A Retrospective Study on Gender-Related Differences in Clinical Events of Sickle Cell Disease: A Single Centre Experience

Chilota Chibuife Efobi[1], Chisom Adaobi Nri-ezedi[2], Chika Sandra Madu[3], Chukwuka Charles Ikediashi[4], Emeka Stanley Obi[5] and Obiora Ejiofor[6]

[1]Department of Haematology, Faculty of Basic Clinical Sciences, Nnamdi Azikiwe University, Nnewi, Anambra, Nigeria. [2]Department of Paediatrics, Faculty of Medicine, Nnamdi Azikiwe University, Nnewi, Anambra, Nigeria. [3]Department of Haematology, College of Medicine, Chukwuemeka Odumegwu Ojukwu Univeristy Awka, Anambra, Nigeria. [4]Department of Family Medicine, College of Medicine, Chukwuemeka Odumegwu Ojukwu Univeristy Awka, Anambra, Nigeria. [5]Department of Healthcare Administration, College of Public Health, East Tennessee State University, P O Box 70705. Johnson City, TN 37614. [6]Department of Paediatrics, College of Medicine, Chukwuemeka Odumegwu Ojukwu University Awka, Anambra, Nigeria.

ABSTRACT

Background: Sickle cell disease (SCD) is a genetic disorder, prevalent in Sub-Saharan Africa, especially in Nigeria with a high rate of mortality and morbidity due to poor socioeconomic structure amongst other factors. Devising risk stratification through inexpensive means may serve as an important tool for early detection and management of complications of SCD. Objective: To determine the impact of gender on the clinical events amongst children living with SCD. **Materials and Methods**: This was a retrospective study carried out at Chukwuemeka Odumegwu Ojukwu University Teaching Hospital, Awka, Anambra, Nigeria. Medical notes were obtained from medical records department. Data on demographic variables, weight, full blood count result, blood transfusions history, hospital admissions and complications were obtained. p value of < 0.05 was considered statistically significant. **Results:** 45 cases were reviewed, of which 23 (51.1%) were males and 22 (48.9%) were females with a mean age of 9.8±3.9 years. The mean haemoglobin concentration, WBC, neutrophil, lymphocyte, and platelet counts of the study group were 9.94± 4.58 g/dl, 13.86 ±8.15x109/l, 6.71± 4.37x 109/l, 6.79±4.51 x109/. There was no statistically significant relationship with gender (p values: 0.457, 0.495, 0.893, 0.319, 0.137 respectively. Frequency of vaso-occlusive crisis and chronic leg ulcer were more in males, although this was not statistically significant (p=0.291, 0.699 respectively). Females were shown to have more cases of osteomyelitis but was not statistically significant (p=0.459). **Conclusion:** We found no statistically significant relationship between gender and clinical events in SCD patients, although other studies reported otherwise. A larger, multicentre study is recommended.

Keywords: Anemia, Sickle Cell; Male; Female; Nigeria; Child

OPEN ACCESS

Correspondence:
Emeka Stanley Obi
East Tennessee State University, P O Box 70705. Johnson City, TN 37614
4236728858
obies1@etsu.edu

Specialty Section:
This article was submitted to Clinical, a section of TJMR

Received: *May 12, 2023*
Accepted: *July 18, 2023*
Published: *June-July 2023*

Citation:
C C Efobi, C A Nri-ezedi, C S Madu, C C Ikediashi, E S Obi and O Ejiofor. A Retrospective Study on Gender-Related Differences in Clinical Events of Sickle Cell Disease: A Single Centre Experience Trop J Med Res. 2023:22(1);137-144. DOI: 10.5281/zenodo.8312700

