Original Article

Age-Related Complications among Individuals with Sickle Cell Anemia Attending a Tertiary Health Facility in Northwestern Nigeria

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Abstract

Background: Sickle cell disease (SCD) is the most common monogenetic disorder worldwide. With an annual birthrate of approximately 150,000 in Nigeria, the burden is expected to increase by 75% in 2050. With improved care, patients live longer but may have more complications. This study seeks to determine the prevalence of some complications of sickle cell anemia (SCA) and how age relates to these complications. **Methods:** This was a 2-year retrospective review of clinic records of patients with SCA attending the hematology clinic of Barau Dikko Teaching Hospital, Kaduna State, Nigeria. Data on sex, age at last birthday, age at diagnosis of SCA, number of crises in past 6 months, proteinuria, steady-state hemoglobin concentration, chest infections, stroke, and oxygen saturation (SPO_2) were collated. **Statistical Analysis:** Data were analyzed using SPSS version 21 (IBM Corp., 2012, Armonk NY, USA). Continuous and categorical variables were assessed using the Shapiro–Wilk test and percentages. Differences in presenting ages between variables were determined using Mann–Whitney U-tests. Level of statistical significance was set at $P \leq 0.05$. **Results:** A total of 109 patients were retrieved, 68.8% (75/109) were females with a median (interquartile range [IQR]) age of 22 (18, 29) years. The median (IQR) number of crises in the preceding 6 months was 0 (0, 3). The prevalence of proteinuria, chest infections in the preceding 6 months, severe anemia, low oxygenation, and stroke were 9.5% (4/42), 6.5% (5/77), 7.0% (5/71), 58.9% (33/56), and 1.3% (1/77), respectively. A positive correlation existed between number of crises and presenting age ($r = 0.317$; $P = 0.005$). Patients with proteinuria, severe anemia, chest infections, and low SPO_2had higher mean rank presenting age while patients with stroke had lower mean rank presenting age. **Conclusion:** Older age is significantly associated with severity of SCD. Age-targeted interventions guided by evidence-based practices are important in slowing down disease progression and severity.

Keywords: Age, complications, sickle cell anemia

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Introduction

Sickle cell disease (SCD) is the most common monogenetic disorder worldwide.[1] It is a disease of major public health importance in sub-Saharan Africa; the region that harbors more than one-third of global disease burden and where access to basic health-care interventions is limited. With an annual birthrate of approximately 150,000 in some countries, unless specific actions are taken, the burden of SCD is projected to increase by ≥75% in 2050, particularly in Nigeria and the Democratic Republic of the Congo.[2] Effective management of SCD involves genetic counseling, neonatal screening, and early diagnosis, combined with parental education and health maintenance.[3] It is estimated that 90% of children born with SCD in sub-Saharan Africa will die before their 5th birthday.[4] In high-income countries, newborn screening, penicillin prophylaxis, screening for stroke, and several interventions done as standard of care for individuals with SCD have changed the narrative of the disease from that of

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a life-threatening disease of children to a chronic disease of adults,[5] with an overall improvement in health outcomes for this group of people. Unfortunately, the same is not replicated in sub-Saharan Africa, as there are very few newborn screening programs as well as a dearth of standard of care practices guided by well-documented recommendations incorporated into the care of all individuals with SCD. Few tertiary health-care facilities have made attempts at incorporating some of these standard care practices;[6] however, this is far below the requirement, and those that present to such institutions represent only a small proportion of the true burden of SCD.

The aim of this study is to assess the proportions of patients with proteinuria, severe anemia, chest infections, and stroke as well as to determine any differences in age among patients with these presentations. This will form a basis for instituting some recommended age-targeted health management interventions, as the standard of care with the hope of slowing down the progression of these complications.

Methods

This was a retrospective review of clinic records of patients with sickle cell anemia (SCA) attending the hematology outpatient clinic of Barau Dikko Teaching Hospital, Kaduna State, Nigeria. Records of SCA patients who attended the adult sickle cell clinic over a 2-year period (January 1, 2017–December 31, 2018) were utilized. Patients who met the following criteria were included in the study: (i) the diagnosis of homozygous SCD and (ii) at least three clinic visits during the period of review. Data on gender, age as at last birthday, age at diagnosis of SCA, number of crises in the past 6 months, proteinuria, steady-state hemoglobin (Hb) concentration, frequency of chest infections, stroke, and oxygen saturation (SPO_2) were collated. Severe anemia and low oxygen saturation were defined as Hb concentration <6 g/dl and oxygen saturation ≤94%, respectively.[7,8]

Statistical analysis

Data were analyzed using SPSS version 21 (IBM Corp., Released 2012, Armonk NY, USA). The distribution of continuous variables was assessed using the Shapiro–Wilk test. These were summarized as means ± standard deviation or medians and interquartile ranges (IQRs) (25th percentile value, 75th percentile value [IQRs]) and modes. Categorical data were summarized as percentages. Differences in the distribution of present age between binomial variables were determined using Mann–Whitney U (MWU)-tests. Level of statistical significance was set at $P \leq 0.05$.

