Original Article

Evaluation of transcranial Doppler abnormalities in children with sickle cell disease in El-Obeid Specialized Children's Hospital

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Abstract

Objectives: This study aims to evaluate transcranial Doppler abnormalities in children with sickle cell disease (SCD) in a specialized children's hospital in El-Obeid. **Materials and Methods:** This is a cross-sectional study done on 119 patients (2–18 years of age were included) who attended the sickle cell clinic in a specialized children's hospital in El-Obeid from December 2016 to February 2017; when patients do not have recent stroke symptoms, blood flow velocities were measured in both proximal internal carotid and middle cerebral arteries (MCAs) using non-imaging Doppler method, and time average mean velocities were recorded along with hemoglobin concentration and of the patients. **Results:** None of the study population had MCA 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. About 20.1% of patients showed low velocities in one or both MCAs; 4.2% had abnormal MCAs' interhemispheric ratio; 4.2% of study population showed absent flow in one of their MCAs, reflecting previous occlusion. About 4.2% had poor temporal window. It was difficult to measure the velocity in one of the four vessels in 5.9% of the patient due to uncooperativeness. There was statistically significant relationship between hemoglobin concentration and blood velocity in the left MCA. **Conclusion:** Despite the international recommendations, using transcranial Doppler ultrasonography (TCD) as a stroke screening tool in children with SCD in Sudan is still not a well-known practice. Successful strategies to improve TCD screening rates must be encouraged in all healthcare institutions.

Keywords: Children, El-Obeid, sickle cell disease, transcranial Doppler

Introduction

Sickle cell disease (SCD) 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 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 of 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. Chronic morbidities include cerebrovascular disease, pulmonary hypertension, osteonecrosis, nephropathy, and organ failure.[3]

Stroke is a common complication of SCD, 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 SCD have evidence of asymptomatic cerebral infarction on

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magnetic resonance imaging of the brain. These individuals may have significant neuropsychological deficit or other neurologic problems such as headache, motor difficulties, and abnormal electroencephalogram.[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.[3]

The available options for prevention of stroke symptoms in patients at risk include hypertransfusion therapy, hydroxyuria, and bone marrow transplantation.[4] We can detect children who are developing cerebral vasculopathy using transcranial Doppler ultrasonography (TCD) to provide effective intervention. TCD measures blood flow velocity in the large arteries of the circle of Willis. Velocity is generally increased by 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.[3]

Materials and Methods

Study design

This was a cross-sectional, descriptive study.

Study area

The study was done at El-Obeid Specialized Children's Hospital in El-Obeid City which is the capital of North Kordofan State; the hospital was founded in the year 1986 by a man of charity Dr. Dawood Alsalih with the 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 El-Obeid City. The first opening of the hospital was as an external clinic in 1989 AD.

El-Obeid Center for sickle cell anemia started first on 28/2/2013 and is the only center specializing in SCD in western Sudan, offering free medical services represented through vitamins and antibiotics and follow-up of patients; the center also offers educational services for patients and acts as research center.

Study duration

The study started from December 2016 and ended in February 2017.

Study population

This study included all the children with SCD attending the sickle cell clinic in El-Obeid Specialized Children's Hospital during the study period.

Inclusion criteria

Children 2–18 years of age attending the clinic 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 children attending the clinic at the study duration; they were 119 patients in total.

Sampling technique

The 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 the study variables was filled using the information provided from sickle cell clinic records and patients' files.

Study variables

The study variables included 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 the right and left proximal internal carotid arteries, and the interhemispheric ratio (IHR) of the middle cerebral arteries' (MCAs) TAMV.

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 using Pearson's correlation method, and the 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 SCD, 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 care takers before data collection, and ethical clearance was obtained from Sudan Medical Specialization Board (SMSB) and other relevant authorities like El-Obeid Specialized Children's Hospital.

