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Neuropsychological Changes in Children with Sickle Cell Disease and Their Correlation to the Imaging Studies

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Authors' contributions

This work was carried out in collaboration among all authors. Author MY designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors HF and MES managed the analyses of the study. Authors HN and MO managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Early detection of neuropsychological changes in children with sickle cell disease (SCD) is essential to improve their quality of life.
Aim of the Work: To assess neurological and psychological disorders in children with sickle cell disease (SCD) using multimodal approach through clinical, laboratory, neuroimaging and neurophysiological studies in a trial to detect etiological risk factors**.**
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 (27 male and 23 female; age range 2-18 years) with SCD and 25 healthy children matched age and sex. All subjects were subjected to full

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history taking, neurologic examination using pediatric neurological sheet, laboratory investigations, neuroimaging including: CT and /or MRI, MRA and/or CT angiography, also MR, EEG and Stanford-Binet Intelligence scales-Fifth Edition.

Results: Most of patients presented with headache 66%, cognitive decline 48%, seizures 28%, and visual affection 24%. Less common presentations were, ischemic and hemorrhagic stroke 6% and 4% respectively. SCD children showed many abnormalities on neurological examination and on different modalities of MR imaging on the brain with positive correlation (X2=7.641, p-value <0.001*, r=0.248) with many risk factors. Prophylactic blood transfusion in SCD patients with abnormal TCD had a role in reducing the incidence of stroke.

Conclusion: Children with SCD were presented with variable neuropsychological disturbance that correlated with the brain imaging.

Keywords: SCD; neuropsychological; imaging.

1. 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) study is useful in detecting subclinical cerebral infarction [13]. It was found in a cohort of individuals with SCD, that those with seizures had increased perfusion and electroencephalographic abnormalities, suggesting that vasculopathy and focal hypoperfusion might be factors in the development of SCD-associated seizures [11].

According to this findings, this study was carried for early detection of neurological disorders in SCD children with their impact on life for early prevention and proper treatment of these disorders.

2. 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. Besides, MRV when needed in some patients. Electrophysiological studies included: EEG.

2.1 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 [14,15].

3. RESULTS

There were many neurological complications among patients that included headache, cognitive decline, seizures, diminution of vision and stroke. Headache was the most frequent complication (66%) followed by cognitive decline (48%) among patients. This was followed by seizures in 28% of patients with 18% presented by focal seizures and 10% presented by generalized seizures. Diminution of vision presented in 24% of patients. Meantime stroke represented the least frequent complication among patients with three of them presented by ischemic arterial stroke, two presented by ischemic venous stroke and two presented by hemorrhagic stroke (Table 1).

Neurological examination of patients revealed many abnormalities. Transient ischemic attacks represented the most frequent abnormality (18%) with 10% presented by side weakness and 4% presented by side numbness together with speech disorder in 4% of patients. This was followed by weakness and cranial nerve affection (10%). Right side numbness represented the least frequent abnormality (2%) (Table 2).

MRI brain in patients was normal in most patients (68%). It showed vascular insult, either ischemic arterial stroke in 22% of patients, or ischemic venous stroke in only 4% of patients, and hemorrhagic stroke in only 4% of patients. It also showed marked atrophic changes without vascular insult in only 2% of patients (Table 3) (Figs. 1,2,3 and 4).

Table 1. Neurological complications among patients

Neurological complications		Patients' group (n=50)	
		Patients(no.=50)	
		Number	Percentage
Headache	**Positive**	33	66.00
Cognitive decline[1]	**Positive**	24	48.00
Seizures	**Focal**	9	18.00
	Generalized	5	10.00
Diminution of vision[2]	**Positive**	12	24.00
Stroke	**Ischemic arterial**	3	6.00
	Ischemic venous(sinus)	2	4.00
	Hemorrhagic	2	4.00

[1]Especially knowledge and working memory; [2] proliferative retinopathy

Table 2. Neurological examination abnormalities of patients

Neurological examination abnormalities	Patients' group (n=50)	
	Number	Percentage
Transient ischemic attacks	9	18
Side weakness	5	10
Side numbness	2	4
Speech disorder	2	4
Motor weakness (hemiplegia)	5	10
Speech or language disturbance	4	8
Cranial nerve affection (UMN facial palsy)	5	10
Sensory affection (right side numbness)	1	2

