Original Article

Two-Dimensional Ultrasound Assessment of Long-Term Intra-Abdominal Organ Changes in Children with Sickle Cell Anemia during Steady State: A Comparative Study

CS Nwosu, CA Nri-Ezedi[1], C Okechukwu[2], TO Ulasi[1], EO Umeh, UR Ebubedike, ME Aronu, AL Obi-Nwosu[3], AO Odita[1], NV Agu[4], SC Ngonadi[4], NC Emedike[5], KM Uke[5], AC Emegoakor[5]

Departments of Radiology, [1]Paediatrics and [3]Family Medicine, Faculty of Medicine, Nnamdi Azikiwe University Awka, Anambra State, [2]Department of Paediatrics and Child Health, Rivers State University Teaching Hospital, Port-Harcourt, Rivers State, Departments of [4]Paediatrics and [5]Radiology, Nnamdi Azikiwe University Teaching Hospital, Nnewi, Anambra State, Nigeria

Received: 30-May-2023;
Revision: 06-Aug-2023;
Accepted: 18-Sep-2023;
Published: 29-Dec-2023

Abstract

Background: Sickle cell anemia (SCA) is a hereditary blood disorder with global prevalence, including in Nigeria. Despite advancements in SCA care management, understanding the long-term impact on organs during steady state has remained inconclusive. **Aim:** This study aimed to investigate the long-term changes in intra-abdominal organs of SCA children compared with non-SCA children during steady state using two-dimensional ultrasound assessment. **Materials and Methods:** A total of 116 children (58 SCA and 58 controls) were enrolled between June 2021 and July 2022. Clinico-demographic data were collected through an interviewer-administered questionnaire. Two-dimensional ultrasound was used to measure the liver, spleen, kidneys, and inferior vena cava in all subjects. Age-matched controls had AA or AS genotypes. **Results:** Of the 58 patients with SCA, 65.5% were males with an overall mean age of 8.1 ± 3.4 years, while among the non-SCA cohort (n = 58), 48.3% were males with an overall mean age of 8.7 ± 3.9 years. There was no statistically significant difference in the age and gender distribution between the SCA and non-SCA cohorts (P = 0.390 and P = 0.091, respectively). SCA subjects had a larger mean hepatic size than non-SCA subjects (12.09 cm ± 2.23 vs. 11.67 cm ± 1.96; P = 0.276) but smaller mean splenic size (8.01 cm ± 1.89 vs. 8.19 cm ± 1.61; P = 0.577) and inferior vena cava diameter (1.16 cm ± 0.29 vs. 1.25 cm ± 0.33; P = 0.100). Left kidney length and breadth were significantly greater in SCA patients (8.91 ± 1.16 vs. 8.27 ± 1.30; P = 0.006 and 4.15 ± 0.92 vs. 3.79 ± 0.48; P = 0.008, respectively). **Conclusion:** This study highlights the utility of two-dimensional ultrasound assessment in monitoring intra-abdominal organ changes in SCA children, suggesting its cost-effective benefits in monitoring health outcomes in SCA patients.

Keywords: *Health outcomes, intra-abdominal organs, long-term effects, sickle cell anemia, steady state, ultrasound*

Introduction

Sickle cell disease (SCD) is an autosomal recessive genetic disorder characterized by an abnormal amino acid substitution in the normal globin chain.[1] This genetic condition occurs globally with a higher disease burden in sub-Saharan Africa, India, Saudi Arabia, and Mediterranean countries.[2] SCD is characterized by red blood cells (RBCs) with abnormal hemoglobin, resulting in rigid sickling of the cell, followed by vascular occlusion and ischemia.[1] The repeated sickling of the RBCs that occurs in the deoxygenated state has the potential to result in chronic

Access this article online

Quick Response Code:

