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Retinal changes in children and adolescents with sickle cell disease attending a paediatric hospital in Cairo, Egypt: risk factors and relation to ophthalmic and cerebral blood flow

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Background: Sickle cell disease (SCD) is characterised by occlusion of small blood vessels. This study aimed to assess retinal changes in patients with SCD and its correlation with time-averaged mean flow velocity (TAMV) in middle cerebral arteries (MCA) and ophthalmic arteries (OA).

Methods: Sixty SCD patients (aged 3–18 years) attending a paediatric hospital in Cairo, Egypt, during March 2010 to November 2011, were compared with 30 healthy controls. All underwent clinical and fundus examination by indirect ophthalmoscopy, and assessment of TAMV in MCAs and OAs by transcranial Doppler, repeated 1 year later for those with conditional velocities.

Results: HbS/β was diagnosed in 32 patients and HbSS in 28; 50 patients had normal fundus and 10 had bilateral non-proliferative retinopathy. Risk factors for retinopathy included HbSS, age, previous stroke, non-compliant hydroxyurea (HU) therapy, frequency of sickling crises and HbS level. TAMVs were increased in MCAs, but not in OAs, in sicklers. TAMVs in MCAs and OAs increased with non-compliant HU therapy, previous stroke, age, frequency of sickling crises and level of HbS. No significant interhemispheric difference was found.

Conclusion: Sickle retinopathy was correlated with TAMV in MCAs but not in OAs. A significant difference was found between initial and follow-up TAMVs in the MCAs, after 1 year of regular HU and transfusion therapy, in those with conditional velocities.

Keywords: Sickle cell disease, Retinopathy, Ophthalmic blood flow, Cerebral blood flow, Transcranial Doppler, Egypt

Introduction

Sickle cell disease (SCD) is a chronic haemolytic anaemia characterised by the occlusion of small blood vessels, tissue ischaemia and effects to various organs including the eyes and brain.[1] Retinal hypoxia, ischaemia, neovascularisation and fibrovascularisation may result from the microvascular occlusion. These vaso-occlusions depend on the degree of blood viscosity, which is proportional to the rate of sickling and the haemoglobin concentration.[2] The most significant ocular changes are those that occur in the fundus, which can be grouped into proliferative and non-proliferative retinal changes. Formation of new vessels is the most important precursor of potentially blinding complications,[3,4] preceding development of vitreous haemorrhage or retinal detachment. Eye manifestations may be asymptomatic, with unawareness of disease progression, and may have devastating consequences.[3]

Stroke is a devastating complication of SCD,[5] affecting 5–10% of patients before adulthood.[6] The most frequent cause of cerebrovascular accident is blockage of the intracranial internal carotid artery and the middle cerebral artery (MCA). Haemorrhagic stroke is less common, occurring in approximately 3% by the age of 20 years.[7] Transcranial Doppler (TCD) ultrasound screening is widely used to identify children with SCD at high risk of stroke.[8] TCD studies measure flow velocity within the large intracranial arteries, which are the vessels most often involved in sickle cerebral vasculopathy and stroke.[9] Patients with high mean flow velocities in major brain arteries have an increased risk of stroke.[8] A blood flow velocity >200 cm/s in the MCA is reported to correlate with a high risk of stroke in African–American HbS/HbS patients.[5] Periodic screening of time-averaged mean flow velocity (TAMV) in the distal internal carotid arteries or MCAs using TCD is considered the only clinically useful prognostic tool available for primary stroke prevention.[6] The aim of this study was to assess retinal changes in children with SCD and its correlation with TAMV in MCAs and ophthalmic arteries (OA) as well as with other clinical and laboratory variables.

Materials and methods

This work was a cohort, prospective, 1-year follow-up study including 60 patients aged <18 years with SCD (HbS/β and HbSS disease). Patients were recruited from regular attendees of the Pediatric Hematology Clinic of the Pediatric Hospital of Ain Shams University (Cairo, Egypt) during March 2010 to November 2011.Thirty age-matched and gender-matched healthy subjects were enrolled as a control group. Both genders were included. The study excluded SCD patients in sickle crises as well as patients with associated diabetes, hypertension, sickle nephropathy or ophthalmological symptoms. Informed consent was obtained from the guardian of each patient or control before participation in the study.

