EUROPEAN ACADEMIC RESEARCH
Vol. XII, Issue 9/ December 2024

Impact Factor: 3.4546 (UIF)
DRJI Value: 5.9 (B+)

ISSN 2286-4822
www.euacademic.org

Clinical Profile and Fetal Hemoglobin in Sudanese Child and Adolescents with Sickle Cell Anemia - SS Pattern

NADA Y ALI
University of El Imam EL Mahdi, Faculty of Medical Laboratory Sciences
HAIDER ELHADI
University of Gezira, Faculty of Medicine
BABIKER A MOHAMED
Karary University, Faculty of Medicine
AHMED M. ELKHALIFA
ELHAM ALI IBRAHIM ELAMIN
RAHMA ABD ELFATAH
ABDELHAKAM G. TAMOMH
University of El Imam EL Mahdi, Faculty of Medical Laboratory Sciences

Abstract

Background and Objectives: *Despite all treatment efforts of sickle cell anemia (SCA) in Sudan, SCA crisis are still responsible for significant morbidity and early mortality. However patients usually seek care in the acute setting for a seemingly uncomplicated pain episode (pain crisis or vaso-occlusive crisis), this event is primary risk factor for potentially life threatening SCA. This study aimed to evaluate clinical profile and fetal hemoglobin of Sudanese patients with sickle cell anemia with SS pattern.*

Methodology: *This is cross sectional hospital based study. Included 340 Sudanese child and adolescents aged 1–18 years having SS pattern attended to Kosti Teaching Hospital, Sudan, during 2018 – 2023. Demographic and clinical data collected by structured questionnaire while Hb F level measured by cellulose acetate paper electrophoresis. Data analyzed using IBM SPSS advanced statistics version 21.*

Results: *In the current study all patient 340 (100%) presented in crisis. Jaundice 139 (40.9%), splenomegaly 66 (19.4%), pneumonia 62 (18.2%), Bone pain 25 (7.4%), vasooclusive 17 (5.0%), chest pain 16 (4.7%), Joint pain 15 (4.4%). Hb F level ranged from 1% up to 32 % , A 91.2% (310) were less than 20% and 8.8 % (30) more than 20% with mean 10.9 % (± 2.1) for total population, a significant negative correlation between Hb F and disease severity was reported P. value (0.032).*

Conclusion: *The study concluded that clinical events (crisis) must diagnosed early and a good interventions should made also awareness among parents about sickle cell disease must be improved.*

Keywords: Sickle Cell Anemia (SCA). SS Pattern. Crisis. Sudanese Child. Hb F. Vaso-occlusive crisis.

INTRODUCTION:

Sickle cell anaemia (SCA) defined as a prototypical monogenic disorder due to autosomal recessive inheritance of a single base substitution (A-T) at the first exon of *HBB*. It results in replacement of negatively charged, hydrophilic glutamic acid by a hydrophobic amino acid, valine, in position 6 (*HBB*; glu (E) 6 val (A); *GAG-GTG*; rs334),

leading to defective haemoglobin tetramers which polymerize and aggregate during deoxygenation, changing soft discoid flexible red blood cells (RBCs) into stiff sickle-shaped cells.(1) Sickle cell anaemia (SCA) is the common inherited haemoglobin (Hb) disorders. Worldwide, a 300,000 infants are born usually.(13) In Sudan the first case of HbS gene was reported at 1950.(2) Latterly, studies showed that the frequencies of sickle cell gene vary from region to another in the country as well as in the same region. The available literature reported a wide range of sickle cell disease (SCD) frequencies in different areas in Sudan ranging from 0.8% in central Sudan to 30.4% in Western Sudan. The Messeryia tribe (branch of Baggara) in Darfur and Kordofan showed the highest rate of sickle cell disease (SCD), it is estimated that one in every 123 children is at risk of having SCD.(3) Sickle cell anemia (SCA), albeit monogenic, has heterogeneous phenotypic expression, mainly related to the level of hemoglobin F (HbF). However, while clinical heterogeneity of Sickle cell anaemia has been recognized, scientific research over the years tried to elucidate the role of several factors responsible for its clinical variability. The importance of fetal hemoglobin (HbF;□ 2 □□2) in sickle cell disease, started more than 70 years ago when Janet Watson observed that infants with sickle cell disease developed few symptoms and their deoxygenated RBCs took longer to sickle and did not deform extensively as their sickle cell trait-carrying mother's cells. Janet Watson later attributed these observation to high HbF levels in the infant blood.(4)

