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Silent Brain Changes in Children with Sickle Cell Disease

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ABSTRACT

Background: Cerebrovascular steno-occlusive disease constitutes one of the most dangerous complications of sickle cell disease (SCD). It could result in overt or silent cerebral infarctions (SCI).

Objective: The aim of this study was to demonstrate silent parenchymal and vascular brain changes that are incidentally observed in neurologically free SCD children using screening MRI and MRA.

Patients and methods: This prospective cross-sectional study was conducted on 78 children diagnosed with SCD who were neurologically free. Magnetic resonance imaging (MRI) and Magnetic Resonance Angiography (MRA) were done to all the participant children. **Results:** Thirty (38.4%) of our children demonstrated pathologic parenchymal features on their MRI. There were 29 (37.17%) patients had pathologic changes in MRA; 6 of them had isolated vascular abnormality, whereas the remaining patients had concurrent parenchymal abnormalities. There was significant high positive correlation between low hemoglobin and presence of silent cerebral infarction (SCI). Moya-moya vasculopathy showed significant positive correlation with arterial occlusion and old SCI. HB SS phenotype was significantly correlated with moya-moya vasculopathy, arterial occlusion and old SCI. **Conclusions:** Silent cerebral and cerebrovascular changes in SCD children are frequent abnormalities requiring utilization of MRI and MRA to find out their exact prevalence and their risk factors.

Keywords: Sickle cell disease, Silent brain infarction, Moya-moya vasculopathy, Screening MRI, Screening MRA.

INTRODUCTION

Sickle cell disease (SCD) is an inherited haemoglobinopathy, which is a severe monogenic condition that affects millions of people worldwide, and characterized by formation of abnormal hemoglobin called Hb S, repeated cycles of sickling and unsickling, multiple episodes of vascular obstruction, and hemolytic anemia [(1)]. During sickling process, interaction between the rigid sickle cells and the vascular wall leads to, intravascular thrombosis and subsequent end-organ ischemia [(1, 2)]. Stroke caused by vaso-occlusion is a major complication of SCD. Its risk is greatest early in childhood during the first decade and is most significant at the age of two to five years. Children with sickling are more susceptible to have stroke 250 times than for those without SCD [(3)]. Silent cerebral infarction (SCI) could be seen in some cases, which often go unnoticed but may cause significant neurological damage and disability up to 17% to 25% of SCD patients [(4)].

Silent stroke is much more common than manifested one, which has declined in the last decade with the use of chronic transfusion therapy and transcranial Doppler (TCD) ultrasonography [(5, 6)]. It is believed that SCI may increase the risk of overt stroke. In brief, the major hypothesis is that prophylactic blood transfusion therapy in children with SCD with silent cerebral infarcts will result in at least 86% reduction in the rate of subsequent overt strokes or new or enlarging cerebral infarcts as defined by MRI of the brain [(6-8)].

By definition, SCIs are clinically silent, they have normal neurologic examination and, in some cases, normal TCD study, subsequently. SCI are identified incidentally or through screening magnetic resonance imaging (MRI). Furthermore, cerebrovascular steno-occlusive disease could result in moya-moya vasculopathy, which could be considered as another silent change developed when the arterial narrowing occurs over a long period of time allowing for formation of collateral pathways [(6, 9)]. The aim of our study was to screen silent parenchymal and vascular brain changes in neurologically free children diagnosed with SCD using MRI and MRA.

PATIENTS AND METHODS

This was a prospective cross-sectional study that was conducted from May 2022 to November 2022 after being ethically approved by the institution committee (Approval no: 512/2022).

Study participants

Seventy-eight children diagnosed with SCD were included in the study, all of them had regular follow ups in the Pediatric Hematology Outpatient's Clinic, Minia University Children Hospital, Egypt. All patients underwent thorough medical history tacking, complete clinical and neurologic examination as well as laboratory tests including CBC, differential white blood cell count, serum ferritin, and renal function tests. MRI and MRA were done to all the participant children. Informed written consent was obtained from the parents of each patient prior to participating in the study. **Inclusion criteria:** SCD children below 18 years who were neurologically free with no history of neurological dieses.