Results

Demographic characteristics

A total of 109 patients' records were retrieved [Table 1].

The median (IQR) number of crises in the preceding 6 months was 0 (0, 3). The mean steady-state Hb concentration was 7.8 ± 1.3 g/dL. The median (IQR) SPO_2 was 93% (90.0%, 97.5%).

Table 1: Summary of some demographic characteristics

Gender
8.8% (75/109) were females
Age
Median (IQR): 22 (18-29) years
Mode: 18 years (10/109-9.2%)
Age at diagnosis
Median (IQR): 1 (0.59-7.25) years
Mode: 1 (49/102-48.1%)
Age at diagnosis (*n*=102), *n* (%)
<1 year - 14 (13.7)
1-5 years - 59 (57.8)
>5 years - 29 (28.4)

IQR: Interquartile ranges

The prevalence of proteinuria, chest infections in the preceding 6 months, severe anemia, low oxygenation, and stroke were 4/42 (9.5%, 95% confidence interval [CI] – 1.3%, 21.1%), 5/77 (6.5%, 95% CI – 1.3%, 13.5%), 5/71 (7.0%, 95% CI – 2.8%, 11.9%), 33/56 (58.9%, 95% CI – 47.4%, 75.0), and 1/77 (1.3%, 95% CI – 0.0%, 3.9%), respectively.

Age correlates positively with number of crises in the last 6 months

The number of crises in the last 6 months increased with increasing age of the participants as depicted by a positive, weak, and statistically significant correlation; $r = 0.317$; $P = 0.005$.

Lower steady-state hemoglobin concentration and oxygen saturation are associated with older age

Older participants had lower steady-state Hb concentration and SPO_2(≤94%). Spearman rank correlation analyses revealed negative correlations between age of participants and steady-state Hb concentration (rho = −0.180, $P = 0.133$) as well as age of participants and SPO_2(rho = −0.059, $P = 0.661$), respectively. However, both relationships were not statistically significant [Table 2].

Severity of sickle cell disease is associated with older age

Series of MWU analyses revealed that participants with proteinuria, severe anemia, chest infections, and low SPO_2 had higher mean rank ages compared to those without these conditions; (34.50 vs. 20.13, MWU = 24.000, $P = 0.023$), (57.20 vs. 34.39, MWU = 59.000, $P = 0.014$), (42.30 vs. 38.77, MWU = 163.500, $P = 0.741$), and (31.65 vs. 23.98, MWU = 483.500, $P = 0.083$), respectively [Table 3].

Stroke is associated with younger age

Patients with stroke were younger than those without stroke (8.00 vs. 39.41, MWU = 7.000, $P = 0.208$) [Table 3].

Discussion

Our study demonstrates that the median age of diagnosis of SCD in our setting is 1 year; however, the majority (>70%) were diagnosed between the ages of 1–5 years similar to the report of Mukinayi *et al*. in the Democratic Republic of the Congo,[9] as well as Southwestern Nigeria,[10] with higher ages in Senegal; 4

Table 2: Spearman correlation analyses

Present age (years)	Age at diagnosis (years)	Number of crises (in the last 6 months)	Average steady-state Hb concentration (g/dL)	SPo_2 last visit
ρ	−0.122	0.317	−0.180	−0.059
P	0.222	0.005	0.133	0.661

Hb: Hemoglobin

Table 3: Distribution of present ages of participants across categories of complications

	Mean rank present age	MWU statistic	*P*
Proteinuria			
Present	34.50	24.000	0.023
Absent	20.13		
Chest infection			
Yes	42.30	163.500	0.741
No	38.77		
Chronic leg ulcer			
Yes	54.30	256.500	0.116
No	37.94		
Stroke			
Yes	8.00	7.000	0.208
No	39.41		
Severe anemia			
Yes	57.20	59.000	0.014
No	34.39		
Oxygen saturation			
≤94%	31.65	483.500	0.083
>94%	23.98		