All included patients were subjected to medical history and clinical examination with special emphasis on age, gender, history of splenectomy (for HbS/β patients) or sickling crisis, transfusion index, and/or hydroxyurea (HU) therapy with determination of patient compliance (defined as receipt of >75% of prescribed dose/kg). History of stroke, avascular necrosis and acute chest syndrome were recorded. Stroke was defined by a focal neurological deficit lasting >24 h with medical documentation, or a deficit lasting <24 h with evidence of acute infarction by neuroimaging. Symptoms of stroke included weakness or numbness that affects one side of the body, sudden behavioural changes, loss of vision, confusion, loss of speech or the ability to understand spoken words, dizziness, headache, seizures, vomiting and coma. The diagnosis of acute chest syndrome was defined as a new pulmonary infiltrate on chest radiography and two or more of chest, upper abdominal or rib pain; dyspnoea; fever; tachypnoea; grunting; nasal flaring; or retractions.

Diagnostic criteria of sickle cell disease

The definition of SCD or β-thalassaemia was based on age at presentation, complete blood count (Coulter Electronics, Hialeah, FL, USA), reticulocyte count and markers of chronic haemolysis (reticulocyte count, lactate dehydrogenase enzyme) as well as qualitative and quantitative haemoglobin analysis by HPLC.[10]

Follow-up data

SCD patients with conditional TAMVs (defined as TAMV of 170–199 cm/s)[5] were followed-up for a mean period of 1 year (after compliance with HU and transfusion therapy).

While in a steady state, all patients and controls underwent fundus examination and TCD examination. Fundus examination was by binocular indirect ophthalmoscopy (Welch Allyn, Skaneateles Falls, NY, USA) with a 20 diopter lens (Volk, Mentor, OH, USA) under mydriasis (with Gutt tropicamide 1%, epinephrine 10%)[11] in which the pupil was dilated, then the patient was asked to position the head in the head mount of the fundus camera (examination photography by fundus and fluorescein camera; TRC-50CX; Topcon, Tokyo, Japan) and to stare at a fixation device so the eyes were still. While the eye-care professional was taking the pictures, the patient saw a series of bright flashes. After the test, the ophthalmologist made a careful interpretation of the images. If the results of the examination were inconclusive, the procedure was repeated. All abnormal fundus findings were verified by another ophthalmologist. Fundus examination takes approximately 5–10 min.

TCD ultrasound was performed using a pulsed Doppler device operating at 2 MHz (Multi-Dop; DWL Electronische Systeme GmbH, Sipplingen, Germany) by the same investigator. Insonation was done for the MCAs and OAs using temporal and orbital windows, respectively. MCA and OA identification followed search techniques described previously by Aaslid et al.[12] and Fujioka and Douville.[13] The highest mean flow velocity of each artery was recorded separately. Final evaluation of the ultrasonographic findings followed the criteria of Seibert et al.[14] predictive for cerebrovascular complications in patients with SCD. Those with conditional velocities were subjected to regular blood transfusion and intake of HU at the maximum tolerated dose (20–30 mg/kg/day),[9] with repetition of TCD after a mean period of 1 year. Fluorescein angiography was done if the fundus examination was abnormal.

The ophthalmologist and the Doppler specialist were blinded to the status of the examined subjects; similarly for the status of TCD for the ophthalmologist and the fundus status for the Doppler specialist.

Statistical analysis

Analysis of data was done by IBM computer using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Normally distributed numerical data were presented as mean ± SD. χ^2 was used to test the association variables for categorical data. Assessment of the statistical significance of the difference between two population means was by Student's t test when involving independent samples and by paired t test for matched or paired samples. Correlation was done using Pearson's test. The correlation coefficient (r) defines the strength and direction of the linear relationship between two variables. p Values of <0.05 and <0.01 were considered significant and highly significant, respectively.