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Exclusion criteria: Children with any risk factor of stroke including congenital or rheumatic heart disease, children with prosthetic valves, vascular malformation, prothrombotic disorders and autoimmune disease. Also, children with MRI contraindication as aneurysm clips, cochlear implant, etc.

MRI and MRA techniques

MRI and MRA of the brain were performed on Ingenia 1.5-T Philips MRI scanner using head coil. Young children who required sedation were sedated with chloral hydrate and immobilized on the table during the study. The MRI protocol included **Axial FLAIR** (TR/TE 8000/92 ms, matrix 240 x 143, slice thickness/gap 5/1 mm, duration 3:34 min). **Sagittal T1WI** (TR/TE 550/15 ms, matrix 168 x 131, slice thickness/gap 5/1 mm, duration 1:54 min). **Axial T2WI** (TR/TE 5190/100ms, matrix 265 x 147, slice thickness/gap 5/1 mm, duration 00:39 min). **Coronal T2WI** (TR/TE 3163/100 ms, matrix 180 x 187, slice thickness/gap 5/1 mm, duration 2:32 min). **Axial DWI** (TR/TE 6000/110 ms, matrix 192 x 190, slice thickness/gap 5/1 mm, duration 1:18 min). **Axial SWI** (TR/TE 49/40 ms, matrix 272 x 220, slice thickness/gap 2/-0.8 mm with slice oversampling, duration 4:13min). **Axial 3D** time of flight **(TOF) MRA** of cerebral arteries and circle of Willis using fast felid echo (TR/TE 26/7 ms, flip angle 20, matrix 265 x 206, FOV = AP 160 mm/ RL 160 mm/ FH 91 mm, duration 2:31 min), frontal, lateral and cranial reformatted images were obtained using maximum intensity projection (MIP).

Image analysis

Overview of the whole brain parenchyma was done on all MRI sequences notably the FLAIR and DWI searching signal abnormality areas compatible with silent recent or old infractions, recent infarction was diagnosed in presence of diffusion restriction, old infarction was diagnosed in presence of FLAIR hypointense CSF signal cavity surrounded with hyperintense gliosis or when focal area of FLAIR hyperintensity of gliosis was observed with or without focal parenchymal atrophy. When FLAIR hyperintense lacunar foci were observed at either deep white matter or white matter watershed areas, they were addressed as ischemic foci. The axial source images of TOF MRA as well as all MIP reformatted images were assessed for presence and location of arterial narrowing and/or occlusion; also they were assessed for presence of moya-moya collateral vasculopathy. Overt disease was not assessed in this study as all patients were neurologically free.

Ethical consent: An approval of the study was obtained from Benha University Academic and Ethical Committee. After explaining our research objectives, written informed consents were obtained from all study participants. This study was conducted in compliance with the code of ethics of the world medical association (Declaration of Helsinki) for human subjects.

Statistical analysis

Our results were recorded, tabulated, and statistically analyzed using SPSS-20 (Statistical Package for Social Sciences) software version 21. Descriptive statistics were expressed for quantitative data by mean and standard deviation. They were presented for categorical data as number and percentage. Analyses were done for quantitative data using t test. However, for qualitative data, Chi-square test or Fisher Exact test was employed when appropriate. The degree of relationship between the variables was calculated using the Pearson correlation analysis. Correlation coefficient (r) ranges from (0–1): weak (r = 0–0.24), fair (r = 0.25–0.49), moderate (r = 0.5–0.74), strong (r = 0.75–1). P ≤ is considered significant.

RESULTS

The current study was carried out on seventy eight children, thirty five (44.87%) males and forty three (55.13%) females. The mean age of all patients was 11.58 ± 2.62 years (range 6-15years). Twenty six (33.3%) patients had homozygous phenotype HB SS whereas fifty two (66.6%) were heterozygous. sixteen (20.5%) patients had normal hemoglobin level for age with their mean hemoglobin concentration was 10.15 ± 0.9 g/dl. Thirty (38.4%) children including eighteen children with HB SS phenotype demonstrated pathologic parenchymal features on their MRI (Tables 1-3) (Figure 1, 2). There were 29 (37.17%) of our children had one or more pathologic changes in MRA, most of which were found in the anterior circulation, while the posterior circulation affection in the current study was rare and found only in 5 (6.4%) patients. There were six patients had isolated vascular abnormality without parenchymal signal changes in other MRI sequences, whereas the remaining had concurrent parenchymal and vascular involvements. The bilateral steno-occlusive changes were sixteen (20.5%), whereas the unilateral affection was thirteen (16.6%), the moya-moya vasculopathy was unilateral in ten (12.8%) cases and bilateral in five (6.4%) cases. The total number of patients who had abnormal MRI and/or MRA studies was thirty six (46.15%). The remaining forty two (53.84%) patients had normal MRI and MRA studies. (Tables 1, 4, and 5) (Figure 2, 3, and 4).

