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Aim of this work: To assess abnormal TCD velocities in pediatric patients with SCD with their relation to stroke and other complications using multimodal approach through clinical, neuroimaging and neurophysiological studies.

Study design: cross-sectional study. Place and Duration of Study: Sample: Department of Pediatric (Hematology Unit) and Department of Neurology, Tanta University Hospital Egypt, between April 2016 and April 2018.

Methodology: This study was conducted on 50 children with SCD and 25 healthy children matched age and sex. All subjects were subjected to full history taking, neurological examination using pediatric neurological sheet, neuroimaging including: CT and /or MRI, MRA and/or CT angiography, also MRV, transcranial duplex, EEG and Stanford-Binet Intelligence scales-Fifth Edition.

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Classification: NLMC CODE: WH 170

Language: English

London Journals Press

LJP Copyright ID: 392844

London Journal of Medical and Health Research

Volume 21 | Issue 1 | Compilation 1.0

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Results: SCD patients showed many abnormalities on neurological examination and on different modalities of MR imaging on the brain with positive relation with many risk factors. Prophylactic blood transfusion in SCD patients with abnormal TCD had a role in reducing the incidence of stroke.

Conclusion: There was variation in neurological presentation, examination and brain imaging in cases with SCD. There was positive relation between regular blood transfusion in SCD patients and decreased risk for ischemic stroke and abnormal TCD velocity in these patients.

Keywords: SCD, TCD abnormalities, prevention.

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I. INTRODUCTION

Sickle cell disease (SCD) is an autosomal recessive hemoglobin disorder. It is a qualitative hemoglobinopathy resulting from a structural change in the sequence of amino acids on the beta globin chain of the hemoglobin molecule due to a point mutation. It is characterized by hemoglobin polymerization, erythrocyte stiffening, and subsequent vaso - occlusion (1, 2).

The most predominant form of hemoglobinopathy worldwide is sickle cell disease. It is estimated that 75-85% of children born with SCD are born in Africa (3, 4). It is common among people of Equatorial African where the prevalence ranges from 10 to 40% of the population, Saudi Arabian and Mediterranean ancestry, and now it's widespread in America and Europe (5, 6). The prevalence of SCD is 0.3% in Egypt, where the carrier rate varies from 9 to 22% (7).

In the deoxygenated condition, the hemoglobin tetramer polarizes and the cell shape becomes distorted, resulting in rigid red blood cells. Cell damage leads to hemolytic anemia and to occlusion of vessels in multiple organs, including the brain (8).

Children with sickle cell disease, present with a wide variety of neurological syndromes, including ischemic and hemorrhagic stroke, transient ischemic attacks, soft neurological signs, seizures, headache, coma, visual loss, altered mental status, cognitive difficulties, and covert or 'silent' infarction (9).

Although the prevalence of seizures in children with sickle cell disease is about10 times that of the general population, there are few prospectively collected data on its pathogenesis (10). Seizures occur in 12 to 14% of patients with sickle cell disease (SCD), herald stroke in 10 to 33%, and are associated with silent infarction (10.11).

Several Studies of cerebral blood flow (CBF) with 133 Xenon inhalation have shown that encephalopathic patients with SCD having seizures show regional hypoperfusion which may resolve at follow-up (12).

Magnetic resonance imaging (MRI) and transcranial Doppler (TCD) flow studies are useful in detecting subclinical cerebral infarction (13). The ability to predict strokes by detecting arterial stenosis with TCD and the role of chronic transfusion in prophylaxis from such strokes has led to the recommendation that TCD can be used for routine screening and that transfusion can be instituted on detection of arterial stenosis (14).

II. PATIENTS AND METHODS

This study was carried out between April 2016 and April 2018 on 50 children diagnosed by hemoglobin electrophoresis as sickle cell disease admitted at hematological unit and underwent follow up at outpatient clinic of Hematology Unit, Pediatric Department. They were aged from 2 to 18 years old including 27 males and 23 females.

There was also a control group of 25 healthy children matched with the age (3 to 16 years old) and gender including 16 males and 9 females who attended general outpatient clinic of Pediatric Department for a comparative study. Informed consent was taken from the guardian of all children and the study was approved from Faculty of Medicine, Tanta University ethical committee.

Inclusion criteria: Children suffered from sickle cell disease who developed various neurological disorders or were at risk for developing such disorders e.g. low hemoglobin, high white cell count, increased baseline of reticulocytes, previous transient ischemic event, hypertension and history of chest crisis.