Website: www.njcponline.com

DOI: 10.4103/njcp.njcp_411_23

Address for correspondence: Dr. CA Nri-Ezedi, Department of Paediatrics, Nnamdi Azikiwe University Teaching Hospital, Nnewi, Anambra State, Nigeria.
E-mail: ca.nri-ezedi@unizik.edu.ng

How to cite this article: Nwosu CS, Nri-Ezedi CA, Okechukwu C, Ulasi TO, Umeh EO, Ebubedike UR, *et al.* Two-dimensional ultrasound assessment of long-term intra-abdominal organ changes in children with sickle cell anemia during steady state: A comparative study. Niger J Clin Pract 2023;26:1861-7.

hypoxic–ischemic insult to all the major organs of the body. Age, dietary state, socioeconomic status, and the intake of disease-modifying drugs all play a role in determining the extent of organ impairment in sickle cell anemia (SCA).[3,4]

Although advancements in sickle care management have led to improved survival rates, the long-term impact of SCA on organs during steady state remains a topic of concern. During steady state, SCA patients are asymptomatic and may not exhibit any signs or symptoms of organ damage or dysfunction. However, studies have shown that organ damage can occur during steady state, and early detection is crucial in preventing further damage and managing complications.[5] There have been reports of regional differences in organ size and parenchymal echotexture among SCD patients.[5] One of the first notable effects of sickle cell on the body organs is its effect on the spleen.[6] There is progressive infarction, fibrosis, atrophy, and, eventually, loss of splenic function. This process begins in infancy and persists up to about 5 years of age when total functional asplenia ensues.[6] The spleen undergoes an initial enlargement in the first decade of life, then subsequently shrinks in size, and, in some cases, may become completely invisible on ultrasound scan.[7] Additionally, congestion and sequestration of sickled RBCs in the liver can result in liver enlargement. The kidneys can also be enlarged following progressive injury, leading to global or segmental glomerulosclerosis, glomerular hypertrophy, and duplication of the glomerular basement membranes, interstitial fibrosis, tubular atrophy, and papillary necrosis.[8]

Sonographic evaluation of abdominal organs is an important workup in managing SCD patients.[9] Ultrasonography is a simple, noninvasive affordable, and easily accessible imaging technique that can be used to determine the size and gross structure of the internal body organs.[10] This study therefore compared the body organs—spleen, liver, and kidneys—of children with SCA in steady state to those of their age-matched non-SCA counterparts.

Methodology

Study design

This was a hospital-based prospective study conducted for 9 months (June 2021 to July 2022).

Study population

The study population consisted of two groups: 58 patients and 58 controls. The patients were children aged 5 to 15 years with SCA in steady state who came for follow-up at the Haematology Clinic of the Department of Paediatrics, Nnamdi Azikiwe University Teaching Hospital, Nigeria. Steady state was defined as that period when the patient with SCA is free from infection, pain, or other disease processes.[11] It includes the following criteria: no history of fever in the preceding 4 weeks, no history of painful crises that required treatment in the hospital in the preceding four consecutive weeks, no history of blood transfusion during the previous 4 months, and no history of intercurrent illness, such as infection and inflammation in the previous 4 weeks.

The controls were children aged 5 to 15 years with Haemoglobin AA (HbAA) or Haemoglobin AS (HbAS) genotype matched for age with the study patients recruited from the Children Outpatient Clinic of the Department of Paediatrics.

Sampling

Patients who met the selection criteria were enrolled consecutively until the desired sample size was obtained. The control group was then selected after matching for age. For each case, at least two matched controls were listed and assigned numbers at random. Using the simple random sampling method via a computer-generated table of random numbers, one of the controls was selected. This process was continued until an equal number of controls, matched in a 1:1 ratio with the patients, were obtained.

Data collection

An interviewer-administered questionnaire comprising sociodemographic variables of interest and biometric data (weight, height, and arm span) was used for data collection.

