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Prevalence of cerebral stroke among patients diagnosed with sickle cell disease at King Abdulaziz University Hospital in Jeddah, Saudi Arabia

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ABSTRACT

Background: Sickle cell disease (SCD) is a common inherited blood disease described by persisting episodes of ischemia and reperfusion injury. Stroke in SCD patients is a debilitating complication with resultant structural and functional defects. This serious complication should be investigated and prevented to improve the quality of life in SCD patients. *Objective:* Our aim in this study was to determine the prevalence of overt stroke among SCD pediatric patients at King Abdul-Aziz University Hospital (KAUH), Jeddah, Saudi Arabia. *Method:* This retrospective study was conducted by reviewing SCD pediatric patients' medical records of patients from January 2010 until July 2018 at KAUH. The target population was SCD patients who had a diagnosis of stroke before the age of eighteen years. Descriptive statistics including proportions and percentages were calculated to provide an overview of the demographic and clinical characteristics of SCD patients. *Result:* A total of 412 patients were enrolled in this study. There were 65 patients with a diagnosis of stroke. 34 were male and 31 were female (52.3% and 47.7% respectively) with mean age of 15.8 years (SD ± 6.6). The prevalence of stroke among SCD pediatric patients was 15.8%. Mortality rate was 7.7% (5 of 65) in patients who had stroke. Common clinical characteristics were identified in SCD patients with stroke such as low Hemoglobin F level (Hb F) (Mean 9.7±7.6). Among SCD patients with stroke, increased frequency of vaso-occlusive crisis (VOC) and acute chest syndrome (ACS) were found in 44 patients and 17 patients (67.7% and 26.25 respectively). Ethnicity was a significant risk factor of stroke incidence, higher incidence of stroke was found among Middle Eastern patients, followed by African and Asian (52.3%, 46.2% and 1.5% respectively). *Conclusion:* The prevalence of cerebral stroke among children diagnosed with SCD was 15.8% at KAUH in Jeddah. Stroke-related mortality was significantly high. Associated co-morbidities were common findings among these children.

Keywords: Sickle cell, stroke prevalence, Saudi Arabia.

1. BACKGROUND

Sickle cell disease (SCD) is a common chronic autosomal recessive disorder described by persisting episodes of ischemia and reperfusion injury (Enninful-Eghan, Moore *et al.*, 2010). The information about the prevalence of SCD in Saudi Arabia is indefinite. Studies have reported that SCD is a common genetic disorder in this part of the world and there is a significant variation in its prevalence across the different regions in this country(Al-Qurashi, El-Mouzan *et al.*, 2008; Alhamdan, Almazrou *et al.*, 2007; el-Hazmi, 1992; el-Hazmi & Warsy, 1999; Lehmann, Maranjian *et al.*, 1963). The eastern region has the highest prevalence of SCD, followed by southwestern province(Jastaniah, 2011). SCD is the most common cause of overt stroke in children. Stroke is a debilitating complication with resultant structural and functional defects. It is accountable for 7–11% of SCD-associated deaths (Platt, Brambilla *et al.*, 1994; D. R. Powars, Chan *et al.*, 2005). The risk of developing stroke is estimated to be 250 times higher in children diagnosed with SCD (Broderick, Talbot *et al.*, 1993; Ohene-Frempong, Weiner *et al.*, 1998). The use of transcranial Doppler ultrasonography (TCD) screening for prevention of stroke has profoundly decreases the frequency of overt stroke (Bernaudin, Verlhac *et al.*, 2011; Enninful-Eghan, Moore *et al.*, 2010). With the continuing search for a curative therapy of SCD; hydroxyurea remains essential in SCD management (Rees, Williams *et al.*, 2010; Yawn, Buchanan *et al.*, 2014). It increases the levels of fetal hemoglobin thus reducing the tendency for red blood cells sickling leading to a significant reduction in the incidence of stroke among SCD patients (Moeen, Thabet *et al.*, 2018; Rigano, De Franceschi *et al.*, 2018). There is a lack of sufficient information regarding the prevalence of stroke among patients with SCD in Saudi Arabia. Such a predictable risk should be investigated and prevented to improve the quality of life in SCD patients.

