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Evaluation of transcranial Doppler abnormalities in children with sickle cell disease in Elobied Specialized Children's Hospital.

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Abstract

Background: Sickle cell disease is one of the most common inherited diseases in Sudan, and it is the most common cause of childhood stroke, occurring with the highest frequency before the age of 6 years. Children with SCD who are developing high stroke risk can be detected months to years before the stroke using non-invasive transcranial Doppler ultrasonography providing a means of selecting and prophylactically treating SCA children at highest risk.
Objectives: This study aims to evaluate transcranial Doppler abnormalities in children with sickle cell disease in El-Obied specialized children hospital.
Materials and methods: This is a cross sectional study done on the 119 patients who attended the sickle cell clinic in El-Obied specialized children hospital during time period from December 2016 to February 2017, ages from 2-18 years was included, when patients does not have recent stroke symptoms, blood flow velocities was measured in both proximal internal carotid and middle cerebral arteries using non-imaging Doppler method, TAMVs was recorded along with hemoglobin concentration and of the patients.
Results: 0% of the study population had middle cerebral artery velocity higher than 200 cm/s, also no high conditional velocity (170-199 cm/s) was recorded so no patient was at high risk to develop stroke. 20.1% of patients showed low velocities in one or both middle cerebral arteries, as well, 4.2% had abnormal middle cerebral arteries interhemispheric ratio, 4.2% of study population showed absent flow in one of their middle cerebral arteries, reflecting previous occlusion. 4.2% had poor temporal window. It was difficult to measure the velocity in one of the 4 vessels in 5.9% of the patient due to uncooperativeness. There was statistically significant relationship between hemoglobin concentration and blood velocity in the left middle cerebral artery.
Conclusion: Despite the international recommendations, using TCD as stroke screening tool in children with sickle cell disease in Sudan is still not a well-known practice. Successful strategies to improve TCD screening rates must be encouraged in all health care institutions.

Keywords: Transcranial Doppler, Sickle cell disease, Children, Elobied.

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Introduction

Sickle cell disease is a hemoglobinopathy that is recessively inherited commonly among people of Equatorial African, Saudi Arabian and Mediterranean ancestry and now widespread in the Americas and Europe [1]. The expected incidence of sickle cell disease (SCD) at birth is 1 in 625 [2]. It is characterized by chronic hemolytic anemia and intermittent vaso-occlusive events. These events result in tissue ischemia, which leads to acute and chronic pain as well as damage to many organs in the body. Complications include ischemic and hemorrhagic stroke, acute chest syndrome, painful vaso-occlusive crises, splenic sequestration, aplastic crises, and bacterial sepsis due to hyposplenia [3]. Chronic morbidities include cerebrovascular disease, pulmonary hypertension, osteonecrosis, and nephropathy and organ failure [4].

Stroke is a common complication of sickle cell disease, which occurs in approximately 7% of children with SCD. The incidence is 0.7% per year during the first 20 years of life, with the highest rates in children 5-10 years of age. An additional 20% of patients with sickle cell disease have evidence of asymptomatic cerebral infarction on MRI of the brain. These individuals may have significant neuropsychological deficit or

other neurologic problems like headache, motor difficulties and abnormal EEG [2]. The most commonly recognized stroke syndrome in children with SCD is large-artery infarction. These "big strokes" are the result of a vascular process involving the large arteries of the circle of Willis leading to territorial infarctions from perfusion failure or possibly artery-to-artery embolism [4].

Available options for prevention of stroke symptoms in patients at risk include hyper transfusion therapy, hydroxyuria and bone marrow transplantation [5]. We can detect children who are developing cerebral vasculopathy using transcranial Doppler ultrasonography (TCD) in order to provide effective intervention. Transcranial Doppler ultrasonography measures blood flow velocity in the large arteries of the circle of Willis. Velocity is generally increased by the severe anemia in these patients, and it becomes elevated focally at the stenotic segment of the vessel. Children with SCD who are developing high stroke risk can be detected months to years before the stroke using TCD [4].

Materials and Methods

Study design

This was a cross sectional, descriptive study.

Study area

Elobeid Specialized Children's Hospital in Elobeid City which is the capital of North Kordofan State, the hospital has been founded in the year 1986 by a man of charity Dr Dawood Alsalih with assistance of the people of Kuwait, under the supervision of patient's subsidy fund in Sudan. The hospital covers two slices; children and other age groups. It is considered the only specialized children hospital in Kordofan province, which provides services for all children in Kordofan province and eastern Darfur. The hospital is attended by about 40,000 inhabitants of the western neighborhoods of the Elobeid City. The first opening of the hospital was as external clinic in 1989 AD.

