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Prevalence of Stroke in Patients with Sickle Cell Anemia, a Single Center's Experience

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Abstract

Introduction: Stroke is a common complication occurring in approximately 10% of children with sickle cell anemia (SCA). A major breakthrough in SCA is the use of hydroxyurea for prevention of stroke and advances in trans-cranial doppler (TCD) for early detection of stroke coupled with blood transfusion program as primary prevention.

Methods: This is a retrospective review of patients with SCA who developed stroke over the last 5 years in King Salman Armed Forces Hospital (KSAFH). Data was entered into SPSS v.20. Descriptive analysis of the data is presented in tabulated and graphical form. Chi Square or Fischer Exact test was used to find out possible association between the variables. $P < 0.05$ is considered as statistically significant.

Results: We reviewed 237 patients, 10 (4.2%) have stroke. TCD was performed in 75 patients (32%), 5 (2.1%) were abnormal. MRI brain was done for 15 patients with stroke and abnormal TCD, 60% of the patients had ischemic stroke. Forty percent of the patients presented with headache and 20% with convulsions. Neurologic deficit occurred in 4 patients (26.6%). Leukocytosis was the most frequent risk factor 66.6%.

Conclusion: Prevalence of stroke in children at KSAFH is 4.2% which is comparable with other studies. This can be attributed to regular use of hydroxyurea and introduction of TCD as the most essential screening tool for stroke in patients with SCA.

Keywords: *Sickle Cell Anemia; Stroke; Trans-Cranial Doppler; Hydroxyurea; Saudi Arabia*

Introduction

Stroke is a common and devastating complication in patients with sickle cell anemia (SCA). Prevalence of stroke in SCA is 3.75% and median age of patients who suffer stroke is 5 years [1,2]. It is estimated that 11% of patients with SCA would develop stroke by age of 20 years and 24% by 45 years. Moreover, recurrent stroke occurs in two third of SCA within 2 - 3 years [3]. Stroke can occur as a result of ischemia, hemorrhage or present as silent infarctions. Ischemic strokes are secondary to vasculopathy and arterial stenosis and are predisposed by transient ischemic attacks, hypertension and nocturnal hypoxemia, while hemorrhagic strokes results from subarachnoid hemorrhage, intraventricular hemorrhage or as combination and are associated with older ages, low hemoglobin and prior blood transfusion within 2 weeks [4,5]. Silent infarctions are defined as increased T2 signal abnormalities on brain magnetic resonance imaging (MRI) without obvious deficits [1].

Patients with stroke can present with motor disabilities (hemiparesis, abnormal gait), focal seizures, speech defect or signs of increased intracranial tension like headache and vomiting.

Blood transfusion program has reduced the risk of stroke recurrence from 46 - 90% to less than 10% [6]. Furthermore, the major success in SCA through implementation of trans-cranial doppler (TCD) screening has decreased the risk of stroke development in patients with SCA. TCD can detect high velocities in major cerebral arteries which are associated with increased stroke risk 10 - 20 times that of general sickle cell population of same ages [6].

Materials and Methods

This is a retrospective review of medical record of patients with SCA. Target population is pediatric patients with SCA under regular follow up from 1 to 14 years of age who have confirmed diagnosis of SCA by hemoglobin electrophoresis. Data collected for patients under regular follow up in 5 years period from 2012 till 2017. Study location is King Salman Armed Forces hospital (KSAFH) which is located in Tabuk/KSA and serves as a tertiary hospital and referral center for the northwestern region of Saudi Arabia. Patients with confirmed stroke clinically and by imaging and those screened by TCD on primary prevention with blood transfusion were retrieved and reviewed separately. All demographic, clinical and imaging data were collected and entered into SPSS v.20. Frequencies and percentages of the descriptive analysis of the data are presented in tabulated and graphical form. Chi Square or Fischer Exact test was used to find out possible association between the variables. $P < 0.05$ is considered as statistically significant.

