

## Predictors of splenic size in children with Sickle Cell Anaemia in Steady-state using ultrasonography in Maiduguri, Nigeria

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### ABSTRACT

**Background:** North-eastern Nigeria has the second-highest regional prevalence of sickle cell gene in the country after the South-west. This high prevalence has been believed to be sustained by the high rates of consanguineous marriages and intermarriages between the ethnic group in this region particularly the Kanuris and Shuwa Arabs. The dearth of data on splenic sizes among these patients living in this malaria-endemic sub-region. Narrative reports from the African region in general, have suggested that splenomegaly tends to persist to a comparatively much older age in these patients, attributed to the effect of recurrent malaria infection and/or hyperactive malarial splenomegaly syndrome. **Objectives:** This study was aimed to determine the sizes of the spleen in children with homozygous sickle cell disease using ultrasonography and the variations that occur in advancing age, and to compare it with foetal haemoglobin levels (HbF). **Methods:** Children with homozygous sickle cell disease aged 5-15 years, attending the Paediatric Haematology clinic of the University of Maiduguri Teaching Hospital (UMTH) were consecutively selected over six months. Demographic data, clinical details of previous crises and transfusions were recorded and had their foetal haemoglobin (HbF) quantified for all the subjects with the use of the Betke method of Alkali denaturation. Splenic sizes were determined using an ultrasound scanner (Aloka SSD 3500, Japan) with a 3.5 MHz sector transducer and ultrasound gel was used to optimize the image. A slightly lateral decubitus position during deep inspiration was used to expose the area of interest appropriately. Longitudinal size measurement was taken in the oblique plane between the most superior medial and the most inferior lateral borders of the spleen and the coronal size were determined along with the eleventh intercostal space. Values obtained was correlated with the height, a standard in assessing the longitudinal dimension of the spleen. **Results:** A hundred and twenty children with SCA in steady-state were evaluated, comprising 59 boys and 61 girls. Their ages ranged from 5-15 years, with a mean of  $10.1 \pm 3.5$  years. Autosplenectomy was seen in 12 (10%) of our patients who were seven years and above while seven (5.83%) had splenomegaly. The mean HbF of the total population studied was low  $6.2\% \pm 0.98$  and the difference in the mean HbF level of patients with autosplenectomy ( $6.6\% \pm 0.96$ ) compared to those with splenomegaly ( $6.1\% \pm 0.54$ ) was not statistically significant ( $p$ -value = 0.28) **Conclusion:** The Foetal haemoglobin level was not significantly related to the presence or absence of splenomegaly in these children, although those with splenomegaly had lower mean HbF than those with autosplenectomy. It is recommended that early determination of HbF and possibly commencing hydroxyurea may improve the care of children with HSCD.

**Keywords:** Autosplenectomy, foetal haemoglobin, homozygous sickle cell disease, splenic size, ultrasonography.

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DOI: 10.31173/bomj.bomj\_2106\_18

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## Introduction

Sickle cell disease (SCD), is a haemoglobin disorder inherited in a Mendelian autosomal recessive fashion. The homozygous variant, sickle cell anaemia (SCA) results from the inheritance of the haemoglobin S variant from both parents, as a single nucleic acid substitution of valine for glutamic acid in the sixth codon of the 146 amino acids of the  $\beta$ -chain of the haemoglobin. It is the most common hereditary disorder in the world and Nigeria has the largest population of SCA patients worldwide. The prevalence of the carrier state (sickle cell trait) is reported to be between 19% and 32.6% in different parts of the country.<sup>1,2</sup> Numerous Nigerian population-based studies reported an estimated prevalence of the homozygous sickle disease to be between 1.6% and 3% in newborns with an incidence of approximately 150,000 newborns per year.<sup>3-5</sup> The abnormal gene for the inheritance of sickle cell disease commonly occurs in tropical regions with intense malaria transmission.

A recent study in Maiduguri North-eastern Nigeria showed a prevalence of 6.8%, and this was attributed to the high rates of intermarriages between ethnic groups that have the highest carrier rate of the disorder.<sup>6</sup> In addition, consanguineous marriages in the North-eastern region of Nigeria also contribute to the high rate of transmission of the abnormal gene to the newborn.