Results

The 60 patients with SCD included 34 males and 26 females (male:female ratio of 1.3:1). The control group consisted of 16 males and 14 females (ratio 1.1:1). The mean age of patients was 10.3 ± 7.4 years (range 3–18 years) and that of controls was 10.7 ± 3.8 years (range 5–18 years). None of the 60 patients was splenectomised or had any ophthalmological symptomatology. The pattern of SCD among the patients revealed that 32/60 patients (53%) had HbS/β (20 had HbS/β^+ and 12 had HbS/β^0), and 28/60 patients (47%) had HbSS disease. HbSC was not found in any of the patients.

Among the patients, the mean reticulocyte count was 7.0% (range 4–15%). The mean lactate dehydrogenase level was 650 IU/L (range 400–1100 IU/L). The mean HbF in HbS/β patients was 35% (range 12–50%). Normal fundus examination was found in 50 (83%) patients and 10 (17%) showed bilateral non-proliferative retinopathy manifested as venous engorgement and kinked blood vessels in the fundus examination. Only one female patient aged 18 years had lateral and vertical vascular deflection in both eyes, suggestive of hypertensive retinopathy. She experienced 4–12 sickling crises per year and was proved to have sickle cell nephropathy and was receiving

antihypertensive drugs. Her fluorescein angiography picture showed bilateral retinal pigment epithelium mottling with abnormal vessel tortuosity, as shown in Figure 1. Risk factors for the presence of retinopathy were HbSS, previous stroke, age, non-compliance with HU therapy, frequency of sickling crises and level of HbS, with no gender difference, as shown in Table 1. All of the control subjects had normal fundus pictures.

Compared with controls, TAMVs were increased in MCAs in patients ($p < 0.001$), but not in OAs, as shown in Table 2. TAMVs in MCAs and OAs were significantly increased with

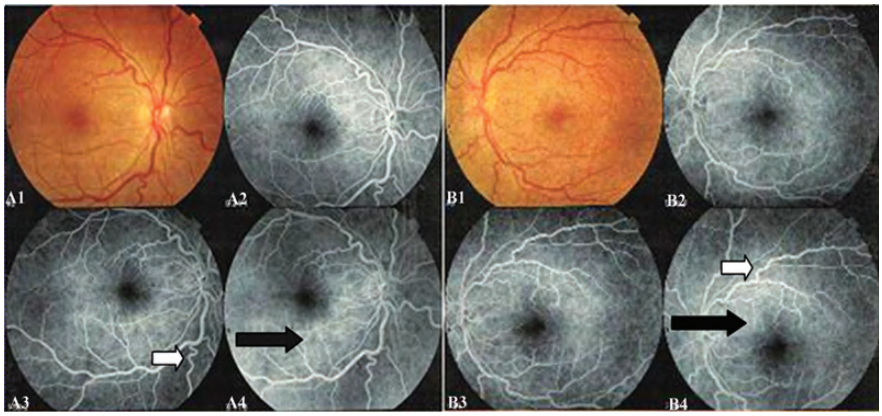

Figure 1. The right eye (A1–A4) and the left eye (B1–B4) of a patient with sickle cell disease. The photos A1 and B1 (conventional fundus pictures) show bilateral retinal pigment epithelium (RPE) mottling with abnormal vessel tortuosity. Photos A2, A3 and A4 and B2, B3 and B4 show fundus fluorescin angiography during various phases of dye transit confirming vascular tortuosity (white arrows) and RPE changes (black arrows) and showing no leakage.