Study Objectives

Primary objective

To determine the prevalence of overt stroke among children diagnosed with SCD at King Abdul-Aziz University Hospital (KAUH), Jeddah.

Secondary objectives

To determine the mortality rate among SCD pediatric patients presented with stroke and if there is an associated risk factors or laboratory indices can be related to stroke Incidence among SCD children.

2. METHOD

Setting

This is a retrospective review study approved by the biomedical ethics committee at KAUH, Jeddah, Saudi Arabia. The participants of the study have included all patients' records been diagnosed with SCD from January 2010 until July 2018. Patients who were diagnosed with sickle cell trait were excluded from this study. In KAUH, each patient is given a unique medical record number (MRN) of admission, and on subsequent admissions, the same number is issued.

A retrospective records review was done by five reviewers using the hospital medical records to look for previous history and risk factors associated with the incidence of cerebral stroke among SCD patients, before their ages have turned to eighteen years old. A total of 412 patients' records were extracted and reviewed to determine the prevalence of cerebral stroke among SCD patients during their childhood life. The range of patient's age varied from 3 months to 18 years old. Children presented with symptoms and signs of sickle cell disease were tested. The confirmation of SCD was done by hemoglobin electrophoresis. Some children were tested for SCD based on the presentation of stroke. All cases of cerebral stroke were diagnosed by reviewing the white matter changes found in their cranial MRI images. SCD patients who were confirmed to have a cerebral stroke were managed by controlled exchange monthly transfusion program and hydroxyurea,

Study variables

Data were collected from the medical records of KAUH, department of hematology using a standardized questionnaire that has been developed and reviewed by the consultant hematologists in KAUH. The following data were extracted for each patient: socio-demographic characteristics such as age, gender, nationality and clinical diagnosis information including age of diagnosis, genotype, Hemoglobin electrophoresis results and previous history of cerebral stroke along with the hematological indices within one year of the last stroke episode, such as: red blood cell count, hemoglobin S level, hemoglobin A2 level, hemoglobin F level, hematocrit level, reticulocytes count, white blood cell count, platelets count, erythrocyte sedimentation rate, peripheral blood smear and the presence of Howell–Jolly bodies. Other associated data of co-morbidities such as voso-occlusive crises, acute chest syndrome, and priapism were also collected and analyzed.

Data analysis

Data entry and coding is done using Microsoft excel sheet. The analysis is done using the Statistical Package for the Social Sciences (IBM SPSS Statistics Version 21). Descriptive statistics are calculated for continuous variables, means, standard deviations and minimum and maximum values are used; for categorical variables frequencies are reported. Student t-test or Mann-Whitney U test are used to compare means, and Chi-square or Fisher's exact test for comparisons between frequencies where appropriate. These tests are done with the assumption of normal distribution where a p-value of < 0.05 will be considered statistically significant. Results are expressed as medians [range], means ± standard deviation (SD) or numbers (%).

3. RESULT

A total of 412 patients' records were identified. All children have been diagnosed with sickle cell disease from 2010 until July 2018 at King Abdul-Aziz University Hospital in Jeddah, Saudi Arabia. The study population consisted of 215 male (52.2%) and 197 female (47.8%) with a mean age of 15.1 years (SD ± 6.7).

Children with cerebral stroke had been diagnosed based on the findings of their cranial MRI images. A total of 65 SCD children had a diagnosis of cerebral stroke. The prevalence of cerebral stroke among children diagnosed with SCD was 15.8%. 34 were male, and 31 were female (52.3% and 47.7% respectively) with a mean age of 15.8 years (SD ± 6.6). Stroke-free population consisted of 134 male and 132 female (50.4% and 49.6% respectively) with a mean age of 13.7 years (SD ± 6.6). The mean age at diagnosis of SCD in children presented with cerebral stroke was 4.3 years (SD ± 4.0) and 3.5 years (SD ± 3.7) in stroke-free children as shown in Table 1 and figure 1.