Definitions: Normal TCD is time-averaged maximum mean (TAMM) velocities < 170 cm/sec, conditional TCD is TAMM velocities 170 - 199 cm/sec, abnormal TCD is TAMM velocities ≥ 200 cm/sec.

Results

Two hundred and thirty-seven patients with SCA (134 male 56.5%) are under active follow up, age is 1-14 years and mean age is 7.87 ± 3.96 years (Figure 1). Ten patients (4.2%) have stroke (male: female = 4:1), (median age at presentation 8 years, 86.6% of patients ≤ 10 years old) and 5 patients (2.1%) have been detected to have abnormal cerebral blood velocities by TCD, all 15 patients (6.3%) (male: female = 2:1) are on chronic blood transfusion (Figure 2). TCD was performed in 75 patients (32%), normal in 61 (81.3%), conditional in 9 (12%) and abnormal in 5 (6.6%). MRI brain and magnetic resonance angiography (MRA) were done for all 15 patients with internal carotid artery (ICA) being the most common artery affected with frequency of 60%. Early moyamoya changes were identified in 2 patients (13.3%). Sixty percent of the patients had ischemic stroke, 13% with silent infarctions, 20% with high TCD velocities with no MRI ischemic or hemorrhagic lesions and only one patient had combined hemorrhagic and ischemic stroke. Forty percent of the patients presented with headache, 20% with convulsions and 20% with limb weakness, other clinical presentations are demonstrated in table 1. Neurologic deficit occurred in 4 patients (26.6%), hemiplegia and epilepsy were the most common deficits with frequencies of 26.6% and 20% respectively and the most statistically significant deficits when correlated to non-compliance to hydroxyurea ($p < 0.05$), neurologic deficits are illustrated in table 2. Despite on blood transfusion program, 4 patients (26.6%) had recurrent stroke. Coexistence between neurologic consequences and recurrent stroke has a statistical significance ($\chi^2 = 6.51$, $p = 0.01$). Leukocytosis was the most important risk factor 66.6% followed by frequent acute chest syndrome (ACS) 46.6%, other risk factors include; recent ACS 40%, frequent vaso-occlusive crisis (VOC) 40%, recent VOC 33.3%, anemia 26.6% and hypertension in 6.6%. Association between risk factors and both recurrence of stroke and neurologic deficits are statistically significant ($p < 0.05$).