Elobeid Center for sickle cell anemia started first on 28/2/2013 and is the only center specializing in sickle cell disease in western Sudan, offering free medical services represented in Vitamins and Antibiotics and follow-up of patients, the center also offers educational services for the patients, and acts as research center.

Study duration

Study started from December 2016 and ended in February 2017.

Study population

This study included all of the children with sickle cell disease attending the sickle cell clinic in Elobied specialized children hospital during the study duration.

Inclusion criteria

Children attending the clinic aging 2-18 years were included.

Exclusion criteria

Children having recent stroke symptoms at the study duration were excluded.

Sample size

The sample size was determined by time frame to include all of children attending the clinic at study duration, they were 119 patients.

Sampling technique

Total coverage of the study population during the duration of the study was attempted.

Data collection tools

A data collection sheet designed to contain all of the study variables was filled using the information provided from sickle cell clinic records and patients files.

Study variables

Patient's age, gender, weight, hemoglobin concentration, time average mean velocity TAMV of the proximal right and left middle cerebral and internal carotid arteries and right and left proximal internal carotid arteries, the interhemispheric ratio of the middle cerebral arteries TAMV (Table 1).

Table 1. *Descriptive statistics of study variables.*

Variables	N	Range	Minimum	Maximum	Mean	Std deviation
Age	119	16	2	18	9.6134	4.35522
Hb	119	7.8	4	12.4	7.3303	1.20954
RICA	112	134	27	161	72.7946	28.35526
LICA	111	139	11	150	73.0721	25.97436
RMCA	109	123	36	159	103.7431	30.61753

LMCA	112	125	33	158	106.1071	27.43095
IHR	107	2.33	0.32	2.65	1.0339	0.37334
Valid N (List wise)	101					

Data analysis

SPSS was used to calculate the mean and ranges of the intracranial arteries TAMV, correlation between TAMV and patient's age, weight and gender was explored with Pearson correlation method, level of significance was set at P<0.01.

Study outcomes

The outcomes of this study are the means and ranges of the TAMV of the intracranial arteries among children with sickle cell disease, the patterns and how frequent are the abnormal TAMV values, and the correlation significance between TAMV of the intracranial vessels and the other study variables.

Ethical considerations

A written form of informed consent was signed by all participants or their carers before data collection, and ethical clearance will be obtained from SMSB and other relevant authorities as Elobeid specialized children hospital.

Results

119 patients attended sickle cell clinic during study period. Females made 52.9% of them and males were 47.1%. The youngest patient was 2 years old and the maximum age was 18 with mean age of 9.6 ± 4.3 years. Hemoglobin concentrations recorded ranged from 4.6 to 12.4 g/dl with mean of 7.33 ± 1.2 g/dl. Time average mean of maximum velocities recorded for the proximal right internal carotid arteries ranged from 27 to 161 cm/s, mean 72.8 ± 28.3 cm/s. For the proximal left internal carotid arteries, minimum velocity was 11 cm/s and the maximum was 150 cm/s with mean of 73.07 ± 25.9 cm/s. For the right middle cerebral arteries velocities ranged from 36 to 159 cm/s the mean was 103 ± 30.6 cm/s, and for the left middle cerebral arteries they ranged from 33 to 158 cm/s with 106 ± 27.4 cm/s mean. The range of right to left interhemispheric ratios of the middle cerebral arteries recorded was 0.32 to 2.65 with mean of 1.033 ± 0.4.

Describing the patterns of transcranial Doppler abnormalities encountered during the study using a non-imaging 2 MHz probe, no patient showed high abnormal velocity in the middle cerebral arteries (more than 200 cm/s), or the high conditional velocity (170-199 cm/s). The low velocity (less than 70 cm/s) was seen in the RMCA of 10 patients 8.4%, in the LMCA in 9 patients 7.5%, and in both arteries in 5 patients 4.2%.

Regarding the MCA right to left ratios, values above or below the mean ± 2 standard deviations (0.37) which are out of the tolerance interval, was assigned to be abnormal, i.e. less than 0.29 or more than 1.77, as it is a normally distributed value and 95% of population should be within the tolerance interval, the values more than 1.77 was recorded in 5 patients 4.2%. No patient showed IHR below 0.29. Another author assigned IHR values less than 0.5 to be abnormal, it was recorded in 6 patients 5.6%.