There were significant difference between SCD children with and without silent brain changes as regards low hemoglobin, sickle cell phenotype, mean number of pain events, and the use pf hydroxyurea (Table 1)

Table (1): Baseline characteristics of the studied children

Characteristic	Studied SCD children (n=78)	Group I (With silent brain changes) (n=36)	Group II (Without silent brain changes) (n=42)	p value
Age (years)	11.58 ± 2.62	11.21 ± 1.92	11.75 ± 2.13	0.21
Gender (Male/Female)	35/43	17/19	18/24	0.17
Genotype				**0.05***
Hemoglobin SS	26 (33.3%)	18(50%)	8(19%)	
Hemoglobin SB+	52 (66.6%)	18(50%)	34 (81%)	
Hemoglobin (gm/dl)	10.15 ± 0.9	10.3 ± 0.5	10.01 ± 0.4	0.11
Severity of anemia				
No anemia (Hb > 11 g/dl)	16 (20.5%)	5(13.9%)	11(26.2%)	
Mild anemia (Hb 10–10.9g/dl)	40 (51.3%)	15(41.2%)	25(59.5%)	**0.04***
Moderate anemia (Hb 7.0–9.9g/dl)	14 (18%)	10(27.7%)	4 (9.5%)	
Severe anemia (Hb <7gldl)	8 (10.2%)	6(16.7%)	2(4.8%)	
Transfusion dependence (n%)	15(19.2%)	7(19.4%)	8(19%)	0.21
Mean Pain event counts (n) (range)	3(0-6)	4(1-6)	1(0-4)	**0.04***
Medications (n%)				
Hydroxyurea	17(21.7%)	6(16.6%)	11(26.2%)	**0.01***
Folic Acid	55(70.5%)	26(72.2%)	29(69%)	0.23
Ibuprofen	43(43.5%)	20(55.5%)	23(54.7%)	0. 31
Paracetamol	45(57.7%)	23(63.8%)	22(52.3%)	0.33

*Significant, SCD: sickle cell disease

Table (2): Parenchymal brain changes in conventional MRI

Pathologic brain changes in conventional MRI	(n=30)	%
Silent acute lacunar infarction (hyperintense DWI)	3	3.84 %*
Silent old infarction (either FLAIR hypointense cavity or FLAIR hyperintense gliosis) +/- atrophy	16**	20.5%
FLAIR hyperintense lacunar ischemic foci at either deep white matter or white matter watershed areas	19**	24.35%*

*Two patients with acute lacunar infarction had concurrent FLAIR lacunar hyperintensities.
**There were six patients had concurrent silent old infarction/infarctions and FLAIR lacunar hyperintensities.

Table (3): Anatomic location of silent brain infarction in conventional MRI

		no. of cases	%	Total no. of cases	%
Silent acute lacunar infarction	External capsule	2	2.5%	3	3.8 %
	Basal ganglia	1	1.28%		
Silent old infarction	Deep white matter frontal	9	11.5%	16	20.5%
	Deep white matter parietal	5	6.4%		
	Basal ganglia	2	2.5%		