MWU: Mann-Whitney U-test

and 9.8 years, respectively.[11,12] The practice of newborn screening in other countries has given an opportunity for early interventions such as penicillin V prophylaxis and parental education, resulting in a decrease in under-five mortality from 25% to <3%.[13-15] With the absence of newborn screening in sub-Saharan Africa, the disease has contributed significantly (~5%) to the overall under-five mortality in the African continent.[16]

This study demonstrates that older age is associated with an increased number of pain crises. Although pain crises are a hallmark of SCD and one of the foremost causes of hospital presentation in individuals with SCD,[17,18] what is not established in this study is whether the crises can be associated with either standard of care or other social interventions. Frequent painful episodes are a predictor of disease severity and mortality in the landmark Cooperative Study of SCD study.[19] Despite improvements in the management of SCD, including the use of disease-modifying therapies such as chronic blood transfusion and hydroxyurea, frequent pain episodes still remain an independent risk factor for premature death in individuals with SCD.[18] In low-resource settings, pain management is suboptimal, and the use of disease-modifying therapies is not frequent. Initially, pain management begins at home with the use of "over-the-counter" analgesics. However, adopting the stepladder approach to pain management by developing a pain management plan that enables patients to move up the analgesic ladder with increasing intensity of pain, the use of nonpharmacologic methods such as keeping warm and massage and knowing when to present to the hospital may help in ameliorating the intensity and frequency of painful crises in our setting.

Data from this study indicate that the older the patient, lower the Hb concentration, and lower the SPO_2(≤94%). A cardinal manifestation of SCD is chronic hemolysis that occurs as a consequence of HbS that polymerizes when deoxygenated.[20] The concomitant effect is that of chronic anemia and its related complications; strokes,[21,22] severe cognitive deficits,[23] renal insufficiency,[24] as well as left ventricular diastolic dysfunction.[25] Severe anemia is an independent risk factor for death among children with SCD in low-resource settings,[26] where the burden of the disease is highest.[27] Furthermore, low Hb concentration has been associated with poor lung function that is progressive with a restrictive pattern exclusive of SCD patients, especially in low-resource settings.[28,29] Although low SPO_2(SPO_2 ≤94%) is not a true reflection of hypoxia, in a low-resource setting, it could be the one valuable marker of hypoxia, and its demonstration with age in this study may be as a result of chronic anemia or other cardiopulmonary complications including pulmonary hypertension, acute chest syndrome, or as components of chronic sickle lung disease.[28,29]

Our study demonstrates that participants with proteinuria are older than those without proteinuria. This is an expected finding as proteinuria is a predictor of chronic kidney disease, which develops with repeated renal infarction that results from sickling, ingestion of nonsteroidal anti-inflammatory drugs, and renal infections among others.[30-32] The prevalence of proteinuria in our study (9.5%) is lower than that reported among other SCD populations; 11% in South West Nigeria and[11] 60.9% in Cameroon.[32] The retrospective nature of our study may explain this lower prevalence as many cases of proteinuria may have been missed in the records. However, our finding of a positive correlation between age and proteinuria corroborates the reports of Arogundade;[11] Geard;[32] and Powars.[30] The relative risk for mortality in patients with SCD and renal insufficiency has been demonstrated to be 1.42 (95% CI, 1.12–1.81; $P = 0.02$).[30] Early detection of renal disease in SCD and institution of preventive strategies have been shown to decrease the progression of renal disease.[33]

Our study indicates that stroke occurs more in younger individuals with SCD. SCA is one of the leading causes of stroke (overt and silent) in children.[1] Approximately 11% of children with SCA have a 10% annual risk of developing

stroke, if no primary stroke prevention intervention is done.[34] In addition, in Sub-Saharan Africa, it is estimated that 11% of children will develop a stroke before their 20th birthday.[21] Based on hospital data, the prevalence of stroke in Nigeria is about 6%–8%.[35,36] The finding of stroke occurring in younger age in this study supports the need for instituting the evidence-based practices (EBPs) for primary stroke prevention, which involves screening for elevated transcranial Doppler (TCD) ultrasound velocity coupled with regular blood transfusion therapy for those with elevated velocities for at least 1 year or the use of hydroxyurea.[37,38] This strategy has worked well in high-income countries by decreasing risk of stroke by 92%,[39] but yet to be readily available in low-income regions like Nigeria as demonstrated by Galadanci *et al*. in 2014. This gap was largely attributed to the lack of trained TCD-ultrasonographers and shortages of TCD machines.[6] However, strategies to address some of these gaps are being developed in sub-Saharan Africa, and with appropriate government support, stroke prevention may soon become incorporated into the usual care for eligible individuals with SCA.[40,41]

Limitations

Being a retrospective study, our findings are unable to establish at what point these complications occur. This will be addressed in a longitudinal prospective study, where the incidence and evolutions of these parameters can be further characterized.

