بسم الله الرحمن الرحيم
Omdurman Islamic University Journal of Applied Sciences
(OIUJ)-(ASC)
للعلوم التطبيقية مجلة جامعة أم درمان الاسلامية
https://journal.oiu.edu.sd/index.php/oiuj
https://doi.org/ 10.52981/oiujas.v22i2.3652
2026; 22(2)50-59
ISSN: 3122-5640

Hypercoagulability Markers in Sudanese Children with Homozygous Sickle Cell Disease: D-Dimer and Protein C Assessment

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To cite this article:

Habeebala Musa and Ibrahim Khider Ibrahim, Hypercoagulability Markers in Sudanese Children with Homozygous Sickle Cell Disease: D-Dimer and Protein C Assessment , Omdurman Islamic University Journal, Sudan

ISSN: 3122-5640

https://doi.org/ 10.52981/oiujas.v22i2.3652

ABSTRACT:

Background

Sickle cell anemia (SCA) is an inherited blood disorder that is characterized by chronic haemolysis and episodes of acute clinical complication. SCA is associated with hypercoagulable state with increased thrombin generation and elevated D-Dimer level which is reported as a marker for SCA related complication.

Materials and Methods

This cross-sectional case–control study included 70 children with homozygous sickle cell disease in steady state and 30 healthy controls. This study aimed to determine the protein C level, D-Dimer level and hemoglobin concentration in Sudanese children with SCA in a steady state and to correlate it with the hematological parameter. Following informed consent, one hundred subjects; seventy children with SCA in steady state were classified according to their ages in to three groups (6-11years)(12-17years) and (18-23years) and according to their gender, thirty healthy subjects as controls were enrolled. Hemoglobin

concentration was performed by automated cell counter (Sysmex XP-300.). Protein C and D-dimer were measured using XRC-fully automated coagulometer.

Results

Mean Protein C level was significantly lower among SCA cases (34.5± 13.0) when compared with the controls (49.4± 5.1) (p value 0.000). Mean D-Dimer level was significantly higher among SCA cases (0.67 ± 0.21) when compared with the controls (0.37± 0.07) (p value 0.000). Mean Hemoglobin concentration was significantly lower among SCA cases (7.9 ± 0.93) when compared with the controls (12.7± 1.2) (p value 0.000). There was significant correlation between D-Dimer level protein C and Hemoglobin concentration.

Conclusion

In conclusion, the study confirms the hypercoagulable state in SCA. The study highlights hematological reference values for Sudanese patients with SCA.

Keywords: Hypercoagulability. Sudanese Children. D-Dimer.

INTRODUCTION

Sickle cell anaemia (SCA) is an inherited blood disorder in which the clinical manifestations arise from the tendency of abnormal haemoglobin (Sickle haemoglobin or HbS) to polymerize and deform red blood cells into a characteristic sickle shape. [1] This property is due to a single nucleotide change in the β - globin gene leading to a substitution of valine for glutamic acid at position 6 of the β -globin chain.[2] The homozygosity of sickle cell genes (HbSS) results in SCA, while the heterozygosity results in other sickle cell diseases (SCD) which include sickle cell trait with one sickle cell gene and a normal haemoglobin gene (HbAS).[3] Pathophysiological studies have shown that the dense, dehydrated red cells play a central role in acute and chronic clinical manifestations of SCA, in which intravascular sickling in capillaries and small vessels leads to vaso-occlusion and impaired blood flow. [4-5]Numerous studies provide laboratory evidence of a hypercoagulable state in sickle cell patients. [6-7-8]This hypercoagulable state has been documented by various abnormalities of coagulation markers. [9]An important component of the hypercoagulable state is increased thrombin production. [10]Thrombin generation is

coupled with increased fibrinolytic activity leading to increased D-dimer levels and plasmin-anti-plasmin complexes.

Although several studies have demonstrated a hypercoagulable state in sickle cell disease, most available data originate from non-Sudanese populations, with limited pediatric-focused evidence from Sudan. Moreover, few studies have simultaneously evaluated both Protein C deficiency and D-dimer elevation in children with homozygous sickle cell disease during the steady state. Given the genetic, environmental, and healthcare differences that may influence coagulation profiles, locally generated data are essential. Therefore, this study aimed to assess Protein C levels, D-dimer concentrations, and hemoglobin levels among Sudanese children with homozygous sickle cell disease in steady state and to compare these parameters with healthy controls.