Table 1 Demographic data

		Stroke children (Frequency %)	Stroke free children (Frequency %)	P value
Gender	Male	34 (52.3)	134 (50.4)	0.483
	Female	31 (47.7)	132 (49.6)	

Mean age in years	15.8 ± 6.6	13.7 ± 6.6	0.024
Mean age at diagnosis in years	4.3 ± 4.0	3.5 ± 3.7	0.163
Mortality rate	5 (7.7)	5 (1.9)	0.018

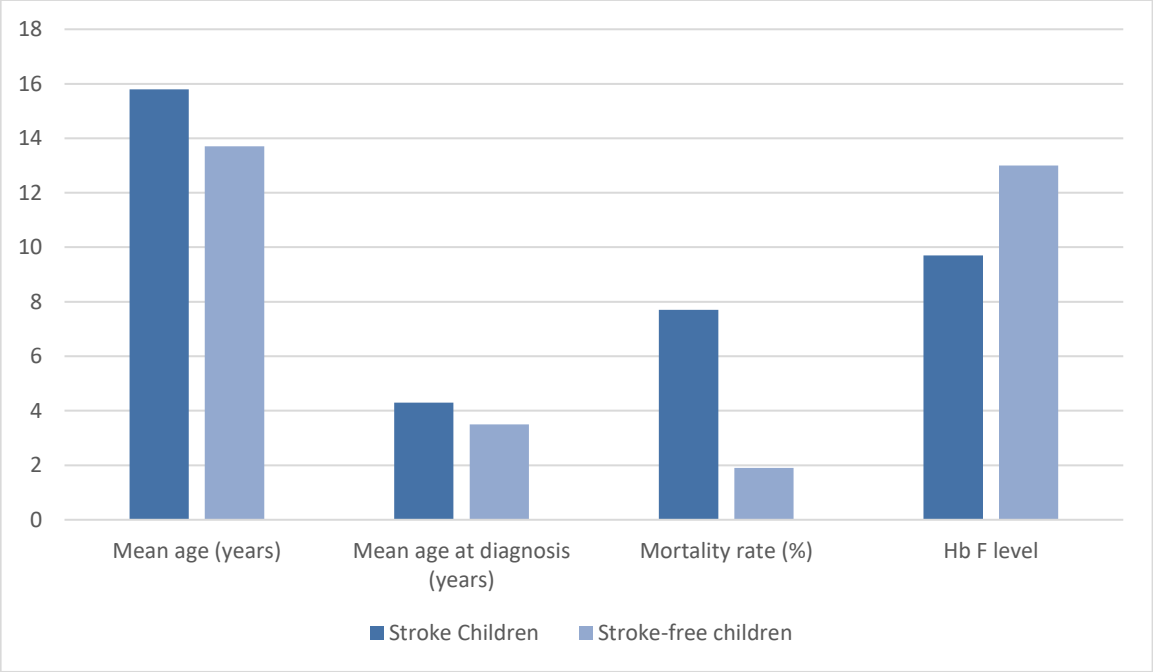

Figure 1 Comparison between Stroke Group vs. Stroke-free Group among SCD Patients

The mortality rate was significantly higher in children presented with cerebral stroke. It accounted for 7.7% of SCD children presented with stroke compared to 1.9% instroke-free children (p = 0.018). The different ethnicities between SCD children have been accounted as a significant risk factor in an association with stroke development, with a higher prevalence of cerebral stroke among Middle Eastern children, followed by African and the Asian group was least affected (52.3%, 46.2% and 1.5% respectively; p = 0.001) as shown in Table 2. Hemoglobin F (Hb F) was another significant risk factor associated with stroke development among SCD children, with a mean value of 9.7 (SD ± 7.6) in SCD children presented with stroke and 13 (SD ± 9.3) in stroke-free children (p = 0.023).

Table 2 Risk factors associated with stroke incidence

Risk factors		Stroke children (Frequency %)	Stroke-free children (Frequency %)	P value
Ethnicity	Middle eastern	34 (52.3)	193 (72.8)	0.001
	African	30 (46.2)	64 (24.2)	
	Asian (least affected)	1 (1.5)	8 (3)	
Level of hemoglobin F	Hb F	9.7±7.6	13±9.3	0.023
	Hb A2	3.3±0.8	3.4±0.9	0.444
Blood Type	O+	31 (48.4)	129 (54)	0.316
	AB+	5 (7.8)	10 (4.2)	
	B+	7 (10.9)	23 (9.7)	
	B-	2 (3.1)	1 (0.4)	
	A+	19 (29.7)	66 (27.6)	

