Duplex Ultrasonography of the Carotid Arteries, in Sickle Cell Disease Children: The Relation to Disease Types and Hematological Parameters

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Abstract: Background: The role of trans-cranial Doppler to detect asymptomatic children who are at increased risk to develop stroke is considered as an evolution in the sickle cell disease (SCD)-related brain injury managment. **This work aims** to detect the role of trans-cranial and extra-cranial Doppler of carotid arteries in children with SCD and its relation to hematological parameters. **Patients & Method:** This prospective observational study carried out in the polyclinic health center of King Feisal University, Al-Ahasa, KSA, in a period from 2011 to 2013. It included 72 patients known to have SCD. Their mean age was (8±3.7yrs). They were (32) males (40) females. Velocities in the carotid arteries measured by both intracranial & extra-cranial duplex ultrasonography. **Results:** High time Average Maximum Mean Velocity (TAMMV) (>190m/s) was detected in 5.4%.Where 62.3% had average flow (<90m/s) and 26.3% had blood flow between 90-190 cm/s. There was significant correlation between the TAMMV, Peak Systolic Velocity (PSV) and Peak Diastolic Velocity (PDV) in both right and left carotid arteries in intracranial and extra-cranial Duplex. Blood flow velocities between intracranial Middle cerebral artery (MCA) and extra cranial proximal internal Carotid artery (pICA) showed significant positive correlation between their TAMMV(r: 0.938 & P< 0.001). It also positively correlated with PSV and PDV. TAMMV was positively correlated with WBCs count, Platelets and Reticulocyte %. Blood flow velocities were more in patients with SCD than those with SCD-thalassemia. **Conclusion:** Duplex Ultrasonography detected a considerable percentage of children who were at increased blood flow velocities. Extracrainal Duplex of proximal internal carotid artery considered as sensitive and easy method to detect these children.

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Key Words: Duplex ultrasonography, Carotid arteries, Sickle cell disease, Children.

Abbreviation: SCD: sickle cell disease, SCDT: Sickle cell disease – Thalassemia, MCA: Middle Cerebral Artery, pICA: Proximal Internal Carotid Artery, TAMMV: Time Average Maximum Mean Velocity, PSV: Peak Systolic Velocity, PDV: Peak Diastolic Velocity

Introduction:

Sickle cell anemia (SCA) is an inherited, severe disease, resulting in early mortality and morbidity. SCA is characterized by several different types of hemoglobinopathies, with the most severe disease occurring in persons with hemoglobin SS (HbSS) or sickle-b0-thalassemia (HbSb0) *(Eckrich et.al; 2012).* Sickle cell disease (SCD) is a global hereditary disease in Saudi Arabia especially in Southern, Western, and Eastern areas where the gene frequently of this disease is quite prevalent. The frequency of sickle cell gene in Al-Hofuf area ranges from 0.15-0.25. Homozygous SCD prevalence ranges from 1.0-1.5% (Alabdulaal et.al; 2007). Stroke is one of the most severe life-threatening complications that affect children with SCD. The peak incidence of overt stroke in SCD is 1.02 per 100 patients between the ages of two and five years (Adams 2007). In spite that children often make a good motor recovery, significant cognitive impairment is almost inevitable (Lo et.al; 2008).

Trans cranial Doppler (TCD) is a novel non-invasive technique. It is done by using a 2-MHz transducer through the temporal window that allows evaluation of the cerebral arteries blood flow in adults and in children with a closed anterior fontanel (Verlhac, 2011).

High blood velocities in the middle cerebral artery (MCA) were strongly associated with increased risk of stroke as proved by Trans cranial Doppler (TCD) scanning. Increased blood velocities identified by TCD typically precede any apparent stenosis on angiography. It has been suggested that failure to regulate blood flow is one of the primary problems that precede the developing of vasculopathy (Verlhac, et.al; 2009).

