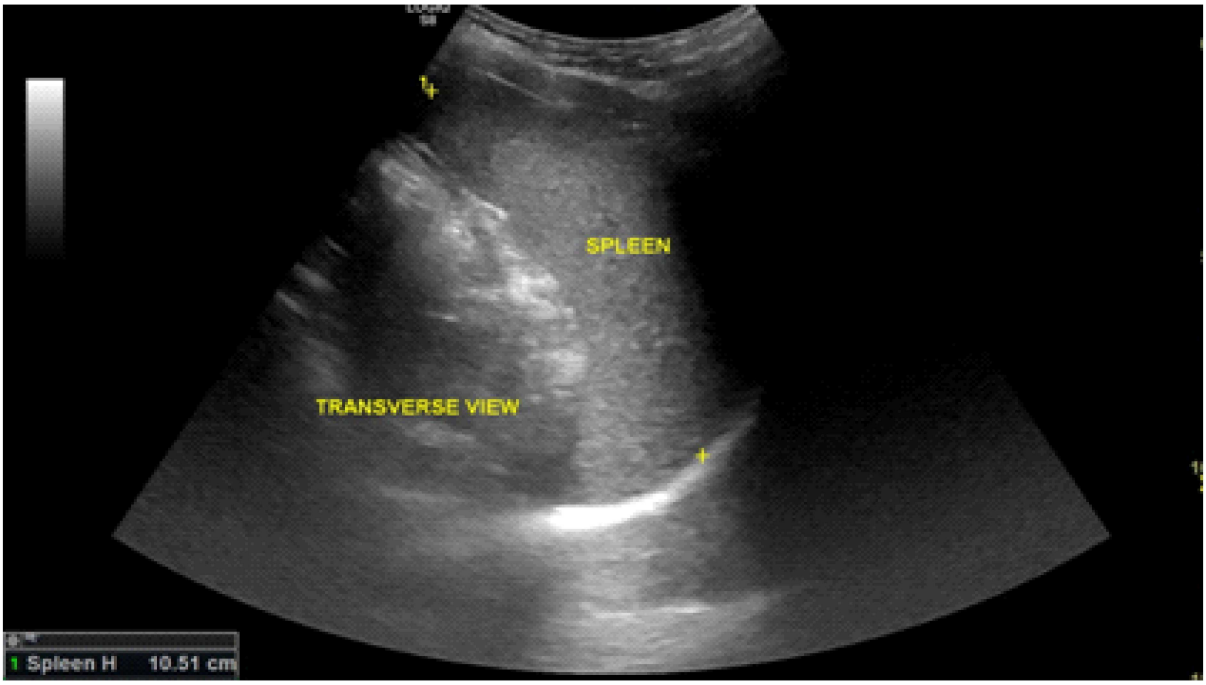

Figure 2: B-mode abdominal ultrasound of the spleen showing the measurement of the transverse diameter (calipers)

Table 1: Socio-demographic Characteristics of study participants

Variables	Cases Freq (%)	ControlsFreq (%)	Chi-square (X^2) test	p-value
Age Group (years)				
2-17	56 (43.8%)	19 (14.8%)		
Above 17	72 (56.2%)	109 (85.2%)	**25.817**	**0.000***
Mean (±SD)	21.2±12.1 years	32.1±13.6 years		
Sex				
Male	50 (39.1%)	46 (35.9%)	**0.267**	**0.606**
Female	78 (60.9%)	82 (64.1%)		
Marital status				
Single	100 (78.1%)	61 (47.7%)		
Married	27 (21.1%)	67 (52.3%)		
Divorced/Separated	1 (0.8%)	0 (0.0%)		
Educational status				
Tertiary and above	41 (32.0%)	89 (69.5%)		
Secondary	62 (48.4%)	22 (17.2%)		
Primary	25 (19.5%)	16 (12.5%)		
Uneducated	0 (0.0%)	1 (0.8%)		

***p<0.05 (significant)**

Table 2: Mean splenic length, width and transverse diameter in both patients and controls.

Mean Variables	Patients (n=128)	Control (n=128)	t-test	p-value
Splenic length (cm)	5.4 ± 4.3	9.0 ± 1.51	-9.037	0.000*
Splenic-width (cm)	2.6 ± 2.1	4.8 ± 1.1	-10.771	0.000*
Splenic-transverse diameter (cm)	5.2 ± 4.0	8.9 ± 1.5	-10.017	0.000*

***p<0.05 (significant)**

The measurements were taken at the level of the splenic hilum so as to have a reference point for the spleen.[18]

The splenic parenchymal architecture as seen on ultrasound was evaluated and documented for the presence of infarcts and hyperechoic parenchymal architecture within the spleen.