Enrolled study participants then had an abdominal ultrasound scan (USS) performed at the radiology department by a consultant radiologist. Before the USS, study participants were to fast for at least 6 hours. With patients lying supine on a couch, the abdomen was exposed from the xiphisternum to the lower suprapubic region, coupling gel was applied to the abdomen, and a low-frequency probe (3.5–5.5 Mhz) was used to evaluate the abdominal organs. The right and left oblique positions were bused as alternate positions if the organs are not clearly visualized in the supine position.

The liver span was measured in the longitudinal plane with the center of the right kidney in the longitudinal plane of imaging. Hepatomegaly was noted as >15.0 cm taken on the long axis.[12,13] The long axis of the spleen was measured at the level of the hilum. If the spleen was not visualized in its position, it was defined as autosplenectomy.[5,10,14] Splenomegaly was defined as >13.0 cm for children above 15 yrs. The long axis of the kidneys was evaluated on the right and left

sides. The bipolar dimensions of the kidneys were then checked against age-matched values.

A 2D ultrasound machine ALOKA Prosound SSD-3500SX (ALOKA Inc., Tokyo, Japan 2008) with Doppler capability fitted with a curvilinear transducer with a frequency of 3.5–5 MHz was used for this study. A high-frequency 7.5-MHz linear transducer was used to study superficial organs, and the 3.5–5 MHz curvilinear transducer was used for the deeper abdominal organs and structures.

Statistical analysis

The data were analyzed using Statistical Package for the Social Sciences, version 23.0 (New York, USA, 2016), and visualized using R version 4.2.2. Frequency tables and percentages were used to illustrate the sociodemographic characteristics of study participants. We presented categorical variables using frequency and percentage. Student's *t*-test was utilized to examine the relationship between numerical variables of interest between two groups, whereas the Chi-square analysis was utilized to examine the relationship between categorical variables of interest. Analyses of predictor variables against the outcome of whether a child has sickle cell were conducted using logistic regression. The level of statistical significance was set at P value < 0.05.

Ethical approval

Ethical approval was obtained from the Ethics Committee of the Nnamdi Azikiwe University Teaching Hospital, Nnewi, Reference Number NAUTH/CS/66B/VOL. 2/174.

Results

There were 116 children recruited for this study. Fifty-eight (50%) of these subjects have SCA, compared with the same distribution of age-matched controls. Table 1 depicts the baseline characteristics of the participants in the study, of whom 66 (56.9 percent) are males and 50 (43.1) are females. The age range of the subjects was 3 to 15 years, with a mean of 8.4 3.7 years. There are no significant differences between the SCA and non-SCA groups in terms of age and gender distribution. However, subjects with SCA were on average 6 kg lighter than those without SCA, and this difference was statistically significant (P = 0.007).

Comparison of organ dimensions between non-SCA and SCA subjects

Table 2 displays the ultrasound-based mean sizes of the liver, spleen, inferior vena cava, and kidneys in non-SCA and SCA study participants. Overall, the mean dimensions of the liver and kidneys were larger in SCA patients than in non-SCA patients. The width of the right kidney and the length and width of the left kidney exhibited statistically significant differences (P < 0.05). These differences were strongly significant for the left kidney characteristics (P = 0.006 for length and P = 0.008 for width, respectively). Although the right kidney length of SCA patients was 0.3 cm longer than that of non-SCA patients, this difference was not statistically significant (P = 0.213). The smaller mean splenic size and inferior vena cava diameter in SCA

Table 1: Baseline characteristics of subjects

	Non-sickle %/SD	Sickle %/SD	*P*
n	58 (50)	58 (50)	-
Age (years)	8.7±3.9	8.1±3.4	0.390
Age category			
3–7	24 (41.4)	28 (48.3)	
8–11	20 (34.5)	20 (34.5)	0.614
Above 11	14 (24.1)	10 (17.2)	
Gender			
Male	28 (48.3)	38 (65.5)	0.091
Female	30 (51.7)	20 (34.5)	
Weight	31.81±12.1	26.22±9.7	0.007

