Clinical profile of paediatric sickle cell disease at a reference hospital in North–eastern Nigeria

Abstract: Background: Sickle cell disorders (SCD) are the commonest inherited haemoglobin (Hb) disorders. Globally, about 300,000 babies are born annually with these conditions. The clinical profiles of SCD have been described in many parts of the world. These however have not been adequately investigated in some parts of Nigeria. This study evaluated the clinical features, Hb phenotype and complications of children with SCD being managed at a Paediatric haematology clinic in Northern Nigeria.

Methods: A prospective observational study of steady state SCD patients aged 2–16 years, was conducted from January, 2019 – October, 2020. Historical and examination findings were documented. Analysis of data was done with the Statistical Package for Social Sciences (SPSS) version 20.0.

Results: One hundred children were studied. Mean age was 6.97 ± 3.63 years. Male: female ratio was 1.6:1. Mean weight and mean height were lower than reference standards (t = -1.20, p = 0.14), (t = -0.66, p = 0.27) respectively. Mean age at diagnosis was 13.24 ±14.83 months, and at first presentation was 13.86 ±17.51 months, 58.5% of subjects were adequately vaccinated for age, while 92% had a Hb phenotype of SS. Acute chest syndrome occurred more frequently in children aged 9-12 years (χ² = 11.59, P < 0.001), and in those with severe bacterial infections (χ² = 7.41, p = 0.006).

Conclusion: The complications of Paediatric SCD in this part of North-Eastern Nigeria mirrors those in other parts of the country. Socio-economic class, Hb phenotype and vaccination status had no influence on the development of complications.

Key words: Sickle cell disease, Acute chest syndrome, Pain crisis, Severe bacterial infections, Socio-economic class.

Introduction

Sickle cell disorders (SCD) are easily the commonest inherited haemoglobin disorder known. Globally, about 300,000 babies are born annually with these conditions.1 Nigeria has the highest burden in the world with a prevalence of 20–30/1000 live births yearly.2,3 SCD accounts for about 25% of under-5 deaths in Sub-Saharan Africa.4

The clinical profiles of SCD have been described in many parts of the world.5 Yet these have not been adequately investigated in some parts of Nigeria. Prior research weakly explored the impact of socio-demographic and clinical features on the development of complications. Moreover, to our knowledge there is no previous study on Paediatric SCD in this part of North-Eastern Nigeria.5,6 This lack of local data is of significance given that SCD is known to be associated with disparity in severity of clinical presentation, often prede-termined by genetic and environmental factors.7,8 It is thus essential to pinpoint local clinical features, as well as socio-demographic factors and their impact on the development of complications.

This study evaluated the clinical features, haemoglobin (Hb) phenotype and complications of children with SCD presenting in steady state, to the Paediatric haematology clinic of a reference hospital North-Eastern Nigeria. The impact of the patients’ gender on the clinical presentation and that of some clinical and socio-demographic factors on the occurrence of complications were also assessed.

Subjects, materials and methods

Ethics

The study was conducted in compliance with the ethical standards of the Helsinki Declaration of 1975 (as
amended). Institutional ethical clearance was obtained from the Research ethics and Review Committee (ref. number FMCA/COM/36/Vol.iii). Prior to recruitment, written informed consent and/or assent were obtained from the parent/caregiver of each participant and some participants respectively, after providing necessary details about the research. All patients’ information was handled confidentially. The subjects neither suffered any harm nor did they incur any extra financial burden on account of this study.

**Study design**

This was a prospective observational study of children with steady state sickle cell disorders and aged 2 – 16 years. The subjects were recruited from the Paediatric Haematology and Oncology clinics of the Federal Medical Centre Azare, Bauchi state during routine follow-up care over a 22-month period (January, 2019 – October, 2020). All the patients who met the inclusion criteria were consecutively recruited into the study.

**Sampling and Sample size determination**

**Inclusion criteria**

1. Children with SCD presenting at steady state to the Paediatric Haematology and Oncology clinics.
2. Children whose parents/ caregivers gave written informed consent.
3. Age two years and above.