SCD is heterogeneous in its phenotypic expression, there is marked intraindividual and interindividual variability. Interindividual variability ranges from asymptomatic to severe illness. Also there is variability within an individual, with changes in the type and frequency of clinical events with age. Finally, there is variability in clinical events according to the geographical area due to the differences in environmental factors such as climate, socioeconomic status, and nutrition which influence the course of disease. Reasons of this heterogeneity are not fully understood. Interindividual variation in fetal hemoglobin (HbF) levels is the main modifiers that influence the clinical heterogeneity observed in SCD patients. (5) Generally the clinical pattern of disease is characterized by quiescent periods interspersed with acute events, referred to as crises. SCD a multisystem disorder, mostly affecting every organ system of the body. The clinical consequences have been divided into four groups: haemolysis and haematological complications, vasoocclusion, infection, and organ dysfunction.(14) Nimer, *et al*., 2019 (6) in their inspiring study entitled Fetal Hemoglobin and Disease Severity in Sudanese Sickle Cell Anemia Patients, conducted at Ahmad Qassem Teaching Hospital (Khartoum, Sudan), reported low level of Hb-F in Sudanese patients with sickle cell anemia (SS pattern) and 90% of patients developed complications.(6) According to their research methodology applied, this result affected by exclusion criteria used in determining the study population as they excluded all Patients under Hydroxyurea and those with a history of blood transfusion for at least three months. Individualized management of the SCA crisis and complications is a great challenge should be the goal of treatment. In this paper we try to assess the complications associated with sickle cell anemia (SS pattern) in (Kosti, Sudan), to reduce morbidity and mortality rate through early interventions.

METHODOLOGY:

The study population for this cross sectional hospital based study is sickle cell child and adolescents having SS pattern attended to Kosti Teaching Hospital, Sudan, during 2018

– 2023, aged 1–18 years. Patients younger than six months and older than 18 years of age, were excluded also patients with other haemoglobinopathies and sickle cell trait. The study approved by research committee of Faculty of Medical Laboratory Sciences, University of Gezira. The informed consent form written in Arabic was given and explained to the parents in local language. Taken the local cultural context into account, a verbal response was sufficient to be included in the study.

Using simple random sampling method and sample size calculation formula, [7] 340 children and adolescents with SCA who satisfied the inclusion criteria were included in this study.

$$N = \frac{Z^2 \times P \times Q}{d^2}$$

(N= Sample size. Z= 1.96. Q= 1-P. P= Expected prevalence rate (33). d= Desired absolute precision=0.05)

$$N = \frac{1.96^2 \times 0.33 \times (1 - 0.33)}{0.05^2} = 339.7$$

Demographic and clinical data collected by structured questionnaire filled by the researcher through translation to local language. A 2,5 ml of venous blood was collected in EDTA anticoagulated tube from each patient. The blood mixed well with an anticoagulant then analyzed immediately by cellulose acetate paper electrophoresis.

CELLULOSE ACETATE PAPER ELECTROPHORESIS:

Five microliters of lysed sample was transferred into well plates using a unit applicator; the sample was applied into the cellulose acetate membrane, along with suitable controls, and immediately placed in the electrophoresis chamber. The chamber was connected to a power supply and electrophoresed for 15 min at 350 V. This was used to separate and identify the different hemoglobins by their migration within an electric field. The amino acid composition of hemoglobin variants results in differences in their surface electrical charges, corresponding to different separation rates. [8]

Data analyzed using IBM SPSS advanced statistics version 22 (SPSS Inc., Chicago, IL). Numerical data expressed as mean and standard deviation or median and range as appropriate. Qualitative data expressed as frequency and percentage. Chi-square test was used to examine the relation between qualitative variables. For not normally distributed quantitative data comparison between three groups were done using nonparametric ANOVA. *P-value* was considered significant at 0.05.