Table 3. Magnetic resonance imaging findings among patients

Variable	Patients' group (n=50)	
MRI brain findings	**Number**	**%**
Normal	**34**	**68**
Ischemic arterial stroke	11	22
Old lacunar infarctions	8	16.00
Recent lacunar infarctions	2	4.00
MCA infarction	1	2.00
Ischemic venous stroke(Hemorrhagic infarction)	2	4.00
Hemorrhagic stroke	2	4.00
Left frontal hematoma	1	2.00
SAH(perimesencephalic)	1	2.00
Marked atrophic changes without vascular insult	1	2.00

MRI: Magnetic resonance imaging, MCA: Middle cerebral artery; SAH: Subarachnoid hemorrhage

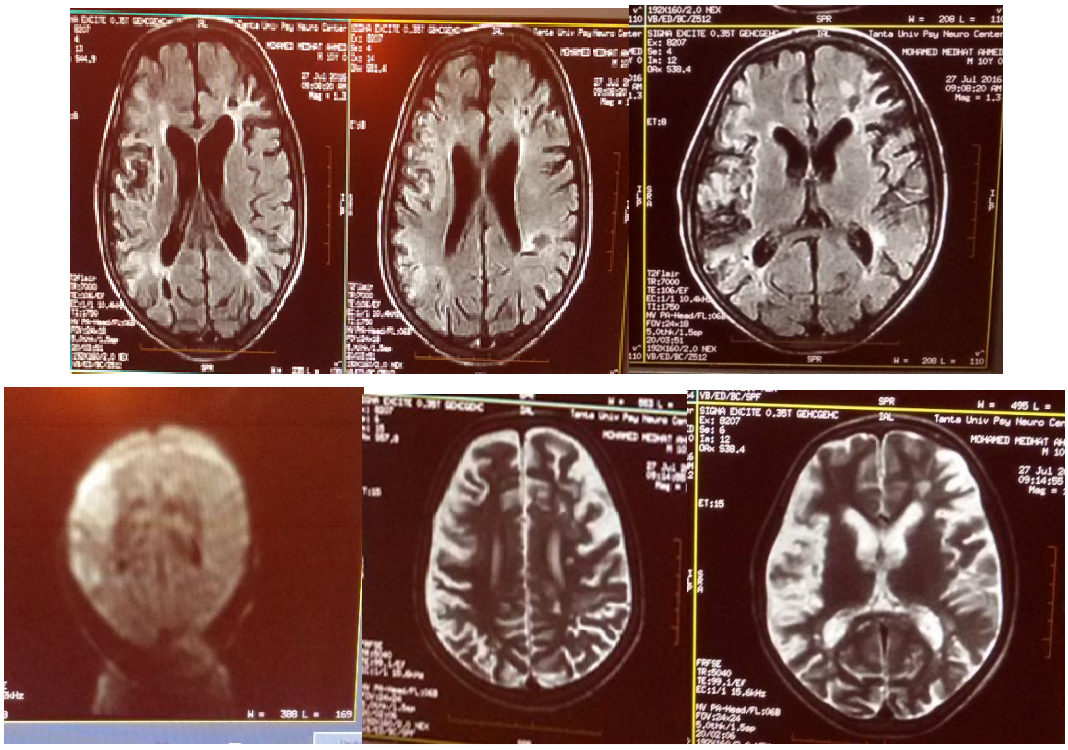

Fig. 1. MRI brain: upper panel showing axial flair demonstrating old right middle cerebral artery infarction besides multiple lacunar infarctions on the left side. Lower panel showing DWI and T2WI demonstrating right middle cerebral artery infarction besides multiple lacunar infarctions on the left side and marked atrophic changes in this case

