European Journal of Clinical Medicine
Vol 5 | Issue 6 | December 2024
ISSN 2736-5476

RESEARCH ARTICLE

Brain MRI Abnormalities in Saudi Children with SCA, Retrospective Cohort, Single-Center Experience

Mai Al Qasimi[1,*], Mohamad Rayis[1], Sofia Muzzafar[2], Rawan Alnofee[3], Rana Alaskar[3], Ahmed Eidaan[3], and Bader Abdulkareem[3]

ABSTRACT

Background: **Sickle cell anemia (SCA) is a severe healthcare issue in Saudi Arabia. A considerable proportion of SCD patients may experience neurological complications over their lifetime, including infarction, silent ischemia, intracranial hemorrhage, then brain atrophy, and cognitive impairment.**

Aim: **To identify the clinical and brain-imaging findings in SCD subjects with suspected neurological complications in Saudi Arabia and the impact of Hydroxyurea (HU) and chronic transfusion program.**

Methods: **This cohort was undertaken at King Fahad Medical City, Riyadh, between October 2022 and September 2023. A total of 100 consecutive patients aged 2–18 years with homozygous sickle cell disease were included. All subjects underwent an MRI.**
Result: **Abnormal brain MRI was found among 30% of the subjects, and the most common abnormal findings were SCI (16%) and CVA + moyamoya (9%). Of the patients, 46% received HU, and 25% received chronic transfusion programs. The HU group has less CVA + Moya-Moya and less SCI ($p = 0.002$) and tended to have normal TCD ($p = 0.001$). TCD was commonly abnormal among 66.7% of patients with CVA + moyamoya and 56.3% of SCI patients ($p < 0.001$).**

Conclusion**: Neurologic sequences of SCD are a major health issue in Saudi Arabia and impact children's quality of life. The most common complications were SCI and CVA combined with moyamoya.**

Keywords: Brain MRI, Infarction, SCA, Silent ischemia.

Submitted: October 21, 2024

Published: December 12, 2024

10.24018/clinicmed.2024.5.6.357

[1] *Pediatric Hematology and Oncology, Comprehensive Cancer Center, King Fahad Medical City, Riyadh, Saudi Arabia.*
[2] *Neuroradiology, King Fahad Medical City, Riyadh, Saudi Arabia.*
[3] *Pediatrics, King Fahad Medical City, Riyadh, Saudi Arabia.*

* ***Corresponding Author:***
e-mail: mai22alqasimi@gmail.com

1. Introduction

Sickle cell disease (SCD) is a disorder of hemoglobin with an autosomal recessive nature [1] due to a single gene mutation on the short arm of chromosome 11 results in replacement of glutamic acid by valine in the beta-globin gene, leading to the generation of hemoglobin S (HbS) [2]. Which has a reduced solubility compared to adult and fetal hemoglobin. This hemoglobin, in turn, results in the abnormal shape of red blood cells (RBCs) [3]. Subjects with sickle hemoglobin (HbS) in homozygous or heterozygous conditions are affected by SCD [3]. SCD occurs due to the inheritance of two sickle cell (S) mutant genes or one (S) mutated gene and another hemoglobin or beta-globin variant. Those having homozygous hemoglobin (S) genes are indicated as Sickle cell anemia (SCA) patients [4]. SCD is a common hematological illness in Saudi Arabia, especially in the Southwestern and Eastern provinces [5]. In Saudi Arabia, there are two haplotypes have been discovered: the Arab-Indian (AI) and Benin haplotypes [6].

Sickle RBCs attach to the vascular endothelium; hence, the blood flow is impeded and increases the capillary transit time. Such adhesion of cells can stimulate the propagation of vaso-occlusion [7]. The sickled nature of RBCs makes them less deformable, and as a result, they obstruct microcirculation and lead to tissue infarction [8]. Cerebrovascular accident (CVA) is a severe consequence of SCD [9], and it is one of the neurological complication of SCD which also can manifest as moyamoya syndrome

(MMS), silent cerebral ischemia (SCI), or ischemic/hemorrhagic stroke [10].

MMS is a condition affecting cerebral vasculature, which is caused by progressive stenosis of the terminal portion of internal carotid artery (ICA), middle cerebral artery (MCA), or anterior cerebral artery (ACA). Those with MMS have a risk of progression to ischemic strokes, resulting in poor outcomes [11]. Pediatrics are more susceptible even before two years of age [12].