The spleen is a reticuloendothelial tissue that enlarges in a variety of clinical conditions in children, however, determination of spleen sizes that are clinically impalpable by percussion has been mostly inaccurate.<sup>7</sup> Following advances in the ultrasonographic assessment of splenic size became feasible for both palpable and the impalpable ones with the possibility of accurate measurement and reliability. The 21st-century dynamic nature of radiological imaging techniques, especially ultrasonography has opened up a new approach to the assessment of various organs of the body particularly the spleen, which is an organ of considerable impact on the clinical course of sickle cell anaemia.<sup>8</sup> The importance of ultrasonography in the evaluation of the pathologic conditions of the spleen has been attributed to its wide availability, absence of radiation and non-requirement for contrast media, as well as its simplicity of use and a lack of stress to the patient.<sup>8</sup> Therefore, ultrasonographic scanning became the method of

choice for the determination of the precise position, shape, size as well and volume of virtually all solid intra-abdominal organs, which has eventually been used as a diagnostic tool and recording of changes within the solid intra-abdominal organ.<sup>9</sup>

Splenomegaly is common in children with SCA. In young children with SCA in the tropics with the intense transmission of malaria, this is due to the combined effects of recurrent malaria infestation, extramedullary haematopoiesis, congestion, and rarely splenic sequestration.<sup>10</sup> However, this splenic enlargement in early life progressively regresses as a result of recurrent and chronic infarction which eventually leads to loss of function, scarring and fibrosis. Finally, the spleen becomes reduced to a merely wrinkled remnant often buried in adhesions, the pulp being entirely replaced by thick-walled vessels and fibrous tissue covered by a grossly thickened capsule and autosplenectomy, occur by the age of 8-10 years.<sup>8</sup> After the age of eight years, less than 10% of American homozygous sickle cell disease patients have palpable spleens.<sup>11-13</sup> Conversely, this is not always the case among African children; current reports have indicated that splenomegaly persists till an older age in Africans and this has been attributed to the effect of recurrent malaria infection especially in the presence of the hyperactive malarial syndrome.<sup>10,14,15</sup> There is a relative dearth of data from Nigeria regarding the ultrasonographically determined spleen size in children with sickle cell anaemia.<sup>8</sup> Furthermore, there is no data available from the Northeast region of Nigeria despite, having a high prevalence of homozygous sickle cell disease in the region.<sup>6</sup> This study was aimed at determining the size of the spleen in children with homozygous sickle cell disease using ultrasonography and to use HbF as a biomarker of splenic function.

## Materials and Methods

This was a prospective study of consecutively selected children with homozygous sickle cell disease at the Paediatric Haematology clinic of the University of Maiduguri Teaching Hospital (UMTH) over six months. The study population included children with homozygous sickle cell disease in steady-state as defined by Akinola et al,<sup>16</sup> on folic acid, proguanil, and penicillin V. A protocol incorporating a questionnaire was administered to each patient aged five to 15 years to record their



demographic data, frequency of crises and previous blood transfusion. The foetal haemoglobin (HbF) was quantified for all the subjects with the use of the Betke method of Alkali denaturation.<sup>17</sup> This test utilizes the characteristic of HbF to resist denaturation in an alkaline solution. The lysed red blood cell solution is added to the cyanomethaemoglobin reagent and then exposed to an alkaline reagent, sodium hydroxide, for a specified period. During this time, normal haemoglobin is denatured or destroyed, while the HbF remains intact. Ammonium sulphate is then added to halt the denaturation process and to precipitate the denatured haemoglobin. The solution is filtered, measured spectrophotometrically, and compared with the spectrophotometric readings of the original cyanomethaemoglobin solution to determine the percentage of HbF present.

**Study design:** This was a cross-sectional descriptive study.

**Study site:** The study was conducted at the Paediatric Haematology clinic of UMTH.

**Study population:** The children aged five to 15 years. For each case. Participants were recruited consecutively as they presented at the clinic after meeting the inclusion criteria.

**Sample size:** This was determined using Taylor's formula,<sup>18</sup> and *p* was taken from a previous study by Adekile et al from Nigeria who reported the splenomegaly rate of SCA to be 8.6%.<sup>19</sup> Thus, 120 homozygous SCD children were enrolled in the study.

**Inclusion criteria:** Children aged five to 15 years with homozygous SCD confirmed by Hb electrophoresis that were healthy in steady-state after giving consent/assent.