Access Code

http://tjmr.org.ng

INTRODUCTION

Sickle cell disease (SCD) is one of the most common haematological disorders worldwide and is linked to a number of episodes of acute illness and progressive organ damage.[1] It is caused by the substitution of valine for glutamic acid at the 6th position of the beta-globin chain, leading to the generation of the abnormal haemoglobin called - HbS. It has several consequent manifestations which may be acute or chronic and include vaso-occlusive crisis, acute chest syndrome, stroke, infections, pulmonary hypertension, nephropathy, avascular necrosis of the bones, retinopathy, chronic osteomyelitis, and chronic leg ulcers.[1]

Although it is a global public health issue, commonly seen in the Middle East, Mediterranean regions, Southeast Asia, and sub-Saharan Africa,[2] its greatest burden is in Nigeria, India, and the Democratic Republic of Congo, with these three countries contributing up to 90% of all cases globally.[3] The global prevalence rate averages between 5-7% but in sub-Saharan Africa, it rises up to 10-45%.[2] Furthermore, while it has no known sex predilection since it is transmitted as an autosomal recessive disorder,[4] there have been some reports of gender variations in its mortality and morbidity, which may be related to biological and social factors.[5,6]

There have been various reports by several authors on gender difference in frequency of VOC amongst SCD patients.[1,5,6,7,8,9] Therefore, pattern of gender distribution may play a role in the management of complications of the disease, by offering insights into its management. Gender as a risk factor of some manifestations of SCD may aid in early detection and prompt management. Considering the growing reports of gender-related differences in SCD manifestations, the divergent findings from various study geographical contexts, and the possible benefits that this knowledge will accord the management of SCD, it becomes beneficial to contribute to the literature from a Nigerian context. This study, therefore, aims to determine the impact of gender on the clinical events amongst children living with SCD.

MATERIALS AND METHODS

Study area: This study was conducted at the Chukwuemeka Odumegwu Ojukwu University Teaching Hospital, Awka. It is a state government owned Teaching Hospital and supplies health care needs for Residents in Awka and neighbouring towns and states.

Study design: This was a retrospective observational study, carried out at the Department of Paediatrics, Chukwuemeka Odumegwu Ojukwu University Teaching Hospital, Amaku, Awka, Anambra State.

Case notes of sickle cell disease patients seen from January 2020 to April 2022 were obtained from the medical records department of the hospital. Data obtained from the case note include sociodemographic variables, weight, full blood count results and complications. These were input on excel sheet.

Inclusion criteria: Case notes of all sickle cell disease patients

Exclusion criteria: Case notes of those not diagnosed of SCD

Data Analysis: Collated data were cleaned and analyzed using Python 3.10.0. Parametric numerical variables were summarized using means and standard deviations, while non-parametric variables were represented with medians and interquartile ranges. Frequencies and their percentages reflected the summary of categorical variable distributions.

Student's t-test and ANOVA were used to determine the statistical inference between numeric subsets while Fischer's exact test and Pearson chi-square analysis employed for categorical variables. A p-value of <0.05 was considered statistically significant for this study.

RESULTS

A total of 45 case notes were reviewed for the study, of which males were 23(51.1%), while females were 22(48.9%). Male to female ratio is 1:0.9. Table 1

shows the weight distribution of the study group. Table two shows the laboratory indices of the study group. There was no statistically significant differences between gender, haemoglobin concentration, total white cell count and platelets. (p=0.457, 0.495, 0.137 respectively). A number of clinical presentations of SCD were found amongst the study group of which vaso-occlusive crisis was the commonest and had more male (56.52%) involvement, although this was not statistically significant.(p=0.291). Males had a higher incidence of chronic leg ulcer when compared to the females, although the difference was not statistically significant.(p=0.699) as seen in table 3.

