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Research Article

Frequency of Stroke among Children with Sickle Cell Disease in Southern Region of Saudi Arabia: Single Center Experience

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Abstract: Background: Sickle cell disease (SCD), being an autosomal recessive disorder of hemoglobin, carries a varied worldwide prevalence. It is characterized by a range of complications hemolytic crisis, vaso-occlusive crisis, splenic sequestration, acute chest syndrome and occasionally stroke.

Objective: To ascertain the frequency of stroke in pediatric population with sickle cell disease (SCD).

Materials and Methods: Retrospective observational study, was conducted in Pediatric Medicine Department, King Fahad Armed Forces Hospital Southern Region, Khamis Mushait, Kingdom of Saudi Arabia, from1st July 2018 to 30th June 2023. The data was collected for last five years regarding pediatric patients of sickle cell anemia and aged one to 14 years.

Result: Among 322 patients of sickle cell disease, 116 were female and 206 male with mean age 6 years 2 months. Each patient had an average of 2.3 admissions during the course of the disease. The most common diagnosis was vaso-occlusive crisis for the inpatient care. The mean hemoglobin was 9.24 g/dL. Transcanial doppler identified recording of high velocity in middle cerebral artery in 2% of sickle patients. 6 patients (1.9%) were found to have stroke with mean age of 9 years 10 months, with obliteration of middle cerebral artery in 4 patients (66%).

Conclusion: Among the children of southern region of Saudi Arabia, the frequency of stroke in SCD patients was 1.9%.

Keywords: Anemia, Complications of sickle cell disease, Hemoglobin, Sickle cell disease, Stroke, Transcranial doppler.

INTRODUCTION

Sickle cell disease (SCD) is characterized under autosomal recessive disorder of hemoglobin [1]. It was first described in 1949 [2]. Its prevalence varies worldwide, In USA, the reported prevalence is 329 cases in one million of the population [3]. In contrary, the incidence is comparatively higher in the African and middle-eastern population, as it affects 2400 per 1,000,000 Saudi children and adolescents [4]. SCD is more commonly encountered in the eastern and southwestern regions of the Kingdom [5].

Sickle cell disease is characterized by a range of complications. Children with this entity are admitted with hemolytic crisis, vaso-occlusive crisis, splenic / hepatic sequestration, acute chest syndrome, stroke, septicemia, priapism and osteomyelitis [6]. It can result in stroke through varying mechanisms – certain entailing to morphology of RBCs and others due to vascular wall injuries and coagulopathy [7]. Sickle cell hemoglobin causes sickling of RBCs which can infer as sludging with occlusion of blood vessels and resulting in brain ischemia [8]. Moreover, it can induce flow-related hemodynamic injury to the endothelial cells, which promotes clot formation [9]. The documented risk of stroke peaks in the first decade of life as it is most apparent between the age of 2 and 5 years [10]. The ischemic stroke is most commonly encountered as it constitutes 54% of all strokes in SCD [11]. In contrary, hemorrhagic stroke is more prevalent among patients in second decade [12].

Despite SCD being common in the Kingdom of Saudi Arabia, data is lacking in Southern region of Saudi Arabia in regards to the prevalence of stroke in such children. We conducted a retrospective review of children admitted with SCD in order to surface the frequency of stroke in SCD children and to ascertain the related complications.

MATERIALS AND METHODS

We conducted a retrospective cross-sectional study at King Fahad Armed Forces Hospital Southern Region Khamis Mushait, a tertiary care hospital and referral center, in southern region of Kingdom of Saudi Arabia. The data was collected for last five years 1st July 2018 to 30th June 2023, after due permission from local Research Ethics Committee (REC certificate number AFHSRMREC/2022/Hematology,Pediatrics Dept/635). Target population was pediatric patients from the age of one to 14 years, who have confirmed diagnosis of sickle cell anemia by hemoglobin electrophoresis and under regular follow up.

Detailed information from electronic record of the sickle cell disease patients undergoing follow up with hematology team was gathered. A well-structured data collection pro-forma was

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integrated for collecting information on demographic characteristics and clinical diagnosis – along with related complications during the past years. World Health Organization definition of stroke was utilized – rapidly evolving clinical signs from focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours with no apparent cause other than of vascular origin [13]. Both ischemic and hemorrhagic stroke were included.