Poor temporal window demonstrated in 5 patients 4.2% and another 5 (4.2%) showed absent flow in one of their MCAs in spite of window presence. One of the 4 arteries could not be examined because of uncooperativeness in 7 patients 5.9%.

Using Pearson's test to correlate between study variables with significance value less than 0.01, significant correlation found only between hemoglobin concentration and TAMV of LMCAs, and between TAMV in LMCAs and RMCAs (Table 2). Correlation between TAMVs and age and patient's weight was not significant.

Table 2. *Correlation between study variables using Pearson's test.*

		Age	Hb	Wt	RMCA	LMCA	IHR
Age	Pearson correlation	1	0.077	0.791**	0.086	0.024	0.055
	Sig. (2-tailed)		0.403	0	0.372	0.805	0.571
	N	119	119	65	109	112	107
Hb	Pearson correlation	0.077	1	0.15	-0.121	-0.327**	0.108
	Sig. (2-tailed)	0.403		0.233	0.209	0	0.268
	N	119	119	65	109	112	107
Wt	Pearson correlation	0.791**	0.15	1	-0.211	-0.176	-0.009
	Sig. (2-tailed)	0	0.233		0.109	0.172	0.946
	N	65	65	65	59	62	58

RMCA	Pearson correlation	-0.086	-0.121	-0.211	1	0.386**	0.472**
	Sig. (2-tailed)	0.372	0.209	0.109		0	0
	N	109	109	59	109	107	107
LMCA	Pearson correlation	0.024	-.327**	-0.176	0.386**	1	-0.559**
	Sig. (2-tailed)	0.805	0	0.172	0		0
	N	112	112	62	107	112	107
IHR	Pearson correlation	0.055	0.108	0.009	0.472**	-0.559**	1
	Sig. (2-tailed)	0.571	0.268	0.946	0	0	
	N	107	107	58	107	107	107

**Correlation is significant at the 0.01 level (2-tailed)

Discussion

Sickle cell center in El-Obied specialized children hospital started at 2013, taking care of about 1100 patients, 600 of them are compliant to the regular follow up every 4-8 weeks according to patient situation. During the study period from December 2016 to February 2017, when TCD screening firstly initiated in the clinic, 119 patient visited the clinic, the counts of both genders were almost similar, a lot of them were siblings or cousins, reflecting the genetic nature of the disease and the high prevalence in the district, due to the high consanguinity rates in Sudan and the rate of first cousin marriages, which is the highest when compared with the other Arab countries (which exceeds 40%). Moreover, the traditional tribal society is still existent in Sudan.

The lack of public health measures and services for the prevention of genetic disorders in general; the selective termination of pregnancy of an affected fetus is illegal in Sudan [6].

Comparing the means of blood velocities in middle cerebral arteries in this study with the mean velocity in healthy children 90 cm/s, patients with sickle cell disease has shown higher values, this can be explained by the brain vascular response to compensate the chronic hypoxia resulting from the chronic anemia status [7]. A study done on 145 Nigerian children with sickle cell anemia has found that the mean velocities in children with HbSS was 152 ± 27 cm/s [8] which is much higher than our patients, 103 ± 30.6 and 106 ± 27.4 cm/s. There is no clear explanation of this difference, but one probability that the Nigerian study was done on patients carrying HbSS hemoglobin type, while the phenotype of hemoglobin was not one of the inclusion criteria of our study, and patients with HbSC hemoglobin who can represent a part of our sample usually have milder disease than HbSS patients.

Regarding the different patterns of abnormal TCD findings, in the Nigerian study 4.7% of patients showed TAMV higher than 200 cm/s, while none of our patients showed this finding, the reasons for this disparity are not quite clear. Could it be the HbSC patients that may represent part of the study sample, or that some patient in the study with normal velocities had suffered a stroke prior to the availability of routine TCD screening? A long-term follow-up of the children may provide some answers.

The TAMV values less than 70 cm/s or IHR values less than 0.5 as recorded in 20.1% and 5.6% respectively can be indicative of severe stenosis at an area proximal to the scanned part of the vessel, according to the guidelines of STOP trial these patients should be rescanned after a month [3].

