

STROKE AMONG SICKLE CELL DISEASE PATIENTS IN MADINA MATERNITY & CHILDREN'S HOSPITAL

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Stroke, defined as an acute, clinically evident neurologic event, occurs in 7% to 8% of children with Hb SS any time after the first year of life.¹⁻⁴ It is one of the serious complications of sickle cell disease. Presenting symptoms vary, but hemiparesis or monoparesis, aphasia or dysphasia and seizures, are the most common presentations.⁴ Stroke usually develops as an isolated event but may also occur during episodes of vaso-occlusive crisis, during febrile illnesses, or with acute anemic events, such as aplastic crisis or splenic sequestration.^{3,4}

Risk factors for stroke were previously unknown, however, a few have recently been reported.³⁻⁵ The Madina region in Saudi Arabia, particularly the Khaiber province, is one of the major pockets of the sickle cell gene, besides the Eastern Province and Tihama Asir region.⁶ The Madina Maternity & Children's Hospital (MMCH) is a 400-bed hospital with a 200-bed pediatric section. It is the main referral hospital for the Madina region, as well as surrounding villages. The age limit for pediatric admission is 13 years, and the approximate number of children served by the hospital is 350,000, in an estimated population of 800,000.

The purpose of this study was to demonstrate our clinical experience with strokes in our sickle cell disease (SCD) patients, and to compare our data with other available studies.

Patients and Methods

All the children with SCD disease known to have stroke were included in this study. Stroke was defined as a neurological deficit lasting for more than 24 hours, excluding transient ischemic attacks, seizures without neurological deficit, meningitis and encephalitis. The diagnosis of SCD was based on cellulose acetate electrophoresis at alkaline pH. Ninety patients with SCD were registered in the Pediatric Hematology Unit at

MMCH from 1993 to 1997. Nine of them had stroke and all were followed for a minimum of 18 months. Four patients were referred from other peripheral hospitals in Madina. The medical records of these patients were studied retrospectively. The following variables were studied: age at onset, sex, nationality, presenting neurological signs and symptoms, associated crisis or illness, Hb electrophoresis, steady-state leukocyte count, steady-state hematocrit, platelet count, reticulocytes, red blood cells count and indices, brain CT scan, acute management undertaken, neurological outcome, recurrence, and mortality.

Results

Stroke occurred in nine out of 90 children with SCD, indicating a prevalence rate of 10%. Eight of the patients were Saudis and one was a Yemeni. They comprised seven males and two females, with a male to female ratio of 3.5:1. Six patients (67%) presented between the age of five and 10 years, and three (33%) presented below the age of five years. Six patients (67%) had homozygous (Hb SS) disease and three (33%) had sickle cell β -thalassemia. Neurological presentations were as follows: four patients (45%) presented with seizure and hemiplegia; three patients (33%) presented with hemiplegia alone; one patient (11%) presented with aphasia and another with severe headache; and eight patients (89%) presented without any associated crisis or illness. Only one patient (11%) presented with associated painful crisis.

Table 1 summarizes the laboratory data of all nine patients before the onset of stroke. It shows that six patients (67%) had a steady-state hematocrit level of less than 25%, and only two patients (22%) had a steady-state leukocyte count of more than 15,000/cmm. Brain CT scan showed abnormal findings of cerebral infarction in eight patients (89%). Only one patient had normal CT scan finding at presentation. Three patients (33%) had exchange transfusion at presentation, and six patients (67%) received simple blood transfusion. The neurological outcome after acute event was as follows: four patients (44%) had complete resolution; five patients (56%) had neurological sequelae; and three patients had a recurrence (33%). There was no mortality.

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Discussion

This study is the first in the Madina Region that highlights the experience of one of the most serious complications of SCD. Although nine SCD children with stroke reported over a five-year period, this does not represent all the cases seen in this region, as some cases would have been referred to other hospitals. Other cases may not have been diagnosed because of lack of clinical experience and diagnostic facilities at the peripheral hospitals. To our knowledge there have only been a few reported cases of stroke in children with SCD in Saudi Arabia.^{7,8} Our study probably presents the largest number of strokes reported in children with SCD in Saudi Arabia.