**Exclusion criteria**

1. SCD patients with acute illnesses.
2. Children diagnosed with a disease other than SCD.

The sample size was calculated with the formula: \[ n = \frac{z^2pqd^2}{\varepsilon^2} \] where; \( n \) = desired sample size, \( z \) = standard normal deviation at 95% confidence, \( p \) = prevalence, \( q \) = 1-\( p \) and \( d \) = acceptable margin of error. The initial calculated sample size was 322.7. However, the finite population correction (for populations less than 10,000) was applied and a minimum sample size of 90.3 was determined. Nonetheless, this figure was approximated to 100.

The study subjects were recruited and examined by consultant Paediatricians, and medical officers posted to the Department of Paediatrics, who then entered the information so obtained, into a structured questionnaire designed for the study. Subjects were recruited once and seen as many times as necessary to complete the questionnaire within the study period. Care was taken not to negatively impact the patients’ waiting time in the clinic. Information obtained included; age in years (at last birth day), sex, weight, height, parents’ educational status and occupations, age at diagnosis and at first presentation to our facility. Others were liver span, splenic size (below the left costal margin), number of blood transfusions in the 12 months prior to recruitment, and Hb phenotype which was obtained from the records. Vaccination status (according to the NPI schedule), history of priapism in infancy, history of acute chest syndrome (ACS), avascular necrosis of the femoral or humeral head, stroke, number of acutely significant painful episodes requiring hospital visit in the preceding 12 months if any, number of haemolytic crises in the last 12 months if any, number of splenic sequestration if any, aplastic crises, number of severe bacterial infections documented in the last 12 months if any, history of hepatopath, cholecystitis, chronic leg ulcers and priapism were obtained from the records.

Socioeconomic class was determined using the occupations and highest academic qualifications of the parents. Complications were defined in conformity with standards. An acutely significant painful episode was defined as a painful event requiring a hospital visit and the use of oral and/or parenteral analgesics. Dactylitis/hand-foot syndrome was defined as painful non-pitting swelling of the hand/foot/digits. Avascular necrosis (AVN) was defined as an osteonecrosis or aseptic necrosis of the head of femur or humerus confirmed by radiography as irregularity of the articular surfaces of the head of femur/ humerus. ACS was defined as an acute illness characterized by fever and respiratory symptoms (dyspnea, chest pain) and together with new pulmonary infiltrates on chest radiograph. Haemolytic crisis was described as a marked drop in haemoglobin concentration with evidence of increased red blood cell destruction such as worsening pallor and jaundice, as well as reticulocytosis. Splenic sequestration was defined as a rapid enlargement of the spleen associated with anemia and hypovolaemic shock. Stroke (cerebrovascular disease) was described as acute neurologic symptoms/signs secondary to occlusion of and/or hemorrhage from cerebral vessels confirmed on computerized tomography (CT) scan. Aplastic crisis was defined as a transient aplastic situation characterized by clinical and laboratory evidences of severe anemia and reticulocytopenia.

Cholelithiasis was verified on abdominal ultrasonography in those with severe abdominal pain. Severe bacterial infections were taken as pneumonia, sepsis, meningitis, urinary tract infections, osteomyelitis, and septic arthritis confirmed by positive cultures and /or radiograph. Chronic leg ulcer was described as ulceration of the skin and under lying tissue of the lower extremities. Priapism was defined as sustained, unwanted, and painful penile erection.

Hepatic and splenic enlargements were elicited by palpation. A liver span of greater 8 cm was taken as hepatomegaly while those above 14cm were regarded as such for children above 15 years. Splenomegaly was defined as splenic enlargement beyond 1cm below the left costal margin. The weights and heights of the patients were measured with a surgilac floor mounted stadiometer combined with weighing scales. Height was measured with the
child standing erect and barefooted, with the occiput, scapulae, buttocks, calves, and heels touching the device. Readings were recorded in centimeters (cm). Steady State SCD was defined as the absence of crisis or any clinically significant event in a SCD patient in the three months prior to recruitment into the study.

Statistical analysis

Analysis of the collected data was done with the Statistical Package for Social Sciences (SPSS) version 20.0. Presentation of data was made using tables and prose. Means ± standard deviations were computed for continuous data, and the means were compared with the T test (mean weights and heights were compared to reference standards), while categorical variables were compared with the Chi-square or Fisher’s exact tests as appropriate. A P value < 0.05 was regarded as statistically significant.