**Exclusion criteria:** Children whose parents or caregivers did not give consent to participate in the study were excluded. Also excluded from the study were children below the age of 5-years because autosplenectomy is not expected. Children with a history of blood transfusion within the previous three months and those on hydroxyurea therapy for any indication were also excluded, as this is expected to confound the anticipated results of this study.

**Ethical considerations**

Approval was obtained from the Hospital Research and Ethics Committee of UMTH. Written informed consent was obtained from the caregivers after adequate education. Participation was, therefore,

absolutely voluntary and those who refused consent to participate were still having their children or wards being followed up appropriately at the clinics. The information and results obtained were kept confidential.

All the subjects had abdominal ultrasound scan measurement for the longitudinal and coronal dimensions of the spleen. Ultrasound scan examination was carried out without sedation using a high-resolution real-time ultrasound scanner (Aloka SSD3500, Japan) with a 3.5 MHz sector transducer. Each subject was scanned in a slightly right lateral decubitus position exposing the area of interest appropriately. Ultrasound gel was then applied to the area to optimize the image. The spleen size was measured during deep inspiration to minimize masking by the left lung. Longitudinal splenic size measurement was performed in the oblique plane between the most superior medial and the most inferior lateral borders of the spleen. The coronal splenic size was obtained by scanning along with the eleventh intercostal space. Values obtained was correlated with the body height which is considered to be the best criteria that correlate with the longitudinal dimension of the spleen.<sup>20</sup> The obtained spleen size was classified based on the Konus et al,<sup>20</sup> reference value for spleen size in children. Values between the 5th and 95th percentile are regarded as normal splenic size. When the size was above the 95th percentile it was considered to be enlarged while a size below the 5th percentile was regarded as a shrunken spleen and non-visualization in the absence of surgical splenectomy was regarded as auto-splenectomy. All Ultrasound scans were performed by the same radiologist, to exclude observer variation. None of our patients studied had a surgical splenectomy in the past.

Data obtained were analyzed using the Statistical Package for Social Sciences (SPSS) version 18 (SPSS, Chicago, Illinois, USA). Means, standard deviation, frequencies and percentages were presented in tables and charts as appropriate. The significance of the difference between means values was determined using Student's *t*-test. *P*-values of <0.05 at a 95% confidence interval was implied to have statistical significance.

**Results**

One hundred and twenty children with sickle cell anaemia in steady-state were evaluated, they comprise 59 boys and 61 girls. Their ages ranged

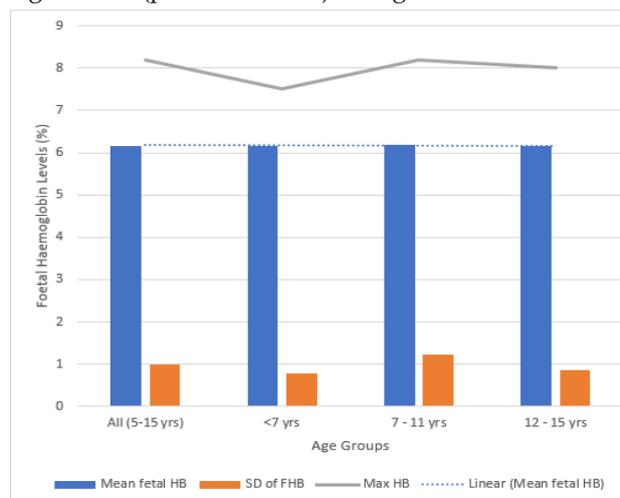
from 5-15 years, with a mean of  $10.1 \pm 3.5$  years. Of these, 25 (20.8%) were <7 years, 44 (36.7%) were in the 7-11 years of age while 51 (42.5%) were in the 12-15 years. The ultrasound scan status of the spleen with the number of patients is shown in Table 1. Only

12 (10%) of the patients had autosplenectomy. All those with autosplenectomy were 7 years and older. Seven (5.8%) of the SCA children had splenomegaly as determined by ultrasonographic examination.