The evolution that occurs in SCD-related brain injury has been the important role of TCD ultrasonography to detect asymptomatic children who are at an increased risk of developing stroke. That followed by administration of chronic transfusion to prevent its occurrence (Lowe & Bulas 2005). In fact Trans-cranial Doppler (TCD) ultrasonography makes primary stroke prevention a reality (Lagunju et.al; 2012).

Routine trans-cranial Doppler studies are accepted as an important screening test in the care of children with sickle cell anemia. Although some difficulties faced during, assessing the distal extra-cranial, petrous, and cavernous internal carotid artery can result in missing some strokes (Deane et.al 2010).

Extra-cranial internal carotid artery (proximal part) (pICA) is easily to be screened through trans-cervical route. It takes five to ten minutes and in general, it is well tolerated.

The significance of extra-cranial proximal internal carotid artery (pICA) disease in children with sickle cell anemia is not well known. Abnormalities well described in cerebrovascular disease in adults without sickle cell anemia (Goldstein 2003). Some strokes in children with sickle cell anemia occur without detectable intracranial vasculopathy; for example, a study using angiography found that 4 out of 14 children with sickle cell anemia and strokes had normal intracranial angiograms (Switzer et.al;2006). Extra-cranial internal carotid artery abnormalities may explain some of these strokes in children without obvious intracranial vasculopathy ((Deane et.al 2010).

The use of Doppler Ultrasonography in studying proximal ICA in Al-Ahasa region, KSA until now is not will establish. Its' significant to detect abnormal velocity, its relation to genetic type and hematological parameters in our patients are not studied before. This study aims to detect the role of trans-cranial and extra-cranial Doppler of the cerebral and carotid arteries as non- invasive technique in children with SCD and its relation to hematological parameters.

Patients & Methods:

This prospective observational study carried out in the polyclinic health center of King Feisal University, Al-Ahasa, KSA, in a period from 2011 to 2013. The permission obtained from the ethical & research committees at the polyclinic. This study included all Children who were known to be SCD, or Sickle cell disease Thalassemia (SCDT) (HbSS, HbS0ß as proved by electrophoresis) wither they came for follow up, acute exacerbation or any acute illness. Children with SCD who had a history of repeated blood transfusion and children with in vaso-occlusive crises. We exclude children with SCD less than 3 years in age because of inconvenience to perform the scanning. Patients who had a history of major head trauma or stroke, and patients with history of seizure disorders or other neurological disorders.

After explaining for the parents the idea of the research and obtaining their verbal consent to share in it. These patients subjected to complete medical history and thorough physical examination. Blood sample obtained from them to assess hematological parameters. TCD was done either on the same day or at the next clinic appointment.

Doppler measurements:

Trans-cranial and Extra-cranial internal carotid color-duplex ultrasound examinations were done using (SonoAce X8; Medison, Korea). Transducers with 1.8– 3.6-MHz were used for trans-cranial Doppler US. Linear-array 11-MHz transducer was used for carotid US. Radiology Consultant with more than 20 years of experience in ultrasonography performed the scan.

Trans-cranial Doppler ultrasonography was done through trans-temporal window or extra-cranial Doppler to the internal carotid artery through the neck. Children were not allowing sleeping during examination. Middle cerebral artery (MCA) and proximal internal carotid artery (pICA) identified by using published standard (Verlhac, 2011). The time-averaged maximum mean velocity (TAMMV) and Peak Systolic Velocity (PSV) and Peak Diastolic Velocity (PDV) were calculated. Detection of any terciousity or abnormal turbulence of these vessels was reported.

Statistical analysis:

Data analysis was done using the statistical program SPSS 19.0 (Chicago, Il, USA). The relation between pICA & MCA measurements, right and left side were compared. Correlations between Doppler velocities and varies hematological parameters was done by Pearson's coefficient. Doppler velocities were either analyzed non-parametrically, Results with $P<0.05$ considered statistically significant.

Results:

During the period of the study, 72 patients presented to the pediatric clinic. Their mean age was (8±3.7yrs) ranges from (3-13yrs). They were (32) males and (40) females. There was no significant difference between males & females in most of clinical, laboratory or Doppler findings.