SCI is a brain lesion that may occur by six months of age and can be detected incidentally [13], [14]. Almost 11% of SCD cases will experience an overt stroke before the age of 20 years unless they receive early management, typically occurs at the ("watershed") border zones of vascular territories, which are supplied by smaller end-arterial branches and therefore vulnerable to ischemia. The latter may be caused by a proximal stenosis, as is typically the case in SCD. A distinction can be made between cortical watershed zones, where vascular territories border on each other, and deep watershed zones, for example, between lenticulostriate perforators and deep penetrating cortical branches of the MCA or between deep white matter branches of the ACA and MCA [15].

Transcranial Doppler (TCD) ultrasound is a non-invasive approach to record the velocity of blood flow in the basal cerebral arteries. It is a repeatable, portable, and inexpensive technique; therefore, it is more convenient for monitoring cerebral blood flow [16], [17]. For SCD cases aged 2–16 years, TCD is recommended to be performed regularly to help with early prediction and prevention of stroke [18]. However, TCD is unavailable across the globe, and it can be unavailable in some developing countries [15]. Magnetic resonance angiography/imaging (MRA/MRI) is currently recommended to detect silent stroke among pediatrics with SCD [19].

As no local study was addressed in Saudi sickle cell anemia (SCA) patients regarding the prevalence of neurological complications and their correlation with radiological findings and phenotype, especially with the improvement of imaging techniques and quality of picking up pathologies, the objective of this research was to identify the clinical and brain-MRI findings addressed in Saudis SCA patients along with the prevalence of these findings and their correlation with TCD findings and the severity of the disease phenotype, and the impact of Hydroxyurea and Chronic Transfusion Program management plan.

2. Materials and Methods

This retrospective cohort was established at King Fahad Medical City, Riyadh, between October 2022 and September 2023. One hundred cases of homozygous sickle cell illness, aged 2–18 years, were enrolled in the Pediatric Hematology clinic. Ethics committee approval was obtained.

Data were collected over four months and extracted from the hospital computer system (EPIC), as well as an old system (CORTTEX), which permitted the extraction of the patient's data. Clinical information was retrieved from the medical notes and medical records, including demographic data, such as age, gender, and management with chronic transfusion or hydroxyurea. Laboratory data, which are the average levels of hemoglobin and LDH, was also collected. Then, all Data were recorded on a comprehensive Excel sheet.

All children who attended the Pediatric Hematology clinic were recommended to undergo a brain MRI study during their follow-up. Then, Radiological Data included 1st TCD and Brain MRI screening, which were set up at King Fahad Medical City, Riyadh, and patients who didn't undergo TCD and MRI studies were excluded from the research.

Brain MRIs were examined by a single radiologist consultant. The interpretations were recorded in the Excel sheet as Normal, CVA, Moya-Moya, and SCI.

Data analysis was processed using SPSS version 26. Numerical data are expressed as mean ± SD. Qualitative variables were represented by frequency and (%). An Independent t-test was adopted to compare values among the two categories. A P-value of 0.05 was used for significance. The chi-squared test was used for categorical values. Fisher exact test was used for evaluating the association and correlation.

A comparison between the clinical characteristics and the patient's gender was conducted using the Fischer Exact test. Also, the relationship between hydroxyurea, MRI findings, and TCD in terms of the clinical characteristics of the patients was performed using the Fischer Exact test.

TABLE I: Demographic and Clinical Characteristics of the Patients$^{(N = 100)}$

Study data	N (%)
Age in years (mean ± SD)	9.41 ± 3.59
Gender	
Male	49 (49.0%)
Female	51 (51.0%)
MRI	
CVA + Moyamoya	09 (09.0%)
CVA	03 (03.0%)
Moyamoya	02 (02.0%)
SCI	16 (16.0%)
Normal	70 (70.0%)
TCD	
Normal	75 (75.0%)
Abnormal	18 (18.0%)
Conditional	07 (07.0%)
Hydroxyurea	
Yes	46 (46.0%)
No	54 (54.0%)
Chronic transfusion program	
Yes	25 (25.0%)
No	75 (75.0%)
Average HGB	
<7%	07 (07.0%)
7%–9%	71 (71.0%)
>9%	22 (22.0%)
Average LDH	
Not done	02 (02.0%)
200 to 400	16 (16.0%)
400 to 600	51 (51.0%)
600 to 800	31 (31.0%)