Table 1. Fundus examination in 60 patients with sickle cell disease (SCD) in relation to their clinical and laboratory parameters

Variable		Fundus examination		
		Normal fundus (n = 50)	Retinopathy (n = 10)	Test of significance
Gender	Female	21 (42)	5 (50)	$\chi^2 = 0.217$
	Male	29 (58)	5 (50)	NS
Pattern of SCD	HbSS	21 (42)	7 (70)	$\chi^2 = 3.963$
	HbS/β^0	9 (18)	3 (30)	NS
	HbS/β^+	20 (40)	0	
History of stroke	Negative	50 (100)	6 (60)	$p < 0.001$[a]
	Positive	0	4 (40)	
Avascular necrosis	Positive	0	5 (50)	$p < 0.001$[a]
Acute chest syndrome	Positive	0	1 (10)	NS[a]
Hydroxyurea therapy	Compliant[b]	49 (98)	0	$p < 0.001$[a]
	Non-compliant[b]	1 (2)	10 (100)	
Age (years)	Range	3–18	6–18	$t = 4.369$
	Mean ± SD	9.98 ± 7.51	12.9 ± 6.79	$p < 0.001$
Frequency of sickling crises/year	Range	2–12	10–14	$t = 8.062$
	Mean ± SD	5.38 ± 2.58	12.2 ± 1.48	$p < 0.001$
HbS (%)	Range	43–82	82.4–85	$t = 5.255$
	Mean ± SD	66.9 ± 9.97	83.6 ± 1.07	$p < 0.001$
Hb (g/dL)	Mean ± SD	8.9 ± 1.8	7.1 ± 0.8	$t = 3.085$
				$p < 0.001$

Data are number (%), unless otherwise indicated.
NS: not significant.
[a]Fisher's exact test.
[b]Patient compliance was defined as receipt of >75% of prescribed dose/kg.

Table 2. Comparison between time-averaged mean flow velocity (TAMV) in middle cerebral arteries (MCA) and ophthalmic arteries (OA) in sickle cell disease patients and controls

Arteries	TAMV (cm/s)				t test	p value
	Patients (n = 60)		Controls (n = 30)			
	Range	Mean ± SD	Range	Mean ± SD		
RT-MCA	75–188	135.98 ± 32.54	44–75	60.6 ± 10.68	−5.723	<0.001
LT-MCA	73–180	134.98 ± 32.18	43–77	60.67 ± 11.03	−6.779	<0.001
RT-OA	20–54	27.113 ± 6.912	19–40	26.33 ± 4.071	−0.660	NS
LT-OA	19–50	28.633 ± 8.413	18–45	25.6 ± 4.005	−6.742	NS

LT: left; NS: not significant; RT: right.

non-compliance with HU therapy and previous occurrence of stroke but not with transfusion frequency. Age, frequency of sickling crises and level of HbS showed significant correlations with TAMVs both in MCAs and OAs. HbF level showed significant correlations with TAMV in MCAs but not with TAMV in OAs (Table 3). No significant interhemispheric difference was found between TAMVs in right and left MCAs or between right and left OAs.

The 10 patients with conditional TAMVs in the MCAs at study entry had been converted to normal velocities (<170 cm/s) after 1 year of regular transfusion therapy and intake of HU with no history of primary or secondary stroke. A significant difference was found between initial and follow-up TAMVs in bilateral MCAs and AOs (Table 4). Sickle retinopathy was correlated with TAMVs in MCAs but not in OAs (Table 5).

Discussion

Fundus examination in the 60 patients revealed the absence of proliferative sickle retinopathy, in accordance with Omolase et al.[2] and Akinsola and Kehinde[11] who reported no cases with proliferative retinopathy in children with SCD. Meanwhile, 10 had non-proliferative sickle retinopathy. This agreed with studies done by Rosenberg and Hutcheson,[15] Omolase et al.,[2] Gill and Lam[16] and Kaimbo et al.,[17] who found that sickle retinopathy develops in the range of 16.7–96.3% for non-proliferative sickle retinopathy and 0–11.1% for proliferative sickle retinopathy. Among the 10 patients with sickle retinopathy, 7 had HbSS and 3 had HbS/β^0. This is in agreement with Rosenberg and Hutcheson[15] who found sickle retinopathy to occur more commonly among patients with HbSS, and with Eruchalu et al.[18] who demonstrated that young children with HbSS with severe clinical symptoms can develop sight threatening retinopathy. In contrast, Gill and Lam[16] and Reynolds et al.[19] reported that although HbSS patients are associated with most acute life-threatening systemic manifestations, they have few ocular complications, while HbS/β patients have few systemic manifestations and severe ocular disease. This may be attributed to the rate of sickling, blood viscosity and haematocrit, which was explained by Lutty and McLeod[20] by the fact that the haematocrit in HbS/β patients is significantly higher than in HbSS patients. HbSC was not found among the patients in the current study as the haemoglobin variants, other than HbS, such as HbC are rare in Middle East Arab countries, as demonstrated by El-Hazmi et al.[21]