Results

Patients’ age, gender, anthropometry and parental socio-economic class

One hundred children with SCD were recruited. The mean age was 6.97 ± 3.63 years. There were 61(61%) boys and 39(39%) girls giving a male: female ratio of 1.6:1. The mean weight of the subjects was lower than the reference standards but the difference did not reach statistical significance (t= -1.20, p= 0.14). Forty percent were between 102cm and 124cm tall, while 12(14.1%) were less than 89cm tall. The mean height of the subjects was also lower than the reference standards, this as well did not differ significantly (t= -0.66, p= 0.27). There was no representation of the upper socio-economic class among the parents of the study subjects, whereas 38(38%) belonged to the lower socio-economic class. These are shown in Table 1.

Clinical characteristics of SCD

Table 2 illustrates the clinical characteristics of the study subjects. The mean age at diagnosis was 13.24 ±14.83 months, while the mean age at first presentation to our facility was 13.86 ±17.51 months. Forty-eight subjects (58.5%) were adequately vaccinated for age, while 92 (92%) had an Hb phenotype of SS. Ten (10%) subjects were on hydroxyurea therapy, 22(22%) had steady state hepatomegaly, and 27(27%) had steady state splenomegaly. Ten (10%) had an episode of ACS within the 12-months preceding recruitment, while 40(40%) had at least one acute bacterial infection.

Gender and clinical features of SCD

The number of blood transfusions per year for both genders did not differ significantly (p= 0.70), steady state
splenic and hepatic sizes also did not differ significantly (p= 0.49, 0.41 respectively). The mean age for boys of 7.27 ±3.91 years and that for girls(6.49± 3.14 years) did not differ significantly as well (p= 0.09). Table 3 outlines the gender differences in clinical features.

**Impact of socio-demographic and clinical features on the occurrence of severe bacterial infections and haemolytic crises**

Table 4 shows that age, Hb phenotype, parental socio-economic status, vaccination status, presence of steady state hepatomegaly and splenomegaly had no statistically significant impact on the development of severe bacterial infections and haemolytic crises.

**Influence of socio-demographic and clinical features on the occurrence of acute chest syndrome and pain crises**

ACS occurred more frequently in children aged 9-12 years of age as well as those who had severe bacterial infections. The associations between ACS and age (χ²= 11.59, p ˂ 0.001), and with severe bacterial infections (χ²= 7.41, p= 0.006) were statistically significant. Table 5 also demonstrates that a history of dactylitis in infancy increased the frequency of occurrence of pain crises in this cohort of SCD patients (χ²= 3.65, p= 0.01). All the other clinical and socio-demographic features did not significantly impact the occurrence of ACS and pain crises.

### Table 3: The impact of patients’ gender on clinical features

| Clinical feature                        | Gender | P- value |
|----------------------------------------|--------|----------|
| Mean age (years)                       | 7.27± 3.9 Male    | 6.49 ± 3.1 Female    | 0.09 |
| Mean weight (Kg)                       | 19.08 ± 8.4 Male    | 18.14 ± 6.5 Female    | 0.53 |
| Mean height (cm)                       | 113.6 ± 22.5 Male    | 113.21 ± 18.8 Female    | 0.93 |
| Splenic size (Steady state)            | 0.44 | 0.44 |
| Normal                                 | 25 (65.8) Male    | 13 (34.2) Female    | 0.41 |
| Splenomegaly                           | 35 (57.4) Male    | 26 (42.6) Female    | 0.41 |
| Liver size                             | 0.70 | 0.70 |
| Normal                                 | 45 (68.4) Male    | 32 (31.6) Female    | 0.70 |
| Hepatomegaly                           | 15 (68.2) Male    | 7 (31.8) Female    | 0.70 |
| Number of blood transfusions in 12 months | 39 (60.0) Male    | 26 (40.0) Female    | 0.23 |
| None                                   | 12 (57.1) Male    | 9 (42.9) Female    | 0.23 |
| One                                    | 5 (62.5) Male    | 3 (37.5) Female    | 0.23 |
| Three                                  | 5 (83.3) Male    | 1 (16.7) Female    | 0.23 |
| Mean number of pain crises in 12 months | 3.20 ± 2.7 Male    | 2.55 ± 2.05 Female    | 0.68 |
| Mean number of haemolytic crises in 12 months | 1.83 ± 1.4 Male    | 2.09 ± 1.9 Female    | 0.68 |