Exclusion criteria: Children with other hemoglobinopathies diagnosed by hemoglobin electrophoresis.

- Children with sickle cell disease having an inborn error of metabolism already diagnosed in conjunction or screening of suspected cases of serum pyruvate, lactate or homocysteine in serum or urine to be excluded.
- Children suffering from neurological disorders especially stroke who already diagnosed as coagulopathy or vasculopathy other than sickle cell disease.

All children were subjected to: Full medical history taking, thorough neurological examination using pediatric neurological sheet, and Stanford-Binet Intelligence scales-Fifth Edition as an evaluation tool for intellectual functioning. Laboratory investigations included: complete blood picture count with differential, reticulocyte count, and renal & hepatic function tests.

Neuroimaging studies included: CT and /or MRI of the brain. Also, MRA and /or CT angiography of cerebral blood vessels when needed in some patients and transcranial color coded duplex(TCCD)(using timed average mean of maximum velocity parameter(TAMMV)). Besides, MRV when needed in some patients. Electrophysiological studies included: EEG.

Statistical analysis

The collected data were organized, tabulated and statistically analyzed using SPSS software statistical computer package V17. For quantitative data, the range, mean and standard deviation were calculated. For qualitative data, comparison between two groups and more was done using Chi-square test ($\chi 2$). Significance was adopted at $p < 0.05$ for interpretation of results of tests of significance (15,16).

III. RESULTS

There was statistically highly significant difference regarding transcranial duplex findings among patients compared with control group, with the largest number of patients (n= 28) (56%) matching with low velocity. Patients with high velocity only represented 8% of patients followed by those with very low velocity (4%)(Table 1) (Figure 1,2).

There was statistically highly significant difference regarding relation between regularity of blood transfusion and occurence of ischemic arterial stroke among patients. The highest percentage (66.67%) of patients at risk of stroke was in those with yearly blood transfusion followed by risk for patients(33.33%) with irregular blood transfusion(Table 2).

There was positive correlation between transcranial duplex abnormalities and risk for cognitive decline, MRI brain, EEG abnormalities and stroke with the highest predictive value for stroke risk (Beta: -0.644) (Table 3).

Table 1: Transcranial duplex findings among patients and control groups:

Variable	Groups				Chi-Square	
Transcranial duplex findings	Patients(n=50)		Control(n=25)			
	Number	%	Number	%	χ^2	P-value
Very low velocity	2	4.00	0	0.00	32.813	<0.001*
Low velocity	28	56.00	0	0.00		
Normal velocity	15	30.00	25	100.00		
Conditioned velocity	1	2.00	0	0.00		
High velocity	4	8.00	0	0.00		

-Very low: All vessels: < 20cm/sec - Low: All vessels: < 70cm/sec.-
Normal: All vessels: < 170cm/sec.-
Conditional: >170 /sec but < 200 cm/sec dICA, MCA, intracranial bifurcation.-
-Abnormal or high: > 200cm/sec MCA, intracranial bifurcation, dICA.