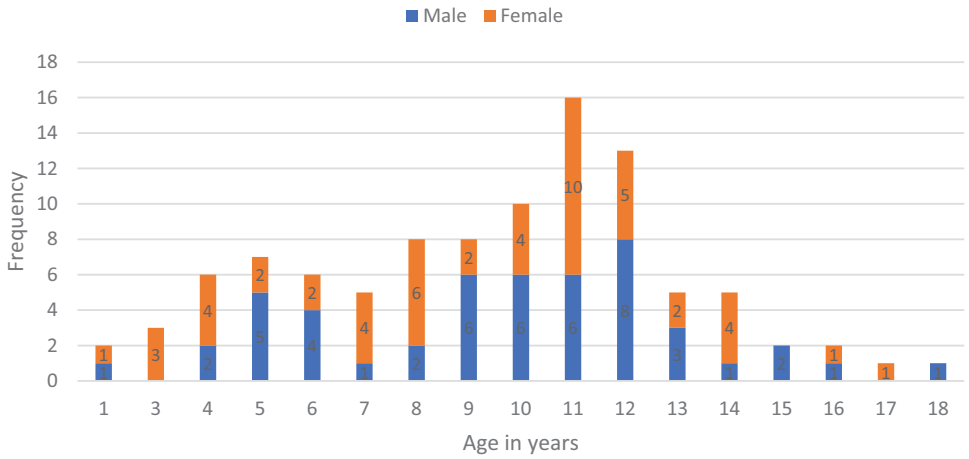

Fig. 1. It displays the distribution of age by gender.

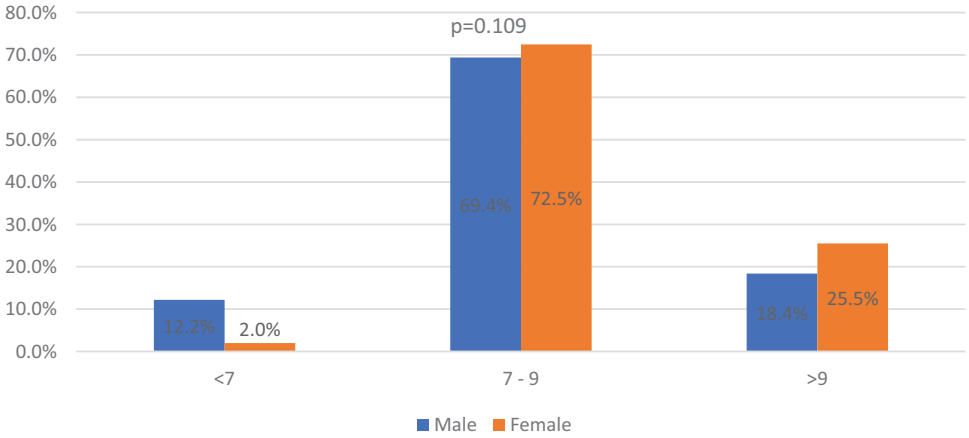

Fig. 2. It illustrates the distribution of hemoglobin (HGB) levels by gender.

3. Results

This study reviewed 100 children with SCA. As illustrated in Table I, the patient's mean age was 9.41 (SD 3.59) years. More than half (51%) were females. The most common findings based on MRI was CVA + moyamoya (9%). TCD findings were mostly normal (75%). Patients who received hydroxyurea were 46%, while those who had chronic transfusion programs were 25%. Most of the patients had Hgb between 7% and 9%. The average LDH was between 400 and 600 (51%).

In Fig. 1, 10 female patients were aged 11 years old, while 6 were male patients of the same age.

In Fig. 2, although female patients had more hemoglobin between 7 and 9%, the overall results weren't significant (p=0.109).

In Table II, it was observed that male patients were more associated with having normal TCD ($p = 0.001$) and without having a chronic transfusion program ($p < 0.001$).

In Table III, the use of hydroxyurea was significantly more common among those who had normal MRI findings ($p = 0.002$), those who had normal TCD findings ($p = 0.002$), and those without having a chronic transfusion program ($p = 0.012$).

In Table IV, it was observed that there was no significant relationship between TCD among average Hgb ($p = 0.254$) and average LDH ($p = 0.532$).