Table 1: Background Characteristics

Variable	Total	Male	Female	p-value
	n=45	*n=23*	*n-22*	
Age	.....	10.35 ± 4.28	9.18 ± 3.51	0.325
Weight (kg)	30.43 ± 9.99	31.72 ± 10.82	29.08 ± 9.08	0.381
Weight SDS	-0.46 ± 1.4	-0.58 ± 1.26	-0.32 ± 1.55	0.543
Weight Distribution				
Underweight	8 (17.8)	4 (17.4)	4 (18.2)	
Healthy weight	29 (64.4)	17 (73.9)	12 (54.5)	0.257
Overweight	5 (11.1)	2 (8.7)	3 (13.6)	
Obese	3 (6.7)	0 (0.0)	3 (13.6)	

Table 2: Laboratory Indices

Variable	Total	Male	Female	p-value
	n=45	*n=23*	*n-22*	
Haemoglobin (g/dl)	.....	10.44 ± 6.07	9.41 ± 2.19	0.457
Packed Cell Volume (L/L)	27.49 ± 7.74	27.17 ± 9.02	27.82 ± 6.32	0.782
White blood count	13.86 ± 8.15	14.69 ± 7.57	13.0 ± 8.81	0.495
Neutrophil	6.71 ± 4.37	6.8 ± 4.14	6.62 ± 4.71	0.893
Lymphocyte	6.79 ± 4.51	7.45 ± 4.52	6.1 ± 4.5	0.319
Monocytes	3.59 ± 2.42	3.51 ± 1.78	3.68 ± 2.99	0.817
Eosinophils	0.22 ± 0.24	0.26 ± 0.25	0.18 ± 0.22	0.237
Basophils	0.37 ± 0.71	0.29 ± 0.4	0.45 ± 0.93	0.446
Platelets	272.02 ± 86.6	290.87 ± 87.79	252.32 ± 82.71	0.137
Neutrophil-Lymphocyte ratio	1.13 ± 0.79	1.03 ± 0.76	1.23 ± 0.82	0.402
Platelet-Neutrophil ratio	67.17 ± 55.42	71.25 ± 60.88	62.91 ± 50.15	0.619
Platelet-Lymphocyte ratio	56.85 ± 37.67	52.93 ± 29.79	60.95 ± 44.83	0.482
Severity Score	4.0 ± 2.02	10.35 ± 4.28	9.18 ± 3.51	0.325

Table 3: gender and SCD presentations

SCA Outcomes	Total	F	M	p-value
Dactylitis				
No	39 (86.7)	19 (86.36)	20 (86.96)	
Yes	6 (13.3)	3 (13.64)	3 (13.04)	0.999
VOC				
No	24 (53.3)	14 (63.64)	10 (43.48)	
Yes	21 (46.7)	8 (36.36)	13 (56.52)	0.291
ACS				
No	41 (91.1)	20 (90.91)	21 (91.3)	
Yes	4 (8.9)	2 (9.09)	2 (8.7)	0.999
Splenic sequestration				
No	43 (95.6)	21 (95.45)	22 (95.65)	
Yes	2 (4.4)	1 (4.55)	1 (4.35)	0.999
Haemolytic crisis				
No	37 (82.2)	18 (81.82)	19 (82.61)	
Yes	8 (17.8)	4 (18.18)	4 (17.39)	0.999
Stroke				
No	44 (97.8)	21 (95.45)	23 (100.0)	
Yes	1 (2.2)	1 (4.55)	0 (0.0)	0.489
Chronic leg ulcer				
No	37 (82.2)	19 (86.36)	18 (78.26)	
Yes	8 (17.8)	3 (13.64)	5 (21.74)	0.699
Avascular Bone Necrosis				
No	44 (97.8)	22 (100.0)	22 (95.65)	
Yes	1 (2.2)	0 (0.0)	1 (4.35)	0.999
Osteomyelitis				
No	37 (82.2)	17 (77.27)	20 (86.96)	
Yes	8 (17.8)	5 (22.73)	3 (13.04)	0.459
Heart failure				
No	44 (97.8)	22 (100.0)	22 (95.65)	
Yes	1 (2.2)	0 (0.0)	1 (4.35)	0.999
Retinopathy				
No	44 (97.8)	22 (100.0)	22 (95.65)	
Yes	1 (2.2)	0 (0.0)	1 (4.35)	0.999
Nephropathy				
No	43 (95.6)	21 (95.45)	22 (95.65)	

DISCUSSION

SCD affects mostly people of African descent and mortality is higher in Sub- Saharan Africa due to several factors including ignorance, poverty, inadequate medical care, etc.[10] Devising risk stratification through inexpensive means may serve as an important tool for early detection and prompt management of complications of SCD. In this case, we tried to determine an association between gender and clinical presentations of SCD.