Table (4): Vascular abnormalities in MRA

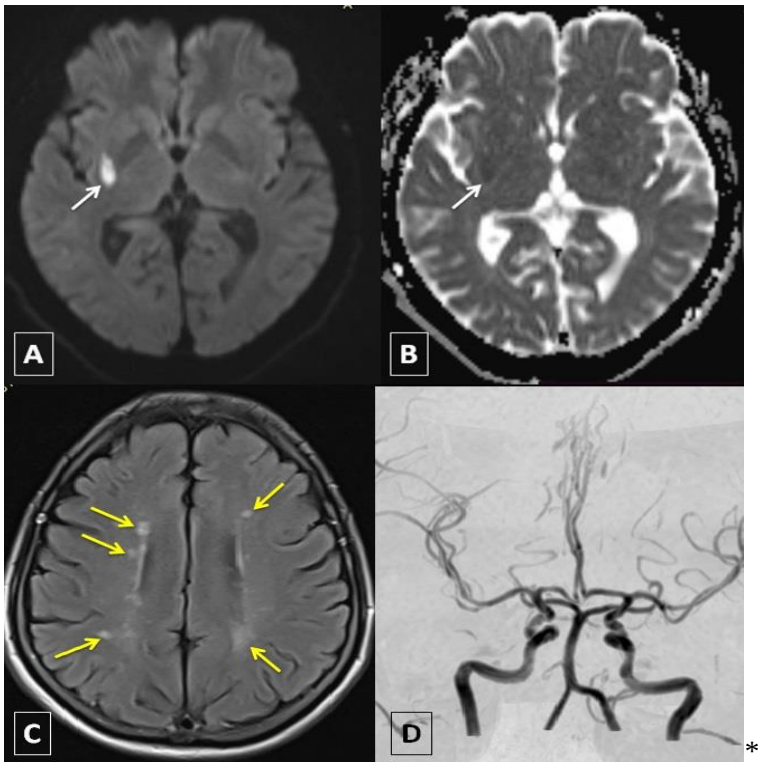
Vascular abnormalities in MRA	No. of cases	%
Vascular narrowing	15	19.2%*
Vascular occlusion	18**	23%*
Moya-moya vasculopathy	15**	19.2%

*There were four patients had arterial narrowing and concurrent occlusion at other anatomic locations.

**Most of patients (13/15) with moya-moya vasculopathy had nearby arterial occlusion whereas the other 2 patients had nearby arterial narrowing.

Table (5): Anatomic location of vascular abnormalities in MRA

		No. of steno-occlusive lesions (n = 46)	No. of abnormal MRA per case (n = 29)
Vascular narrowing	ICA	13	15*
	ACA	4	
	Middle cerebral artery (MCA)	5	
	Vertebral artery	1	
Vascular occlusion	Distal ICA	15	18*
	Proximal ICA	4	
	Vertebral artery	2	
	Basilar artery	2	



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There were four patients had arterial narrowing and concurrent occlusion at other anatomic locations.

Figure (1): Eleven year-old neurologically free male patient with SCD underwent MRI and MRA of the brain as a part of pre-procedural workup prior to bone marrow transplant. (A, B) DWI and corresponding ADC map that showed lacunar area of diffusion restriction at right external capsule (white arrow) consistent with silent acute lacunar infarction. (C) Axial FLAIR demonstrate multiple FLAIR hyperintense lacunar areas (yellow arrows) involving the periventricular and deep white matter bilaterally. (D) Frontal MIP reformatted MRA shows normal caliber patent ICAs as are all cerebral arteries.