The age of onset of sickle retinopathy in the current study had a mean of 15.9 years (range 12–18 years), in agreement with Kaimbo et al.[17] who reported that the chance of occurrence of sickle retinopathy increases with patient age. Meanwhile, Eruchalu et al.[18] showed a significant retinal disease in children as young as 8 years. In addition, this study showed that sickle retinopathy was correlated with frequency of pain crises, history of stroke and irregular use of HU therapy, in agreement with Rosenberg and Hutcheson[15] who correlated sickle retinopathy with frequency of crises but not with the frequency of cerebrovascular accident. In contrast, Gill and Lam[16] found no correlation between sickle retinopathy and the presence of systemic occlusive manifestations. No gender difference was found among the patients in the current study with sickle retinopathy, in agreement with Eruchalu et al.[18] and Kaimbo et al.[17] In contrast, Rosenberg and Hutcheson[15] reported that sickle retinopathy was found to be more common in males.

TAMVs in MCAs in the current study were significantly higher among patients with SCD than that in the control group, reflecting a difference in cerebral blood flow in patients with SCD (even without previous cerebrovascular disease) and healthy children, in accordance with Melo et al.[22] No significant interhemispheric difference was found in this study, in agreement with Colombatti et al. [5] Gender difference had no impact on TCD velocities among the studied patients, in accordance with Arkuszewski et al.[8] However, Vavilala et al.[23] and Tontisirin et al.[24] demonstrated that girls between 4 years and 8 years of age had higher MCA flow velocity than age-matched boys, explained by the inherent differences in cerebral metabolic rate and/or estimated cerebrovascular resistance between the genders. The mean of TAMVs in MCAs in the current study was >170 cm/s in 10 patients, but not in OAs. This discrepancy between TAMVs in MCAs and in OAs demonstrated that the hyperdynamic effect of chronic anaemia was not homologous in all arteries and that the risk of stroke was not dependent on a TCD recording from a specific artery, confirmed by Arkuszewski et al.[8] Of the 10 patients with conditional velocities in the MCAs, 4 had a history of stroke.

Table 3. Time-averaged mean flow velocity (TAMV) in middle cerebral arteries (MCA) and ophthalmic arteries (OA) in sickle cell disease (SCD) patients in relation and correlation to different parameters

			TAMV (cm/s)			
			RT-MCA	LT-MCA	RT-OA	LT-OA
Pattern of SCD	HbSS	Mean	129	126.607	28.857	30.929
		SD	44.342	43.233	9.034	11.102
	HbS/β	Mean	142.094	142.313	26.281	26.625
		SD	14.84	14.974	4.082	4.294
	t test	t	−1.574	−1.929	1.454	2.028
		p value	NS	NS	NS	NS
HU compliance	Compliant	Mean	126.592	126.184	26.082	26.694
		SD	27.746	28.584	4.353	3.927
	Non-compliant	Mean	177.818	174.182	33.727	37.273
		SD	13.963	10.88	11.765	15.589
	t test	t	−5.928	−5.451	−3.644	−4.288
		p value	<0.001	<0.001	<0.001	<0.001
History of stroke	Negative	Mean	132.768	131.875	26.536	27.125
		SD	31.216	31.033	5.288	4.671
	Positive	Mean	181	178.5	40.75	49.75
		SD	8.083	2.38	13.251	18.839
	t test	t	−3.06	−2.981	−4.603	−6.996
		p value	<0.001	<0.001	<0.001	<0.001
TAMV in sickle patients in correlation with clinical and laboratory parameters						
Age (years)		r	0.675	0.668	0.381	0.288
		p value	<0.001	<0.001	<0.001	<0.001
Transfusion index (mL/kg/year)		r	−0.146	−0.131	−0.091	−0.13
		p value	NS	NS	NS	NS
Frequency of sickling crises/year		r	0.705	0.698	0.545	0.5
		p value	<0.001	<0.001	<0.001	<0.001
HbS%		r	0.659	0.659	0.311	0.211
		p value	<0.001	<0.001	<0.001	<0.001
HbF%		r	−0.376	−0.363	−0.178	−0.212
		p value	<0.001	<0.001	NS	NS