Vaso-occlusive crisis is one of the commonest presentations of SCD.[11] Previous studies have found either a male[5] or female predominance[6,7] in the frequency of the occurrence of vaso-occlusive crisis, which is in contrast with our own findings. However, our report corresponded with reports by Ugwu et al[1] who reported no statistically significant difference between the two genders. Of these other studies,[5,6,7,8] the striking occurrence is the similarity between our study and that of Ugwu et al[1] in terms of geographical context, whereby both studies were conducted in Nigeria, but in different centres and age groups, while the other studies were conducted in other countries including Italy,[5] the United States,[7] and Saudi Arabia,[8] This raises further questions on the variation of gender differences by geographical locations or intrinsic characteristics such as race or genetic makeup.

Furthermore, similar to other previous studies,[1,5,7] we found no statistically significant difference between the mean white cell count, platelet count of SCD patients, and gender of the study group. This is in contrast with findings of a study carried out in Ghana and reported a higher white cell count in males when compared to females.[12] Nevertheless, regarding the haemoglobin level, findings from our study did not correspond with the study population in the United States[7] where there were some statistically significant gender differences with a higher haemoglobin concentration observed in males when compared to females. However, our non-significant gender differences correspond to other studies including the local[1] and international studies.[5,8]. It has been shown that hematological features and clinical severity of SCD are affected by gender, genetic, and environmental factors.[12]

We found no statistically significant difference between leg ulcer and gender, unlike other studies[1,7] where males had more leg ulcers than females. This difference may be explained by the fact that our study population was the paediatric age group, unlike Masese et al.[7] and Ugwu[1] who used adult subjects for their studies. This age difference has also been supported by previous studies[13,14] which did not only show a male predominance pattern but also an increasing incidence rate with age, and an incidence rate of 3% per year between 10 and 19 years and 14.5-19% per year after 20 years. This may be explained by the fact that males tend to seek financial independence early and hence are exposed earlier to hazardous elements, while seeking for a means of livelihood and therefore increasing their risk of having leg ulcers.

Regarding osteomyelitis, our study corresponded with Ceglie et al.[5] with no statistically significant difference between the two genders but now contrasts with the findings by Ugwu et al,[1] (which shares a similar geographical context as our study). This pattern of no significant gender difference in osteomyelitis manifestation in SCD may probably be explained by the difference in age of the study group, as some previous studies[15,16] have noted that the risk of osteomyelitis is higher with increasing age and herein, the study by Ugwu et al,[1] was performed amongst SCD adults while our study and that of Ceglie et al. [5] were performed in children. However, these studies that linked osteomyelitis incidence to age were performed on healthy subjects, and considering the pathophysiology of osteomyelitis in SCD patients, where osteomyelitis is strongly linked to the immunodeficiency that is often secondary to splenectomy that occurs in some SCD patients even at an age as young as 5 years[17], age may not really be a true explaining factor in this case.

Compared to other studies,[1,5] our study found a similar occurrence of no statistically significant

gender related differences in the occurrence of splenic sequestration, avascular necrosis, nephropathy, and stroke. This contrasts with findings from other studies, that found that splenic sequestration and nephropathy were more in females.[18,19] These studies also had adults as their study group. However, we also found no significant difference in the occurrence of cardiac events, while this corresponds with Meloni et al,[20] it did not correspond to the findings by Masese et al.[7] and Ceglie et al.[5] who both found male dominance in the occurrence. Salzano et al,[18] also found that chest pain was commoner in males.