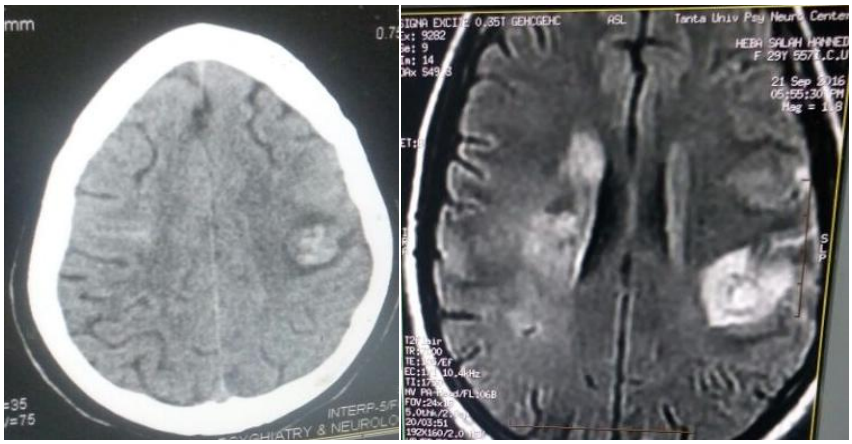

Fig. 2. Non-contrast CT to the right side showing left hemorrhagic infarction. Flair MRI on the left side showing bilateral and multiple infarctions with evident hemorrhagic infarction on the left side in this patient

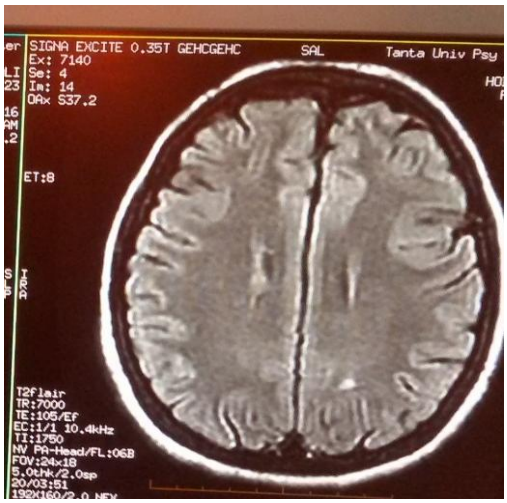

Fig. 3. MRI brain with axial flair showing left recent infarction as silent infarction in this case.

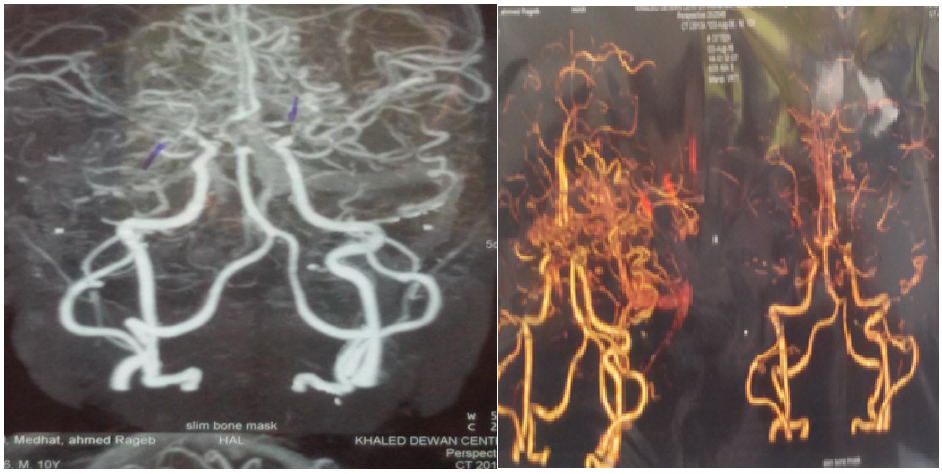

Fig. 4. CT angiography showing Moyamoya syndrome in this case

Table 4. Relation between MRI brain findings and EEG findings among patients

MRI brain findings	EEG findings										Chi-square	
	Normal		Focal activity		Multifocal activity		Focal with secondary generalization		Generalized activity			
	N	%	N	%	N	%	N	%	N	%	χ^2	*P-Value*
Normal	31	79.49	3	50.00	0	0.00	0	0.00	0	0.00	91.888	<0.001*
Ischemic arterial stroke	6	15.38	2	33.34	2	66.66	1	100.00	0	0.00		
Old lacunar infarctions	5	12.82	1	16.67	1	33.33	1	100.00	0	0.00		
Recent lacunar infarction	1	2.56	1	16.67	0	0.00	0	0.00	0	0.00		
MCA infarction	0	0.00	0	0.00	1	33.33	0	0.00	0	0.00		
Ischemic venous stroke (Hemorrhagic infarction)	1	2.56	0	0.00	1	33.33	0	0.00	0	0.00		
Hemorrhagic stroke	1	2.56	1	16.67	0	0.00	0	0.00	0	0.00		
Left frontal hematoma	1	2.56	0	0.00	0	0.00	0	0.00	0	0.00		
SAH(perimesencephalic)	0	0	1	16.67	0	0.00	0	0.00	0	0.00		
Marked atrophic changes without vascular insult	0	0.00	0	0.00	0	0.00	0	0.00	1	100.0		