MATERIALS AND METHODS

his study was designed as a **cross-sectional case–control study**, conducted to compare coagulation markers (Protein C and D-dimer) and hemoglobin concentration between Sudanese children with homozygous sickle cell disease (HbSS) in steady state and apparently healthy controls (HbAA).

Following informed consent, one hundred children were included: seventy known sickle cell patients (HbSS) in a non-crisis steady state, defined as a ≥4 weeks from an acute illness and ≥10 weeks post-transfusion, thirty apparently healthy controls (HbAA). Subjects with recent surgery, trauma, known history of diabetes mellitus, cardiopulmonary disease, autoimmune disease and malignancy were excluded from the study. Five ml of venous blood was collected from each subject: 2.5 ml in 3.8% trisodium citrate (9:1 vol/vol), kept on ice until centrifugation at 2500g for 30 minutes at 4°C, plasma samples were immediately frozen and stored at - 80°C for subsequent coagulation analysis; and 2.5 ml in EDTA for the blood count. Laboratory analysis was performed at the Department of Haematology, Aliaa Specialist Hospital. Hemoglobin concentration was performed by automated cell counter (Sysmex XP-100). D-dimer was measured using XRC-fully automated coagulometer. Statistical analysis was performed using statistical package for social science (SPSS) software. Evaluation of patient's data was performed using the t-test

and Pearson correlation test. Results with p value < 0.05 were considered statistically significant.

Written informed consent was received from all participating patients. The whole design, procedure and informed consent of this study were approved by the Research Ethics Committee of Omdurman Military Hospital.

RESULTS

Demographic characteristics

A total of 100 participants were enrolled in the study, comprising 70 children with homozygous sickle cell disease (SCD) in steady state (cases) and 30 healthy children (controls). The age distribution is shown in Table 1. Among the cases, 26 (37.1%) were aged 6–11 years, 31 (44.3%) were aged 12–17 years, and 13 (18.6%) were aged 18–23 years. In the control group, 12 (40.0%), 13 (43.3%), and 5 (16.7%) participants fell into the same respective age groups. Gender distribution was identical among cases, with 35 (50.0%) females and 35 (50.0%) males, whereas the control group consisted of 18 (60.0%) females and 12 (40.0%) males.

Comparison of Protein C and D-dimer levels between cases and controls

As shown in Table 2, the mean Protein C level was significantly lower in SCD cases (34.5 ± 13.0) compared with controls (49.4 ± 5.1) (p = 0.000). Conversely, the mean D-dimer level was significantly higher in cases (0.67 ± 0.21 µg/mL) than in controls (0.37 ± 0.07 µg/mL) (p = 0.000).

Distribution of D-dimer levels

The categorical analysis (Table 3) revealed that 53 (75.7%) of the SCD cases had D-dimer levels greater than 0.5 µg/mL, while all controls (100%) had levels below 0.5 µg/mL. This association between elevated D-dimer levels and SCD status was statistically significant (p = 0.000).

Distribution of Protein C levels

As presented in Table 4, 50 (71.4%) of SCD cases had Protein C deficiency (low levels), compared with none in the control group. All controls (100%) had normal Protein C levels, whereas only 20 (28.6%) of SCD cases had normal levels. The difference was statistically significant (p = 0.000).

Table 1. Demographic characteristics of sickle cell disease cases and controls

Age group	Study population		
	Case	Control	Total
6-11 year	26	12	38
12-17 years	31	13	44
18-23 years	13	5	18
Total	**70**	**30**	**100**
Gender	**Study population**		
	Case	**Control**	**Total**
Female	35	18	53
Male	35	12	47
Total	70	30	100

Table 2. Comparison of hemoglobin concentration, Protein C, and D-dimer levels between cases and controls

Parameter	Case (mean ± Std)	Control(mean ± Std)	*P.value*
Protein C	34.5± 13.0	49.4± 5.1	0.000
D-dimer	0.67 ± 0.21	0.37± 0.07	0.000