Body weight of the children studied didn't also differ with gender in as much as many of them were within expected weight. This is contrasts with the study done in Philadelphia that reported males had a lower body weight than females.

While other studies have found some differences in at least one complication, our study has not shown such a pattern. This overall non-gender related pattern may be due to some methodology limitations in our study such as a small sample size of only 45 subjects, which was limited to the paediatric age group and a retrospective data collection time frame of only two years. A longer time frame may have increased our sample size and offered more reliable data insights; however, the records could only afford comprehensive SCD data for the studied time frame. Additionally, findings from this study may not be readily generalizable because the data for this study was obtained from a single centre. Hence, a future multi-centre study with a large sample size which will involve both the adult and paediatric age group, will aid in robustly investigating the gender differences in SCD manifestations in children.

Furthermore, certain possible and important determinants, such as social factors, lifestyle, and health literacy, were not considered in this study. This is because, based on the study's retrospective design, these details were not available and accessible to us. It is already known that SCD patients who care better for themselves by adhering to their care regimens have better and more stable clinical state than those who do not.[21] These determinants have also been shown by previous studies to influence the health behaviours and health-related quality of life of various groups including males versus females.[22-25] Another possible confounding factor that could not be assessed because of the retrospective nature of the study is the frequency of clinic visits.

CONCLUSION

We found no statistically significant association between clinical manifestations of SCD and gender. This may have been influenced by the small sample size and age of the study population. However, it is therefore important to conduct a more broad-based study, possibly a multicentre study, involving both adult and paediatric age groups, to determine the possibility of using its findings as a screening tool for early detection of SCD complications and possibly design a protocol for prophylactic measures for genders identified with any of these complications.

Acknowledgements: Profound gratitude to the Chukwuemeka Odumegwu Ojukwu University Teaching Hospital's medical record department for her diligence and cooperation in sourcing and supplying the case notes for this study.

Author Contributions: CCE conceptualized the study. CSM, CCI were responsible for the data curation while CAN contributed to the formal analysis and methodology. CSM, CSI, ESO were involved in writing the original draft while CCE, CAN, OE did the review and editing. Finally, project administration was done by ESO.

Data availability: The data used to support this findings are available from the corresponding author upon reasonable request.

Funding: No funding sources

Conflict of interest statement: None declared

Ethical Approval: The study was approved by the Institutional Ethics Committee.