Table 5. Relation between MRI brain findings and stanford binet intelligent quotient grades among patients

MRI Brain findings	Stanford Binet Intelligent quotient grades										Chi-Square	
	Mild impaired		Borderline		Low average		Average		High average			
	N	%	N	%	N	%	N	%	N	%	X^2	*P-Value*
Normal	1	7.14	7	100.00	3	100.00	22	88.00	1	100.00	41.993	0.043*
Ischemic arterial stroke	8	57.13	0	0.00	0	0.00	3	12.00	0	0.00		
Old lacunar infarctions	5	35.71	0	0.00	0	0.00	3	12.00	0	0.00		
Recent lacunar infarction	2	14.28	0	0.00	0	0.00	0	0.00	0	0.00		
MCA infarction	1	7.14	0	0.00	0	0.00	0	0.00	0	0.00		
Ischemic venous stroke (Hemorrhagic infarction)	2	14.28	0	0.00	0	0.00	0	0.00	0	0.00		
Hemorrhagic stroke	2	14.28	0	0.00	0	0.00	0	0.00	0	0.00		
Left frontal hematoma	1	7.14	0	0.00	0	0.00	0	0.00	0	0.00		
SAH (perimesencephalic)	1	7.14	0	0.00	0	0.00	0	0.00	0	0.00		
Marked atrophic Changes without vascular insult	1	7.14	0	0.00	0	0.00	0	0.00	0	0.00		

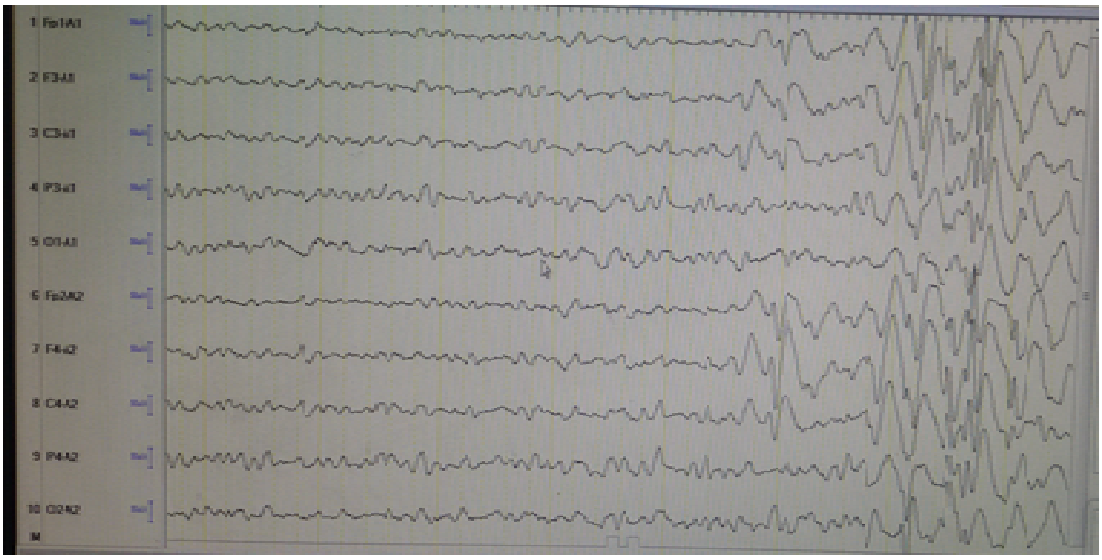

Fig. 5. Abnormal EEG showing generalized epileptogenic activity in the form of spike, sharp and slow wave complex in this case