We found a relatively high prevalence of stroke among our patients (10%), as compared to other studies (7%-8%).¹⁻⁴ The majority of our patients were male, which is consistent with other studies.^{3,7} The reason for male predominance is unknown. The youngest patient in our study was a three-year-old male, and the age group mostly affected was between three and 10 years, also consistent with other studies.³ The reason why this age group is particularly prone to stroke is unknown, however, in view of the known high values of cerebral blood flow and metabolism in childhood, it has been suggested that when this is compounded by anemia, the hypercirculatory state of abnormal red cells may make patients in this age group particularly prone to ischemic infarction.⁹ One-third of our patients had sickle β -thalassemia, in contrast to Balkaran et al., who reported all his cases as Hb SS disease.³ About 89% of our patients presented without any associated sickle cell crisis or other illnesses, a finding consistent with other studies.⁴ Steady-state leukocyte count was high in only 22%, in contrast to Balkaran's study. About 67% of our patients had a steady-state hematocrit level less than 25%. A low hematocrit level is thought to be associated with increased cerebral blood flow and increased cerebral blood volume, which is considered a risk factor for stroke in SCD.^{9,10} CT scan of the brain was abnormal in 89% of our patients, and all the abnormalities were cerebral infarction. The reason for the high yield was probably due to late referral in some cases, so the CT scan was done a few days after the onset of stroke. Six patients (67%) received simple blood transfusions upon presentation, because four of them were referred late from other peripheral health centers and two presented late to our hospital. Although the recommended management by many centers is prompt exchange transfusion or erythrocytapheresis to lower the percentage of sickle hemoglobin to less than 30%,^{2,11} other centers treat acute stroke with cautious simple transfusion, especially stable patients without progressive neurologic symptoms.¹² Five patients (56%) had neurological sequelae, and none of them had received exchange transfusion at onset of stroke, as mentioned earlier, because of late presentation. All those who received exchange transfusion had complete

TABLE 1. Steady-state hematological data.

Patient #	WBC x 10 ⁹	HCT %	MCHC g/dL	MCV (fL)	Reti %	RBC x 10 ¹²	Plt x 10 ⁹	Hb S %	Hb F %	Hb A ₂ %
1	9.5	30	31	95	4	3.14	475	70	0	2.7
2	18	23	32	89	7	2.98	415	79	17	2.9
3	10	20	33	92	3.5	2.22	192	70	0	2.9
4	11.2	21	37.2	76	8	2.87	536	80	16	2.5
5	11.4	25.8	32	82	3	3.13	540	85	12.9	1.6
6	10.5	24	34	84	10	3.24	230	88	11	4
7	21.6	23	32.5	93.6	15	2.67	486	85	0	4.7
8	7	27	34.9	86.3	10	3.22	180	62	0	4.5
9	11	24	35	82	8	2.98	329	60	23	2.3

recovery. So the high percentage of neurological sequelae in our study is probably the result of failure to perform exchange transfusion at acute onset of stroke. Despite the fact that all our patients were on chronic red blood cell transfusion, there was recurrence in 33%, which is greater than the estimated risk of 10% recurrence in patients who are receiving chronic transfusion therapy,^{1,13} but lower than the 46% quoted by Balkaran et al.³ The reason for the high recurrence rate is probably due to a less intense transfusion regime, because of irregular follow-up of some patients, which results in failing to maintain sickle hemoglobin under 30%. We had no mortalities among our patients.

In conclusion, we found that a low steady-state hematocrit level in sickle cell patients was a risk factor for stroke, as was reported in other studies,¹² but that a high leukocyte count is not a risk factor, as has been reported by others.³ We also conclude that exchange transfusion is the treatment of choice of acute stroke to reduce the risk of neurological sequelae, and that regular chronic transfusion is an important mode of therapy to reduce risk of recurrence. As stroke is one of the most serious complications of SCD, it would be important to prevent the first attack of stroke by identifying high-risk patients by using noninvasive diagnostic methods. Adams et al. have reported that transcranial ultrasonography can identify children with SCD who are at risk for cerebral infarction, and suggest that periodic ultrasound examination and the selective use of transfusion therapy could make the prevention of first stroke an achievable goal.¹⁴ As well, detection of silent infarction by magnetic resonance imaging (MRI) has been reported,¹⁵ and will identify a high-risk patient, but would leave open the argument of whether or not chronic transfusion would be beneficial, as there is no reliable data to support the use of transfusion therapy for such groups of patients.

As the pathophysiology of stroke in sickle cell anemia remains unclear, our study did not contribute to the pathologic basis of stroke in SCD because of limited local diagnostic facilities. A collaborative prospective study with other tertiary care centers is required to measure protein C and protein S activities in children with SCD, as they have

been reported to be significantly decreased in children with SCD who have had stroke.¹⁶ Also, homocystine in urine and plasma need to be assessed among our patients, as most of them had poor compliance with folic acid supplementation, and homocystinuria is a well-known cause of thrombotic hypercoagulability state, which accounts for a significant proportion of unexplained strokes.¹⁷ Finally, we recommend the prevention of SCD and other hemoglobinopathies in Saudi Arabia by genetic counselling through health education, reduction of consanguineous marriages and implementation of premarital screening for hereditary blood diseases.

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