Table 3. Distribution of D-dimer levels among cases and controls

D.dimer	Study population		Total
	case	control	
Less than 0.5	17	30	**47**
More than 0.5	53	0	**53**
Total	70	30	**100**
P.value :0.000			

Table 4. Distribution of Protein C levels among cases and controls

Protein C	Study population		Total
	case	control	
Low	50	0	**50**
Normal	20	30	**50**
Total	70	30	**100**
P.value :0.000			

Discussion

Sickle cell disease is a chronic hemolytic disorder that is marked by tendency of hemoglobin molecules within red cellsto polymerize and deform the red cell into a sickle (or crescent) shape resulting in characteristic Vaso occlusive eventsand accelerated hemolysis [11].

The level of D-dimer was significantly higher in 53/70 of the patients; and significant elevation was observed in patients with VOC when compared with steady state, thisare in keeping with many reports of elevated D-dimerin SCD[12,13,14]. Elevated plasma D-dimer levels indicate increased plasmin degradation of cross-linked fibrin, and are therefore an indirect indication of increased thrombin activity and fibrin formation. Increasing of thrombin activity and fibrin formation these increasing are features of steady-state sickle cell disease, and that they furtherincrease during painful crisis[15]. With regard to protein C, patients with SCD our study reported decreased levels in most of the patients (50/70). This finding is in agreementwith previous report among SCD patients [16,17]. Protein C is natural inhibitors proteins and mechanism of lowered remains unknown but most authors explainedthe reduced levels of these natural anticoagulant proteinsin SCD as a result of hepatic dysfunction that can decrease synthesis of protein C, in additionconsumptive coagulopathy[18].Also, our finding similar to findings by El-Hazmi et al., concluded that the lower protein C levels in SCD is eitherdue to decreased production or increased consumptionthough this reduction does not seem to play a role inproducing thrombo-embolic disorders[19].

Fakunle *et al.*,[20] Hagger *et al*., [21,22] and Francis RB [23] reported similar findings in separate studies with significantly high D-dimer levels in patients with SCA in steady state compared to controls. It is possible that the marked increase in D-dimer levels observed in this study was due to multiple sites, with varying severity, being involved in thrombi formation in individuals with SCA.[23] It is also possible that some of the patients with SCA during this study had some form of crises as reflected in their D-dimer level. However, a study by Akinola *et al*. in patients with SCA in steady state showed biochemical as well as rheological changes that are consistent with minor episodes of microvascular stasis, and these episodes were insufficient to cause overt vaso-occlusive crisis.[24]Although high D-dimer levels do not necessarily imply thrombosis because some factors may contribute to its increase in plasma like inflammation, infections, or surgery. However, normal levels exclude thrombosis with a high probability and the negative predictive value is often >90%. [25]

In the present study Hb was decreased among all cases, Reduced hemoglobin concentration (Hb) observed in this study among patients with SCA is similar to the studies reported separately by Ladu *et al*., [26] Omoti,[27] and Chikhlikar *et al*.[28] Reduced Hb in patients with SCA has been associated with continuous hemolysis of red blood cells thereby reducing their survival to 10–20 days and splenic sequestration. Therefore, reduced Hb concentration in patients with SCA serves as a reflection of both degree of anemia and degree of hemolysis

Study Limitations

This study has several limitations. First, the cross-sectional design limits the ability to establish causal relationships between hypercoagulability markers and clinical outcomes. Second, the relatively modest sample size and single-center setting may limit generalizability. Third, additional coagulation markers such as Protein S, antithrombin III, and thrombin generation assays were not assessed. Finally, subclinical inflammation or undetected minor vaso-occlusive events may have influenced D-dimer levels despite enrollment during the steady state.

Conclusion

This study demonstrates that Sudanese children with homozygous sickle cell disease exhibit significantly lower Protein C levels and markedly elevated D-dimer concentrations compared with healthy controls, confirming the presence of a hypercoagulable state in this population. The strong association between these hemostatic markers and SCD highlights the potential utility of Protein C and D-dimer as laboratory indicators for monitoring thrombotic risk. Establishing local reference values and integrating coagulation profiling into routine clinical assessment may aid in early identification and prevention of SCD-related complications.

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