Data collected was entered and analyzed using the Statistical package for social sciences (SPSS) software version 21 (SPSS inc. Chicago, IL, USA.) spread sheet. The categorical variables such as the demographic data was presented in standardized formats such as frequency tables,percentages, and graphs for qualitative variables. Mean and standard deviation were used to present quantitative variables such as splenic length, splenic width, splenic transverse dimension and splenic parenchymal echogenicity.The relationship between ultrasound splenic parenchymal echogenicity in both the cases and control was tested using chi-square, and Independent T- test was usedto test the relationship of the splenic dimensionsin both the cases and control. A p-value of less than or equals to0.05 was statistically significant. The confidence interval used was 95%.

Results

Two hundred and fifty-six subjects were recruited for the study (128 HbSS patients and 128 HbAA controls). The age range of the subjects with HbSS was between 9 and 33 years with a mean of 21.2 ± 12.1 years while the age range for the control group, HbAA was between 19 and 46 years with a mean of 32.1 ± 13.6 years. Both groups had a slight female preponderance, 78(60.9%) and 82(64.1%) in the HbSS and HbAA groups respectively (Table 1). Most of the subjects with HbSS (100,78.1%) were single while only 47% of the controls were single. The only divorced/separated subject was in the HbSS group (Table 1).

The mean splenic dimensions of the HbSS subjects were significantly lower when compared with

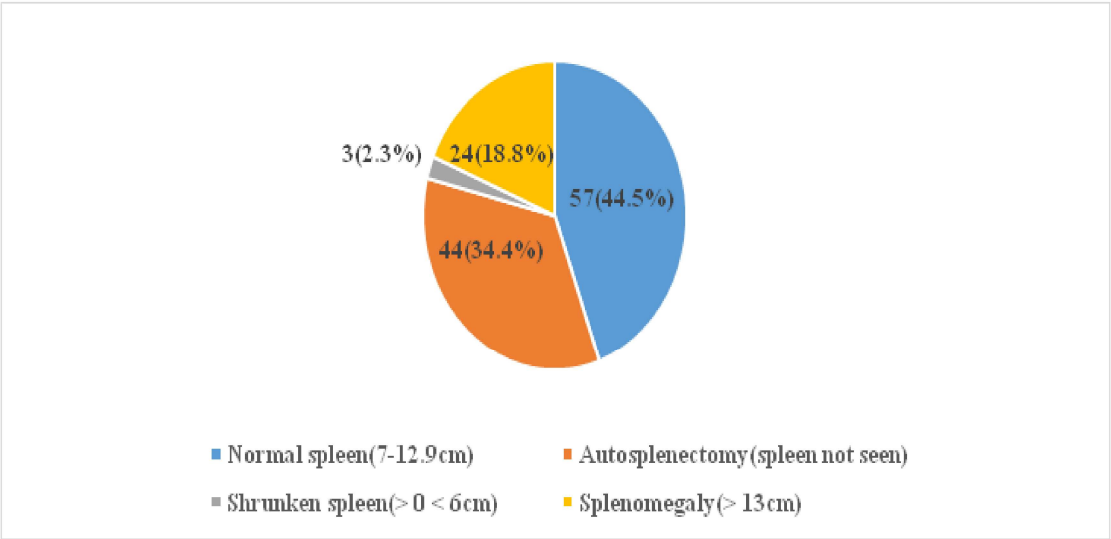

Figure 3: A pie chart showing the distribution pattern of the splenic size in HbSS patients studied.

Table 3: Distribution of sonographic autosplenectomy among HbSS of different age groups

Age range (years)	Total number for each age range	Frequency	Percentage n=44(%)	Cummulative Frequency (%)
2-10	26	1	2.3	2.3
11-20	43	14	31.8	34.4
21-30	32	16	36.4	70.5
31-40	17	6	13.6	84.1
41-50	6	4	9.1	93.2
51-60	4	3	6.8	100
Total	**128**	**44**	**100%**	**-**

