ORIGINAL ARTICLE

Transcranial Doppler in Screening of Sickle Cell Disease in Basrah: A Cross-sectional Descriptive Study

Basim A.A Alhijaj [1*], Wissam J. Yeser [2], Huda M. Othafa [2]

[1] *Consultant Pediatrician, Head of Basrah Center for Hereditary Blood Disease, Al Zahraa Medical College, IAMRS Secretary, Basrah, Iraq*

[2] *Specialist Radiologist, Al-Basrah Center for Hereditary Blood Diseases, Basrah Teaching Hospital, Basrah, Iraq*

*Corresponding Author: Basim A.A Alhijaj
Email: basim.abdulkarem@avicenna.uobasrah.edu.iq

Received: 13 October 2023 / Accepted: 27 November 2023

Abstract

Purpose: This cross-sectional study aimed to assess the effectiveness of Transcranial Doppler (TCD) screening as a primary preventive measure against overt strokes in sickle cell patients at the Basrah Center for Hereditary Blood Diseases. The study's objectives were to analyze descriptive statistics of enrolled patients and investigate potential correlations between TCD values and various factors, such as age, sex, mean hemoglobin levels, and High-Performance Liquid Chromatography (HPLC) domains.

Materials and Methods: TCD screening was introduced at the Basrah Center for Hereditary Blood Diseases in 2012, utilizing an imaging ultrasonic machine. Four years later, it transitioned to a non-imaging technique, significantly expanding the service. The screening was carried out by two specially trained senior radiologists, resulting in more than 300 annual examinations.

Results: Among the enrolled patients, no abnormal TCD values (above 200) were recorded. However, 23 patients exhibited conditional values (170-200), with a higher prevalence among males and homozygous SCA individuals. These patients had a mean Hb F of 18.2%, Hb S of 70.2%, a mean age of 8.9 years, and an Hb level of 7.45 gm/dL.

Conclusion: Transcranial Doppler screening at Basrah Center for Hereditary Blood Diseases has proven effective in preventing overt strokes in sickle cell patients. The absence of abnormal TCD values in the enrolled patients suggests that early intervention and monitoring through TCD can be a valuable tool in managing sickle cell disease. Further analysis revealed potential associations between conditional TCD values and specific factors, such as age, sex, mean hemoglobin levels, and HPLC domains, which warrant continued investigation for a better understanding of risk factors in sickle cell patients.

Keywords: Transcranial Doppler; Time-Averaged Mean Maximum; Sickle Cell Disease; Stroke.

DOI:

1. Introduction

1.1. Background

Sickle Cell Disease (SCD) is a blood disease that is inherited as an autosomal recessive disease, it is endemic in certain regions throughout the globe like, Saudi Arabian, and Mediterranean ancestry, Equatorial Africa, and because of the immigration now widespread in the Americas and Europe. The expected incidence of SCD at birth is 1 in 625 [1].

Sickle cell disease is associated with cerebrovascular accidents in different degrees in 7%. 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 [2]. The guidelines adopted by ASH (American Society of Hematology) in 2020 aimed to supply hematologists with a consensus about prophylaxis and evaluation of the CNS impact of sickle cell diseases, evidence-based discussions had yield nineteen conclusions and recommendations three of them immediately effect on current clinical care and follow-up. These recommendations include the use of transcranial Doppler ultrasound screening and hydroxyurea for primary stroke prevention in children with Sickle Cell Anemia (SCA), Hemoglobin SS (HbSS), and hemoglobin Sb0 (HbSβ°) thalassemia [3].

Transcranial Doppler ultrasonography (TCD) plays a role in the estimation of the patients' risk of having an overt stroke through the assessment of the blood velocity in the internal carotid and the middle cerebral artery [4].

An elevated Time-Averaged Mean Maximum (TAMM) blood flow velocity >200 cm/sec in Children with sickle cell anemia will put them at increased risk for a cerebrovascular event. A TAMM measurement of <200cm/s but above 180 cm/sec represents a conditional threshold [5].

A repeat measurement is suggested within a few months because of the high rate of conversion to a TCD velocity >200 cm/sec in this group of patients [4, 6].

In the Basrah governorate of southern Iraq, 6.48% of the population are carriers of the sickle hemoglobin (HbS) gene, giving a gene frequency of 0.0324 [7, 8], and more than (5270) registered patients with sickle cell diseases of both adult and pediatric age groups, with a relative risk for having a stroke in sickle cell patient of (2.1 %) [9], Changes on TCD ultrasonography have been proposed as significant predictors of cerebrovascular complications in SCD. However, consensus with regard to the TCD criteria to recognize abnormalities in cerebral vasculature is lacking [10].