HU: hydroxyurea; LT: left; NS: not significant; RT: right.

Table 4. Comparison between initial and 1-year follow-up time-averaged mean flow velocity (TAMV) in middle cerebral arteries (MCA) and ophthalmic arteries (OA) in sickle cell disease patients with initial TAMV of 170–199 cm/s

	Initial TAMV (cm/s)		1-year follow-up TAMV (cm/s)		Paired t test	
	Range	Mean ± SD	Range	Mean ± SD	t	p value
RT-MCA	170–188	181.6 ± 6.47	110–165	141.1 ± 18.22	7.24	0.007
LT-MCA	170–180	177.3 ± 3.56	112–160	140.4 ± 17.24	6.52	0.006
RT-OA	20–54	27.113 ± 6.912	20–36	26.5 ± 5.421	2.81	0.020
LT-OA	19–50	28.633 ± 8.413	16–33	26.3 ± 5.618	2.8	0.021

LT: left; RT: right.

Table 5. Time-averaged mean flow velocity (TAMV) in middle cerebral arteries (MCA) and ophthalmic arteries (OA) in the presence of retinopathy

Artery	Fundus examination	TAMV (cm/s)		Paired t test	
		Range	Mean ± SD	t	p value
RT-MCA	Normal	44–188	118.326 ± 56.056	−5.723	<0.001
	Retinopathy	170–180	175 ± 7.071		
LT-MCA	Normal	43–182	117.907 ± 55.64	−6.779	<0.001
	Retinopathy	175–179	177 ± 2.828		
RT-OA	Normal	20–54	31.512 ± 11.44	−0.66	NS
	Retinopathy	27–54	40.5 ± 19.092		
LT-OA	Normal	19–50	32.419 ± 12.827	−6.742	NS
	Retinopathy	24–50	38.8 ± 6.364		

LT: left; NS: not significant; RT: right.

This is in agreement with Hankins et al.[25] who reported that children with SCD and conditional TAMVs have increased risk of primary stroke.

This study demonstrated that patients with conditional TCD velocities at initial evaluation had been converted to normal velocities (<170 cm/s) after 1 year of regular transfusion therapy and intake of HU with no history of secondary stroke. In agreement, Enninful-Eghan et al.[26] and Mazumdar et al.[27] reported that annual TCD ultrasound screening until the age of 10 years with transfusion for children at high risk until 18 years of age is advised for an optimal stroke prevention strategy. On the other hand, Ali et al.[28] supported the role of HU as a useful intervention for the prevention of stroke recurrence in SCD when transfusion programmes are not available or practical; and Zimmerman et al.[9] documented that HU can decrease elevated TCD flow velocities, often into the normal range, in SCD. However, the SWITCH trial found that HU with regular phlebotomy was found to be unlikely to prevent recurrent strokes better than standard therapy combining blood transfusion with deferasirox.[29]

TAMVs in MCAs in the patients in this study increased with age. This is in agreement with Hankins et al.[25] Despite the absence of a correlation between TAMVs in OAs and the occurrence of sickle retinopathy in these patients, a significant correlation was found between the presence of sickle retinopathy and increased TAMVs in MCAs.