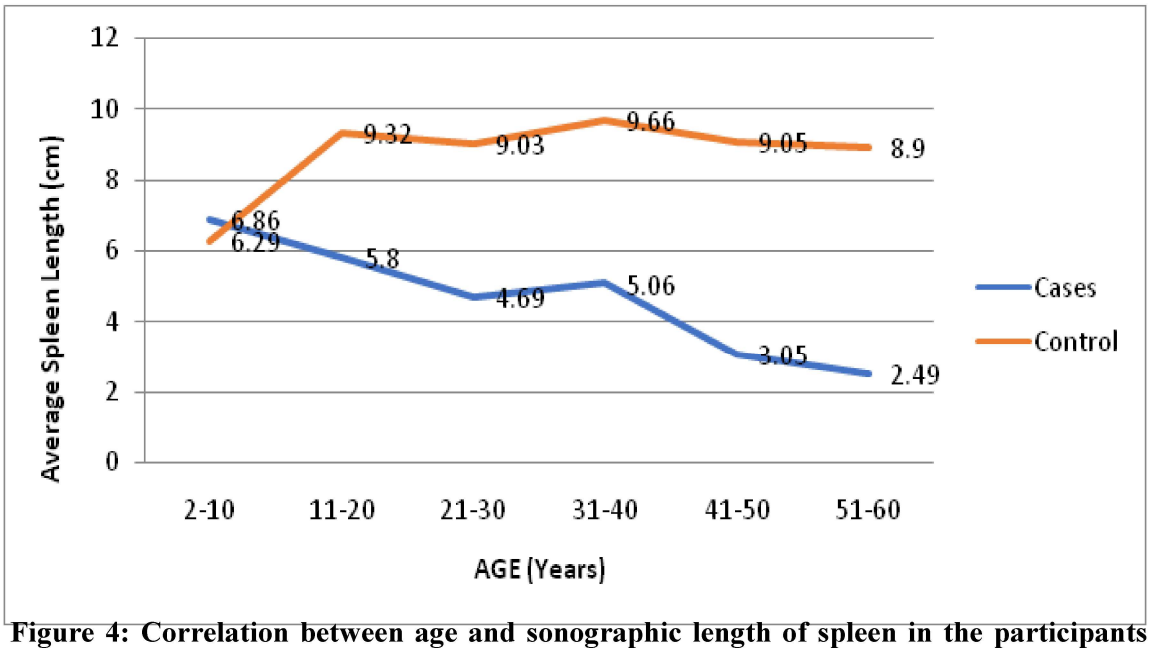

Figure 4: Correlation between age and sonographic length of spleen in the participants

Table 4: Sonographic parenchymal findings of spleen among participants

Parenchyma findings	Cases Freq	%	Control Freq	%	Chi-square test	p-value
Normal**	64	50.0	124	96.9	72.090	0.000*
Hyperechoic**	16	12.5	4	3.1	7.810	0.009*
Fibrotic scar	-	-	-	-	-	-
Infarction**	6	4.7	0	0.0	6.144	0.029*
Calcification	-	-	-	-	-	-

***p<0.05 (Significant)** ****p-value is obtained from Fisher's exact test**

the HbAA subjects (5.4 ± 4.3cm vs 9.0 ± 1.5cm; p=0.000), (2.6 ± 2.1cm vs 4.8 ± 1.1cm; p=0.000) and (5.2 ± 4.0cm vs 8.9 ± 1.5cm; p=0.000) for mean splenic length, width and transverse diameter respectively in the HbSS group (Table 2).

Splenomegaly was seen in 24(18.8 %) of the HbSS subjects with only 4(3.1%) seen among the HbAA subjects. There was no case of shrunken spleen or autoplenectomy among the HbAA group whereas 3(2.3%) and 44(34.4%) of the HbSS subjects had shrunken and autosplenectomy respectively. Normal splenic size was the most common size pattern seen in both groups however it was significantly lower among the HbSS group (57, 44.5%) when compared with the HbAA group (124, 96.9%)). (Figures 1).

The highest incidence of autosplenectomy among the HbSS subjects was found in the 3rd decade of life 16 (36.4%), followed by the 2nd decade of life 14 (31.8%). Subjects in the 1st decade of life had the lowest incidence 1(2.3%) in this study and it was only seen in a 10-year-old subject.

Normal splenic parenchymal echogenicity was seen in 50% of the HbSS. This was statistically significantly lower in the subjects than controls with 96% (p=0.000). Abnormal parenchymal findings (splenic infarct (4.7%), Hyperechogenicity(12.5%) were statistically significantly higher in the HbSS group (17.2%) when compared with HbAA (3.1%) (Table 4**)**

Splenic length decreased as the age increased among the HbSS group while it increased with age among the HbAA group (Figure 2).

Discussion

Ultrasound evaluation of the spleen in sickle cell anaemia patients is an invaluable method of assessing the size and parenchymal echogenicity which can be a pointer to the spleen functioning ability. It is a safe, easily assessable, and affordable method even in resource poor communities.

In this study, splenic sizes of subjects with HbSS were noticed to reduce with increasing age and the mean splenic sizes were significantly lower in them when compared with the HbAA subjects. This was similar to findings from studies by Ugwu*et al*[20] in Gombe, Babadoko*et al*[7] in Zaria and Fasola*et al*[21] in Ibadan where the mean splenic length observed in the sickle cell patients studied was lower than those of the control. This may likely be as a result of frequent vaso-occlusive crises occurring in sickle cell anaemia patients with resultant infarction of the spleen. However, this was contrary to the findings by Olatunji *et al* [16] and Eze *et al* [10] whosestudiesshowedgreatermeansplenic size (splenomegaly) in HbSS patients whencomparedwithHbAA. This persistent splenomegaly may be related to tropical Africa splenomegaly which is caused by malaria parasite (*Plasmodium falciparum*).