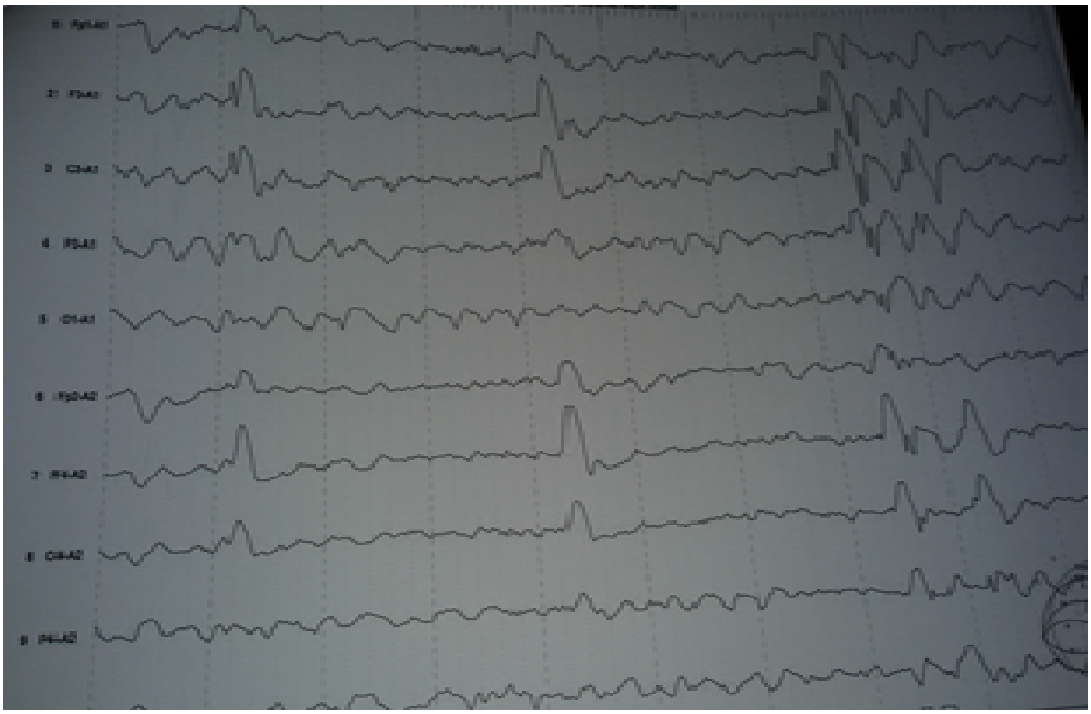

Fig. 6. Abnormal EEG showing multifocal epileptogenic activity in the form of spike, sharp and slow wave complex in this case

There was statistically highly significant difference regarding relation between MRI brain findings and increased risk for abnormal EEG findings among patients. Patients with ischemic arterial stroke had the most frequent risk for focal activity (33.34%), multifocal activity (66.66%) and focal activity with secondary generalization (100%). Also, patients with marked atrophic changes had the most frequent risk for generalized activity (100%) (X^2=91.888, p-value <0.001*) (Table 4) (Figs. 5 and 6).

There was statistically significant difference regarding relation between MRI brain findings and Stanford Binet Intelligent quotient grades among patients. Most patients within the grade mild, impaired had ischemic arterial stroke especially old lacunar infarctions in MRI (57.13%, 35.71% respectively), followed by equal percentage for those with ischemic venous stroke and hemorrhagic stroke (14.28%). In contrast to this patients within the grade borderline, low average and high average had normal MRI (100%) (X2=41.993, p-value 0.043*) (Table 5).

4. DISCUSSION

This study showed that the most common neurological complication was headache that represented 66% of the presenting features in patients. This was in agreement with Dowling MM et al., [16] who reported that headache was one of the most common neurologic symptoms in SCD, both acutely and chronically in 36% in children with sickle cell anemia.

Cognitive decline was the next most common neurological complication that represented 48% of the presenting complications in patients. This was in agreement with Berkelhammer LD et al., [17] who reported a higher frequency of impairments on executive functions in children with SCD when compared to the normal population; 25% of the SCD patients had a significant cognitive deficit.