1.2. Historical Background

TCD screening started to be issued in the Basrah Center for Hereditary Blood Diseases in 2012 by using an imaging ultrasonic machine that had been changed to a non-imaging technique after 4 years greatly expanding the service and increasing the number of patients examined for more than 300 annual examinations to be done operated by 2 professionals specifically trained senior radiologist

Analysis of the TCD data in the Middle East area had been conducted in different series involving Iraq, Persian Gulf, Turkey, Oman, Kuwait, and most comforting data regarding having risky values were obtained [9-12].

In all these cohorts, the samples studied seemed to be rather small with regards to the number of patients registered and TCD examined in Basra, which is why the research group was motivated tower tabulation and analyzing the data of the local TCD screening program which involved more than 1223 patient examined even in a simple descriptive pattern.

1.3. Objectives

A cross-sectional study that aims to:

1) Elaborate the descriptive statistics of the patients enrolled in Transcranial Doppler screening in Basrah Center for Hereditary Blood Diseases

2) Correlates higher values to certain factors including age, sex, mean hemoglobin values, and High-Performance Liquid Chromatography (HPLC) domains.

2. Materials and Methods

2.1. Study Design

A cross-sectional study conducted to analyze data from the Transcranial Doppler study, demonstrating the data in a descriptive pattern.

2.2. Population

Patients who regularly visit the outpatient clinic of the Basrah Center for Hereditary Blood Diseases, out of 1223 data, only 1173 patients were enrolled; the rest were excluded because their data was incomplete or not suitable for analysis. Patient data which was electronically recorded via Microsoft Access Wizard had been obtained, verified, and tabulated by the researchers.

2.3. Machine

2 MHZ probe digital portable transcranial Doppler device by Atys®. The examination was performed by a Non-imaging technique (AtysMedica l17, Parcd'Arbora 69510 Soucieu en Jarrest France, Waki-EWaki1Tc) medical operated by two professional and trained senior radiologist in a sequential program of annual reading for each patient registered in the center according to a local guideline

2.4. Statistics

The data were collected for each patient via a locally designed Microsoft Access Wizard which were all transformed into the Statistical Package for the Social Sciences (SPSS) 23 database for being tabulated, analyzed, and graphed.

Number of figures/tables is mentioned according to their entrance in the text and all of the figure sub-parts are mentioned in the body of text.

3. Results

More than 1173 patients enrolled were examined with a 2MHZ probe digital portable transcranial Doppler device.

The burden of the TCD work in this cross-sectional study is demonstrated in Figure 1.

Demographic data of the enrolled patients are shown in Table 1.

The mean age was 8.7 years ±3.4 for the examined patients ±, most of the patients were of the 6-12 years old group, male, and sickle cell anemia (homozygous).

Almost there were no values exceeding the upper limit to the international score of TCD different

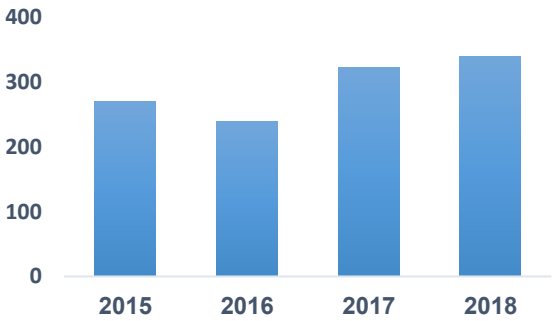

Figure 1. Annual distribution of the cases studied over 4 years

Table 1. Demographic characteristics of the examined patients

Variables		No.	Percentages
Age	Group		
	2-5 years	232	19.8%
	6-12 years	739	63.0%
	more than 12	202	17.2%
Sex	male	712	60.7%
	females	461	39.3%
Diagnosis	SCA	771	65.7%
	S β°	385	32.8%
	s trait	4	0.3%
	S/D disease	13	1.1%

arteries values (i.e., above 200 cm/s) many patients showed a conditional value (i.e., 170-200 cm/s).

A higher mean value was recorded in both middle cerebral arteries (RT and LT) followed by the inferior cerebral arteries (RT and LT) and the lowest values were recorded in the anterior cerebral arteries (Figure 2, Table 2).

Table 3 shows the characteristics of those cases that showed conditional values.

A total of 23 patients were found to have a conditional value (170-200cm/s) which represents 1.91% of the total enrolled patients.