Endothelial dysfunction and impaired nitric oxide bioavailability have been implicated in the pathogenesis of sickle cell anaemia,[30] yet many pathophysiological features in SCD are still unclear, in particular in the genesis of vasculopathy.

The present study recommended annual screening of children with SCD by TCD. All SCD patients with high TAMV (>200 cm/s) or with a conditional TAMV of 170–199 cm/s could have benefited from monthly blood transfusion with regular HU therapy, although a multicentre study on a larger number of patients with SCD is recommended to confirm these results. TCD should be done bilaterally and on more than one artery. Routine yearly fundus examination is essential for SCD children to avoid the occurrence of unnoticeable serious complications in the eye.

In conclusion, non-proliferative retinopathy, detected in 16.7% of SCD patients, was correlated with history of stroke, poor compliance with HU therapy, frequent sickling crises, higher HbS level, and TAMV in MCAs and not with TAMV in OAs, with no gender difference. TAMVs were increased in MCAs, but not in OAs, in SCD patients. TAMVs in MCAs correlated with the frequency of sickling crises, HbS and HbF level, non-compliant HU therapy, previous stroke and age, but were not correlated with transfusion frequency or TAMVs in OAs. No significant interhemispheric difference was found in TAMVs of MCAs and OAs. Regular transfusion and HU therapy decreased conditional TAMVs in MCAs in sicklers.

Authors' contributions: AAGT conceived the study; AAGT, NGA and AAMA designed the study, supervised the follow-up of patients, and analysed and interpreted the clinical haematological findings; BAEK carried out the fundus examination for all SCD patients and controls, and analysed and interpreted the ophthalmological findings; ASS carried out the transcranial Doppler examination and neurological examination for all SCD patients and controls, and analysed and interpreted the transcranial Doppler and neurological findings; AAGT, NGA and AAMA drafted the manuscript. All authors critically revised the manuscript for intellectual content and read and approved the final version. AAGT and AAMA are guarantors of the paper.

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Ethical approval: The procedures applied in this study were approved by the Ethical Committee of the Pediatric Hospital, Faculty of Medicine, Ain Shams University (Cairo, Egypt).

References

1 Elagouz M, Jyothi S, Gupta B, Sivaprasad S. Sickle cell disease and the eye: old and new concepts. Surv Ophthalmol 2010;55:359–77.

2 Omolase CO, Paul-Odo B, Omalse BO. Ocular findings of sickle cell eye disease patients in Owo. Middle East J Family Med 2010;8:1448–96.

3 Fadugbagbe AO, Gurgel RQ, Mendonca CQ et al. Ocular manifestations of sickle cell disease. Ann Trop Paediatr 2010;30:19–26.

4 Reynolds SA, Rodman J. Hematological disorders and the retina. Rev Optom 2008;(Suppl):3–4.

5 Colombatti R, Meneghetti G, Ermani M et al. Primary stroke prevention for sickle cell disease in north-east Italy: the role of ethnic issues in establishing a transcranial Doppler screening program. Ital J Pediatr 2009;35:15.

6 Flanagan JM, Frohlich DM, Howard TA et al. Genetic predictors for stroke in children with sickle cell anemia. Blood 2011;117:6681–4.

7 Wolf M, Cangemi C, Drachtman R, Masterson M. Primary hemorrhagic stroke in a 12-year-old female with sickle cell disease and normal transcranial Doppler. Pediatr Hematol Oncol 2008;25:451–6.

8 Arkuszewski M, Krejza J, Chen R et al. Sickle cell disease: reference values and interhemispheric differences of nonimaging transcranial Doppler blood flow parameters. AJNR Am J Neuroradiol 2011;32:1444–50.

9 Zimmerman SA, Schultz WH, Burgett S et al. Hydroxyurea therapy lowers transcranial Doppler flow velocities in children with sickle cell anemia. Blood 2007;110:1043–7.