Seizures represented 28% of the presenting complications in patients Focal seizures occurred in about 18% of patients and generalized seizures occurred in about 10% of patients. This was in agreement with Adams RJ., [18] who found that seizures occurred in 12 to 14% of patients with sickle cell disease (SCD).

Diminution of vision represented about 24% of the presenting complications in SCD group. This was in agreement with Babalola O.E and Wambebe C.O et al., [19], Lal A et al., [20] who found that proliferative retinopathy (PSR) occurred most frequently in HbSC disease with an incidence of approximately 33%. PSR could also be seen in patients with HbSS disease, though less commonly.

The discrepancy between these incidences and our results, may be due to limited age group, method of selection of patients and the comprehensive workup for diagnosis and investigations even in asymptomatic patients.

Other less common complications included ischemic arterial stroke that represented 6% of the presenting features in patients. This was in agreement with Gueguen A et al., [21] who reported that stroke occurred in 8 % to 11% of school aged children and adolescents with SCD. Ischemic venous stroke represented 4% of the presenting complications in patients especially after urgent imaging. This was in agreement with Sébire G et al., [22] who found that venous sinus thrombosis was probably underdiagnosed because many patients did not undergo acute vascular imaging; if emergency MRA was available and the results were found to be normal, magnetic resonance venography or CT venography should be considered.

Hemorrhagic stroke represented 4% of the presenting complications in patients. This was in agreement with Kossorotoff M et al., [23] who reported that prevalence of cerebral hemorrhage in children with sickle cell disease and hemorrhagic stroke in children and adults with SCA was 3% and 10%, respectively.

Study of the neurological examination of the present work revealed that there were many abnormalities on neurological examination. They included transient ischemic attacks (TIA) that represented 18% of SCD patients. Transient ischemic attacks were the most common abnormal findings with 10% presented by side weakness and 4% presented by side numbness together with speech disorder in 4% of patients.

This was in agreement with Deus L et al ., [24] who reported that patients with SCD were at high risk of transient ischemic attacks or mini-stroke which lasted a few minutes with most symptoms and signs disappeared within an hour, although many of these individuals were found to have had recent cerebral infarction or atrophy on imaging.

Other less common abnormal findings included: hemiplegia (represented 10% of patients), speech or language disorder (represented 8% of patients), cranial nerve affection (UMN facial palsy) (represented 10% of patients), right side numbness (represented 2% of patients).

This was in agreement with Deus L et al., [24] who reported that clinical stroke was 250 times more common in children with SCD than in the general pediatric population. This was also in agreement with Amlie C et al., [25] who reported that common presenting symptoms and signs included hemiparesis, monoparesis, aphasia or (dysphasia), seizures, severe headache, cranial nerve palsy, stupor, and coma.

In the current study, many abnormalities were detected on different modalities of magnetic resonance imaging on the brain of patients that included old lacunar infarctions (16% of patients), recent lacunar infarction (4% of patients), MCA infarction (2% of patients), hemorrhagic infarction(4% of patients), left frontal hematoma(2% of patients), SAH (perimesencephalic) (2% of patients) and marked atrophic changes(2% of patients).

This was in agreement with Edward C et al., [26] and Kossorotoff M et al., 2015 who reported that MRI of the brain was the preferred strategy over a CT scan to detect both hemorrhage and cerebral infarct. MRI, particularly diffusion weighted, was a sensitive method for the detection of cerebral infarction and ischemia and had become the method of choice for the confirmation of stroke. It could detect cortical atrophy and reduced grey matter volume in the cortex and basal ganglia.

In this study, there was statistically significant difference regarding grades of Stanford Binet Intelligent Quotient among patients and control groups, with the largest number of patients present in the grade average (50%) followed by grade mild impaired (28%) then grade borderline (14%). This was in agreement with Angelo Onofria et al., [27] who reported that SCD might impair intellectual activity; 25% of the SCD patients had a significant cognitive deficit. An incidence of mild mental deficiency was elevated at least 11-fold in a small sample of patients with SCD, and no clinical history of stroke.

5. CONCLUSION

Patients with SCD complicated with many neurological abnormalities which were represented on different imaging modalities. There was a positive relation between MRI brain abnormalities in SCD patients and increased risk for seizures, abnormal EEG activities and cognitive decline.

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 willbe 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.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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