High TAMMV was detected in 5.4% (4 cases) where the average velocities in the middle cerebral artery (MCA) and proximal internal carotid artery (pICA) more than 190 cm/s. Where 62.3% (48 cases) had average flow in the MCA & pICA (< 90cm/s), and 26.3% (20cases) had blood flow was 90-190 cm/s. Levels determined according (Adams,2005b).

Data obtained from the right & left side to the MCA by trans-cranial Doppler is analyzed using Pearson correlation coefficient (Table1). The TAMMV of the RT & LT. MCA significantly correlated (R: 0.980 and p < 0.001). There are also significant correlation between PSV and PDV in the RT. & Lt. MCA R (0.956- 0.550) and P (0.000-0.001) respectively.

Table (1) Pearson correlation of Blood flow velocities in RT, LT MCA& RT, LT. extra-cranial ICA obtained with imaging TCD in studied group

Parameter	Rt. side	Lt side	R	P.Value
MCA				
TAMMV *cm/s* ***Mean±SD*** ***(range)***	105.49±38 (60-200)	101.66±36 (65-190)	0.980	0.01
PSV*cm\s* ***Mean± SD*** ***(range)***	134.5±24. (102-190)	136.81±26 (103-197)	0.956	0.001*
PDV*cm\s* ***Mean± SD*** ***(range)***	46.98±7.82 (29-67)	47.7±8.03 (28-63)	0.550	0.01
pICA				
TAMMV*cm\s* ***Mean± SD*** ***(range)***	94.95±32.95 (60-197)	94.41±33.45 (61-198)	0.996	0.001*
PSV*cm\s* ***Mean± SD*** ***(range)***	134.64±27.1 (104-197)	133.26±24.5 (103-189)	0.991	0.001*
PDV*cm\s* ***Mean± SD*** ***(range)***	49.1±6.77 (37-62)	48.5±6.73 (36-62)	0.578	0.001*
VMCA/VpICA ratio				
TAMMV *cm/s* ***mean±SD***	1.1±0.14	1.08±0.13	0.673	0.001*
PSV*cm\s* ***Mean± SD***	1±0.06	1.0±0.04	0.865**	0.001*
PDV *cm\s* ***Mean± SD***	0.96±0.13	0.98±0.13	0.951*	0.001*

MCA: Middle Cerebral Artery, **pICA**: proximal Internal Carotid Artery, **TAMMV**: Time Average Maximum Mean velocity **PSV**: Peak Systolic Velocity, **PDV:** Peak Diastolic Velocity

Velocities in both right and left proximal internal carotid artery (pICA) are analyzed also and shows that TAMMV in the Rt. side was 94.95±32.95 and in the Lt. it was 94.41±33.45, with correlation coefficient of (r: 0.996 & P 0.000) (Table 1). It also demonstrates significance correlation between Rt. and Lt. pICA in the PSV and PDV. The ratio of velocity between the MCA and pICA is estimated and found that Mean MCA Velocities / Mean pICA Velocities were around 1 in all findings.

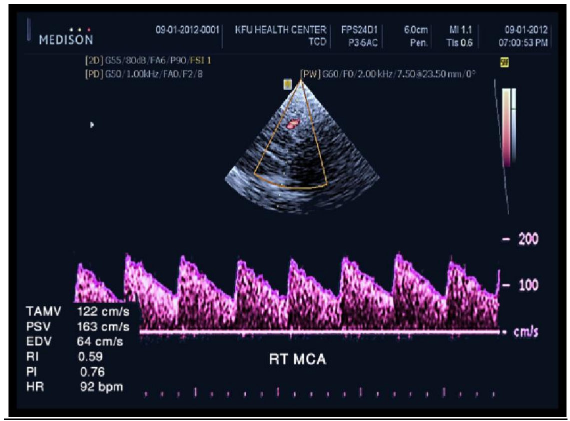

Figure 1: Trans-cranial Color Doppler Ultrasonography with the waveform of the right middle cerebral artery for 9 year-old boy with sickle cell anemia