RESULTS:

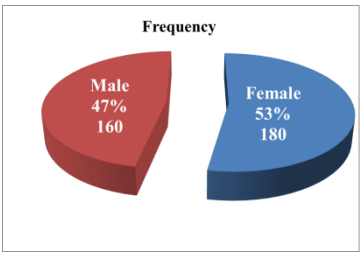

Figure 1: Study population according to sex

Table 1: Distribution of study population according to their age.

Age group	Frequency	Percent (%)
1-5 years	140	41.2
6-10 years	100	29.4
> 10 years	100	29.4
Total	340	100.0

Table 2: Hemoglobin F % mean and Standard deviation:

	Minimum	Maximum	Mean	Std. Deviation
Hb F %	1	32.%	10.9	± 2.1

Table 3: Hb F % according to sex:

Sex	Mean	No
Male	(10,8%)	160
Female	(9.45%)	180
Total	(10.9%)	340

Table 4: Hb F (%) level in study population

Hb F %	No	%
Less than 20%	310	91.2
More than 20%	30	8.8
Total	340	100

Table 5: Hb F according to age group

Age group	Mean	N	Std. Deviation
1-5 years	.89 (13%)	140	.51
6-10 years	.95 (14.2%)	100	.58
> 10 years	.53 (7.2%)	100	.35
Total	.80 (10.9%)	340	.53

A significant negative correlation between Hb F and age was reported, *p value* (0.001)

Table 6: Clinical presentation (SCA crisis) of study population:

	Frequency	Valid Percent
Pneumonia	62	18.2
Jaundice	139	40.9
Splenomegaly	66	19.4
chest pain	16	4.7
Vasooclusive	17	5.0
Joint pain	15	4.4
Bone pain	25	7.4
Total	**340**	**100.0**

A significant negative correlation between Hb F and disease severity was reported *P. value* (0.032).

Table 7: Crisis according to age group.

Crisis No (%)	Age group			Total
	1-5 years	6-10 years	> 10 years	
Pneumonia 62 (18.2%)	26	22	14	62
Jaundice 139 (40.9%)	56	42	41	139
Splenomegaly 66 (19.4%)	31	32	3	66

Chest pain 16 (4,7%)	4	1	11	16
Vasocclusive 17 (5 %)	15	0	2	17
Joint pain 15 (4.4%)	5	0	10	15
Bone pain 25 (7.4%)	3	3	19	25
Total 340 (100%)	140	100	100	340

DISCUSSION:

This study includes 340 Sudanese child and adolescents with sickle cell anemia (SCA) having SS pattern ,180 (52.9%) were females whereas 160 (47.1%) were males, (male to female ratio was 0.9:1), Similar results was found in study conducted by Gloire Mbayabo, *et al*. [10] Participants age ranged from 1- 18 years and the mean age was (7.8 ± 4.7). They classified into three group 1-5 years 140 (41.2%), group (2) was 6-10 years included 100 (29.4%) and group (3) was > 10 years included 100 (29.4%). All of them attended Kosti Teaching Hospital. Most patients belonged to the age group of 1-5 years representing 41.2%, this result supported by Jain *et al* [11] who reported that the highest incidence of acute events may be due to cross-infection and 56% of them were younger than three years old.