10 Mosca A, Paleari R, Ivaldi G et al. The role of haemoglobin A_2 testing in the diagnosis of thalassaemias and related haemoglobinopathies. J Clin Pathol 2009;62:13–7.

11 Akinsola FB, Kehinde MO. Ocular findings in sickle cell disease patients in Lagos. Niger Postgrad Med J 2004;11:203–6.

12 Aaslid R, Markwalder TM, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. J Neurosurg 1982;57:769–74.

13 Fujioka KA, Douville CM. Anatomy and freehand examination. In: Newell DW, Aaslid R, editors. Transcranial Doppler. New York, NY: Raven Press; 1992: p. 9–32.

14 Seibert JJ, Glasier CM, Kirby RS et al. Transcranial Doppler, MRA, and MRI as a screening examination for cerebrovascular disease in patients with sickle cell anemia: an 8-year study. Pediatr Radiol 1998;28:138–42.

15 Rosenberg JB, Hutcheson KA. Pediatric sickle cell retinopathy: correlation with clinical factors. J AAPOS 2011;15:49–53.

16 Gill HS, Lam WC. A screening strategy for the detection of sickle cell retinopathy in pediatric patients. Can J Opthalmol 2008;43:188–91.

17 Kaimbo KWA, Makuala N, Dralands L, Missotten. Ocular findings in children with homozygous sickle cell disease in the Democratic Republic of Congo. Bull Soc Belge Opthalmol 2000;275:27–30.

18 Eruchalu UV, Pam VA, Akuse RM. Ocular findings in children with severe clinical symptoms of homozygous sickle cell anemia in Kaduna, Nigeria. West Afr J Med 2006;25:88–91.

19 Reynolds SA, Besada E, Winter-Corella C. Retinopathy in patients with sickle cell trait. Optometry 2007;78:582–7.

20 Lutty GA, McLeod DS. Angiogenesis in sickle cell retinopathy. Retinal and Choroidal Angiogenesis 2008;389–405.

21 El-Hazmi MAF, Al-Hazmi AM, Warsy AS. Sickle cell disease in Middle East Arab countries. Indian J Med Res 2011;134:597–610.

22 Melo HA, Barreto-Filho JA, Prado RC, Cipolotti R. Transcranial Doppler in sickle cell anaemia: evaluation of brain blood flow parameters in children of Aracaju, Northeast-Brazil. Arq Neuropsiquiatr 2008;66:360–4.

23 Vavilala MS, Kincaid MS, Muangman SL et al. Gender differences in cerebral blood flow velocity and autoregulation between the anterior and posterior circulations in healthy children. Pediatr Res 2005;58:574–8.

24 Tontisirin N, Muangman SL, Suz P et al. Early childhood gender differences in anterior and posterior cerebral blood flow velocity and autoregulation. Pediatrics 2007;119:e610–5.

25 Hankins JS, Fortner GL, McCarville MB et al. The natural history of conditional transcranial Doppler flow velocities in children with sickle cell anaemia. Br J Haematol 2008;142:94–9.

26 Enninful-Eghan H, Moore RH, Ichord R et al. Transcranial Doppler ultrasonography and prophylactic transfusion program is effective in preventing overt stroke in children with sickle cell disease. J Pediatr 2010;157:479–84.

27 Mazumdar M, Heeney MM, Sox CM, Lieu TA. Preventing stroke among children with sickle cell anemia: an analysis of strategies that involve transcranial Doppler testing and chronic transfusion. Pediatrics 2007;120:e1107–16

28 Ali SB, Moosang M, King L et al. Stroke recurrence in children with sickle cell disease treated with hydroxyurea following first clinical stroke. Am J Hematol 2011;86:846–50.

29 Jeffrey S. Stroke prevention trial in children with sickle cell disease and iron overload halted. Medscape News; 2010. http://www.medscape.com/viewarticle/723291 [accessed 7 January 2013].

30 Akinsheye I, Klings ES. Sickle cell anemia and vascular dysfunction: the nitric oxide connection. J Cell Physiol 2010;224:620–5.