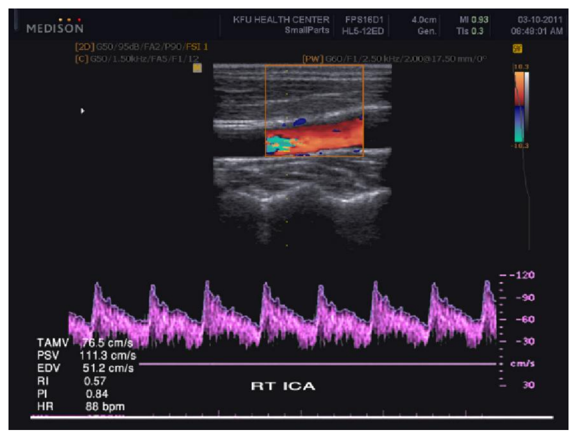

Figure 2: Extra-cranial Color Doppler Ultrasonography with the waveform of the mid-portion of the right internal carotid artery for the same patient of figure 1.

Table (2): Pearson correlation of Blood flow velocities between MCA & pICA obtained with imaging TCD in studied group

pICA MCA	TAMMV (72)	PSV (72)	PDV (72)
TAMMV: R P.value	**0.938**** **0.001**	**0.529**** **0.001**	**0.233**** **0.015**
PSV: R P.value	**0.571**** **0.001**	**0.954**** **0.001**	**- 0.119** **0.321**
PDV: R P.value	**0.233*** **0.049**	**0.151** **0.204**	**0.560**** **0.001**

MCA: Middle Cerebral Artery, **pICA**: proximal Internal Carotid Artery, **TAMMV**: Time Average Maximum Mean velocity **PSV**: Peak Systolic Velocity, **PDV:** Peak Diastolic Velocity

Table (4): Comparison of the mean velocities of cranial vessels in SCD and SCDT patients

Patient Groups Doppler parameters	Sickle cell disease 54 (73.1%)	Sickle cell thalassemia 18 (26.9%)	F	**P**
MCA Velocities (Mean ±SD) TAMMV PSV PDV	 119.0±50.2 146.2±30.7 45.3±7	 98.4±30.311 32.1±22.64 48.01±8.0	 4.367 4.369 1.580	 0.040 0.040 0.213
pICA Velocities (Mean ±SD) TAMMV PSV PDV	 113.1±53.7 148.2±34.4 46.18±4.6	 88.54±19.8 129.18±20.4 49.67±7.1	 8.153 8.147 3.747	 0.006 0.006 .057

MCA: Middle Cerebral Artery, **pICA**: proximal Internal Carotid Artery, **TAMMV**: Time Average Maximum Mean velocity **PSV**: Peak Systolic Velocity, **PDV:** Peak Diastolic Velocity

Table (3): Pearson correlation between the hematological parameters and Doppler finding in the studied group