Conclusion

Older age is significantly associated with the severity of SCD. Age-targeted interventions guided by EBP may be important in slowing down disease progression and severity.

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Conflicts of interest

There are no conflicts of interest.

References

1. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet 2010;376:2018-31.
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;381:142-51.
3. Hsu L, Nnodu OE, Brown BJ, Tluway F, King S, Dogara LG, *et al.* White paper: Pathways to progress in newborn screening for sickle cell disease in Sub-Saharan Africa. J Trop Dis Public Health 2018;6:260.
4. 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:S398-405.
5. Chaturvedi S, DeBaun MR. Evolution of sickle cell disease from a life-threatening disease of children to a chronic disease of adults: The last 40 years. Am J Hematol 2016;91:5-14.
6. Galadanci N, Wudil BJ, Balogun TM, Ogunrinde GO, Akinsulie A, Hasan-Hanga F, *et al.* Current sickle cell disease management practices in Nigeria. Int Health 2014;6:23-8.
7. Bello-Manga H, DeBaun MR, Kassim AA. Epidemiology and treatment of relative anemia in children with sickle cell disease in Sub-Saharan Africa. Expert Rev Hematol 2016;9:1031-42.
8. Howard J, Hart N, Roberts-Harewood M, Cummins M, Awogbade M, Davis B, *et al.* Guideline on the management of acute chest syndrome in sickle cell disease. Br J Haematol 2015;169:492-505.
9. Mukinayi BM, Kalenda DK, Mbelu S, Gulbis B. Awareness and attitudes of 50 congolese families affected by sickle cell disease: A local survey. Pan Afr Med J 2018;29:24.
10. Arogundade FA, Hassan MO, Omotoso BA, Oguntola SO, Okunola OO, Sanusi AA, *et al.* Spectrum of kidney diseases in Africa: Malaria, schistosomiasis, sickle cell disease, and toxins. Clin Nephrol 2016;86:53-60.
11. Arogundade FA, Sanusi AA, Hassan MO, Salawu L, Durosinmi MA, Akinsola A. An appraisal of kidney dysfunction and its risk factors in patients with sickle cell disease. Nephron Clin Pract 2011;118:c225-31.
12. Diop S, Thiam D, Cisse M, Toure-Fall AO, Fall K, Diakhate L. New results in clinical severity of homozygous sickle cell anemia, in Dakar, Senegal. Hematol Cell Ther 1999;41:217-21.
13. Vichinsky E, Hurst D, Earles A, Kleman K, Lubin B. Newborn screening for sickle cell disease: Effect on mortality. Pediatrics 1988;81:749-55.
14. Gaston MH, Verter JI, Woods G, Pegelow C, Kelleher J, Presbury G, *et al.* Prophylaxis with oral penicillin in children with sickle cell anemia. A randomized trial. N Engl J Med 1986;314:1593-9.
15. Kato GJ, Piel FB, Reid CD, Gaston MH, Ohene-Frempong K, Krishnamurti L, *et al.* Sickle cell disease. Nat Rev Dis Primers 2018;4:18010.
16. World Health Organization. Sickle Cell Anaemia. Fifty-Ninth World Health AssemblyA59/9; 2006. Available from: http://www.who.int/iris/handle/10665/20890. [Last accessed on 2019 Apr 27].
17. Brandow AM, DeBaun MR. Key components of pain management for children and adults with sickle cell disease. Hematol Oncol Clin North Am 2018;32:535-50.
18. Darbari DS, Wang Z, Kwak M, Hildesheim M, Nichols J, Allen D, *et al.* Severe painful vaso-occlusive crises and mortality in a contemporary adult sickle cell anemia cohort study. PLoS One 2013;8:e79923.
19. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, *et al.* Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med 1994;330:1639-44.
20. Novelli EM, Gladwin MT. Crises in sickle cell disease. Chest 2016;149:1082-93.
21. Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW, *et al.* Cerebrovascular accidents in sickle cell disease: Rates and risk factors. Blood 1998;91:288-94.
22. DeBaun MR, Kirkham FJ. Central nervous system complications and management in sickle cell disease. Blood 2016;127:829-38.
23. King AA, DeBaun MR, White DA. Need for cognitive rehabilitation for children with sickle cell disease and strokes. Expert Rev Neurother 2008;8:291-6.
24. Gladwin MT. Cardiovascular complications and risk of death in sickle-cell disease. Lancet 2016;387:2565-74.
25. Gladwin MT, Sachdev V. Cardiovascular abnormalities in sickle cell disease. J Am Coll Cardiol 2012;59:1123-33.
26. Makani J, Cox SE, Soka D, Komba AN, Oruo J, Mwamtemi H, *et al.* Mortality in sickle cell anemia in Africa: A prospective cohort study in Tanzania. PLoS One 2011;6:e14699.
27. Piel FB, Hay SI, Gupta S, Weatherall DJ, Williams TN. Global burden of sickle cell anaemia in children under five, 2010-2050: Modelling based on demographics, excess mortality, and interventions. PLoS Med 2013;10:e1001484.
28. Arigliani M, Dogara LG, Zubair R, Castriotta L, Pusiol A, Zuiani C, *et al.* Lung function impairment in pediatric patients with sickle cell anemia from Nigeria is associated with low steady state hemoglobin. Am J Hematol 2019;94:E70-1.