In Table V, it was revealed that there was a significant relationship between MRI findings in terms of TCD findings ($p < 0.001$) and chronic transfusion program ($p < 0.001$). No considerable relationship was noted between MRI findings in terms of age, gender, average Hgb, and average LDH ($p > 0.05$).

4. Discussion

SCD occurs due to the inheritance of two sickle cell (S) mutant genes or one (S) mutated gene and another hemoglobin or beta-globin variant. Those having homozygous hemoglobin (S) genes are indicated as Sickle cell anemia (SCA) patients [4]. SCD is a complex illness that affects several body systems and results in high rates of morbidity and mortality. Neurological complications are common and severe among SCD subjects; SCD can lead to neurologic issues such as stroke, MMS, and SCI [20]. There was no local study addressed in Saudi SCA patients regarding the prevalence of neurological complications and their correlation with radiological findings and phenotype. The objective of the present research was to identify clinical and brain-MRI findings of SCD subjects with suspected neurological complications in Saudi Arabia. This is the first research conducted at the local institute that has provided us with some useful data and laid the groundwork for

TABLE II: Comparison of Clinical Characteristics Between Males and Females(N = 100)

Factor	Male N (%)(n = 49)	Female N (%)(n = 51)	P-value§
Age in years			
<10 years	21 (42.9%)	24 (47.1%)	0.693
≥10 years	28 (57.1%)	27 (52.9%)	
MRI			
CVA + Moyamoya	02 (04.1%)	07 (13.7%)	0.128
CVA	02 (04.1%)	01 (02.0%)	
Moyamoya	01 (02.0%)	01 (02.0%)	
Other	05 (10.2%)	11 (21.6%)	
Normal	39 (79.6%)	31 (60.8%)	
TCD			
Normal	43 (87.8%)	32 (62.7%)	**0.001****
Abnormal	02 (04.1%)	16 (31.4%)	
Controversial	04 (08.2%)	03 (05.9%)	
Hydroxyurea			
Yes	25 (51.0%)	21 (41.2%)	0.422
No	24 (49.0%)	30 (58.8%)	
Chronic transfusion program			
Yes	04 (08.2%)	21 (41.2%)	<**0.001****
No	45 (91.8%)	30 (58.8%)	
Average LDH†			
200 to 400	06 (12.2%)	01 (02.0%)	0.109
400 to 600	34 (69.4%)	37 (72.5%)	
600 to 800	09 (18.4%)	13 (25.5%)	

Note: †Not done was included in the analysis.
§P-value has been calculated using Fischer Exact test.
**Significant at $p < 0.05$ level.

TABLE III: Comparison of Clinical Characteristics Between Hydroxyurea and Non-Hydroxyurea(N = 100)

Factor	Hydroxyurea N (%)(n = 46)	Non-hydroxyurea N (%)(n = 54)	P-value§
Age in years			
<10 years	22 (47.8%)	23 (42.6%)	0.688
≥10 years	24 (52.2%)	31 (57.4%)	
MRI			
CVA + Moyamoya	01 (02.2%)	08 (14.8%)	**0.002****
CVA	01 (02.2%)	02 (03.7%)	
Moyamoya	02 (04.3%)	0	
Other	03 (06.5%)	13 (24.1%)	
Normal	39 (84.8%)	31 (57.4%)	
TCD			
Normal	40 (87.0%)	35 (64.8%)	**0.002****
Abnormal	02 (04.3%)	16 (29.6%)	
Conditional	04 (08.7%)	03 (05.6%)	
Chronic transfusion program			
Yes	06 (13.0%)	19 (35.2%)	**0.012****
No	40 (87.0%)	35 (64.8%)	
Average Hgb			
<7%	05 (10.9%)	02 (03.7%)	0.164
7%–9%	34 (73.9%)	37 (68.5%)	
>9%	07 (15.2%)	15 (27.8%)	
Average LDH†			
200 to 400	07 (15.9%)	09 (16.7%)	0.390
400 to 600	26 (59.1%)	25 (46.3%)	
600 to 800	11 (25.0%)	20 (37.0%)	

Note: †Not done was included in the analysis.
§P-value has been calculated using Fischer Exact test.
**Significant at $p < 0.05$ level.