US Doppler Of Cranial Vessels **-------------------------** ***Hematological Parameters***	**MCA**			**pICA**		
	TAMMV ***Mean±SD*** (103.5±37)	PSV ***Mean±SD*** (135.6±25.4	PDV ***Mean±SD*** (47.3±7.8)	TAMMV ***Man±SD*** 94.68±33.17	PSV m²\s ***Mean±SD*** (133.95±25.7	PDV m²\s ***Mean±SD*** (48.8±6.7)
WBCs×10³\CU ***Mean±SD* (8.3±3.15)** ***R*** ***Pvalue***	0.270 0.03*	0.014 0.91	0.219 0.07	0.249 0.04*	0.025 0.84	0.226 0.06
RBCS×*106\CU* ***Mean±SD* (4.3±.8)** ***R*** ***Pvalue***	-0.119 0.32	-0.014 0.91	0.193 0.11	-0.11 0.36	-0.03 0.8	0.036 0.76
HB conc(mg/dl) ***Mean±SD* (10.97±1.87)** ***R*** ***Pvalue***	- 0.142 0.234	0.046 0.7	0.131 0.27	0.107 0.369	0.009 0.94	0.075 0.53
Plateltes×*105\cu* ***Mean±SD* (358.1±134.3)** ***R*** ***Pvalue***	0.371 0.001**	0.310* 0.01**	0.02 0.88	0.499 0.000*	0.291 0.013**	0.306 0.01**
Retics %: ***Mean±SD* (4.3±2.7)** ***R*** ***P value***	0.176 0.14	0.291* 0.013	0.005 0.968	0.150 0.21	0.280* 0.02	0.077 0.520
HBs% ***Mean±SD* (71.36±9.35)** ***R*** ***Pvalue***	0.182 0.126	0.001 0.996	-0.012 0.92	-0.183 0.123	-0.065- 0.59	0.111 0.35
HbF% ***Mean±SD* (7.03±10.05)** ***R*** ***Pvalue***	-0.043- 0.72	0.023 .849	-0.259-* 0.028	-0.007- 0.95	0.043 0.72	-0.189- .112
HbA2% ***Mean±SD (20.78±13.5)*** ***R*** ***Pvalue***	***0.291**** ***0.013***	***0.085*** ***0.48***	***0.196*** ***0.099***	***0.313**** ***0.007***	***0.122*** ***0.31***	***-0.046-*** ***0.698***

MCA: Middle Cerebral Artery, **pICA**: proximal Internal Carotid Artery, **TAMMV**: Time Average Maximum Mean velocity **PSV**: Peak Systolic Velocity, **PDV:** Peak Diastolic Velocity

Table 2: shows Pearson correlation of Blood flow velocities between intracranial MCA and extra cranial pICA. There is significant positive correlation between mean TAMMV, in the intracranial MCA and extra cranial pICA with R: 0.938& P< 0.001. It also positively correlated with PSV and PDV in pICA.

Analysis of PSV in the MCA shows significant positive correlation between PSV and TAMMV with PSV and TAMMV in pICA. PDV shows no significant correlation between velocities both intracranial MCA extra cranial picas.

Correlation between the hematological parameters and the Doppler findings in our cases table (3). TAMMV in both MCA and pICA is the only parameter that shows positive correlation with WBCs count. Platelets count positively correlated with TAMMV and PSV in both arteries. While Reticulocyte percentage positively correlated with PSV in both MCA and pICA. RBCs count shows non-significant –ve correlation with all Doppler findings in both MCA and pICA.

Multivariate analysis was done to compare the trans-cranial findings in SCD and SCDT showed in Table (4) where there is significant difference between the mean flow velocities in both MCA and pICA in both SCD and SCDT mainly in PSV and TAMMV, where the velocities were higher in SCD.

Discussion:

In Saudi Arabia the prevalence of SCD varies significantly in different regions of the country, the Eastern province represents the highest prevalence, followed by the southwestern provinces. Generally, Stroke is considered relatively rare in childhood (Tsze & Valente, 2011). One of the commonest causes of pediatric stroke is Sickle cell disease occurring in 285 cases per 100,000 affected children (Earley et. al; 1998).

Standard TCD is a low cost method to detect children with sickle cell disease at increased risk of a stroke (Hokazono et.al; 2011 &, Behpour et.al; 2013). Our study found abnormal TCD findings among 5.4% (4 cases) of our patients. In these patients TAMMV in cerebral blood flow was above 190 while no one was above 200cm|s. Lagunju et,al. (2012), reported that despite the higher stroke prevalence in African children with SCD, only 4.7% of the Hb SS cases had abnormal velocities, compared to 8% in the African-American cohort. This can explain by the genetics haplotype differences of SCD.

In KSA Salih et.al; (2006), had reported that TCD was of great value in identifying cerebrovascular disease in three patients with SCD, who later proved to have associated MRI abnormalities. They explained this finding by two different phenotypes of SCD were present in Saudis. In the Eastern Province, the disease is mild, whereas in the Western Provinces it runs a severe course. Also association with B-thalassemia seems to protect from stroke possibly by improving RBC deformability that decreasing hemolysis.