**Table 1: Splenic status of the study population**

Splenic sizes	Spleen status	No. of patients	Percentage
Not visualized	Autosplenectomy	12	10.0
Below 5 <sup>th</sup> percentile	Shrunken	28	23.3
Between 5 <sup>th</sup> & 95 <sup>th</sup> percentile	Normal	73	60.8
Above 95 <sup>th</sup> percentile	Splenomegaly	7	5.83

All patients recalled having had a mass for variable periods that ranges from six months to over three years to the time of the study, and all observed a gradual increase in the abdominal swelling. The studied population had HbF ranged 1.6% - 8.2% with an overall mean of  $6.2\% \pm 0.98$ . The mean HbF level with various age groups is shown in Figure 1. The mean HbF level of those with autosplenectomy was  $6.6\% \pm 0.96$ , while that of those with splenomegaly was  $6.1\% \pm 0.54$ . Although the mean of those with autosplenectomy is higher than that of those with splenomegaly, the difference was not statistically significant ( $p$ -value = 0.28) using Student's *t*-test.



**Figure 1: Variation of Foetal Hb Across Age Groups**

## Discussion

There is increasing interest in issues relating to HbF in HSCD in the last six decades in the huge protective role it plays on the timing and severity of the SCD

symptomatology and the predisposition to bacterial infections, which appears to be the main cause of death in children with HSCD.<sup>12,13,21</sup> The present study has further confirmed previous findings that splenomegaly is much more common in African HSCD patients than in HSCD patients living in the United States and Europe. Northeastern Nigeria, is hyperendemic for malaria. While it had been suggested that persistent splenomegaly in Sub-Saharan African HSCD patients is due, to a reasonable extent, to the effects of the intense malaria transmission.<sup>10</sup> Unfortunately, in Nigeria, where the burden of the HSCD is highest, studies on HbF in children with HSCD are scanty. The findings of this study demonstrate the fact that HSCD children had high HbF levels, this may be due to the adaptive genetic modulators present in children with HSCD that include higher HbF production.<sup>22</sup> Furthermore, there is a delay in the genetically controlled postnatal switch of HbF to HbA in HSCD which consequently leads to a surge in the levels of HbF. The exact mechanism for this delayed switch is unknown, however, it might be related to the accelerated expansion of early erythroid progenitor cells which still possess the ability to express  $\gamma$ -globin. The accelerated expansion of progenitors is directly linked to increased haemolysis and the associated increased erythropoiesis occurring in HSCD.<sup>21</sup> This finding of high levels of HbF in HSCD is similar to reports from South-western Nigeria,<sup>23,24</sup> and Congolese patients.<sup>25</sup> The result of this study also showed the HSCD children to have autosplenectomy

with an incidence of 10%. This finding is consistent with the report of Al-Salem et al,<sup>26</sup> and Al-Jama et al.<sup>27</sup> The report of having autosplenectomy in children older than seven years is also consistent with the findings of Olaniyi and Abjah in Nigerian SCD patients.<sup>23</sup> However, earlier workers had demonstrated that impalpable spleen was visualized on ultrasound in over 50% of subjects with SCA.<sup>1,28</sup> Splenomegaly is expected to be an uncommon finding in SCA children beyond the age of seven years because of autosplenectomy that occurs due to repeated infarction; however, in this present study, about 5.8% of the SCA children had palpably enlarged spleen as verified on ultrasound examination. The mere presence of splenomegaly in these SCA patients does not imply functionality. One of the seven patients with splenomegaly had the abdominal swelling to have prompted the caregivers to bring the patient to our medical facility where the patient was evaluated and ultimately diagnosed to have SCA at the age of eight years. Moreover, splenomegaly predisposes the SCA child to the risk and possibility of infarction, acute splenic sequestration with the requirement of top-up transfusion, hypersplenism, and abscess formation. The SCA patients with massive splenomegaly are predisposed to have compromised function of the spleen particularly against infection with encapsulated bacteria such as pneumococcus and are, therefore, at increased risk of a severe form of bacterial infection especially when they did not receive a pneumococcal conjugate vaccine and are not on prophylactic per oral penicillin V for one reason or the other.

The splenomegaly of sickle cell anaemia is due to the marked sluggishness and increased viscosity of the large pool of sickled haemoglobin which leads to sinusoidal and venules occlusion in the spleen. The ischaemic component of sickling in the capillaries and arterioles probably occurs less frequently and as a late event is associated with the Benin haplotype which is predominant in Nigerian patients with SCA.<sup>29</sup> The variability in splenomegaly in SCA is consistent with the diverse genetic and environmental factors influencing the clinical course of abdominal haematopoietic organs notably the spleen. One of the contributing environmental factors in Nigeria is hyperendemic malaria,<sup>10</sup> while genetic factors may include coexistent  $\alpha$ -thalassaemia which has been noted to reduce the rate