TABLE IV: Comparison Between TCD in Relation to Hgb and LDH(N = 100)

Factor	Normal N (%)(n = 75)	Abnormal N (%)(n = 18)	Conditional N (%)(n = 7)	P-value§
Average Hgb				
<7%	05 (06.7%)	0	02 (28.6%)	0.254
7%–9%	53 (70.7%)	14 (77.8%)	04 (57.1%)	
>9%	17 (22.7%)	04 (22.2%)	01 (14.3%)	
Average LDH†				
200 to 400	13 (17.8%)	01 (05.6%)	02 (28.6%)	0.532
400 to 600	37 (50.7%)	10 (55.6%)	04 (57.1%)	
600 to 800	23 (31.5%)	07 (38.9%)	01 (14.3%)	

Note: †Not done was included in the analysis.
§P-value has been calculated using Fischer Exact test.

future service indicator development for the treatment of SCD patients that we provide, both locally and nationally.

In this research, CVA was detected among 12% of patients, which was in agreement with Al Hawsawi and Ismail 1998 [21] and Zayed et al. [22] and consistent with a global report of CVA prevalence (6% to 17%) of SCD pediatrics and young adults [8].

Moyamoya is a non-frequent cerebral vasculopathy that involves typical angiographic variations. It is a rare neurological complication despite its presence among sickle cell trait cases, but it is found to be more common among sickle cell disease patients [8].

To our knowledge, Moymoya frequency among Saudi children with SCD is not previously estimated, and in our study, we found 11% of SCD children had Moyamoya finding in their Brain MRI Study, and 9/11 (81%) of Moyamoya patients had already CVA. Elmahdi *et al*. reported MMS in 98% of children who had MRA studies for strokes [23]. A previous Saudi study enrolled 385 children with SCA reported a high prevalence of moyamoya as it was detected among 61.5% of the subjects, and it was found at the onset of the first stroke in all cases with MRA abnormalities [22], and this rate was much higher compared to our findings.

SCI is a brain lesion that results from vascular occlusion found incidentally by MRI. It is a precursor of progressive brain damage and symptomatic stroke. It was reported that SCI can be found among 17% of SCD patients based on MRI findings [8]. In this research, the prevalence of SCI was 16% which was lower compared to the previously published rates of 11%–15% in pediatrics less than two years [24], 25% by six years [25], and up to 37% in 14 years [9] and various haplotypes of the beta-globin gene in SCD cases in Saudi Arabia: the eastern province subjects (Arab-Indian) have a milder illness compared to southwestern ones (Benin) and that contributed to HBF high levels [5].

The comparison between males and females in this study displayed no significant variations regarding MRI findings; however, more females tended to experience SCI and CVA combined with moyamoya. Also, a previous study revealed that the rates of moyamoya displayed no great variance between both genders; however, a higher proportion of males (56.3%) had moyamoya compared to females (43.8%) [22].

TABLE V: Comparison Between MRI in Relation to Patients Characteristics$^{(N = 100)}$

Factor	MRI findings					P-value§
	CVA + Moyamoya N (%)$^{(n = 9)}$	CVA N (%)$^{(n = 3)}$	Moyamoya N (%)$^{(n = 2)}$	SI N (%)$^{(n = 16)}$	Normal N (%)$^{(n = 70)}$	
Age in years						
<10 years	05 (55.6%)	01 (33.3%)	01 (50.0%)	07 (43.8%)	31 (44.3%)	0.976
≥10 years	04 (44.4%)	02 (66.7%)	01 (50.0%)	09 (56.3%)	39 (55.7%)	
Gender						
Male	02 (22.2%)	02 (66.7%)	01 (50.0%)	05 (31.3%)	39 (55.7%)	0.128
Female	07 (77.8%)	01 (33.3%)	01 (50.0%)	11 (68.8%)	31 (44.3%)	
TCD						
Normal	03 (33.3%)	03 (100%)	02 (100%)	06 (37.5%)	61 (87.1%)	<**0.001****
Abnormal	06 (66.7%)	0	0	09 (56.3%)	03 (04.3%)	
Conditional	0	0	0	01 (06.3%)	06 (08.6%)	
Chronic-transfusion program						
Yes	01 (11.1%)	02 (66.7%)	01 (50.0%)	05 (31.3%)	66 (94.3%)	<**0.001****
No	08 (88.9%)	01 (33.3%)	01 (50.0%)	11 (68.8%)	04 (05.7%)	
Average Hgb						
<7%	0	01 (33.3%)	0	01 (06.2%)	05 (07.1%)	0.427
7%–9%	06 (66.7%)	01 (33.3%)	01 (50.0%)	11 (68.8%)	52 (74.3%)	
>9%	03 (33.3%)	01 (33.3%)	01 (50.0%)	04 (25.0%)	13 (18.6%)	
Average LDH†						
200 to 400	0	01 (33.3%)	0	01 (06.3%)	14 (20.0%)	0.264
400 to 600	05 (62.5%)	0	0	10 (62.5%)	36 (51.4%)	
600 to 800	03 (37.5%)	02 (66.7%)	01 (100%)	05 (31.3%)	20 (28.6%)	