29. Faleti OA, Akodu SO, Disu EA, Njokanma OF. Pulmonary functions in children with sickle cell anemia in steady state in Lagos, Nigeria. Ann Health Res 2017;3:18-25.
30. Powars DR, Elliott-Mills DD, Chan L, Niland J, Hiti AL, Opas LM, *et al.* Chronic renal failure in sickle cell disease: Risk factors, clinical course, and mortality. Ann Intern Med 1991;115:614-20.
31. Yeruva SL, Paul Y, Oneal P, Nouraie M. Renal failure in sickle cell disease: Prevalence, predictors of disease, mortality and effect on length of hospital stay. Hemoglobin 2016;40:295-9.
32. Geard A, Pule GD, Chetcha Chemegni B, Ngo Bitoungui VJ, Kengne AP, Chimusa ER, *et al.* Clinical and genetic predictors of renal dysfunctions in sickle cell anaemia in cameroon. Br J Haematol 2017;178:629-39.
33. McKie KT, Hanevold CD, Hernandez C, Waller JL, Ortiz L, McKie KM. Prevalence, prevention, and treatment of microalbuminuria and proteinuria in children with sickle cell disease. J Pediatr Hematol Oncol 2007;29:140-4.
34. Adams RJ, McKie VC, Carl EM, Nichols FT, Perry R, Brock K, *et al.* Long-term stroke risk in children with sickle cell disease screened with transcranial Doppler. Ann Neurol 1997;42:699-704.
35. Fatunde OJ, Adamson FG, Ogunseyinde O, Sodeinde O, Familusi JB. Stroke in Nigerian children with sickle cell disease. Afr J Med Med Sci 2005;34:157-60.
36. Lagunju IA, Brown BJ. Adverse neurological outcomes in Nigerian children with sickle cell disease. Int J Hematol 2012;96:710-8.
37. Adams RJ. Lessons from the stroke prevention trial in sickle cell anemia (STOP) study. J Child Neurol 2000;15:344-9.
38. Ware RE, Davis BR, Schultz WH, Brown RC, Aygun B, Sarnaik S, *et al.* Hydroxycarbamide versus chronic transfusion for maintenance of transcranial Doppler flow velocities in children with sickle cell anaemia-TCD with transfusions changing to hydroxyurea (TWiTCH): A multicentre, open-label, phase 3, non-inferiority trial. Lancet 2016;387:661-70.
39. Adams RJ, McKie VC, Hsu L, Files B, Vichinsky E, Pegelow C, *et al.* Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med 1998;339:5-11.
40. Galadanci NA, Umar Abdullahi S, Vance LD, Musa Tabari A, Ali S, Belonwu R, *et al.* Feasibility trial for primary stroke prevention in children with sickle cell anemia in Nigeria (SPIN trial). Am J Hematol 2017;92:780-8.
41. Galadanci NA, Abdullahi SU, Vance LD, Tabari MA, Abubakar S, Belonwu R, *et al*. Implementing a standard-of-care clinic for stroke prevention in children with sickle cell disease in Nigeria: A feasible strategy outside a clinical trial setting. Blood Adv 2017;1:23-5.