REFERENCES

1. Ugwu AO. Gender differences in the complications of sickle cell anemia. International Journal of Medicine and Health Development [Internet]. 2022 [cited 2022 Sep 22];27(1):38–42. Available from: https://www.ijmhdev.com/article.asp?issn=2635-3695;year=2022;volume=27;issue=1;spage=38;epage=42;aulast=Ugwu
2. Adewoyin AS. Management of sickle cell disease: A review for physician education in Nigeria (Sub-Saharan Africa). Anemia. 2015; 18;2015.
3. DeBaun MR, Galadanci NA. Sickle cell disease in sub-Saharan Africa [Internet]. UpToDate. 2022 [cited 2022 Mar 16]. Available from: https://www.uptodate.com/contents/sickle-cell-disease-in-sub-saharan-africa
4. Maakaron JE. Sickle Cell Disease [Internet]. Medscape. 2021 [cited 2022 Mar 16]. Available from : https://emedicine.medscape.com/article/205926-overview
5. 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 Pediatric Cohort: A Single-Center Retrospective Study. Front Mol Biosci, 2019 Dec 5;6:140.
6. Auma CPA, Owino EJ. Influence of gender on quality of life of paediatric patients with sickle cell disease attending a referral hospital in Western Kenya; a preliminary analysis. East Afr Med J. 2021 Jun 17;96(4).
7. Masese R v., Bulgin D, Knisely MR, Preiss L, Stevenson E, Hankins JS, et al. Sex-based differences in the manifestations and complications of sickle cell disease: Report from the Sickle Cell Disease Implementation Consortium. PLoS One. 2021 ;16(10):e0258638.
8. Udezue E, Girsham AM. Differences between males and females in adult sickle cell pain crisis in eastern Saudi Arabia. Ann Saudi Med. 2004;24(3):179.
9. Ilesanmi OO. Gender Differences in Sickle Cell Crises: Implications for Genetic Counselling and Psychotherapy. J Psychol Psychother. 2013;03(04):1000123
10. Grosse SD, Odame I, Atrash HK, Amendah DD, Piel FB, Williams.TN. Sickle Cell Disease in Africa: A Neglected Cause of Early Childhood Mortality. Am J Prev Med. 2011; 41(6): S398–S405
11. Jang, T., Poplawska, M., Cimpeanu, E. *et al.* Vaso-occlusive crisis in sickle cell disease: a vicious cycle of secondary events. *J Transl Med* **19**, 397 (2021).
12. Antwi-Boasiako C, Ekem I, Abdul-Rahman M, Sey F, Doku A, Dzudzor B, Dankwah GB, Hagar Otu K, Ahenkorah J, Aryee R. Hematological parameters in Ghanaian sickle cell disease patients. *J Blood Med*. 2018;9:203-209
13. Monfort JB, Senet P. Leg Ulcers in Sickle-Cell Disease: Treatment Update. Adv Wound Care (New Rochelle) 2020;9(6):348.
14. Minniti CP, Eckman J, Sebastiani P, Steinberg MH, Ballas SK. Leg Ulcers in Sickle Cell Disease. Am J Hematol .2010;85(10):831–3.
15. Allende JMB, Sánchez MG, Caso AA. Osteomyelitis. Medicine (Spain). 2022;13(52):3041–9.
16. Kremers HM, Nwojo ME, Ransom JE, Wood-Wentz CM, Joseph Melton L, Huddleston PM. Trends in the Epidemiology of Osteomyelitis: A Population-Based Study, 1969 to 2009. J Bone Joint Surg Am. 2015;97(10):837–45.
17. Al Farii H, Zhou S, Albers A. Management of Osteomyelitis in Sickle Cell Disease: Review Article. J Am Acad Orthop Surg Glob Res Rev. 2020 Sep;4(9):e20.00002-10.
18. Salzano, FM. Incidence, effects, and management of sickle cell disease in Brazil. J Pediatr Hematol Oncol. 1985; 7(3):p 240-244,
19. Osarogiagbon RU, Haider SN, Jun Tang MS .

Effect of Sickle Cell Disease Type, Age and Gender On the Prevalence of Chronic Organ Damage in Adults with Sickle Cell Disease. Blood. 2009; 114(22): 4607

20. Barden ME, Kawchak DA, Ohene-Frempong K, Virginia A Stallings VA, Zemel BS. Body composition in children with sickle cell disease, AJCN. 2002;76(1):218–225.
21. Walsh KE, Cutrona SL, Kavanagh PL, Crosby LE, Malone C, Lobner K, et al. Medication adherence among pediatric patients with sickle cell disease: A systematic review. Pediatrics 2014;134(6):1175–83
22. Martin C, Pialoux V, Faes C, Charrin E, Skinner S, Connes P. Does physical activity increase or decrease the risk of sickle cell disease complications? Br J Sports Med. 2018;52(4):214–8.
23. Cohen RT, DeBaun MR, Blinder MA, Strunk RC, Field JJ. Smoking is associated with an increased risk of acute chest syndrome and pain among adults with sickle cell disease. Blood 2010;115(18):3852–4.
24. Palermo TM, Riley CA, Mitchell BA. Daily functioning and quality of life in children with sickle cell disease pain: relationship with family and neighborhood socioeconomic distress. J Pain 2008;9(9):833–40.
25. McClish DK, Penberthy LT, Bovbjerg VE, Roberts JD, Aisiku IP, Levenson JL, et al. Health related quality of life in sickle cell patients: the PiSCES project. Health Qual Life Outcomes. 2005;3(50).