Most of these values were shown in the right middle cerebral arteries (60.9%) followed by the LT middle cerebral arteries (34.8%) while two vessels conditional value were demonstrated in five patients (21.7%).

The mean hemoglobin (Hb) of those 23 patients was (7.45 gm/l ±1.1), and there was no value in them above 9 gm/l.

Table 2. Distribution of the Transcranial Doppler (TCD) velocities, and study variables profile

	Mean	maximum	minimum	ST/DEV
mean hemoglobin	8.9	12.1	4.7	1.9
RT ACA	66	150	38	9.3
LT ACA	65.6	30	125	9.7
RT ICA	98.8	49	165	23.3
LT ICA	97.5	40	155	22.9
RT MCA	126.3	41	190	18.1
LT MCA	124.9	55	180	17.06
RT PCA	74.6	38	175	29.6
LT PCA	73.8	32	150	10.7

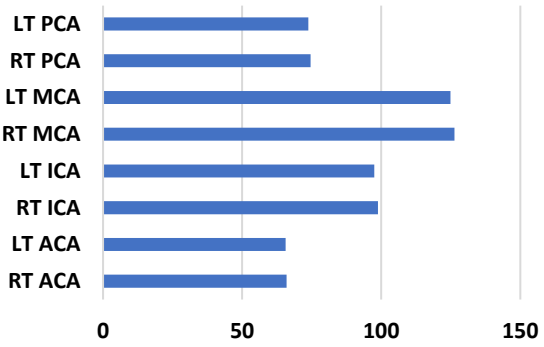

Figure 2. TCD values distribution

Table 3. Conditional TCD value

Vessel Involved	**RT MCA**	14	60.9%
	LT MCA	8	34.8%
	RT PCA	1	4.3%
	TOTAL	23(1.91%)	100
Mean hemoglobin	7.45 gm/l	±1.1	
Mean age	8.9 years	±3.47	
Sex	male	18	78.3%
	female	5	21.7%
Diagnosis	SCA	22	95.7%
	S β°	1	4.3%
HB variant dominates	HB A	5.25	
	HB S	70.8	
	HB F	18.2	
	HB A2	4.3	

The vast majority were males (78.3%) with a male: female ratio of 3.6, homozygous Sickle Cell Anemia (SCA) (95.7%), with a higher hemoglobin S (HbS) ratio (70.8) and low hemoglobin A (HbA) (5.25), While the mean age was (8.9 years±3.47) old patients thirteen of them were above 10 years old.

4. Discussion

The Basra Center for Hereditary Blood Diseases involve the largest cohort of sickle cell diseases on the national level. The study represents the largest cohort of the Transcranial Doppler (TCD) examined patients ,1223 examined patients from them 1173 did enroll in this study, none of them showed an abnormal high value (i.e. above 200cm/s) which is similarly corresponded to what had been found in Oman at which there was no evidense of any abnormal high result of Time-Averaged Mean Maximum (TAMM) in the anterior ceberal artery in all the enrolled cases [10] and Peninsular Arab Patients Series [9] in which a higher mean value was recorded in both middle cerebral arteries (Rt and Lt) and the results also were corresponding similar to Adekunle Adekile *et al.'s* study [9, 13], in Kuwait study (highest mean ± SD values for the middle cerebral artery PSV, EDV, TAMxV, PI, and RI were 130.30 + 26.5, 145.0 ± 21.9) [14], and Latin America cohort [15] followed by the inferior cerebral arteries (Rt and LT) the least values were recorded in the anterior cerebral arteries also it is corresponding large cohort in U.S. done by Naffa *et al.* in which (The most frequent location of highest velocity measurement was noted to be in the Middle Cerebral Artery (MCA) regardless of whether it was measured by PSV or TAMM. This accounted for over 80% of all exams during our study period) [16].

In a Nigerian study, 4.7% of patients showed Time-Averaged Mean Maximum (TAMM) higher than 200 cm/s, while none of our patients showed this finding; the reasons for this disparity are so clear as most of the patients, in Iraq and the Persian Gulf, belong to the sickle Arab genotype while Nigerian patients are of the African type [17, 18].

A total of 23 patients were found to have a conditional value (170-200cm/s) which represents 1.91% of the total enrolled patients.

In comparison to what found in Al Obeid center in Sudan, no conditional or higher leading than 200 were found [19], whereas only 13 (3.1%), all from Iraq, had conditional values (170-200 cm/s) [9].

The mean Hemoglobin (Hb) of those 23 patients was (7.45 gm/l ±1.1), and there was no value in them above 9 gm/l.