Table 2: Comparison of mean organ dimensions between non-SCA and SCA subjects

	Non-sickle	Sickle	*P*
Liver span	11.67±1.96	12.09±2.23	0.276
Splenic size	8.19±1.61	8.01±1.89	0.577
Right kidney length	8.16±1.36	8.46±1.18	0.213
Right kidney width	3.53±0.59	3.73±0.43	0.039*
Left kidney length	8.27±1.30	8.91±1.16	0.006*
Left kidney width	3.79±0.48	4.15±0.92	0.008*
Inferior vena cava	1.25±0.33	1.16±0.29	0.100

Table 3: Variations in the abdominal organ dimensions across different age groups between non-SCA and SCA groups

Age category	Organs	Non-SCA	SCA	*P*
3 to 7 years	Liver span	10.10±1.35	11.24±1.71	0.011
	Splenic size	6.77±0.95	7.94±2.07	0.011
	Right kidney length	6.91±0.84	7.99±1.24	0.001
	Left kidney length	7.01±0.64	8.56±0.94	0.0001
	Inferior vena cava	1.04±0.31	1.10±0.33	0.450
8 to 11 years	Liver span	12.03±1.30	12.89±2.76	0.216
	Splenic size	8.88±0.89	8.14±1.93	0.131
	Right kidney length	8.77±0.75	8.48±0.60	0.183
	Left kidney length	9.12±0.85	9.77±0.96	0.225
	Inferior vena cava	1.38±0.22	1.14±0.25	0.002
Above 11 years	Liver span	13.84±1.11	12.88±1.55	0.089
	Splenic size	9.64±1.36	7.94±1.43	0.009
	Right kidney length	9.46±0.85	9.74±0.98	0.460
	Left kidney length	9.20±0.77	10.18±1.27	0.028
	Inferior vena cava	1.44±0.29	1.35±0.20	0.385

Table 4: Logistic regression analysis of abdominal organ sizes between non-SCA and SCA subjects as the outcome of interest

	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Weight	0.954 (0.921–0.989)	0.009	0.870 (0.819–0.925)	0.0001
Liver span	1.105 (0.923–1.322)	0.277	-	-
Splenic size	0.942 (0.764–1.161)	0.573	-	-
Right kidney length	1.204 (0.899–1.612)	0.212		-
Left kidney length	1.547 (1.121–2.134)	0.008	3.625 (2.071–6.344)	0.0001
Inferior vena cava	0.360 (0.109–1.225)	0.103	-	-