Note: †Not done was included in the analysis.
§P-value has been calculated using Fischer Exact test.
**Significant at $p < 0.05$ level.

Intracranial arteries are majorly impacted in SCD; therefore, TCS is used to quantify the time-average mean of the maximum velocity (TAMMV) for such arteries. Elevated velocity may be associated with the narrowing of arterial diameter [26].

The TCD screening system was established in our institute over 12 years ago, and our local statistics showed that more than three-quarters of our SCD patients had a TCDi examination done at least once during their follow-up. The slightly elevated percentage of high-risk TCD may well be explained by the fact that our cohort didn't enroll in severe cases or those complicated by the general pediatrics team.

A small proportion of our sample (18%) displayed TCD abnormalities; the findings of TCD significantly varied between males and females, where females significantly tended to display abnormal TCD compared to males. In contrast to our findings, a previous study that enrolled 379 children with SCD revealed no significant differences between males and females regarding TCD findings [27].

Lower rates of abnormal TCD were reported in previous studies; one study reported that 3% of 542 infants who underwent TCS displayed high abnormal [28].

TCD findings in our sample were statically correlated with the brain MRI findings, which showed the highest rate of abnormal TCD screening among SCI cases, and conditional TCD patients had normal brain MRIs. Lastly, the CVA and Moyamoya were found to have more abnormal than conditional or normal TCD. It was stated that narrowing the intracranial arteries is a risk for SCI, which is featured by elevated velocity of blood flow [8]. However, it was reported that many SCI patients display normal TCD [29].

In this study, we demonstrated the correlation of TCD and Brain MRI findings with what is well-known about disease severity parameters like average Hgb and LDH levels. Interestingly, found statically no significant correlation between the degree of hemolysis and the imaging finding.

HU is a chemotherapeutic medication that increases hemoglobin F (HbF), and as a result, it has been well-known to improve hematologic parameters and vaso-occlusive complications [30]. In regard to the treatment, our sample included all SCD patients who had Brain MRI and TCD screening and all the imaging done pre-or during treatment (HU or Chronic transfusion program).

Our study revealed significant variations between those who received HU and those who didn't regard TCD findings ($p = 0.002$). A greater proportion of those who received HU tended to have normal TCD, whereas 16 out of 18 who displayed abnormal TCD didn't receive HU. This may indicate the effectiveness of HU treatment. A non-significant variation between those with normal TCD and other findings regarding HU therapy was reported in a previous study ($p = 009$); however, a higher proportion of those who received HU had normal TCD (28.1%) compared to abnormal or conditional TCD (21.9%) [27]. Additionally, in this study, we found that the highest proportion of those who received HU significantly tended to have normal MRI, whereas significant proportions of those who didn't receive HU displayed SCI and CVA + moyamoya.

Transfusion normally is provided to increase Hb in order to improve the oxygen content of blood. Patients with SCD

gain another two benefits of transfusion, including reducing the proportion of HbS-containing cells and increasing the proportion of red cells with normal oxygen affinity [31].

A chronic transfusion program (CTP) was applied to 25% of our patients. Females significantly tended to receive CTP compared to males, and this may relate to the fact that more females displayed complications based on MRI findings. Additionally, we found that the large majority of those who received CTP displayed normal MRI findings, whereas the largest frequency of those who didn't receive CTP had SCI. The association between not receiving CTP and having SCI can be reinforced by the previous report that stated that treatment with chronic transfusion may prevent new SCI among SCD patients [8].