	O-	0 (0)	10 (4.2)	
Genotype	AS	2 (3.1)	8 (3)	0.727
	SS	55 (84.6)	215 (80.8)	
	S B-Thal	8 (12.3)	43 (16.2)	
Transcranial Doppler (cm/s)	Right MCA	87.1 ± 33	82 ± 33	0.647
	Left MCA	88.2 ± 28.6	83.9 ± 3.8	0.657

Blood type was another non-significant risk factor in our analysis, with a higher prevalence of cerebral stroke among SCD children presented with O+ blood type, followed by A+, B + and AB+ (48.4%, 29.7%, 10.9% and 7.8% respectively, p = 0.316). Cerebral stroke development was found to be non-significantly higher in SCD children with S-Beta Thal genotype compared to the other genotypes. Other predicted risk associated factors were shown in Table 2.

The common associated co-morbidities is shown in Table 3. It is found that there is an association between incidence of stroke and priapism among the male SCD children, in which priapism prevalence was significantly higher in SCD children presented with stroke compared to stroke-free children accounting for 7.7% and 2.6% respectively (p = 0.000).

Table 3 Associated comorbidities

Comorbidities	SCD patients with stroke		SCD patients without stroke		P value
	n	Frequency (%)	n	Frequency (%)	
Priapism	5	7.7	7	2.6	0.000

Among SCD children who presented with cerebral stroke (n = 65), 61.5% presented with only one episode of cerebral stroke, while 38.5% had recurrent episodes of stroke during the course of their disease. The presenting symptoms of stroke were variant among the SCD children. Seizure was the most commonly reported symptom of cerebral stroke at presentation, followed by headache and limb weakness accounting for 20.3%, 9.4%, and 9.4% respectively. Other presenting symptoms of cerebral stroke are shown in Table 4.

Table 4 Presenting symptoms of stroke

	n	Frequency (%)
Seizure	13	39.4
Headache	6	18.2
Upper limb weakness	6	18.2
Lower limb weakness	4	12.1
Hemiplegia	1	1.6
Slurred speech	1	1.6
Decreased level of conciseness	2	3.03
Totalof reported cases	33	100

4. DISCUSSION

In this study, we have determined the prevalence of stroke among SCD patients admitted to KAUH. A total of 65 SCD children had a diagnosis of cerebral stroke. Our results showed quite higher prevalence 15.8% in comparison to other studies such as Munube et al., 2016 in Uganda, Jude et al., 2014 in Nigeria, and Njamnshi et al., 2006 in Cameroon, who have resulted in prevalences of 6.8%, 0.74%, and 6.67% respectively (Jude, Aliyu *et al.*, 2014; Munube, Katabira *et al.*, 2016; Njamnshi, Mbong *et al.*, 2006). Gender was not found to be a significant risk factor for the incidence of stroke among SCD patients with an equal male to female ratio; this is similar to the results found in Njamnshi et al. Ohene-Frempong et al. and Munube et al. (Munube, Katabira *et al.*, 2016; Njamnshi, Mbong *et al.*, 2006; Ohene-Frempong, Weiner *et al.*, 1998). Opposing results were reported by Sarnaik et al., 2001, where they found that the prevalence of stroke is higher in female than in male with a male to female ratio of 2:3 (Sarnaik & Ballas, 2001). Another opposing results showed a higher incidence of stroke in boys than in girls (Balkaran, Char *et al.*, 1992).

Recurrence of stroke episodes was observed in 38.5% of SCD patients. Which is much lower than what was reported in 1978 by Powars et al. and Lagunju et al. 2012 that 67% (10 / 15) and 50% (9 / 18) of SCD patients had recurrent stroke episodes respectively (Lagunju & Brown, 2012; D. Powars, Wilson *et al.*, 1978). This variation could be contributed to the better medical care of these groups of patients as these studies were performed before the introduction of the preventive modalities such as the exchange transfusion programs. In our study, most of the patients with a previous history of stroke were started on a preventive exchange transfusion program to prevent further recurrence of stroke episodes. This may justifies the lower recurrence rate. Jude et al. and Njamnshi et al. are in line with our results where they have observed 23.9% and 25% recurrence rates respectively (Jude, Aliyu *et al.*, 2014; Njamnshi, Mbong *et al.*, 2006).