The pathophysiology of sickle cell anaemia depends on the degree of polymerization of deoxygenated sickle hemoglobin, thus the clinical symptoms of patients with HbSS disease are varies considerably from a symptomatic in some patients, to death in infancy in the others. Clinical symptoms include severe anemia (hemolytic and aplastic), susceptibility to infections, organ injury, sequestration, and episodic vaso-occlusions. Death in most patients was attributed to chronic organ damage, acute chest syndrome (such as renal and cardiac failure), cerebrovascular accident, and complications of pregnancy. [12] In the current study all patient 340 (100%) presented in crisis. Jaundice 139 (40.9%), splenomegaly 66 (19.4%), pneumonia 62 (18.2%), Bone pain 25 (7.4%), vasooclusive 17 (5.0%), chest pain 16 (4.7%), Joint pain 15 (4.4%) . This result supported by Nimer, *et al*., 2019 [6] 90% of patients presented SCA crisis and Imoudu A *et al* 2021, [13] and these complications may attributed to polymerization of deoxygenated HbS and to a lesser extent Hb C, vaso-occlusion, haemolysis, as well as an increased predisposition to infections are central to the pathophysiology of these complications. [16] The predominance of the HbSS in study population may have played a significant role in the frequency of complications here, given that HbSC have a less severe course. [17] Vasoocclusion (VOC) was thought to be the underlying cause of painful crises, acute splenic sequestration, and priapism (painful and prolonged penile erection). Painful crises, considered the hallmark of SCD, they are severe pain lasting for two or more hours attributable to SCD due to blockage of microcirculation by sickled red blood cells leading to hypoxic injury and infarction. Normally affect arms, legs, back, abdomen, chest, and head. [14]

In this study 62 (18.2%) participant have Pneumonia 26 (41.9%) of them within 1-5 years old, this result supported by Imoudu A, *et al*, [13] who reported that 40% of the study population had at least one severe bacterial infection. Different factors responsible for increased risk of infections in SCD. Some infections are result of treatment complication itself. Also SCD patients are at high risk of blood transfusion

transmissible infections as they frequently received blood especially human immunodeficiency virus (HIV) and viral hepatitis. In addition to immunologic dysfunction in SCD due to autosplenectomy which result in defective cellular and humoral immunity. About 30% loss of splenic function occurs by first year of life and 90% by sixth year of life. [15]

In the present study the Hb F level ranged from 1% up to 32 % , 310 (91.2%) were less than 20% and 30 (8.8%) more than 20% with mean 10.9 % (± 2.1) for total population, a significant negative correlation between Hb F and disease severity was reported *P. value* (0.032). Houwing, *et al* 2023 [18] reported that the level of HbF varies markedly between sickle cell disease patients ranging from 1% up to > 25% and is genetically controlled. Physiological decrease in HbF and switch to adult haemoglobin controlled by BLC11A gene and ZBTB7A gene. Patients with high HbF% may exhibit severe disease if Hb F is unevenly distributed among F cells (red blood cells with detectable Hb F), with a majority of erythrocytes containing insufficient Hb F concentrations to inhibit HbS polymerization.

Although several studies reported that the level of Hb F is sex dependent and is high in female than in male we observed a lower levels in female (9.45%) compared to the male (10.8%) (Table 3). The reason for this result is not clear. It may be explained by nongenetic factors such as socio economic factors and environmental factors. A significant negative correlation between Hb F and age was reported*, p value* (0.001) this result is consistent with Gloire Mbayabo, *et al* 2023. [10] However Hb F level in the current study was varied according to age group, the study observed (13%) in 1-5 years, (14.2%) in 6-10 years and (10.9%) in patients > 10 years. These differences may be due to various factors affect Hb F production in SCA individuals. Haplotype is one of this factors, Cameroon and Benin haplotypes are commons in Sudan, another factor affects Hb F levels is Hydroxyurea for those under treatment which were not excluded in methodology.

CONCLUSION

The study concluded that clinical events (crisis) must diagnosed early and a good interventions should made also awareness among parents about sickle cell disease must be improved.

Limitations:

As in all research this study has limitations. The nutritional status, socio-demographic factors in addition to psychological deficits were not evaluated.