5. Limitations of the Study

The primary impediment to the generalization of our results is the small sample size at our center, and that makes the statistical tests and identifying significant relationships in the data quite difficult also as this is a retrospective study lacks valuable data, such as possible Brain MRA scans and TCD screening before the first stroke episode. Additionally, the deficiency of previous similar research in Saudi Arabia restrticts the scope of our analysis and comparison of our data with that from other centers. Also, we do not have the full genotyping of cases to elaborate on the geno-phenotype interaction of the two common haplotypes, Benin and Arab-Indian.

6. Directions for Future Research

More prospective and multicenter studies are needed to determine the extent of the neurological complications in SCD pediatrics in Saudi Arabia, as well as a correlation between the variable genetic origin and clinical phenotype of SCD in the East and West regions of Saudi Arabia. These studies may help modify guidelines regarding performing Brain MRA in children with SCD at a younger age in areas without routine Doppler ultrasound and help predict illness severity and risk stratify cases to receive early care or persistent symptomatic care.

Conflict of Interest

Authors declare that they do not have any conflict of interest.

References

[1] Potoka KP, Gladwin MT. Vasculopathy and pulmonary hypertension in sickle cell disease. *Am J Physiol-Lung Cell Mol Phys*. 2015 Feb 15;308(4):L314–24.

[2] Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. *Lancet*. 2010 Dec 11;376(9757):2018–31.

[3] Brewin J, Kaya B, Chakravorty S. How I manage sickle cell patients with high transcranial doppler results. *Br J Haematol*. 2017 Nov;179(3):377–88.

[4] Wudil JB, Usman WJ, Muuta I, Oyewole AO. Assessment of the risk of stroke in children with sickle cell anemia using transcranial doppler ultrasound with imaging in Northwestern Nigeria. *Nig J Paediatr*. 2022;49(4):290–7.

[5] Jastaniah W. Epidemiology of sickle cell disease in Saudi Arabia. *Ann Saudi Med*. 2011 May;31(3):289–93.

[6] Alsultan A, Alabdulaali MK, Griffin PJ, AlSuliman AM, Ghabbour HA, Sebastiani P, *et al.* Sickle cell disease in S audi A rabia: the phenotype in adults with the A rab-I ndian haplotype is not benign. *Br J Haematol*. 2014 Feb;164(4):597–604.

[7] Walmet PS, Eckman JR, Wick TM. Inflammatory mediators promote strong sickle cell adherence to endothelium under venular flow conditions. *Am J Hematol*. 2003 Aug;73(4):215–24.

[8] Al-Jafar HA, Alroughani R, Abdullah TA, Al-Qallaf F. Neurological complications in sickle cell disease. *Int J Clin Exp Neurol*. 2016;4(1):9–18.

[9] Bernaudin F, Verlhac S, Arnaud C, Kamdem A, Chevret S, Hau I, *et al.* Impact of early transcranial Doppler screening and intensive therapy on cerebral vasculopathy outcome in a newborn sickle cell anemia cohort. *Blood, J Am Soc Hematol*. 2011 Jan 27;117(4):1130–40.

[10] Farooq S, Testai FD. Neurologic complications of sickle cell disease. *Curr Neurol Neurosci Rep*. 2019;19:1–8.

[11] Tho-Calvi SC, Thompson D, Saunders D, Agrawal S, Basu A, Chitre M, *et al.* Clinical features, course, and outcomes of a UK cohort of pediatric moyamoya. *Neurology*. 2018 Feb 27;90(9):e763–70.

[12] Verduzco LA, Nathan DG. Sickle cell disease and stroke. *Blood, J Am Soc Hematol*. 2009 Dec 10;114(25):5117–25.

[13] Shinkawa A, Ueda K, Kiyohara Y, Kato I, Sueishi K, Tsuneyoshi M, *et al.* Silent cerebral infarction in a community-based autopsy series in Japan: the Hisayama Study. *Stroke*. 1995;26:380–5.

[14] Kapustin D, Leung J, Odame I, Williams S, Shroff M, Kassner A. Hydroxycarbamide treatment in children with Sickle Cell Anaemia is associated with more intact white matter integrity: a quantitative MRI study. *Br J Haematol*. 2019 Oct;187(2):238–45.

[15] Belisário AR, Silva CM, Velloso-Rodrigues C, Viana MB. Genetic, laboratory and clinical risk factors in the development of overt ischemic stroke in children with sickle cell disease. *Hematol, Trans Cell Therapy*. 2018;40(2):166–81.