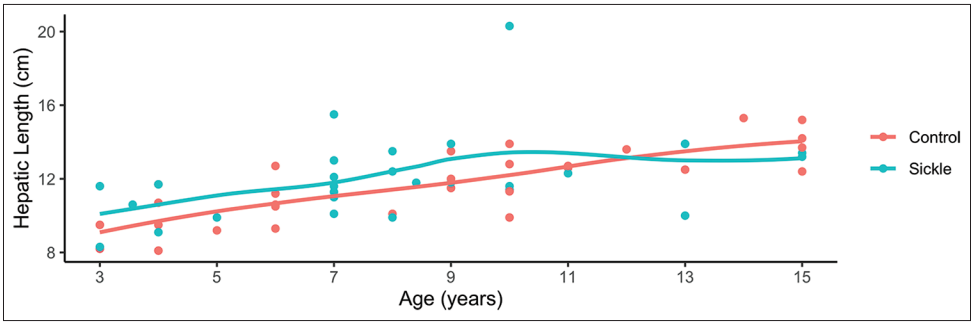

Figure 1: Correlation between liver size and age in non-SCA and SCA subjects

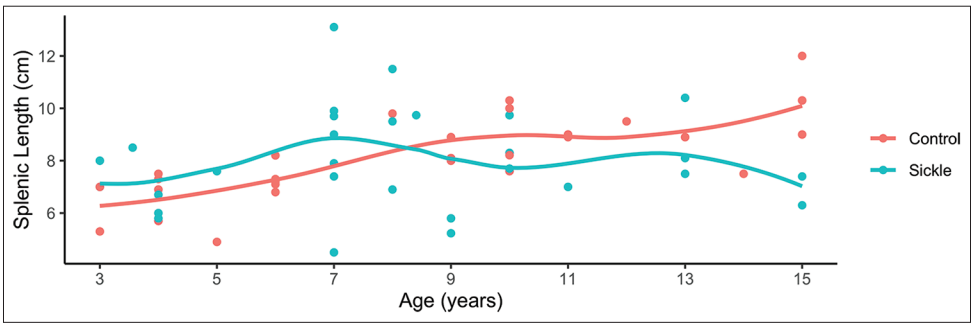

Figure 2: Correlation between splenic size and age in non-SCA and SCA subjects

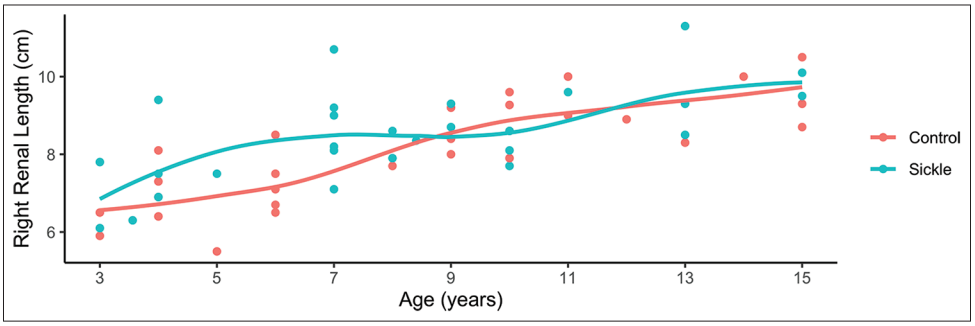

Figure 3: Correlation between right kidney length and age in non-SCA and SCA subjects

patients compared with non-SCA patients were not statistically significant ($P > 0.05$).

Comparison of the pattern of organ size with age

Table 3 illustrates the differences in intra-abdominal organs between SCA patients and healthy controls across age groups. In the younger age group (3–7 years), the mean splenic and hepatic sizes were comparable in both groups, whereas the SCA cohort had significantly larger kidneys than the control group ($P = 0.001$ for the right kidney and $P = 0.0001$ for the left kidney).

In children aged 8 to 11 years, the ultrasonic-derived sizes of abdominal organs were comparable. In contrast, the average splenic size of adolescents with SCA was significantly smaller than that of controls,

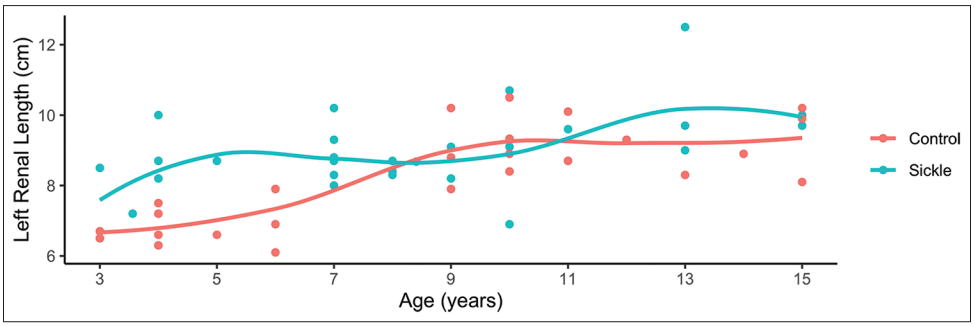

Figure 4: Correlation between left kidney length and age in non-SCA and SCA subjects