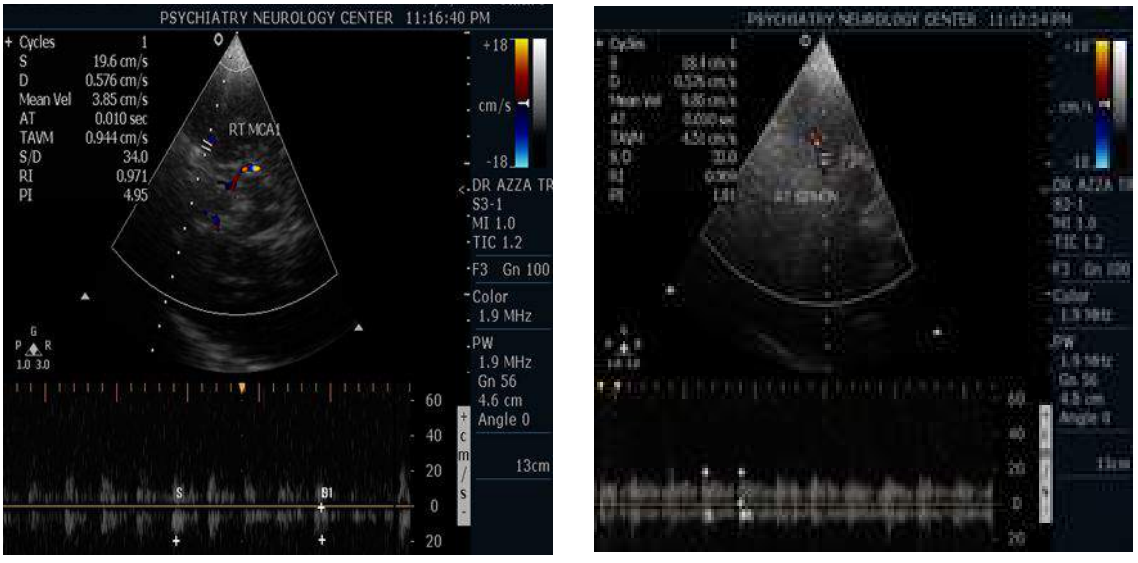

Figure 1: TCCD showing TAMV of right MCA and right siphon less than 20cm/s (very low velocity) in this case

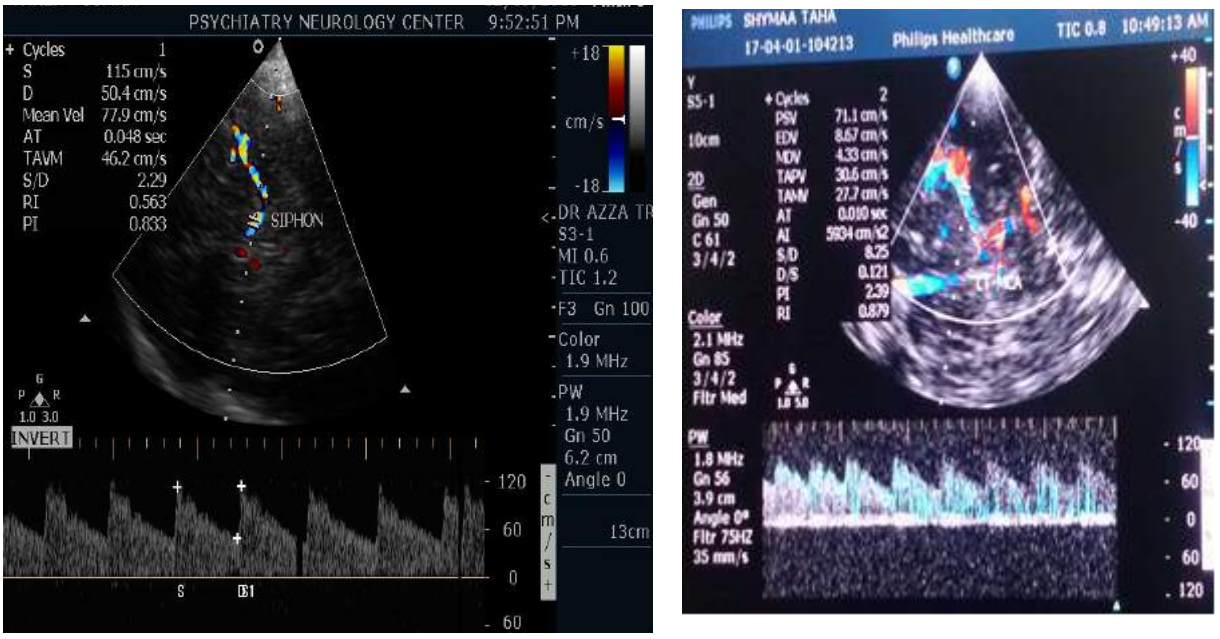

Figure 2: TCCD showing TAMV of left distal ICA (siphon)and left MCA less than 70cm/s (low velocity) in this case.

Table 2: Relation between regularity of blood transfusion and transcranial duplex findings among patients

Regular Blood transfusion	Transcranial duplex										Chi-Square	
	Very low velocity		Low velocity		Normal velocity		High velocity		Conditioned velocity			
	N	%	N	%	N	%	N	%	N	%	X^2	*P-Value*
Regular	1	50	28	100	15	100	4	100	1	100		
Every month	0	0.00	7	25.00	7	46.67	0	0.00	0	0.00	115.221	<0.001*
Every 2 months	0	0.00	11	39.29	5	33.33	0	0.00	0	0.00		
Every 3 months	0	0.00	5	17.86	2	13.33	0	0.00	0	0.00		
Every 4 months	0	0.00	2	7.14	0	0.00	0	0.00	0	0.00		
Every 5 months	0	0.00	1	3.57	0	0.00	1	25.00	0	0.00		
Every 6 months	0	0.00	0	0.00	0	0.00	2	50.00	0	0.00		
Every 7 months	0	0.00	0	0.00	0	0.00	0	0.00	1	100.00		
Yearly	1	50.00	2	7.14	1	6.67	1	25.00	0	0.00		
Irregular	1	50.00	0	0.00	0	0.00	0	0.00	0	0.00		