STATISTICAL ANALYSIS

The data was analytically evaluated using descriptive statistics, including frequency and percentage for categorical variables, and mean and standard deviation for numerical variables. P value ≤0.05 was characterized as significant.

RESULT

During the study, 322 patients of sickle cell disease were selected with 116 (36%) patients being female and 206 (64%) male. The mean age was 6 years 2 months (±3.59). Each patient had an average of 2.3 admissions during the course of the disease with quite variation observed among individual patients (maximum 18 admissions with minimum of nil admission). The most common diagnosis was vaso-occlusive crisis (28%) for the inpatient care (Table **1**). The mean Hb was 9.24 g/dL with mean hematocrit of 29.18%. The other red cell indices are shown in Table **2**. All of the patients received folic acid and oral penicillin V. Hydroxyurea (hydroxycarbamide) was advised to all the patients, however, hydroxyurea was discontinued in 22% of the patients in lieu of drug induced thrombocytopenia. Transcanial doppler was done in 64% patients, with recording of high velocity in middle cerebral artery in 2% of sickle patients. Such patients were managed by regular packed red blood cell transfusion protocol.

Six patients (1.9%) were found to have stroke with mean age of 9 years 10 months (±3.08). Limb weakness was found in all the patients as exhibited in Table **3**. Among those 6 patients, obliteration of middle cerebral artery was the cause of ischemic stroke in 4 patients (66%) as presented in Table **3**. Out of 2 patients, these 6 had recurrent stroke.

Table 1. Diagnosis for the Inpatient Admissions of Sickle Cell Disease Patients.

Diagnosis	Number of Inpatient Admissions n (%)
Vaso-occlusive crisis	210 (28%)
Hemolytic crisis	168 (23%)
Acute chest syndrome	126 (17%)
Splenic sequestration	105 (14%)
Sepsis	63 (9%)
Osteomyelitis	60 (8%)
Stroke	6 (1%)
Total	**738 (100%)**

Table 2. Red Cell Indices in Sickle Cell Disease Patients.

Red Cell Indices	Mean Value (±SD)
Hemoglobin (Hb)	9.24 (±1.35) g/dL
Hematocrit (Hct)	29.18 (±4.28) %
Mean corpuscular volume (MCV)	85.19 (±11.40) fL
Reticulocyte	9.77 (±5.89) %
Leukocytes	11.31 (±4.75) x 109/L
HbS	71.40 (±11.48) %

Table 3. Presenting Symptoms and Involved Cerebral Vasculature in Stroke Patients with Sickle Cell Disease.

Symptoms	No of Patients (%) (n=6)
Weakness	6 (100%)
Headache	2 (33%)
Seizures	-
Difficulty in speech	1 (17%)
Cerebral Arteries Involved in Stroke	
Right middle cerebral artery	2 (33%)
Left middle cerebral artery	1 (17%)
Bilateral middle cerebral artery	1 (17%)
Right anterior cerebral artery	1 (17%)
Left anterior cerebral artery	1 (17%)

DISCUSSION

Sickle cell disease (SCD) is a common genetic hemoglobinopathy and major health disorder in selected distribution [14]. The burden of SCD varies worldwide [15]. However, in the Kingdom of Saudi Arabia it has a high recorded incidence especially more prevalent in the Eastern and Southwestern regions of the Kingdom [16]. SCD encompasses whole range of complications from hemolytic and vaso-occlusive crisis to splenic sequestration and stroke [17]. A comprehensive care for such children is essential in limiting its morbidity and mortality [18]. SCD stands as the most common cause of stroke (39%) in pediatrics as SCD result in multifold increase in risk of stroke in children [19]. This study aimed at describing the risk factors with its related co-morbid conditions which predispose towards the risk of stroke among SCD patients.

Multiple research studies have been conducted worldwide to highlight the prevalence of stroke and other associated complications of SCD. A study conducted in Saudi Arabia revealed 11.5% of the children with SCD had stroke [20]. The prevalence of stroke in SCD reported from Uganda, Sub-Saharan Africa, among the children with SCD was 6.8% [21]. In our observation, we found a relatively low prevalence of stroke (1.9%) with middle cerebral artery being the most commonly involved. Other studies conducted in Cameroun and Nigeria almost similar results were found [9, 22]. A study organized at King Abdulaziz

University Hospital in Jeddah KSA reported prevalence of stroke in patients with SCD as 15.8 % which is much higher as compared to our observation. The female and male children were equally affected, quite contrary to our experience [14]. The observed low incidence of stroke in our study can be lieu to screening Transcranial Doppler (TCD) utilization in identifying potential candidates and steering them towards regular transfusion protocol. The adoptions of various new interventions have apparently derived towards decreasing prevalence of stroke in the developed world. A study had reported a 5% incidence in the meta-analysis of Asian children [23].