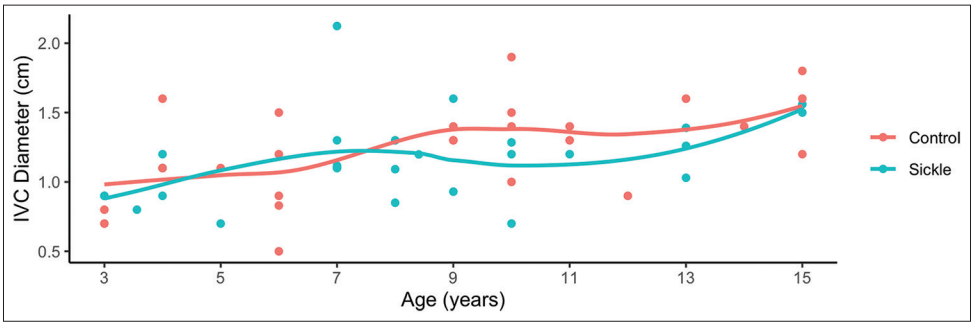

Figure 5: Correlation between inferior vena cava size and age in non-SCA and SCA subjects

while the length of the left kidney was significantly greater ($P = 0.028$).

Figures 1-5 provide additional visual insights into the correlation between age and the organs of interest within both study groups.

Predictive value of the organ sizes

In the univariate and multivariate logistic regression models depicted in Table 4, the predictive values of weight and intra-abdominal organ sizes between non-SCA and SCA patients (as the outcome of interest) were assessed. Following adjustments, weight and left kidney length emerged as the strongest predictors of subjects with SCA, with an increase of one unit in left kidney length associated with a 3.625% increase in the likelihood of having SCA (95%CI: 2.071–6.344).

Discussion

The average hepatic size of the SCA cohort was larger than the cohort without the disease. This finding is consistent with the reports of Ma'aji *et al.*[5] and Luntsi *et al.*[10] who observed larger liver sizes in their sickle cell cohorts. The cause of hepatomegaly in the SCD group has been attributed by previous researchers to repeated sequestration, vaso-occlusion, and possibly therapy complications.[15,16] Because this difference was not statistically significant, further evaluation of the hepatic size across age groups revealed a distinct picture in which there was a decline in size with increasing age, particularly among adolescents. This was in contrast to the non-SCA group, where hepatic size increased proportionally with age.

The average splenic size of the SCA cohort was slightly smaller than that of the non-SCA group. Observations across age groups provided a clearer picture of the trajectory [Figure 2]. In the SCA cohort, splenic size decreased with increasing age, especially during the adolescent period, where significant differences in splenic size between the SCA and non-SCA groups were observed. This result is consistent with the findings of other researchers.[5,10,17,18] After 7 years of age, there was a reduction in splenic size in children with SCA, but no subject in this study underwent complete autosplenectomy. The diminution of the spleen may be due to repeated sickling of RBCs. Repeated splenic crisis causes stagnation in the microcirculation of the spleen, resulting in splenic infarction and ultimately autosplenectomy.

Intriguingly, the kidneys (both right and left) were larger on average in the SCA group compared with the non-SCA group, but these differences were only significant for the left kidney and persisted after weight differences between the two groups were accounted for. This contradicted the findings reported by Muftaudeen *et al.*,[17] Mohanty *et al.*,[16] and Luntsi *et al.*[10] The difference between their findings and those of this study may be because their subjects were adults in a state of crisis, whereas all of the participants in this study

were children in a steady stable state. Up to 25% of the heart's total output is distributed to the kidneys. In children with SCA, this volume increases as a result of the hyperdynamic state caused by chronic anemia. Although it is not immediately apparent why the left kidney was significantly larger than the right in children with SCA, we believe that the normal anatomic variation in which the left kidney is typically larger than the right kidney underlies this effect, which is further exacerbated in children with SCA due to glomerular hyperfiltration.[19] This apparent nephromegaly is believed to precede the onset of microalbuminuria in children, which is a well-known indicator of sickle cell nephropathy.[20] To further establish the potential role of nephromegaly as an early marker of sickle cell nephropathy in children, more robust studies are required, especially in regions with limited resources, as this offers a noninvasive and cost-effective alternative for diagnosing sickle cell nephropathy in affected children.