The vast majority were males (78.3%) with a male: female ratio of 3.6, homozygous Sickle Cell Anemia (SCA) (95.7%), with a higher hemoglobin S (HbS) ratio (70.8) and a low hemoglobin A (HbA) (5.25), while the mean age was 8.9 years±3.47 old patients.

This means that those groups with higher TAMM values were of lower mean hemoglobin, and more male involvement with the same age span of the total cohort but slightly older.

A corresponding result in conditional values was evident in the Adekunle Adekile *et al.* study [9] and in Omani series [10], age, race, transfusion type, and transfusion frequency were significant predictors of the TCD velocities were found in Wali *et al.*

Persian Gulf cohort of 410 patient studied [13], while an Italian study confirmed the relation of the conditional HAMM reading to the lower Hemoglobin (Hb) level and higher hemolytic markers it involved a higher percentage (10.9%) of conditional readings [20], also in Jamaican children with sickle cell who had been studied showed the same correlation with the low hemoglobin profile [21].

The relation of the higher HAMM readings with being of younger age had been also confirmed by Italian series and another study conducted in France in which Créteil newborn cohort did show that the risk of abnormal and conditional transcranial color Doppler imaging (TCDi) was higher in young children and reduced with age [22].

There was a paucity of evidence of a correlation between level of the HPLC domains and the higher TAMM level in TCD but a 2011 Brazilian study reported a negative correlation between Time-Averaged Mean Maximum Value (TAMMV) and hemoglobin (Hb) level in patients with hemoglobin SS (HbSS) and haemoglobin Sβ° (HbSβ°) genotypes in which a higher TAMM reading was recorded in group I (patients with SCA/Sß° thalassemia) than group II (patients with SC hemoglobinopathy/Sß+ thalassemia) [23].

5. Conclusion

1. There was no abnormal high TAMM reading among this study sample.
2. High conditional TAMM readings were recorded in only 1.91 % of the studied sample.
3. High conditional TAMM readings seemed to be correlated to the lower hemoglobin level, young age group, male sex, and homozygous genotype of SCD.

5.1. Recommendations

1. A similar sample size with a more correlational study that covers the impact of therapeutic modalities on the level of TAMM readings
2. Potentiation of the TCD ultrasonography as a screening tool for the sickle cell primary stroke prevention program.

5.2. Limitations

Although this study did overcome certain limitations recorded in similar studies like sample size, different machines and multiple operators to perform the examination, it still did not cover the following important issues that are intended to be addressed in future studies.

1. More risk factors like white Blood cells (WBC), platelets count, and thrombophilia markers about high values.
2. MRI correlational comparison.

The effect of certain protective strategies against primary stroke development like simple or aphaeretic transfusion or hydroxyurea therapy on the level of TCD reading.

Acknowledgment

The authors received no financial support for the research, authorship, and publication of this article.

References

1- Fenella J Kirkham, "Therapy insight: stroke risk and its management in patients with sickle cell disease." *Nature clinical practice Neurology*, Vol. 3 (No. 5), pp. 264-78, (2007).

2- Philip Lanzkowsky, Manual of pediatric hematology and oncology. UK: *Elsevier*, (2005).

3- MR DeBaun *et al.*, "American Society of Hematology 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults." *Blood advances*, Vol. 4 (No. 8), pp. 1554-88, (2020).

4- Andrew D Hershey, RM Migraine Kliegman, BF Stanton, NF Schor, JW St Geme, and RE Behrman, "Nelson Textbook of Pediatrics. 19th Edit." ed: Saunders, Philadelphia, (2011).

5- Miguel R Abboud, Eunsil Yim, Khaled M Musallam, Robert J Adams, and STOP II study investigators, "Discontinuing prophylactic transfusions increases the risk of silent brain infarction in children with sickle cell disease: data from STOP II." *Blood, The Journal of the American Society of Hematology*, Vol. 118 (No. 4), pp. 894-98, (2011).

6- Michael M Dowling *et al.*, "Acute silent cerebral ischemia and infarction during acute anemia in children with and without sickle cell disease." *Blood, The Journal of the American Society of Hematology*, Vol. 120 (No. 19), pp. 3891-97, (2012).

7- Rawshan Zuhair Jaber, Meàad Kadhum Hassan, and Sadeq Khalaf Al-Salait, "Microcytosis in children and adolescents with the sickle cell trait in Basra, Iraq." *Blood research*, Vol. 54 (No. 1), pp. 38-44, (2019).