Acknowledgement

Thanks and gratitude to all members of Kosti Teaching Hospital and Al-Yamama Specialized Hospital for their help and support

Funding

None

REFERENCES:

1. Paikari Alireza and Sheehan Vivien A. Fetal haemoglobin induction in sickle cell disease. *British Journal of Haematology* 2018.; (180); 189–200.
2. El-Hazmi MA, Al-Hazmi AM, Warsy AS. Sickle cell disease in Middle East Arab countries. *Indian J Med Res*; 2011; 134(5):597-610. PubMed Google Scholar.
3. Majdi Mohammed Sabahelzain and Hanan Hamamy. The ethnic distribution of sickle cell disease in Sudan. *Pan African Medical Journal*; 2014; 18:13 doi:10.11604/pamj.2014.18.13.3280.
4. Akinsheye Idowu, Abdulrahman Alsultan, Nadia Solovieff, Duyen Ngo, Clinton T. Baldwin, Paola Sebastiani, David H. K. Chui, Martin H. Steinberg1. Fetal hemoglobin in sickle cell anemia. *bloodjournal.org*. 2015.
5. Serjeant. G. R. The natural history of sickle cell disease. *Cold Spring Harbor Perspectives in Medicine*, 2013; 3(10) Article ID a011783.
6. Shireen Z. Nimer, El Shazali W. Ali, Hiba Khalil. Fetal Hemoglobin and Disease Severity in Sudanese Sickle Cell Anaemia Patients. *African Journal of Medical Sciences*, 2019, 4 (7). ajmsc.info.
7. Onwasigwe C. Principles and Methods of Epidemiology. *Enugu*: El 'Demak Publishers; 2010.
8. ICSH: International Committee for Standardization in Haematology. Haematological Tests. In: Cheesbrough M,. *District laboratory practice in Tropical Countries*, Part 1. Cambridge, UK: Cambridge University press, 1988:282-98.
9. Betke K, Mati HR, Schlicht L. Investigation of abnormal haemoglobins and thalassaemia. In: Dacie JV, Lewis SM, eds. *Practical haematology*. 9th ed. London, UK: Curchill Livingstone, 2001: 231-68.
10. Gloire Mbayabo, Mamy Ngole, Paul Kabuyi Lumbala, Aimé Lumaka, Valerie Race, Gert Matthijs, Tite Minga Mikobi, Koenraad Devriendt, Chris Van Geet & Prosper Tshilobo Lukusa Clinical and biological profile of Sickle Cell Anemia children in a rural area in Central Africa, *Hematology*, 2023; 28:1, 2193770, DOI: 10.1080/16078454.2023.2193770
11. Jain D, Bagul AS, Shah M, Sarathi V: Morbidity pattern in hospitalized under five children with sickle cell disease. Indian J Med Res. 2013, 138:317-21
12. Henry O. Ogedegbe.ß-Globin Gene Cluster Haplotype Analysis as a Predictor of Sickle Cell Disease Severity. *Labmedicine*.2020.
13. Imoudu A, Iragbogie, Yusuf O Maimuna, Ahmad Hayatu, Afegbua S Dalhat and Ismail K Musa Clinical profile of paediatric sickle cell disease at a reference hospital in North– eastern Nigeria *Niger J Paediatr* 2021; 48 (2):74 – 81
14. Makani, J. Ofori-Acquah, S. F. Nnodu, O. Wonkam, A. and Ohene-Frempong K.. Sickle Cell Disease: New Opportunities and Challenges in Africa. *The Scientific World Journal*. 2013. Article ID 193252, doi.org/10.1155/2013/193252.
15. Adewoyin. A. S. Management of Sickle Cell Disease: A Review for Physician Education in Nigeria (Sub-Saharan Africa). Review Article. *Anemia*. 2015. ID 791498, 21pages. doi.org/10.1155/2015/791498.
16. Booth C, Inusa B, Obaro SK. Infection in sickle cell disease: A review. *Int J Infect Dis* 2010;14:2-12.
17. Alleluia MM, Fonseca TCC, Souza RQ, Neves FI, Conceicao 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.
18. Houwing, M. E., de Pagter, P. J., van Beers, E. J., Biemond, B. J., Rettenbacher, E., Rijneveld, A. W., Schols, E. M., Philipsen, J. N. J., Tamminga, R. Y. J., van Draat, K. F., Nur, E., & Cnossen, M. H. Sickle cell disease: Clinical presentation and management of a global health challenge. *Blood reviews*, 2019; 37, Article 100580. https://doi.org/10.1016/j.blre.2019.05.004.