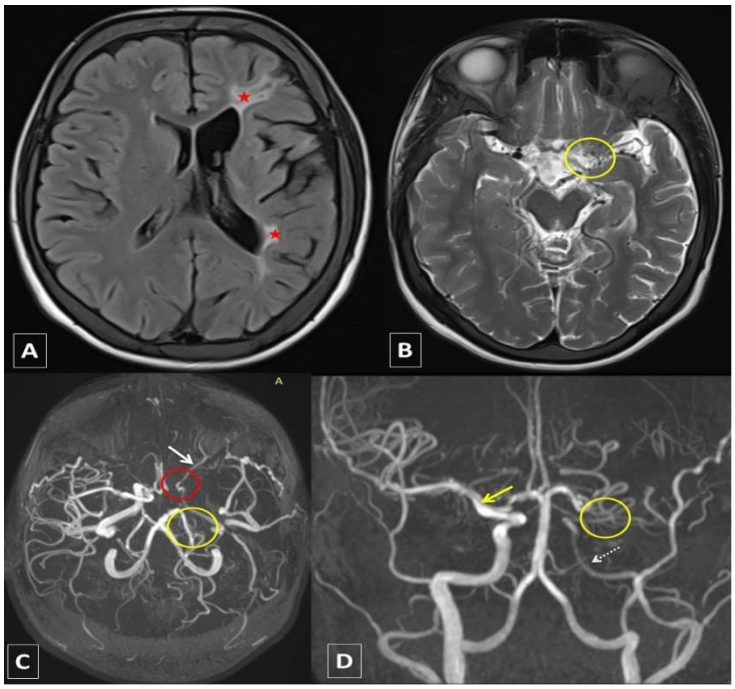

Figure (2): Nine year-old neurologically free male patient on a regular neuroimaging follow up by MRI and MRA. (A) Axial FLAIR image through the corona radiata showed left frontal and parietal peri-ventricular high signal areas (stars) consistent with old SCI. (B) Axial T2WI image through the suprasellar cistern demonstrate left cisternal signal flow voids (yellow circle) representing moya-moya vessels. (C, D) Cranial and frontal MIP MRA images showed right MCA narrowing (yellow arrow), proximal left internal carotid artery (ICA) narrowing (dashed arrows) which become occluded distally (red circle) after giving the left ophthalmic artery (white arrow), note unilateral moya-moya vessels (yellow circle).

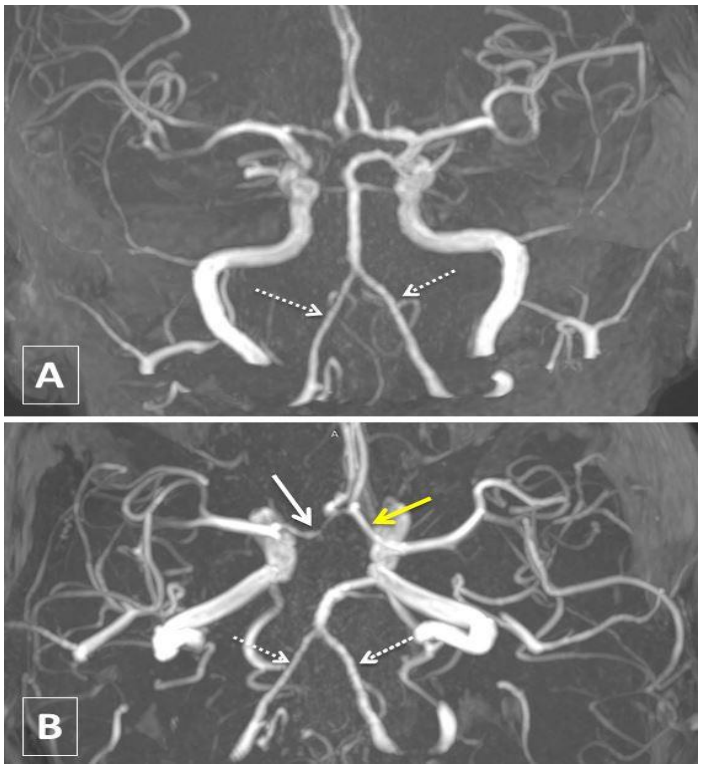

Figure (3): Ten year-old neurologically free female patient on a regular neuroimaging follow up by MRI and MRA. (A, B) Frontal and cranial oblique MIP MRA images showed mild luminal narrowing and beading of both vertebral arteries (dashed arrows), there was further narrowing of right ACA (white arrow) with normal left ACA (yellow arrow) consistent with true right ACA narrowing rather than normal variant hypoplastic ACA. All MR sequences of the brain parenchyma are normal (not shown).