Hb = Haemoglobin
The common complications in the present study were, pain crises, dactylitis, severe bacterial infections and haemolytic crises respectively. ACS, stroke, acute splenic sequestration and sickle cell hepatopathy occurred less frequently. Priapism and chronic leg ulcers were rare in this group of patients. These are in line with previous studies.\textsuperscript{23,25} Polymerization of deoxygenated HbS and to a lesser extent HbC, vaso-occlusion, haemolysis, as well as an increased predisposition to infections are central to the pathophysiology of these complications.\textsuperscript{26,27} The overwhelming predominance of the HbSS type may have played a role in the prevalence of these complications here, given that the HbSC type which is known to have a less severe course only occurred in 2% of subjects.\textsuperscript{25}

Few studies have explored the influence of gender on morbidity in Paediatric SCD. The majority seem to agree that girls have a milder course than boys.\textsuperscript{28,29} It has been speculated that males produce less nitric oxide (NO) than girls.\textsuperscript{28,30} NO is vital in sustaining vasomotor tone, controlling platelet aggregation, inhibiting ischaemic reperfusion injury, and regulating endothelial adhesion molecule expression.\textsuperscript{31} Estrogens are known to enhance NO production and limit its depletion, NO has also been associated with transcriptional control of fetal haemoglobin.\textsuperscript{28} Our data did not indicate a significant association between gender and clinical features. The reason for this is not clear. Nevertheless, it may be explained by our relatively small sample size, and the fact that our sample was skewed towards the male gender.

Severe bacterial infections were common among our patients, 40% of the study subjects had at least one severe bacterial infection. The basis for increased susceptibility of SCD patients to infections is well documented.\textsuperscript{27} Yet, our data did not indicate significant associations between age, Hb phenotypes, vaccination status, socio-economic class, hepatomegaly as well as splenomegaly and the risk of contracting a severe bacterial infection. Adegoke et al.\textsuperscript{24} reported similar results in Osun State, South-Western Nigeria. However, in their
study there was a significant association between mean age and severe bacterial infections. School age children were most likely to contract these infections. In addition, a Spanish study demonstrated that routine vaccination significantly reduces the risk of severe bacterial infections in a cohort of Paediatric SCD patients. The reasons for the dissimilarities in our study is not evident but, one could speculate that our patients were not vaccinated against most of the bacterial agents implicated in these infections.

None of the clinical and socio-demographic factors evaluated was significantly associated with haemolytic crisis in this cohort. Other studies have demonstrated that pre-school age, socio-economic class 3 and HbSS phenotypes are more likely to predict haemolytic crises in paediatric SCD patients. Our data did indicate that the majority of those with haemolytic crises had the HbSS phenotypes but this did not reach statistical significance. The relatively small sample size and less representation of the HbSC type in the current study could explain these discrepancies.

We found that our patients were more likely to develop ACS if they were aged 9-12 years and had previously contracted a severe bacterial infection. Similar studies done previously observed that socio-economic status, age and gender were associated with ACS. Differences here are perhaps due to dissimilarities in study design, sample size, and pattern of Hb phenotype. History of dactylitis in infancy was associated with an increased likelihood of contracting pain crisis in this cohort. This probably underlines the fact that both conditions are triggered by the acute vaso-occlusive phenomenon and hence would possess the same risk factors. Highlighting this association could assist clinicians to predict the prospects of future pain crises early in infancy and hence, institute preventive interventions for reduction of the frequency of pain crises. Other researchers however, did not explore this association.

The present study has documented some baseline parameters of Paediatric SCD in our setting. Nonetheless, limitations to the study were recognized. One of such is the fact that a prospective cohort design would have been better suited to this study. In addition, a multicenter approach with a larger sample would have been more representative. Also, assessment of sensitive markers of inflammation would have been applied in the determination of patients in steady state rather than solely relying on clinical assessment. Future research in this area may be directed at determining the pathophysiology of the complications of SCD and recommending more specific therapies.

**Conclusion**

The complications of Paediatric SCD in this part of North-Eastern Nigeria mirrors those in other parts of the country. ACS was more likely to occur in children with a previous severe bacterial infection. Socio-economic class, Hb phenotype and vaccination status appeared to have no influence on the development of complications.

**Recommendations**

We propose that in the evaluation of children with SCD, dactylitis in infancy could be taken into account as a risk factor for future development of frequent pain crises and in the establishment of personalized preventive interventions. There is also the need for advancement in the prevention of severe bacterial infections.