[16] Naqv J, Yap KH, Ahmad G, Ghosh J. Transcranial doppler ultrasound: a review of the physical principles and major applications in critical care. *Intern J Vasc Med*. 2013;2013(6):I629378.

[17] Nicoletto HA, Burkman MH. Transcranial doppler series part II: performing a transcranial doppler. *Am J Electroneurodiagnostic Technol*. 2009;49(1):14–27.

[18] Loggetto SR, Veríssimo MP, Darrigo-Junior LG, Simões RD, Bernardo WM, Braga JA. Guidelines on sickle cell disease: primary stroke prevention in children and adolescents. Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular Guidelines project: associação Médica Brasileira-2021. *Hematol, Trans Cell Therapy*. 2022 Mar 21;44(1):85–94.

[19] Galadanci AA, DeBaun MR, Galadanci NA. Neurologic complications in children under five years with sickle cell disease. *Neurosci Lett*. 2019;706:201–6.

[20] DeBaun MR, Jordan LC, King AA, Schatz J, Vichinsky E, Fox CK, *et al.* American Society of Hematology 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults. *Blood Adv*. 2020 Apr 28;4(8):1554–88.

[21] Al Hawsawi ZM, Ismail GA. Stroke among sickle cell disease patients in Madina Maternity & Children's Hospital. *Ann Saudi Med*. 1998 Sep;18(5):472–4. doi: 10.5144/0256-4947.

[22] Zayed AM, Al-Muhaimeed S, Al-Otaibi T, Ali EM, Saleh R, Ancheta SJ, *et al.* Moyamoya syndrome in children with sickle cell disease in saudi arabia: a single-center experience. *Cureus*. 2023;15(11).

[23] Elmahdi M, Fadalla T, Suliman M, Elsayed M, Elhaj AM, Hussein H. Moyamoya syndrome and stroke among pediatric sickle cell disease patients in Sudan: a cross-sectional study. *Ann Med Surg*. 2022 May 21;78:103815. doi: 10.1016/j.amsu.2022.103815.

[24] Wang WC, Pavlakis SG, Helton KJ, McKinstry RC, Casella JF, Adams RJ, Rees RC. BABY HUG Investigators: mRI abnormalities of the brain in one-year-old children with sickle cell anemia. *Pediatr Blood Cancer*. 2008;51:643–6.

[25] Kwiatkowski JL, Zimmerman RA, Pollock AN, Seto W, Smith-Whitley K, Shults J, Blackwood-Chirchir A, Ohene-Frempong K. Silent infarcts in young children with sickle cell disease. *Br J Haematol*. 2009;146:300–5.

[26] Parikh T, Goti A, Yashi K, Gopalakrishnan Ravikumar NP, Parmar N, Dankhara N, *et al.* Pediatric sickle cell disease and stroke: a literature review. *Cureus*. 2023 Jan 20;15(1):e34003. doi: 10.7759/cureus.34003.

[27] Rodrigues DL, Adegoke SA, Campos RD, Braga JA, Figueiredo MS, Silva GS. Patients with sickle cell disease are frequently

excluded from the benefits of transcranial doppler screening for the risk of stroke despite extensive and compelling evidence. *Arquivos de neuro-psiquiatria*. 2017;75:15–9.

[28] Telfer P, Dwan K, Simmons A, Evanson J, Gadong N, Newell K, Tangayi S, Leigh A, Tsouana E, Hemmaway C, Kaya B. Transcranial Doppler screening in a regional care network for sickle cell disease in the United Kingdom. *J Pediatr Hematol/Oncol*. 2016 Oct 1;38(7):517–24.

[29] Melek I, Akgul F, Duman T, Yalcin F, Gali E. Neurological soft signs as the stroke risk in sickle cell disease. *Tohoku J Exp Med*. 2006;209(2):135–40.

[30] Al Sabbah MA, Radaideh M, Saleh SM, Al-Doory SA, Abdalqader AM, Mir FF, *et al.* Is hydroxyurea treatment changing the life of children with sickle cell disease? *Dubai Med J*. 2023 Dec 6;6(4): 301–5.

[31] Tanhehco YC, Nathu G, Vasovic LV. Development of curative therapies for sickle cell disease. *Front Med (Lausanne)*. 2022 Nov 24;9:1055540. doi: 10.3389/fmed.2022.1055540.