Notably, the average diameter of the inferior vena cava was substantially smaller than that of the controls. The left and right kidneys drain into the left and right renal veins, with both veins ending in the inferior vena cava. The shorter right renal vein empties directly into the inferior vena cava at a right angle, whereas the significantly longer left renal vein courses through several structures and receives tributaries from various organs before emptying into the Inferior vena cava (IVC). A constricted IVC contributes to an increase in resistance and venous pressure. We believe this phenomenon impedes the venous drainage of both kidneys, leading to a worsening of hypoxia, sickling, and stenosis of the venules, which promotes renal infarction and atrophy.[21-23] As the right renal vein drains directly to the IVC without any tributaries to reduce the net effect of the back pressure from the narrowed IVC, this may explain the marked structural changes evidenced by a smaller right renal size in SCA subjects, in contrast to the left renals, which essentially remained the same in size. It is unclear why the IVC is constricted in this age group, and this must be investigated in future research.

The purpose of this study was to compare the ultrasound-estimated dimensions of vital organs in children with SCA to those of their peers without the disease. Historically, SCA affects the structural and functional integrity of the majority of intraabdominal organs through its complex pathophysiologic mechanisms. With the vast improvement in the routine care of SCA children, we hypothesized that these alterations, especially the structural component, would differ from what is conventionally known. Additionally, there has been a dearth of data on this subject matter in the past decade. The elucidation of the structural profile of the major intra-abdominal organs in this study is timely and reaffirms that despite the improvement in the routine management of SCA, which in our institution includes the routine use of hydroxyurea, proguanil, multivitamins, and penicillin, the structural integrity of affected patients remains compromised by the underlying disease.

A potential limitation of this study is the use of HbAS and HbAA as controls, which could have introduced confounding factors. Nonetheless, the strength of the study lies in its comprehensive and comparative assessment of intra-abdominal organ changes using two-dimensional ultrasound, a cost-effective and noninvasive tool, which offers valuable insights into the long-term effects of SCA on pediatric patients during steady state.

In conclusion, our study demonstrates that SCA can have significant long-term effects on intra-abdominal organs in steady-state children, with these effects appearing to worsen with age. While routine follow-up care at a clinic can help to slow or reduce the incidence of organ complications in SCA patients, our findings suggest that early and periodic imaging studies should be considered to promptly detect adverse structural changes indicative of functional derangements. These results have important implications for enhancing the management and health outcomes of SCA patients and highlight the need for further research to identify effective strategies for monitoring and treating SCA-related complications.

Ethical considerations

Ethical approval for the study was obtained from the Ethical Committee of the Nnamdi Azikiwe University Teaching Hospital: NAUTH/CS/66B/VOL. 2/174. Assent was obtained from children aged 6 years and above, and consent was obtained from the parents or guardians. The principles of ethics were upheld in carrying out the research.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Inusa BPD, Hsu LL, Kohli N, Patel A, Ominu-Evbota K, Anie KA, *et al*. Sickle cell disease-genetics, pathophysiology, clinical presentation and treatment. Int J Neonatal Screen 2019;5:20.
2. Sickle-cell anaemia. Report by the Secretariat Prevalence of Sickle-Cell Anaemia; 2006.
3. Vichinsky E. Chronic organ failure in adult sickle cell disease. Hematology Am Soc Hematol Educ Program 2017;2017:435–9.