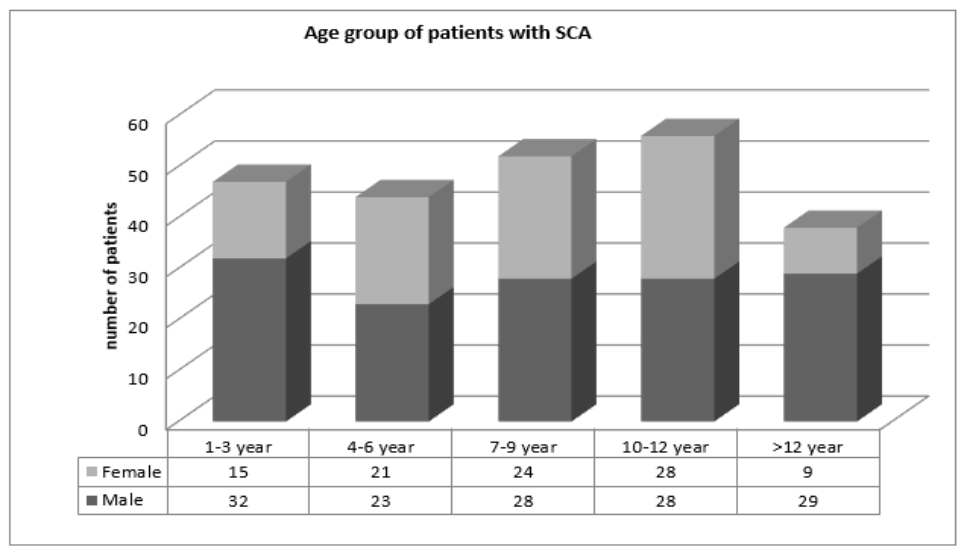

Figure 1: *Age group distribution of patients with SCA.*

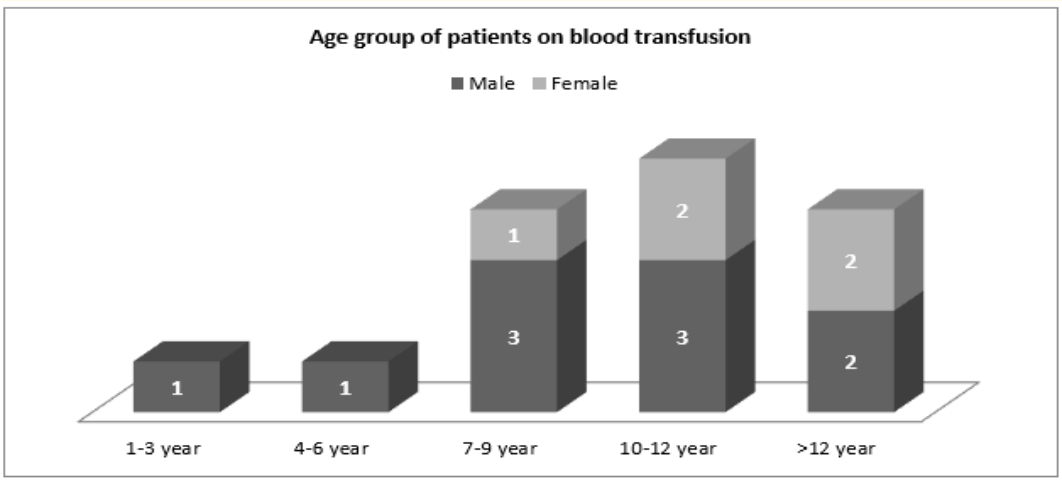

Figure 2: *Age group distribution of patients with SCA having either stroke on secondary prevention by chronic blood transfusion or detected by TCD on primary prevention by chronic blood transfusion.*

Symptoms/signs	Number of patients = total 15	Frequency
Headache	6	40%
Convulsions	3	20%
Limb weakness	3	20%
Vomiting	2	13.3%
Slurred speech	2	13.3%
Squint	1	6.6%
Abnormal gait	1	6.6%
Hypertension	1	6.6%
Transient blindness	1	6.6%
Abnormal movements	1	6.6%

Table 1: *Clinical presentation of patients with SCA who had stroke or at high risk of stroke by TCD and/or MRI.*

Deficit	Number of Patients = Total 15	Frequency (1 Patient can have more than one deficit)	Statistics (Correlated to Hydroxyurea)	
			Chi Square (χ^2)	P value
Hemiplegia	4	26.6%	8.18	0.004
Epilepsy	3	20%	5.62	0.018
Dysarthria	2	13.3%	3.46	0.063
Aphasia	1	6.6%	1.61	0.205
Incontinence	1	6.6%	1.61	0.205
Squint	1	6.6%	1.61	0.025
No deficit	11	73.3%		

Table 2: *Frequency of neurologic deficit in patients with SCA who had stroke or at high risk of stroke by TCD and/or MRI.*

Discussion

Stroke is defined as acute neurologic insult caused by vascular occlusion or hemorrhages that result in ischemia and focal neurologic symptoms or signs lasting more than 24 hours, whereas silent stroke is an MRI evidence of cerebral ischemia in the absence of focal neurologic deficits [7].

Stroke is a common complication in patients with SCA and necessitates prompt action. In our center, patients with SCA who presents clinically with manifestations and risk factors suggesting stroke follow a specific pathway of management. If the symptoms are highly suggestive of stroke, an immediate exchange blood transfusion is carried out if hemoglobin level is ≥ 9 gm/dl otherwise if hemoglobin is low, a simple blood transfusion is carried out first prior to the exchange. Those who have suspicious diagnosis will do an urgent brain MRI and necessary blood works (i.e. hemoglobin electrophoresis) before a decision is taken (this usually takes 24 - 48 hours). The patients who have confirmed stroke will be followed up monthly for blood transfusion aiming to keep HBS level < 30%.