Mortality rate was significantly raised among SCD patients who have suffered one or more episodes of stroke throughout their life compared to stroke-free children, reaching a rate of 7.7% and 1.9% respectively. This is similar to Ohene-Frempong et al. as they showed a rate of up to 10.6% of stroke-related mortality (Ohene-Frempong, Weiner *et al.*, 1998). Different ethnicities among SCD children showed a significant variation in the incidence of stroke. The highest prevalence of stroke was observed among the Middle Eastern population (52.3%), followed by African (46.2%) and Asian (1.5%). Neonato et al. showed 15% prevalence of silent infarcts among SCD patients of primarily African descent (Neonato, Guilloud-Bataille *et al.*, 2000). Other published studies AsIzuora et al, Al-Rajeh et al. and Obama et al. have concluded that Stroke appears to be rare in Saudi Arabian and Nigerian children who were diagnosed with SCD (al-Rajeh, Larbi *et al.*, 1991; Izuora, Al-Dusari *et al.*, 2003; Obama, Dongmo *et al.*, 1994); which is contrary to our findings. Added to these, Marouf et al. from Kuwait showed low incidence of silent infarcts in the Kuwaiti SCD children with an overall prevalence of 3.3% (Marouf, Gupta *et al.*, 2003). This wide variation may show the need to a relook at incidents of stroke in SCD children were a large number of patients should be included.

Our study showed significantly lower levels of Hb F among SCD patients presented with stroke compared to stroke-free patients (mean of 9.65 ± 7.6 g/dl and 12.87 ± 9.2 g/dl respectively) and this is supported by David Calvet et al. 2017 theory which predicted that low levels of Hb F have a role in shortening survival rate and increasing the incidence of silent white matter changes (Calvet, Tuilier *et al.*, 2017). Gender is a factor that influences HbF levels as described by Chang et al.1995 in which female have higher levels of Hb F than male due to genetic bases associated with a specific locus found on chromosome X (Chang, Smith *et al.*, 1995). This theory supports the results of our study, where females had higher levels of Hb F than male with a mean of 12.2 ± 9.3 g/dl and 11.4 ± 8.3 g/dl respectively.

The majority of SCD patients who have presented with previous episode of stroke were found to have other associated co-morbidities. The most common associated co-morbidity was vaso-occlusive crises (67.7%) followed by acute chest syndrome (26.2%). This is similar to Munube et al. that showed a high prevalence of vaso-occlusive crises among SCD patients presented with one or more episodes of stroke during their lifetime (40.0%) (Munube, Katabira *et al.*, 2016). Balkaran et al. has shown that hemiplegia was the most common presenting symptom of stroke among SCD patients occurred in 14 patients out of 17 SCD patients presented with stroke, followed by slurred speech in 10 patients. Convulsions preceded stroke in three patients (Balkaran, Char *et al.*, 1992). In comparison to our results, Seizure was the most common presenting symptom of stroke among SCD patients in our study, accounting for 20.3% and occurred in 13 patients. Hemiplegia and slurred speech were observed in only one patient.

We described for the first time the prevalence of stroke in our population of children with SCD at KAUH in Jeddah KSA. We also represented the high mortality rate among SCD patients who presented with one or more episodes of stroke and some co-morbid conditions that the children with stroke could present with. The information regarding the prevalence of stroke among children with SCD will confirm the need to provide comprehensive care to those children. This will include screening and early identification of children diagnosed with SCD who are at high risk of stroke development, using transcranial Doppler screening (TCD) and the provision of chronic exchange transfusion programs to prevent stroke occurrence and recurrence.

This study was limited by its retrospective nature, which relied on already existing patients' medical records that impose missing values and could alter the exact results. Limitations such as incomplete documentation, loss of follow-ups, and the lack of a united patient's medical profile among hospitals in Saudi Arabia were inevitable. However, the results are representative of SCD patients at KAUH.

5. CONCLUSION

The prevalence of cerebral stroke among children diagnosed with SCD was 15.8% at KAUH in Jeddah, KSA. Stroke-related mortality was significantly high and associated priapism was common findings among these children. We recommend the application of transcranial Doppler Ultrasonography as a secondary screening method for all newly diagnosed SCD patients to identify those who are at high risk of stroke as these measures may prevent its occurrence and recurrence.

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