It is not unusual to have patients with poor or absent temporal bone window, as it is a normal anatomical variant prevalent in 5-30% of people, and can be seen unilaterally in 38% [9] and encountered in 4.2% of the study population, but another contributing factor that diffuse bone sclerosis is one of the known complications of sickle cell disease, As one of these patient had X ray scans of multiple bones, requested for another cause, which showed diffuse increase of bone density [10].

Patients with sickle cell disease who had a stroke in the past have 30% higher chance to develop a new one, compared to 0.5-1% risk in sickle cell patient without stroke history. This can be seen in the 4.2% of study patients who have absent blood flow in window presence, indicating total vessel occlusion with failure of recanalization or collateral formation. These children should be offered more frequent screening [3].

In 5.9% of the patient, most of them were the youngest in the study, it was difficult or sometimes impossible to scan one of the 4 vessels. To make the patient more cooperative, the procedure, as well as the need to remain awake and cooperative during the examination, should be explained to the patient. Some centers allow children to watch a movie during the examination.

When the patient becomes sleepy, the CO_2 levels increase which elevates the mean flow velocity and could give a false-positive result. It is also beneficial to try with more experienced operator, the deficient exam is not valid and should be repeated at another visit [3]. The statistically significant negative correlation between hemoglobin concentration and blood flow velocity in left middle cerebral artery is consistent with the results of the Nigerian study,

where blood flow velocity was negatively correlated with the hematocrit. This can be explained by the compensatory mechanism of the cerebral perfusion under chronic anemia status.

Limitations

Data collection from the paper form of patient's records of the clinic was a complicated process, with a lot of missed values, unrecorded cases; unclear handwriting although clinic staff offered a lot of help, but this can affect the accuracy of the study.

The far geographic distance of study area from the Khartoum and the busy nature of the registrar job made the supervision on data collection process and Doppler examination of the patients difficult and less frequent.

Financial resources are limited, its availability could extend this study to include other laboratory examinations as CBC and hemoglobin electrophoresis, and increase the sample size to give more information and strength to the study.

Conclusion

The mean TAMV of RICA in patients with sickle cell disease was 72.7 cm/s, and 73.0 cm/s in LICA. Regarding the middle cerebral arteries the mean velocity in the right side was 103.7 cm/s, and 106.1 in the left side. The mean right to left interhemispheric ratio of the middle cerebral arteries was 1.03.

0% of the study population had middle cerebral artery velocity higher than 200 cm/s, so no patients had impending stroke, also no high conditional velocity (170-199 cm/s) was recorded so no patient was at high risk to develop stroke.

20.1% of patients showed low velocities in one or both middle cerebral arteries, as well, 4.2% had abnormal middle cerebral arteries interhemispheric ratio, indicating either hyperemic status due to chronic anemia or arterial stenosis, making the close follow up necessary at intervals determined by the local guidelines.

4.2% of study population showed absent flow in one of their middle cerebral arteries, reflecting previous occlusion with failure of recanalization as stated by their medical history. 4.2% had poor temporal window possibly normal anatomical variant or part of diffuse bone sclerosis caused by sickle cell disease.

It was difficult to measure the velocity in one of the 4 vessels in 5.9% of the patient due to uncooperativeness, mostly those of young ages, a problem can be solved by an experienced operator.

There was statistically significant relationship between hemoglobin concentration and blood velocity in the middle cerebral artery reflecting the vascular response to maintain brain perfusion under chronic anemia circumstances.

Recommendations

This study emphasizes the role of transcranial Doppler as a powerful screening tool for strokes in children with sickle cell disease due its advantages over the other imaging modalities, and encourages use of it in Sudanese hospitals.

Sickle cell disease is associated with serious neurological complications and morbidities that can be avoided by raising the awareness of the importance of early screening and follow up of all affected children according to the guidelines.

International protocols of transcranial Doppler examination should be followed closely to guarantee accurate and valid diagnosis. This means to scan the 4 vessels of anterior brain circulation and the basilar and ophthalmic arteries when indicated.

The operators should be keen to improve their performances through continuous training, and by keeping updated with new protocols and medical discoveries.

Doppler machines should be widely available in all hospitals, with regular quality assurance programs.

Archiving systems in sickle cell clinics should be computerized and properly designed to give accurate and detailed information that can be advantageous for both clinicians and researchers.

Transcranial Doppler in sickle cell patients is a rich field that still needs meticulous researching with larger sample sizes and expanded time for more generalizable results.

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