Hydroxyurea is a cytotoxic agent and is the only drug that is effective in reducing painful crisis, raising hemoglobin and HBF level in patients with SCA [8]. Our center started 12 years ago using hydroxyurea for all SCA patients above 2 years of age. Moreover, we keep giving the medication to patients who develop stroke in addition to the regular blood transfusion. Recently, TWiTCH trial demonstrated that hydroxyurea is non-inferior to blood transfusion therapy for primary stroke prevention after an initial year of blood transfusion therapy in children with elevated TCD measurements [9].

The success in using TCD was a major breakthrough in SCA to identify asymptomatic patients at high risk of stroke, and when coupled with blood transfusion, it resulted in substantial decrease in the prevalence of overt stroke from 11% to 1% [10,11]. We started 2 years ago to implement TCD as a screening tool for stroke. It was performed on 75 patients and 5 patients (6.6%) have been identified to be at risk of stroke.

In our study, the prevalence of stroke in patients with SCA is 4.2% which is comparable with other studies. Adeloye., *et al.* reported 4% prevalence at the University of Ibadan Hospital in Nigeria, and George., *et al.* reported a 4.3% prevalence at the University of Port Harcourt in Nigeria [12,13]. However, some studies in Africa showed higher incidence rates. Munube., *et al.* reported a prevalence of 6.8% and similar results were reported 2008 by Kehinde., *et al.* in Lagos University in Nigeria [14,15]. The difference between high and low rates might be attributed to the regular use of hydroxyurea and successful implementation of TCD screening which is lacking in some parts in Africa. A paucity of data exists regarding the prevalence of stroke in SCA patients in Saudi Arabia. Nevertheless, Zakaria., *et al.* stated that the prevalence was 10% when they reviewed 90 patients with SCA in Madnia region in 1998 [16].

Male to female ratio of patient who have stroke in our study is 4:1 and although this value is higher than other studies, it is not statistically significant ($p > 0.05$).

Forty percent of the patients presented with headache, 20% with limb weakness, and 20% presented with convulsions that are of high prevalence in children with SCA (10 times more that of general population) [17]. One patient presented with hypertension and posterior reversible encephalopathy syndrome which is very rare association in pediatric patients with SCA.

Sixty percent of the patients in this study had ischemic stroke and this is consistent with other studies that shows higher incidence of ischemic strokes in pediatric age group unlike the hemorrhagic stroke which occurs mainly at older ages. Jiya., *et al.* reported in their study that 71.4% of stroke that occurred in children with SCA was infarctive based on neuroimaging findings [18]. While Ohene-Frempong estimated the incidence of infarctive stroke to be 53.9% among patients with SCA from 23 clinical centers across the United States [1].

Moyamoya disease (means in Japanese "puff of smoke") is a progressive, occlusive disease of cerebral vessels, mainly the circle of Willis [19]. This unique entity has been described with SCA but scarce data exists regarding its actual prevalence with SCA. However, moyamoya disease is potentially affecting the management process in SCA and acts as a predictor of recurrent stroke. Dobson., *et al.* concluded in their study that 41% of patients with SCA have recurrent stroke despite chronic blood transfusion and moyamoya disease is associated with high risk of recurrence among those patients [20].

Four out of 15 patients (26.6%) in this study had recurrent stroke while on transfusion. All 4 patients are males (not significant $p = 0.09$) and non-compliant to hydroxyurea which is of statistical significance ($p = 0.004$), 3 out of 4 patients (75%) are more than 9 years of age. Contrarily, only two out of the remaining 11 patients who had no recurrent stroke is non-compliant to hydroxyurea therapy. This finding might strengthen the role of hydroxyurea in stroke prevention among patients with SCA. In addition, early moyamoya changes detected by MRA in 2 of the 4 patients suggests their high recurrence rate of stroke and this finding is consistent with the results in Dobson., *et al.* study [20].