The mean age of our children with stroke was 9 years 10 months. One of the study reported mean age of 6 years 1 month in such stroke patients. They have documented 72.1 % children with stroke were identified to have co-morbidities, most notably severe anaemia, bacteraemia and vaso-occlusive crisis [21]. Unlike their study, our stroke patients lacked comorbids. This contrast can be explained from better pneumococcal vaccination coverage and prophylactic penicillin administration. Moreover, a dedicated hematology service in our setup can have a pivotal role in better outcome [24, 25].

Being the tertiary referral center in Southern Region of Saudi Arabia, its gives a validity and strength to the results of our study. The major inherent limitation of our study is its retrospective nature.

CONCLUSION

Among the children of southern region of Saudi Arabia, the frequency of stroke in children with SCD was 1.9%. Treatment with hydroxyurea assists towards reducing the risk of stroke. Moreover, efficient screening with TCD has proved of great value in identifying the children of SCD with future potential of cerebro-vascular complications. Such patients with abnormal TCD, must be strongly considered for prophylactic transfusion program - aiming to limit sickle cell hemoglobin (HbS) less than 30%.

AUTHORS' CONTRIBUTION

- **Badriah Gharamah Al Asmari**: Conception, Literature Search.
- **Mohammed Alpakra**: Study Questionnaire, Critical Revision.
- **Muhammad Saeed**: Study Design, Proof reading.
- **Ali Mujtaba Tahir**: Data Analysis, Drafting.
- **Abla Abdullah Al-Ashik Alshahrani**: Drafting.
- **Sultan Mahdi Alqarni and Yahya Salman Hassan Suhluli**: Data Collection.

CONFLICT OF INTEREST

Declared none.

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REFERENCES

[1] Switzer JA, Hess DC, Nichols FT, Adams RJ. Pathophysiology and treatment of stroke in sickle-cell disease: Present and future. Lancet Neurol 2006; 5(6): 501-12. doi: 10.1016/S1474-4422(06)70469-0.

[2] Adams RJ, McKie VC, Brambilla D, *et al*. Stroke prevention trial in sickle cell anemia. Control Clin Trials 1998; 19(1): 110-29. doi: 10.1016/s0197-2456(97)00099-8.

[3] Piel FB, Steinberg MH, Rees DC, Longo DL. Sickle cell disease. N Engl J Med 2017; 376(16): 1561-73. doi: 10.1056/NEJMra1510865.

[4] Al-Qurashi MM, El-Mouzan MI, Al-Herbish AS, Al-Salloum AA, Al-Omar AA. The prevalence of sickle cell disease in Saudi children and adolescents. A community-based survey. Saudi Med J 2008; 29(10): 1480-3.

[5] Memish ZA, Saeedi MY. Six-year outcome of the national premarital screening and genetic counseling program for sickle cell disease and βthalassemia in Saudi Arabia. Ann Saudi Med 2011; 31(3): 229-35. doi: 10.4103/0256-4947.81527.

[6] Dormandy E, James J, Inusa B, Rees D. How many people have sickle cell disease in the UK? J Public Health 2018; 40(3): 291-5. doi: 10.1093/pubmed/fdx172.

[7] Green NS, Munube D, Bangirana P, *et al*. Burden of neurological and neurocognitive impairment in pediatric sickle cell anemia in Uganda (BRAIN SAFE): A cross-sectional study. BMC Pediatr 2019; 19(1): 381-92. doi: 10.1186/s12887-019-1758-2

[8] Abboud MR. Standard management of sickle cell disease complications. Hematol Oncol Stem Cell Ther 2020; 13(2): 85-90. doi: 10.1016/j.hemonc.2019.12.007.

[9] Njamnshi AK, Mbong EN, Wonkam A, *et al*. The epidemiology of stroke in sickle cell patients in Yaounde, Cameroon. J Neurol Sci 2006; 250(1): 79-84. doi: 10.1016/j.jns.2006.07.003.