4. Adewoyin AS. Management of sickle cell disease: A review for physician education in Nigeria (Sub-Saharan Africa). Anemia 2015;2015: 791498.
5. Ma'aji SM, Jiya NM, Saidu SA, Danfulani M, Yunusa GA, Sani UM, *et al*. Transabdominal utrasonographic findings in children with sickle cell anaemia in Sokoto, Northeastern Nigeria. Niger J. Basic Clin Sci 2012;9:14-7.
6. Brousse V, Buffet P, Rees D. The spleen and sickle cell disease: The sick (led) spleen. Br J Haematol 2014;166:165–76.
7. Al-Salem A. Medical and Surgical Complications of Sickle Cell Anemia. 1st ed. Springer; 2016. ISBN 3319247603.
8. Mammen C, Bissonnette ML, Matsell DG. Acute kidney injury in children with sickle cell disease—compounding a chronic problem. Pediatr Nephrol 2017;32:1287–91.
9. McCarville MB, Luo Z, Huang X, Rees RC, Rogers ZR, Miller ST, *et al*. Abdominal ultrasound with scintigraphic and clinical correlates in infants with sickle cell anemia: Baseline data from the BABY HUG trial. Am J Roentgenol 2011;196:1399–404.
10. Luntsi G, Eze CU, Ahmadu MS, Bukar AA, Ochie K. Sonographic evaluation of some abdominal organs in sickle cell disease patients in a tertiary health institute in Northeeastern Nigeria. J Med Ultrasound 2018;26:31-6.
11. Makani J, Williams TN, Marsh K. Sickle cell disease in Africa: Burden and research priorities. Ann Trop Med Parasitol 2007;101:3–14.
12. Fifty-Ninth World Health Assembly. Sickle Cell Anaemia-Report by the secretariat. A59/9: Provisional Agenda Item 11.4. World Health Organization; 2006. p.1-135.
13. Balci A, Karazincir S, Sangun O, Gali E, Daplan T, Cingiz E, *et al*. Prevalence of abdominal ultrasonographic abnormalities in patients with sickle cell disease. Diagn Interv Radiol 2008;14:133-7.
14. Dorland WAN. Spleen. Dorland's Pocket Medical Dictionary. 28th ed. Philadelphia: Elsevier Saunders; 2009. p. 780.
15. Rusheke AH. Abdominal ultrasonogrphic abnormalities in patients with sickle cell anaemia at MuhInbili National Hopital. M Med (Radiology0 Dissertation, Muhimbili University of Health and Allied Sciences. 2010.
16. Mohanty J, Narayan J, Bhagat S, Panda BB, Satpathi G, Saha N. Sonological evaluation of abdominal organs in sickle cell crisis in Western Orissa. Indian J Radiol Imaging 2004;14:247-51.
17. Muftaudeen B, Eze JC, Sibi M, Miftaudeen MN. Sonographic assessment of some abdominal organs in children with sickle cell disease in Ilorin, Nigeria. J Med Ultrasound 2020;29:94-8.
18. Bharati S, Das S, Majee P, Mandal S. Anaesthetic management of a patient with Sickle B -Thalassemia. Saudi J Anaesth 2011;5:98-100.
19. Naik RP, Derebail VK. The spectrum of sickle hemoglobin-related nephropathy: From sickle cell to sickle trait. Expert Rev Hematol 2017;10:1087-94.
20. Lebensburger JD, Aban I, Pernell B, Kasztan M, Feig DI, Hilliard LM, *et al*. Hyperfiltration during early childhood precedes albuminuria in pediatric sickle cell nephropathy. Am J Hematol 2019;94:417-23.
21. Wesson DE. The initiation and progression of sickle cell nephropathy. Kidney int 2002;61:2277-86.
22. De Jong PE, Statius van Eps LW. Sickle cell nephropathy: New insights into its pathophysiology. Kidney int 1985;27:711-7.
23. Bhathena DB, Sondheimer JH. The glomerulopathy of homozygous sickle hemoglobin (SS) disease: Morphology and pathogenesis. J Am Soc Nephrol 1991;1:1241-52.