Results

Overall, 119 patients attended sickle cell clinic during the study period. About 52.9% of them were females, and males were

47.1%. The youngest patient was 2 years old and the oldest patient was 18 years old, with a mean age of 9.6 ± 4.3 years. Hemoglobin concentrations ranged from 4.6 to 12.4 g/dL with a mean of 7.33 ± 1.2 g/dL. The time average mean of maximum velocities recorded for the proximal right internal carotid arteries (RICAs) ranged from 27 to 161 cm/s, with a mean of 72.8 ± 28.3 cm/s. For the proximal left internal carotid arteries (LICAs), the minimum velocity was 11 cm/s and the maximum was 150 cm/s with a mean of 73.07 ± 25.9 cm/s. For the right middle cerebral arteries (RMCAs), velocities ranged from 36 to 159 cm/s, with a mean of 103 ± 30.6 cm/s; for the left middle cerebral arteries (LMCAs), they ranged from 33 to 158 cm/s with a mean of 106 ± 27.4 cm/s. The range of right to left IHRs of the MCAs recorded was 0.32–2.65 with a mean of 1.033 ± 0.4 [Table 1].

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

Table 1: Descriptive statistics of study variables

Variables	*n*	Range	Minimum	Maximum	Mean	Std deviation
Age	119	16.00	2.00	18.00	9.6134	4.35522
Hb	119	7.80	4.00	12.40	7.3303	1.20954
RICA	112	134.00	27.00	161.00	72.7946	28.35526
LICA	111	139.00	11.00	150.00	73.0721	25.97436
RMCA	109	123.00	36.00	159.00	103.7431	30.61753
LMCA	112	125.00	33.00	158.00	106.1071	27.43095
IHR	107	2.33	0.32	2.65	1.0339	0.37334
Valid *n* (listwise)	101					

Hb: Hemoglobin; RICA: Right internal carotid artery; LICA: Left internal carotid artery; RMCA: Right middle cerebral artery; LMCA: Left middle cerebral artery; IHR: Interhemispheric ratio

Regarding the MCA right to left ratios, the values above or below the mean ± 2 standard deviations (0.37) which are out of the tolerance interval were assigned to be abnormal, that is, 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 were recorded in 5 (4.2%) patients. No patient showed IHR below 0.29. Another author assigned IHR values less than 0.5 to be abnormal; it was recorded in 6 (5.6%) patients.

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

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

Discussion

Sickle cell center in El-Obeid Specialized Children's Hospital was started at 2013, taking care of about 1100 patients; 600 of them are compliant to regular follow-up every 4–8 weeks according to patient situation. During the study period from December 2016 to February 2017, when TCD screening was first initiated in the clinic, 119 patients 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 high consanguinity rates in Sudan and the rate of first-cousin marriages, which is the highest when compared with other Arab countries (which exceeds 40%). Moreover, the traditional tribal society is still existent in Sudan.

Table 2: Correlation between study variables using Pearson's test

		Age	Hb	Wt	RMCA	LMCA	IHR
Age	Pearson's correlation	1	0.077	0.791**	0.086	0.024	0.055
	Sig. (two-tailed)		0.403	0.000	0.372	0.805	0.571
	n	119	119	65	109	112	107
Hb	Pearson's correlation	0.077	1	0.150	−0.121	−0.327**	0.108
	Sig. (two-tailed)	0.403		0.233	0.209	0.000	0.268
	n	119	119	65	109	112	107
Wt	Pearson's correlation	0.791**	0.150	1	−0.211	−0.176	−0.009
	Sig. (two-tailed)	0.000	0.233		0.109	0.172	0.946
	n	65	65	65	59	62	58
RMCA	Pearson's correlation	−0.086	−0.121	−0.211	1	0.386**	0.472**
	Sig. (two-tailed)	0.372	0.209	0.109		0.000	0.000
	n	109	109	59	109	107	107
LMCA	Pearson's correlation	0.024	−0.327**	−0.176	0.386**	1	−0.559**
	Sig. (two-tailed)	0.805	0.000	0.172	0.000		0.000
	n	112	112	62	107	112	107
IHR	Pearson's correlation	0.055	0.108	0.009	0.472**	−0.559**	1
	Sig. (two-tailed)	0.571	0.268	0.946	0.000	0.000	
	n	107	107	58	107	107	107