[10] Parikh T, Goti A, Yashi K, *et al*. Pediatric sickle cell disease and stroke: A literature review. Cureus 2023; 15(1): e34003. doi: 10.7759/cureus.34003.

[11] Kapustin D, Leung J, Odame I, Williams S, Shroff M, Kassner A. Hydroxycarbamide treatment in children with sickle cell anaemia is associated with more intact white matter integrity: A quantitative MRI study. Br J Haematol 2019; 187(2): 238-45. doi: 10.1111/bjh.16063.

[12] Giovanna G, Lucia DF, Laura S, *et al*. Transfusional approach in multi-ethnic sickle cell patients: Real-world practice data from

a multicenter survey in Italy. Front Med 2022; 9: 832154. doi: 10.3389/fmed.2022.832154.

[13] Bello-Manga H, Haliru L, Ahmed KA, *et al*. Primary prevention of stroke in children with sickle cell anemia in Nigeria: Protocol for a mixed methods implementation study in a community hospital. JMIR Res Protoc 2022; 11(6): e37927. doi: 10.2196/37927.

[14] Alzahrani F, Fallatah AM, Al-Haddad FM, *et al*. Risk factors and complications among pediatric patients with sickle cell anemia: A single tertiary center retrospective study. Cureus 2021; 13(1): e12440. doi:10.7759/cureus.12440.

[15] Wali Y, Kini V, Yassin MA. Distribution of sickle cell disease and assessment of risk factors based on transcranial doppler values in the Gulf region. Hematology 2020; 25(1): 55-62. doi: 10.1080/16078454.2020.1714113.

[16] Halawani HM, Al Shahrani RS, Al-Harbi HA, *et al*. Prevalence of stroke among patients with sickle cell disease at King Abdulaziz University Hospital in Jeddah, Saudi Arabia. Med Sci 2020; 24(102): 464-71.

[17] Rigano P, De Franceschi L, Sainati L, *et al*. Real-life experience with hydroxyurea in sickle cell disease: A multicenter study in a cohort of patients with heterogeneous descent. Blood Cells Mol Dis 2018; 69: 82-9. doi: 10.1016/j.bcmd.2017.08.017.

[18] Galadanci NA, Abdullahi SU, Shehi AA, *et al*. Moderate fixed-dose hydroxyurea for primary prevention of strokes in Nigerian children with sickle cell disease: Final results of the SPIN trial. Am J Hematol 2020; 95(9): 247-50. doi: 10.1002/ajh.25900.

[19] Abdullahi SU, Wudil BJ, Bello-Manga H, *et al*. Primary prevention of stroke in children with sickle cell anemia in sub-Saharan Africa: Rationale and design of phase III randomized clinical trial. Pediatr Hematol Oncol 2021; 38(1): 49-64. doi: 10.1080/08880018.2020.1810183.

[20] Salih MH, Abdel-Gader AG, Al-Jarallah AA, *et al*. Hematologic risk factors for stroke in Saudi Arabia in children. Saudi Med J 2006; 27(1): 21-34.

[21] Munube D, Katabira E, Ndeezi G, *et al*. Prevalence of stroke in children admitted with sickle cell anaemia to Mulago Hospital. BMC Neurol 2016; 16: 175-80. doi: 10.1186/s12883-016-0704-2.

[22] Kehinde MO, Temiye EO, Danesi MA. Neurological complications of sickle cell anemia in Nigerian Africans–a case–control study. J Natl Med Assoc 2008; 100(4): 394-9. doi: 10.1016/s0027-9684(15)31271-2.

[23] Kuikel S, Rauniyar R, Kharel S, *et al*. Prevalence of stroke in Asian patients with sickle cell anemia: A systemic review and meta-analysis. Neurol Res Int 2021; 2021: 9961610. doi: 10.1155/2021/9961610.

[24] Gargot J, Parriault M-C, Adenis A, *et al*. Low stroke risk in children with sickle cell disease in French Guiana: A retrospective cohort study. Front Med 2022; 9: 851918. doi: 10.3389/fmed.2022.851918.

[25] Moeen SM, Thabet AF, Hasan HA, Saleh MA. Lower transcranial doppler flow velocities in sickle cell anemia patients on hydroxyurea: Myth or fact. Indian J Hematol Blood Transfus 2018; 34(1): 97-103. doi: 10.1007/s12288-017-0814-z.

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