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**Authors’ contributions**

Imoudu IA conceptualized and designed the study, participated in data collection, analyzed and interpreted the data and drafted the manuscript. Yusuf MO participated in study design, data collection, and data analysis. Ahmad H, Afegbua D and Ismail MK participated in study design. All the authors reviewed and approved the final manuscript.

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References

1. Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. Bull World Health Organ 2008; 86(6): 480-7.

2. Piel FB, Patil AP, Howes RE, Nyangiri OA, Gething PW, Dewi M, et al. Global epidemiology of sickle haemoglobin in neonates: a contemporary geostatistical model-based map and population estimates. Lancet 2013;381(9861):142-51. doi:10.1016/S0140-6736(12)6229-X.

3. World Health Organization. Sickle-cell Anaemia Report by the Secretariat. Fifty-Ninth World Health Assembly 2006: WHO Geneva; 2006. Available from: http://wwwapps.who.int/ gb/archive/pdf_files/WHA59/A59_9-en.pdf. (cited on 2020 Nov 18).

4. Brabin BJ, Premji Z, Verhoeoff F. Analysis of anaemia and childhood mortality. J Nutr 2001;131:636-45.

5. Animasahun BA, Bode-Thomas F, Temiye EO, Njokanma OF. Clinical profile of Nigerian children with sickle cell anaemia. Curr Pediatr Res 2013;17(2):95-9.

6. Saganuwan AS. The pattern of sickle cell disease in sickle cell patients from North-Western Nigeria. Clinical Medical Insights: The therapeutics 2016;8:53-7.

7. Steinberg MH. Predicting clinical severity in sickle cell anaemia. Br J Haematol 2005;129:465-81.

8. Adegoke SA, Kuti BP. Evaluation of clinical severity of sickle cell anaemia in Nigerian children. J Appl Haematol 2013;4:58-64.

9. Chalan J, Biswas T. How to calculate sample size for different study designs in medical research. Indian J Psychol Med 2013;35(2):121-6.

10. Oyedeji. Socio-economic and cultural background of hospitalized children in Ilesha. Niger J Paediatr 1985;12(4):111-7.

11. Ballas SK, Lieff S, Benjamin LJ, Dampier CD, Heeney MM, Hoppe C, et al. Definitions of the phenotypic manifestations of sickle cell disease. Am J Hematol 2010;85:6-13.

12. World Health Organization Growth Reference Study Group. WHO child growth standards based on length/height, weight and age. Acta Paediatrica 2006;450:76-85.

13. Eyong ME, Ikobah JM, Ntea H, Eyong EM. Growth parameters of children in Calabar, a South-South Nigerian city: Are the CDC growth charts useful in clinical practice in this area? Niger J Paediatr 2020;47(1):30-6.

14. Akodu SO, Njokanma OF, Kehinde OA. Cormic index profile of children with sickle cell anaemia in Lagos, Nigeria. Anemia 2014; doi:10.1155/2014/312302. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4016837/pdf/ANEMIA2014-312302.pdf. (cited on 2020 Nov 23).

15. Esezobor CI, Akintan P, Akinlulie A, Adeyemo T. Wasting and stunting are still prevalent in children with sickle cell anaemia in Lagos, Nigeria. Ital J Pediatr 2016; 42:45. https://doi.org/10.1186/s3052-016-0257-4.

16. Payne AB, Link-Gelles R, Azonobi H, Hooper WC, Beall BW, Jorgensen JH, et al. Invasive pneumococcal disease among children with and without sickle cell disease in the United States, 1998 to 2009. Pediatr Infect Dis J 2013;32(12):1308-12. doi:10.1097/INF.OB013e3182a11808.

17. Zemel BS, Kawchak DA, Fung EB, Ohene-Frempong K, Stallings VA. Effect of zinc supplementation on growth and body composition in children with sickle cell disease. Am J Clin Nutr 2002;75(2):300-7.

18. Nunlee-Bland G, Rana SR, Houston-Yu PE, Ondunkor W. Growth hormone deficiency in patients with sickle cell disease and growth failure. J Pediatr Endocrinol Metab 2004;17(4):601-6.