Hb: Hemoglobin; RMCA: Right middle cerebral artery; LMCA: Left middle cerebral artery; IHR: Interhemispheric ratio**Correlation is significant at the 0.01 level (two-tailed)

There is a 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.[5]

Comparing the means of blood velocities in MCAs in this study with the mean velocity in healthy children (90 cm/s), patients with SCD have shown higher values; this can be explained by the brain vascular response to compensate the chronic hypoxia resulting from the chronic anemia status.[6] 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,[7] which is much higher than our patients (103 ± 30.6 and 106 ± 27.4 cm/s). There is no clear explanation for this difference, but one probability is 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, patients with HbSC hemoglobin who can represent a part of our sample usually have milder disease than patients with HbSS.

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 patients with HbSC who may represent part of the study sample, or that some patients 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.

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 Stroke Prevention Trial in Sickle Cell Anemia (STOP) trial, these patients should be rescanned after a month.[8]

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 is that diffuse bone sclerosis is one of the known complications of SCD, as one of these patients had X-ray scans of multiple bones, requested for another cause, which showed diffuse increase in bone density.[10]

Stroke is an important complication of SCD. Approximately 24% of patients have a stroke by the age of 45 years. Blood transfusions decrease stroke risk in patients deemed at high risk by TCD by evidence of elevated intracranial internal carotid or MCA velocity.[11] The STOP study confirmed that TCD could reliably identify those at the highest risk for stroke.[12]

Based on different studies and considering that SCD is the most common monogenic hereditary disease, occurring predominantly among African descendents, guidelines for transcranial Doppler in children and adolescents with SCD were developed to contribute in reducing morbidity and mortality resulting from this pathology in different settings.[13]

Children with SCD are at high risk for stroke.[1-3] The risk is highest in children with elevated blood flow velocity in the distal internal carotid (terminal internal carotid artery) or proximal MCA, as measured with TCD.[14] Chronic blood transfusions, if implemented in a timely fashion in those with flow velocity of 200 cm/s, can reduce the risk of stroke by as much as 92%.[14,15]

The STOP investigators suggested that unilateral high-flow velocity indicates stenosis, whereas bilateral high velocity represents bilateral stenosis, hyperemia, or both.[16]

Patients with SCD who had a stroke in the past have 30% higher chance to develop a new one, compared with 0.5%–1% of risk in patients with sickle cell without stroke history. This can be seen in 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.[8]

In 5.9% of the patients, most of them were the youngest in the study, and it was difficult or sometimes impossible to scan one of the four vessels. To make the patient more cooperative, the procedure, and 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 examination is not valid and should be repeated at another visit.[8] Statistically significant negative correlation between hemoglobin concentration and blood flow velocity in LMCA is consistent with the results of the Nigerian study, where blood flow velocity was negatively correlated with 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, and unclear handwriting; although the clinic staff offered a lot of help, 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, such as complete

blood count 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 SCD was 72.7 cm/s, and in LICA was 73.0 cm/s. Regarding the MCAs, the mean velocity in the right side was 103.7 cm/s, and in the left side was 106.1. The mean right to left IHR of the MCAs was 1.03.

None of the study population had MCA 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.

About 20.1% of patients showed low velocities in one or both MCAs; 4.2% had abnormal MCAs' IHR, indicating either hyperemic status due to chronic anemia or arterial stenosis, making the close follow-up necessary at intervals determined by the local guidelines.

About 4.2% of the study population showed absent flow in one of their MCAs, reflecting previous occlusion with failure of recanalization as stated by their medical history. Around 4.2% had poor temporal window possibly normal anatomical variant or part of diffuse bone sclerosis caused by SCD.

It was difficult to measure the velocity in one of the four vessels in 5.9% of the patients due to uncooperativeness, mostly from young age patients, a problem that can be solved by an experienced operator.

There was statistically significant relationship between hemoglobin concentration and blood velocity in the MCA 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 SCD due its advantages over the other imaging modalities and encourages use of it in Sudanese hospitals.

SCD 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 four 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 patients with SCD is a rich field that still needs meticulous researching with larger sample sizes and expanded time for more generalizable results.

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Conflicts of interest

There are no conflicts of interest.

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