Table 3: Multiple regression analysis according to transcranial duplex abnormalities

	Unstandardized Coefficients		Standardized Coefficients	T	*P-Value*
	B	Std. Error	Beta		
Cognitive decline	0.137	0.229	0.088	0.600	0.552
MRI brain abnormalities	0.165	0.121	0.410	1.364	0.179
EEG abnormalities	-0.389	0.139	-0.421	-2.791	0.008*
Stroke risk	-0.702	0.345	-0.644	-2.036	0.048*
Dependent Variable: Transcranial duplex abnormalities					

IV. DISCUSSION

Transcranial duplex findings of our studied patients revealed that patients presented according to TAMM velocity by either: Very low velocity (4% of patients), low velocity (56% of patients), normal velocity (30 % of patients), conditioned velocity (8% of patients) and high (2% of patients) velocity. There was statistically highly significant difference regarding transcranial duplex findings among patients compared with control group, with the largest number of patients (56%) matched with low velocity.

This was in agreement with Zétola VF., 2012 who reported that in normal children the velocity was in the range of 90 cm/sec in the middle cerebral artery. In children with SCD the velocity was higher due to anemia and it is in the range of 130-140 cm/sec. Above 170 cm/sec, which was about 1.5 standard deviations above the mean, stroke risk increased. Over 200 cm/sec the risk of stroke rised from the baseline rate of 0.5-1%/year to the range of 10-13%/year. Values in between 170 and 200 indicated intermediate risk. Very low velocities on TCD might be found after an overt stroke. This was in agreement with Buchanan ID et al., 2013 who reported that velocities were low or absent by TCD in 10% of the SCD patients perhaps related to vasculopathies such as moyamoya or extracranial vasculopathy.

There was positive relation between regular blood transfusion in patients in this study and risk for abnormal velocity detected in transcranial duplex. The highest percentage of patients with very low velocity were those with yearly (50%) and irregular (50%) blood transfusion. The highest percentage of patients with conditioned velocity were those with blood transfusion every 7 months (100%) and the highest percentage of patients with high velocity were those with blood transfusion every 6 months (50%) followed by those with yearly blood transfusion(25%). In contrast to this, the highest percentage of patients with normal velocity were those with regular blood transfusion every month (46.67%)).

There was statistically highly significant difference between patients with regular blood transfusion and those with irregular blood transfusion as regard abnormal velocity detected on TCD. This was in agreement with Raphael JA et al., 2013 who reported that chronic blood transfusion was effective for the primary and secondary prevention of stroke as well as for reducing the risk of recurrent cerebral infarcts in children with SCD. Stroke patients were continued on monthly RBC transfusions indefinitely, with a goal HbS of less than 30%. Patients who had abnormal TCDs were also treated with monthly transfusions, with a goal HbS of 30%.

V. CONCLUSION

Most patients (56%) had low velocity according to TAMM on transcranial duplex indicating previous stroke. There was positive relation between regular blood transfusion in SCD patients and decreased risk for ischemic stroke and abnormal TCD TAMM velocity (high and very low velocity). There was positive correlation between transcranial duplex abnormalities and risk for cognitive decline, MRI brain, EEG abnormalities and stroke with the highest predictive value for stroke risk (Beta: -0.644)

5.1 Compliance With Ethical Standards

Any unexpected risks appeared during the course of the research will be cleared to the participants, their parents and the ethical committee on time.There are adequate measures to maintain the privacy of participants and confidenality of the data:

A code number to every patient with the name and address will be kept in a special file. The patient name will be hidden when using the research.The results of the study will be used only in a specific manner and not to use in any other aims. Endpoint of the research will be achieved when any of the above mentioned risks threaten the health and the quality of the life of patients.

Informed consent will be obtained from patients 18 years old or older and from the legal guardians of those younger than 18 years. Assent will be obtained from patients between 14 and 18 years old before entering the study.

Consent

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this research and accompanying images.

Ethical Approval

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Competing Interests

Authors have declared that no competing interests exist.

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