19. Wolf RB, Saville BR, Roberts DO, Fissell RB, Kassim AA, Airewele G, et al. Factors associated with growth and blood pressure patterns in children with sickle cell anemia: Silent cerebral infarcts multi-center clinical trial cohort. Am J Hematol 2015;90(1):2-7. doi:10.1002/ajh.23854.

20. Akohoue SA, Shankar S, Buchowsk MS. Energy expenditure, inflammation, and oxidative stress in steady-state adolescents with sickle cell anemia. Pediatric Research 2007;61:233-8.

21. Eke BC, Edelu BO, Ikfebuna AN, Emodi JJ, Ibe BC. Obesity in Preschool-aged children with sickle cell anemia: Emerging nutritional challenge in a resource limited setting. Pediatr Hematol Oncol 2015;32(6):390-8. doi:10.3109/08880018.2015.1030716.

22. Oredugba FA, Savage KO. Anthropometric findings in Nigerian children with sickle cell disease. Pediatr Dev 2002;24:321-5.

23. Inusa BP, Daniel Y, Lawson JO, Dada J, Matthews CE, Sukhleem MS, et al. Sickle cell disease screening in Northern Nigeria: The co-existence of β-thalassemia inheritance. Pediad Therapeut 2015;5:3. DOI:10.4172/2161-0665.1000262.
24. Adegoke SA, Adeodu OO, Adekile AD. Sickle cell disease clinical phenotypes in children from South-Western Nigeria. Niger J Clin Pract 2015;18:95-101.
25. Alleluia MM, Fonseca TCC, Souza RQ, Neves FI, Conceição da Guarda C, Satiago RP, et al. Comparative study of sickle cell anemia and hemoglobin SC disease: Clinical characterization, laboratory biomarkers and genetic profiles. BMC Hematology 2017;17:15.DOI:10.1186/s12878-017-0087-7.
26. Kato GJ, Hebbel RP, Steinberg MH, Gladwin MT. Vasculopathy in sickle cell disease: biology, pathophysiology, genetics, translational medicine, and new research directions. Am J Hematol 2009; 84(9):618-25.
27. Booth C, Inusa B, Obaro SK. Infection in sickle cell disease: A review. Int J Infect Dis 2010;14:2-12.
28. Gladwin MT, Schechter AN, Ognibene FP, Coles WA, Reiter CD, Schenke WH, et al. Divergent nitric oxide bioavailability in men and women with sickle cell disease. Circulation 2003;107:271-8. doi:10.1161/01.CIR.0000044943.12533.A8.
29. Ceglie G, Di Mauro M, Tarissi De Jacobis I, De Gennaro F, Quaranta M, Baronci C, et al. Gender related differences in sickle cell disease in a paediatric cohort: A single-center retrospective study. Front Mol Biosci 2019;6:140.doi:10.3389/fmobi.2019.00140.
30. Alexandre-Heymann L, Dubert M, Diallo DA, Diop S, Tolo A, Belinga S, et al. Prevalence and correlates of growth failure in young African patients with sickle cell disease. Br J Haematol 2019;184:253-62.
31. Kim-Shapiro DB, Gladwin MT. Nitric oxide pathology and therapeutics in sickle cell disease. Clin Hemorheol Microcirc 2018;68:223-7.doi:3233/CH-189009.
32. Rincon-Lopez EM, Gomez MLN, Matos TH, Saavedra-Lazano J, De La Red YA, Ruperez BH, et al. Low risk factors for severe bacterial infection and acute chest syndrome in children with sickle cell disease. Pediatric Blood and Cancer 2019;66 (6):e27667.doi.org/10.1002/pbc.27667.
33. Alkindi S, Al-Busaidi I, Al-Salami B, Ballas SK. Predictors of impending acute chest syndrome in patients with sickle cell anaemia. Sci Rep 2020;10:2470.DOI:https://doi.org/10.1038/s41598-020-59258-y.
34. Da Silva Junior GB, Daher ED, Castro da Rocha FA. Osteoarticular involvement in sickle cell disease. Rev Bras Hematol Hemoter 2012;34 (2):156-164.
35. Ugwu AO, Ibegbulam OG, Nwagha TU, Madu AJ, Ocheni S, Okpala I. Clinical and laboratory predictors of frequency of painful crises among sickle cell anaemia patients in Nigeria. J Clin Diagn Res 2017;11(6):22-5.