of haemolysis in SCA.<sup>30</sup> Other hereditary haemolytic disorders such as glucose-6-phosphate dehydrogenase deficiency also affect the clinical course of SCA as it relates to splenomegaly. Some of the Nigerian children with SCA without splenomegaly might have fallen into these categories of patients and therefore, the need for further study in Nigerian children with SCA. In Nigeria, SCA is reported to be more severe than in some other parts of the world where there is a high prevalence of SCA like Saudi Arabia and the Indian sub-continent. The benign nature of this disorder has been attributed to high levels of HbF and the frequently associated  $\alpha$ -thalassaemia in Saudi Arabia.<sup>26,31,32</sup> Patients who had marked to massive splenomegaly had the same HbF levels when compared with those who had autosplenectomy, a finding in contrast to that of Saudi Arabia report.<sup>26</sup> This has been attributed to the favourable influence exhibited by a high level of HbF through inhibition of HbS polymerization and thus survival of HbF containing cells and less sickling.<sup>33</sup> The average HbF level in our SCA population was 6.2% and was lower than what was observed in other studies in South-western Nigeria,<sup>34,35</sup> and Senegal,<sup>36</sup> where the mean HbF levels were 9.5%, 17% and 25% respectively. The relatively low levels of HbF in the current study may be a possible indicator of severe disease that is correlated with the Benin haplotype that is prevalent in Nigeria. Patients with massive splenomegaly are at risk of acute splenic sequestration crisis (ASSC) which is a major cause of death commonly in the first two years of life.<sup>37</sup> Approximately half of those dying in the first two years of life died as a direct consequence of ASSC.<sup>26</sup> This life-threatening event can be effectively treated with blood transfusions, unfortunately, it has a high tendency and propensity of recurrence with several episodes within a short time. Surgical splenectomy that is frequently required in the long-term management of patients with recurrent ASSC is not a popular practice in our settings. An episode of ASSC, therefore, indicates the use of hydroxyurea in the setting of the paucity of surgical splenectomy for patients with persistent massive splenomegaly to avoid dying from a complication of ASSC. Recurrence of ASSC becomes less frequent after the age of 5 years, and the tendency of autosplenectomy increases as seen in this report with all the 12 children 7-years and beyond with non-visualized spleen on Ultrasound examination. Our findings support the



conservative approach to the management of ASSC instead of surgical splenectomy with its attendant complication. However, splenectomy becomes an important alternative in the settings of limitations in blood availability and paucity of donors in the community like ours.

### Conclusion

Ultrasonographic examination of the spleen is a non-invasive technique devoid of exposing the patient to radiation, a safe, simple, reliable and reproducible method of splenic size assessment in SCA patients. The Foetal haemoglobin level was not significantly related to the presence or absence of splenomegaly in these children, although those with splenomegaly had lower mean HbF than those with autosplenectomy, it appears that no significant relationship exists between spleen size and HbF level in children with HSCD. It is recommended that early determination of HbF and possibly commencing hydroxyurea may add value in the follow-up of patients and improve the care of children with HSCD.

### Acknowledgement

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We are grateful to Professor Jose Pwvimbo Ambe for his willingness and immeasurable support in this work, we are also grateful to Abdulmummini Garba of the Emergency Paediatrics side laboratory of the University of Maiduguri Teaching Hospital for running the Packed Cell Volume of the SCA children.

**Financial discloser:** The authors declared that this study received no financial support.

### Authorship contributions

Halima U. Ibrahim and Abubakar G. Farouk conceived and designed the research. Aminu U. Usman did the ultrasonographic scanning. Abubakar Farouk, Halima U Ibrahim, and Aminu U. Usman analyzed the data. Bello A. Ibrahim, Aminu U. Usman, and Ahmadu M. Sani contributed materials, did literature search and analysis. Mohammed B. Mala did HbF quantification and analysis of data. Abubakar G. Farouk wrote the first draft. All authors corrected, read and agreed to publish the work.

**Conflict of interest:** Authors declared no conflict of interest



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**Cite this Article as:** Ibrahim HU, Farouk AG, Ahmadu MS, Usman AU, Mala MB, Ibrahim BA. Predictors of splenic size in children with Sickle Cell Anaemia in Steady-state using ultrasonography in Maiduguri, Nigeria. **Bo Med J 2020; 18(1): 1-8** **Source of Support:** Nil, **Conflict of Interest:** None declared

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