Several trans-cranial parameters measured in our study that showed that there are significant correlation coefficients between all TCD parameters in the right & left MCA as well as Rt. & Lt. pICA. This is agreed with Krejza et al ;(2012), who reached same results and concluded that there is no statistically significant side-to-side difference in Doppler parameters in any artery. They also added that left sided velocities were usually slightly higher than right sided ones and this agreed with our results (Table 2).

In general, increase velocities in the great cerebral vessels can denote hyperemia or also may denotes stenosis (Prohovnik et.al; 2009). Low hematocrit and hemoglobin in children with SCD can lead to hyperemia and abnormally high flow velocity that mistakenly interpreted as resulting from narrowing. Krejza et al.(2012), stated that the use of side-to-side indices to detect stenosis can be beneficial because they are supposed to be resistant to bilateral physiological changes.

TCD screening has limitations, including the failure to identify all children at increased risk of stroke. Some strokes may be missed due to difficulties assessing the distal extra-cranial, petrous, and cavernous internal carotid artery using the STOP protocol. Comparison between the MCA velocities and pICA velocities in our study denotes that there is significant positive correlation between these velocities. We suggested that Doppler ultrasound of the extra-cranial internal carotid artery is a potentially useful screening tool to identify children at increased risk of stroke who may not be detected by using routine TCD. This is agree with Pawlak et al (2009); who added that it is a safe non-invasive, quick, cheap, and does not require any anesthesia or sedation.

Correlation between the hematological parameters and the Doppler findings in our study demonstrated that the cerebral blood velocities had statistical positive correlation with WBCs count, platelets and reticulocytes. This can be supported by (Leite et. al; 2012 & Jordan et. al; 2012), who stated that an elevated leukocyte count was demonstrated to be an independent predictor of the severity of SCD and was associated with an increased risk of stroke. This is possibly due to the adverse effect of neutrophils on the vascular endothelium. Also In study done by Deane et.al 2010, they found that there was significant correlation (P<0.05) between extra-cranial internal carotid artery PSV and white cell count and reticulocyte count.

One of the predictive factors of stroke development was the hematocrit level and Hb concentration (Jordan et.al; 2012). In our study, there is non-significant negative correlation with hematocrit level and Hb concentration. In SCA hemoglobin concentration is inversely correlated with TCD velocity (DeBaun et.al; 2011), and an elevated TCD is the one of the strongest well-known risk factor for stroke in SCA (Adams, 2005c).

Stroke usually occurs four times more often in patients with sickle cell anemia than in patients with SCD- thalassemia. Several studies found that stroke is less common in children with SCD and coexisting alpha thalassemia (Hsu et.al; 2003&, Ashjazadeh et.al; 2012). In our study, there was significant difference between the TCD velocities in patients with SCD and SCD-thalassemia with high velocities in patients with SCD. Children with SCD found to have higher cerebral blood flow velocities than the normal population in several studies. Several mechanisms have been explaining this including anemia, deficiency of nitric oxide synthesis, and endothelial dysfunction (Bartolucciet.al; 2012). In study done by Abboud et.al; 2013, comparing the cerebral blood flow in patients with SCD and associated thalassemia intermediate they found that maximal blood flow velocity was significantly different among patients & controls.

In conclusion:

TCD screening is currently ideal standard of care for stroke prevention in SCA. Our study demonstrated considerable percentage of children with high velocities that can be a prediction for future stroke. Extra-cranial Duplex for the pICA is an easy method to perform the screening and significant in detecting high velocities. It might be used as an alternative to TCD in older children or in uncooperative patients. Leukocytosis and thrombocytosis considered significant factors that affects the blood flow velocities in cranial vessels. Association between SCD and thalassemia can decrease the blood flow velocities thus can decrease incidence of stroke. Our recommendations: to hematologist in Al -Ahasa TCD should be done routinely for children with SCD.

Conflict of interest:

All authors show no conflict of interest

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