Risk factors that predispose to stroke in SCA include prior transient ischemic attacks, anemia, recent and frequent ACS, recent VOC, hypertension and nocturnal hypoxemia [1]. This was consistent with our findings when every patient with stroke in our study had at least 2 risk factors. Of these risk factors, repeated VOC and repeated ACS are essential predictors of both stroke recurrence and neurological deficits ($p = 0.004$) and are also of statistical significance for occurrence in male gender. None of the patients in our study has α-gene or β-globin haplotype which if present, reduces the risk of stroke development. Moreover, all our patients with stroke have low HBF level (1% - 30%) with median value of 7% which might be due to non-compliance to hydroxyurea therapy and thus considered as an indirect risk factor for stroke development.

Four Patients had permanent neurologic deficit after stroke and surprisingly, all patients are males and non-compliant to hydroxyurea ($p < 0.05$). Those who developed stroke and had no residual deficit are 73.3%, this value might improve with adequate screening and prompt intervention when stroke is suspected and risk factors are taken seriously.

In addition to the risk factors of stroke, there is a correlation between male patients particularly those who are non-compliant to hydroxyurea and to both existence of neurological deficits and recurrence of stroke despite on chronic blood transfusion (Table 3). This finding should be taken into consideration when defining the profile of patients who have or are at high risk of having stroke among patients with SCA.

Patient	Gender	Age	Risk factors	Neurologic deficit	Recurrence	Hydroxyurea
1	M	3	Recent ACS, VOC Recurrent ACS, VOC	No	No	Compliant
2	F	13	NO	No	No	Compliant
3	F	10	Leukocytosis	No	No	Compliant
4	F	9	NO	No	No	Compliant
5	M	14	Recurrent ACS, VOC Leukocytosis	No	No	Compliant
6	M	10	Recurrent ACS, VOC Leukocytosis	Hemiplegia, Squint	Yes	Non-compliant
7	M	5	Leukocytosis, Anemia	No	No	
8	M	11	Recurrent ACS, VOC	Hemiplegia, Dysarthria, Epilepsy	Yes	Non-compliant
9	M	11	Recurrent VOC, ACS Leukocytosis	Hemiplegia, Aphasia, Epilepsy	Yes	Non-compliant
10	M	13	Recent ACS Leukocytosis, Anemia	No	No	Compliant
11	M	7	Recurrent VOC, ACS Leukocytosis	No	Yes	Non-compliant
12	F	11	Recent ACS, VOC, Hypertension Leukocytosis, Anemia	No	No	Compliant
13	M	9	Recent ACS, VOC	Hemiplegia, Dysarthria, Epilepsy	No	Non-compliant
14	M	8	Recent ACS, VOC Leukocytosis, Anemia	No	No	Non-compliant
15	F	13	Recent ACS, VOC Leukocytosis	No	No	Compliant

Table 3: *Profile of patients on chronic blood transfusion including risk factors of stroke, neurologic deficit, recurrence of stroke and compliance to hydroxyurea.*

Conclusion

The prevalence of stroke in patients with SCA in KSAFH Tabuk-KSA is 4.2%. Recurrent ACS, VOC and non-compliance to hydroxyurea not only predisposes to stroke but also are significant predictors of recurrent stroke and neurologic consequences. So, we recommend regular and compliant use of hydroxyurea for all patients with SCA starting from early ages. Furthermore, we emphasis the implementation of TCD in the management guidelines, as an essential imaging tool to identify patients at high risk of stroke. More studies are needed to determine the accurate prevalence of stroke among SCA patients in Saudi Arabia aiming to know the magnitude of problem to establish the necessary setup of comprehensive care for this subtype of patients.

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Competing Interests

The authors declare that they have no competing interests.

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