8- MK Hassan, JY Taha, LM Al Naama, NM Widad, and SN Jasim, "Frequency of haemoglobinopathies and glucose-6-phosphate dehydrogenase deficiency in Basra." *EMHJ-Eastern Mediterranean Health Journal, 9 (1-2), 45-54, 2003*, (2003).

9- Adekunle Adekile, Meaad Hassan, Akram Asbeutah, Mohamed Al‐Hinai, Omar Trad, and Nayef Farhan, "Transcranial Doppler ultrasound in Peninsular Arab patients with sickle cell disease." *Journal of Ultrasound in Medicine*, Vol. 38 (No. 1), pp. 165-72, (2019).

10- Arunodaya R Gujjar *et al.*, "Transcranial Doppler ultrasonography in sickle cell disease: a study in Omani patients." *Journal of Pediatric Hematology/Oncology*, Vol. 35 (No. 1), pp. 18-23, (2013).

11- Sultan Aydin *et al.*, "Associations Between Transcranial Doppler Flow Velocities, Laboratory Parameters, and Clinical Features in Turkish Children With Sickle Cell Disease." *Journal of Pediatric Hematology/Oncology*, Vol. 43 (No. 7), pp. 249-53, (2021).

12- Akram M Asbeutah, Akmal M Zahra, Hanan Al‐Abboh, Abdullah A AlMajran, and Adekunle Adekile, "Repeat transcranial Doppler ultrasound imaging in Kuwaiti children with sickle cell disease after a 10‐year interval: A prospective, cohort study." *Health Science Reports*, Vol. 6 (No. 3), p. e1159, (2023).

13- Yasser Wali, Vishwanatha Kini, and Mohamed A Yassin, "Distribution of sickle cell disease and assessment of risk factors based on transcranial Doppler values in the Gulf region." *Hematology*, Vol. 25 (No. 1), pp. 55-62, (2020).

14- Akram M Asbeutah, Abdullah A AlMajran, and Adekunle Adekile, "Pattern of cerebral blood flow and the interrelationship of vascular parameters of transcranial Doppler imaging in children with sickle cell disease." *Journal of Clinical Ultrasound*, Vol. 47 (No. 3), pp. 128-32, (2019).

15- Gabriel Pinheiro Modolo *et al.*, "Transcranial doppler as screening method for sickling crises in children with sickle cell anemia: a latin America cohort study." *BMC pediatrics*, Vol. 22 (No. 1), pp. 1-8, (2022).

16- Lena N Naffaa, Yasmeen K Tandon, and Neville Irani, "Transcranial Doppler screening in sickle cell disease: the implications of using peak systolic criteria." *World Journal of Radiology*, Vol. 7 (No. 2), p. 52, (2015).

17- Viviane Flumignan Zétola, "Role of TCD in sickle cell disease: A review." *Perspectives in Medicine*, Vol. 1 (No. 1-12), pp. 265-68, (2012).

18- Robert J Adams, "Big strokes in small persons." *Archives of neurology*, Vol. 64 (No. 11), pp. 1567-74, (2007).

19- Walaa Ismail Musa Ismail, Mustafa Elnour, and Alam Eldin Musa Mustafa, "Evaluation of transcranial Doppler abnormalities in children with sickle cell disease in El-Obeid Specialized Children's Hospital." *Journal of Family Medicine and Primary Care*, Vol. 8 (No. 3), p. 1176, (2019).

20- Giulia Reggiani *et al.*, "Relationship between hemoglobin, hemolysis, and transcranial Doppler velocities in children with sickle cell disease: Results from a long‐term natural history study in Italy in the era of multimodal therapy." *European Journal of Haematology*, (2023).

21- Angela E Rankine‐Mullings *et al.*, "Transcranial Doppler velocity among Jamaican children with sickle cell anaemia: determining the significance of haematological values and nutrition." *British Journal of Haematology*, Vol. 181 (No. 2), pp. 242-51, (2018).

22- Françoise Bernaudin *et al.*, "Impact of early transcranial Doppler screening and intensive therapy on cerebral vasculopathy outcome in a newborn sickle cell anemia cohort." *Blood, The Journal of the American Society of Hematology*, Vol. 117 (No. 4), pp. 1130-40, (2011).

23- Mary Hokazono, Gisele Sampaio Silva, Edina Mariko Koga Silva, and Josefina Aparecida Pellegrini Braga, "Results from transcranial Doppler examination on children and adolescents with sickle cell disease and correlation between the time-averaged maximum mean velocity and hematological characteristics: a cross-sectional analytical study." *Sao Paulo Medical Journal*, Vol. 129pp. 134-38, (2011).