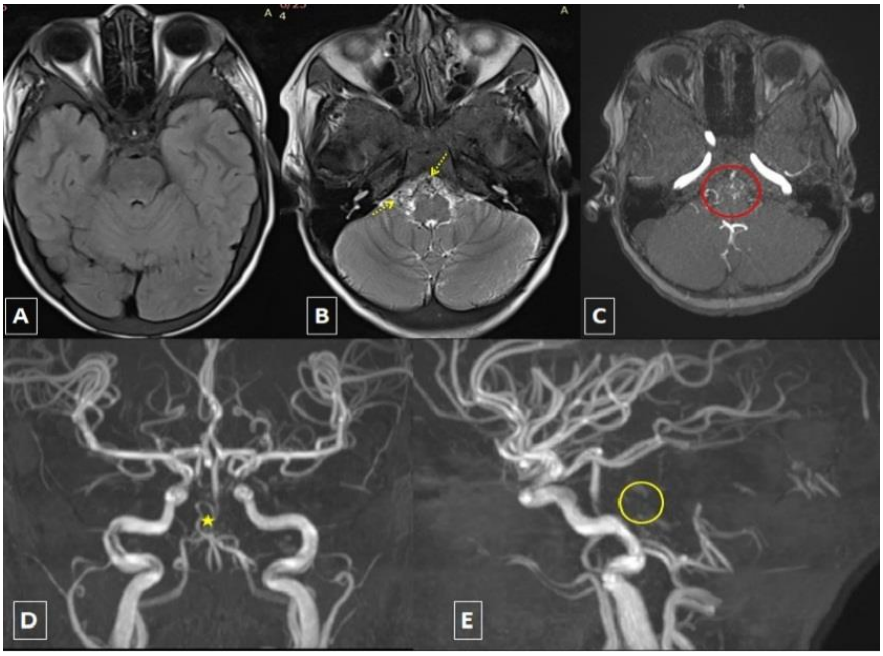

Figure (4): Fourteen year-old neurologically free male with SCD planned for bone marrow transplant underwent brain MRI and MRA as a pre-procedural workup. (A) Axial FLAIR image through the upper portion of the posterior fossa was unremarkable and showed normal signals, all other sequences were unremarkable (not shown). (B) Axial T2WI demonstrate rare occasion of posterior circulation steno-occlusive changes in SCD in the form of multiple low signal flow voids in the pre-medullary cistern (yellow arrows) representing moya-moya vessels. (C) Axial MIP MRA image obtained from TOF MRA source images demonstrated absence of flow from the basilar artery which was replaced by high signals moya-moya collaterals (red circle). (D, E) frontal and lateral MIP reformatted MRA images showed moya-moya collateral vasculopathy (yellow stars) and lack of flow from the basilar artery (yellow circle).

The correlation analysis demonstrated significant high positive correlation between the low hemoglobin and presence of either acute or old SCI. The moya-moya vasculopathy showed significant very high positive correlation with arterial occlusion and significant reasonable positive correlation with old SCI. Regarding SCD phenotypes, HB SS phenotype was significantly correlated with moya-moya vasculopathy, arterial occlusion and old SCI (Table 6).

Table (6): Correlation analysis between silent brain changes and other features

		r	**p value**
Low Hb	Infarction (acute or old)	0.74	<0.0001
homozygous phenotype HB SS versus	Arterial occlusion	0.82	<0.0001
	Moya-moya vasculopathy	0.66	<0.0001
	Old infarction	0.62	<0.0001
Moya-moya vasculopathy versus	Arterial occlusion	0.87	<0.0001
	Old infarction	0.57	<0.0001
	Arterial narrowing	0.35	0.0017

DISCUSSION

Silent brain changes in SCD are frequent clinically-important concealed abnormalities that carry an elevated risk for subsequent overt stroke in the future and an association with lower IQ scores. They are not uncommon as some think, but; their prevalence could be estimated only when using MRI and MRA as screening imaging tools, the current study employed such screening method in neurologically free SCD children in order to demonstrate silent brain parenchymal and cerebrovascular changes.

To the best of author's knowledge, there is no consensus exists regarding the use of MRI for SCI screening, as many institutional protocols found difficulties to support routine MRI studies in neurologically free SCD children. On the other hand, transcranial Doppler (TCD) continues as a cost-effective diagnostic method used in stroke risk screening in SCD children. However, the use of TCD carries some limitations as operator dependency and possible inadequate acoustic window that could be frequently faced in older children, the more important issue in this context is that silent brain changes can develop even in presence of normal TCD study, and this could in turn evoke a paradigm shift regarding the guidelines of neuroimaging screening methods in SCD. In our study, we did not address the association of SCI with TCD, as TCD was not performed regularly in our institution due to logistic weakness [10-13].