Ojo*et al* [11] in their own studies observed no statistical significant difference between the splenic length of the subjects with HbSS and the HbAA. This may likely be due to the small number of patients used in the study with only 40 HbSS and controls used as against 128 subjects.

Fifty percent of the subjects with HbSS studied were observed to have normal splenic size, this percentage is observed to be higher than in studies carried out in Ebonyi and Zaria in Nigeria [7,15] where they recorded 9.5% and 39% normal splenic sizes. This variation may be related to the difference in our sample population as index study used a higher number of cases and controls.

Autosplenectomy was observed in about a third (34.4%) of all the sickle cell patients in this study which is similar to findings by Inah*et al*[22] in Calabar and Ezeike*et al*[15] both in Nigeria as well as Balci*et al*[23] in Turkey where 32.5%, 30% and 33.3% of the sickle cell patients had autosplenectomy respectively. This may suggest the possibility of common sickle cell haplotype in these regions.

On the contrary, lower percentage of autosplenectomy were recorded in studies carried out by Fasola*et al*[21] in Ibadan, Nigeria (20%) and Ahmed *et al*[24] in Khartoum (27.2%). Similarly studies carried out in Saudi Arabia by Al-salem*et al* [25] and Kaushal *et al* [26] in India also observed lower percentages of autosplenectomy among the HbSS studied. This variation may be attributed to the smaller number of sickle cell patients studied.

The inclusion of the paediatric age group in this study enhanced the scientific determination of the age at which autosplenectomy occurs. This study observed that the earliest age of onset of autosplenectomy was in the first decade of life at 10 years. This agrees with a study carried out by Wilson-Okoh*et al*[27]where autosplenectomy was observed to occur in the first decade of life. This may suggest early vaso-occlusive crises with resultant splenic infarction which may be due to early reduction of fetal haemoglobin in them. The increasing occurrence of autosplenectomy which finally peaked in the third decade in this study may be attributed to malaria endemicity in tropical Africa which causes splenomegaly in children. However, a cohort study

where serial abdominal ultrasound will be done annually/biannually in sickle cell anaemia patients in sub-saharan Africa from birth to adulthood for more accurate scientific determination of the age at which autosplenectomy occur in them will be suitable.

Splenomegaly was seen in almost one fifth of the sickle cell patients studied in the index study. The proportion of cases with splenomegaly is similar to what was obtained by Ojo *et al*[11] with 15% of the patients with HbSS studied having splenomegaly. In the paediatrics age group, the index study observed that 37.5% had splenomegaly among the sickle cell patients. This percentage observed among the children in index study is slightly higher than what was obtained in a study carried out in the eastern part of Nigeria (33%) where a greater number of paediatric patients were studied.[10] A study done by Olatunji *et al*[16] where 98 sickle cell patients were studied however reported that splenomegaly was the most common splenic size observed in the HbSS patients, this may be due to the difference in the age of patients studied with lower number of adults studied. Another study by Brown *et al*[1] also observed a 31.7% splenomegaly among children with sickle cell patients though the spleen was assessed by palpation method and not sonographically. This was slightly higher than what was observed in this study, but a clinical and radiological comparison was not done.

The percentage of sonographic splenic infarct in this study was almost twice that observed by Eze *et al*[10]. However, it was lower than what was observed in a study carried out in Turkey by Balci*et al*[23] (6%) . This may be due to the combination of both HbSS and S/Beta (thal) used in their study with the likelihood of the latter also having splenic infarction.

As a result of frequent sickling in the spleen of sickle cell anaemia patients, the parenchymal architecture of the spleen can be affected and differs from the normal homogenous parenchyma seen in the controls (HbAA). This study however, observed that half of the splenic parenchymal architecture seen in the cases was of the normal homogenous parenchyma. This may be due to improved quality of care and knowledge about the disease condition which is readily available than in the past. The normal splenic parenchyma seen in this study among the sickle cell anaemia was more than 5 folds higher than that observed in Enugu by Eze *et al*[10] who found 8.7% however they studied a mixed haemoglobin pattern of HbSS and HbSC. There was a high possibility of patients with HbSC also having abnormal parenchymal architecture and thus lowering the proportion of normal splenic parenchymal observed.

Conclusion

Sonography was found to be an invaluable imaging tool in the assessment of the spleen as both splenic size and parenchymal architectural pattern are important in the well-being of patients with sickle cell anaemia. More than a third of the HbSS studied hadtheir spleen within the normal range limit. The abnormal parenchymal architecture-infarcts were easily demonstrable in the patients with sickle cell anaemia with none observed in the controls.

We recommend that regular abdominal ultrasound scan with emphasis on both the splenic dimensions and parenchymal architecture be included in the routine investigations for patients with sickle cell anaemia in crises and / follow up.

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