The current study figured out a variety of silent cerebrovascular and brain changes that were found unexpectedly in 36 (46.15%) of cases, among them the lacunar ischemic white matter foci and the vascular occlusion were the most common changes. Few reports studied prevalence of SCI in SCD children using brain MRI, **Kwiatkowski *et al.*** [14] who studied silent infarcts in young SCD children using MRI and MRA of the brain found that among 65 neurologically asymptomatic children, there were 18 (27.7%) had silent infarcts, this low SCI rate could be attributed to young age of their patient population compared to our population (mean age was 3.7 ± 1.1 years versus 11.58 ± 2.62 years), and also to the fact that the frequency of SCI has a longitudinal increase with age. The interesting point here is lack of any overt neurologic symptoms despite of high percentage of abnormalities found in the study [15]. However; with close analysis of lesion distribution there would be no conflict, as most of parenchymal brain changes found in the current study were observed within the fronto-parietal deep white matter location away from the neurologically important regions as cerebral cortex and deep grey matter nuclei. Regarding the acute events of SCI in our study, our findings are in agreement with **Quinn *et al.*** [16] who studied the prevalence of acute silent cerebral ischemia in children with sickle cell anemia and found that acute SCI had low prevalence and was detected only in 1.3% of cases.

Regarding the prevalence and distribution of cerebrovascular steno-occlusive in the current study, along with the association between abnormal MRA and SCI in our study, our results have almost in perfect agreement with **Idro *et al.*** [17] who studied cerebrovascular injury in Ugandan children with sickle cell anemia but otherwise clinically free using brain MRI-MRA, they found that silent infarcts and/or vascular stenosis were detected in 55/81 (67.9%), with that stenoses primarily occurred in the anterior circulation. They found high association between abnormal MRA and silent infarcts ($p<0.0001$).

The current study comes out with the result of frequently observed moya-moya vasculopathy, which was often unilateral and frequently associated with vascular occlusion, this finding could be in agreement with **Kauv *et al.*** [18] who studied the characteristics of moya-moya syndrome in SCD by MRA. They found that unilateral moya-moya syndrome and moderate steno-occlusion are features of SCD moya-moya syndrome. The explanation of such frequent unilateral moya-moya vasculopathy in our study could be related to patient's therapy to lower HbS level which could delay the development of the contralateral side.

On correlating silent cerebral and cerebrovascular changes with other clinical and imaging features in the current study, SCI inferred a significant positive correlation with homozygous phenotype (HB SS), low hemoglobin and moya-moya vasculopathy. Theses associations are in agreement with many reports that studied the risk factors for cerebrovascular disease in SCD children. For instance, **Nafile *et al.*** [19] studied silent cerebral infarct in fifty-four sickle cell anemia patients of southern Turkey who had no history of cerebral stroke and had normal neurological examinations. They found that presence of homozygote genotype, and high HbS are risk factors for SCI. Furthermore, **Bernaudin *et al.*** [20] who studied the risk factors for silent cerebral infarcts in sickle cell anemia found that hemoglobin level lower than 7 g/dL is a significant predictive risk factor for SCI. Moreover, **Elmahdi *et al.*** [21] studied moya-moya syndrome in pediatric SCD in Sudan, and found a very high association of moya-moya vasculopathy with cerebral stroke.

The associations of moya-moya vasculopathy in the current study with steno-occlusive and with homozygous phenotype (HB SS), would be expected. The moya-moya vessels are fragile neo-vessels developed as a result of progressive occlusion of the intracranial carotid artery and/or its main branches to overcome diminished cellular perfusion [18].

We found in our study that children who use hydroxyurea showed significant reduction in the incidence of silent brain changes. This agrees with a systemic review by **Hasson *et al.*** [22] who included 10 single arm observational studies with 361 participants, and one RCT study with 60 participants receiving hydroxyurea and they found no deaths attributed to hydroxyurea. The results revealed that 1% (of patients receiving hydroxyurea had stroke. 18% of the hydroxyurea patients had silent stroke and they concluded that hydroxyurea is safe and may prevent silent stroke and stroke in sickle cell disease.

CONCLUSIONS

Silent cerebral and cerebrovascular changes in SCD children are frequent abnormalities requiring utilization of MRI and MRA to find out their exact prevalence and their risk factors. We support the expansion in the use of MRI/MRA as a screening and follow up neuroimaging to be performed at least once in middle and old children with SCD, and routinely in high-risk group.

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