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Research Article

Prevalence and Factors Associated with Arterial and Venous Thromboembolic Events in Patients with Sickle Cell Disease

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Abstract

Background: Hypercoagulability in patients with sickle cell disease is well recognized but the clinical and laboratory characteristics, and the risk factors associated with development thromboembolic-events (TEE), particularly venous thrombosis, are not well studied.

Objectives: The objectives of this study were to determine the prevalence and risk factors associated with TEE among sickle cells patients.

Materials and Methods: We conducted a retrospective analysis of all patients diagnosed with sickle cell disease over a 26-year period at King Khalid University Hospital, Riyadh. The information gathered included demographic data, clinical presentation, laboratory parameters, complications, co-morbidities, treatment and factors associated with TEE development.

Results: Of the 428 SCD patients studied, 207 (48.4%) were male and the mean age of the group was 22.6±11.7 years. Forty-nine (11.4%) patients developed TEE. Venous TEE was documented in 22 (5.1%) patients. The development of TEE was significantly associated with older age, hypertension, Trauma, transient immobility, family history of TEE and a higher HbS.

Conclusion: The prevalence of TEE, particularly venous thrombosis, was high among SCD patient despite their relatively younger age.

Older age, hypertension, Trauma, Transient immobility, family history of TEE and a higher HbS were significantly associated with thromboembolic development.

Keywords: *Sickle Cell Disease; Thromboembolic Events; Arterial; Venous; Thrombosis*

Introduction

Sickle cell disease (SCD) is an inherited hemolytic disorder characterized by the presence of sickle hemoglobin (HbS), which results from the substitution of glutamic acid by valine at the sixth position of the β-globin chain. Sickle cell disease affects millions of people

worldwide and is common in the Eastern and South-Western provinces of Saudi Arabia (SA) [1,2]. However, SCD among Saudis has phenotypic differences from SCD in African Americans, including a high prevalence of splenomegaly, uncommon central nervous system disease, and absence of leg ulcers [2,3]. Patients from the Eastern province of SA have a milder phenotype associated with the presence of high levels of fetal hemoglobin (HbF), which is closely related to the Saudi-Indian haplotype of the HBB gene-like cluster [3-5]. However, patients from the South-Western province have a relatively more severe disease and variable HbF levels [2-5].

The link between SCD and development of thromboembolic events (TEE), particularly venous thrombosis, has not been widely studied. There is increasing evidence that SCD is characterized by a hypercoagulable state [6,7]. Patients with SCD continue to experience stroke and cardiopulmonary complications [8-14] and TEE is a frequent cause of morbidity and mortality among patients with SCD [15]. Recently, it has been reported that patients with SCD manifest laboratory evidence of chronically activated coagulation [16,17]. For example, patients with SCD show distinct increase in several chemokines and cytokines, including tumor necrosis factor-α, interleukin (IL)-1β, IL-6, IL-8, monocyte chemoattractant protein-1, macrophage inflammatory protein-1α, and interferon-γ, either during a painful crisis or at steady state [18]. Also, plasma levels of various growth factors, including human vascular endothelial growth factor, human basic fibroblast growth factor, and human hepatocyte growth factor show a sustained 2- to 3-fold increase in patients with SCD during painful crisis and steady state [18]. There is also some suggestion that Hb-bound von Willebrand factor multimers are elevated in SCD and associated with the pathogenesis of thrombosis and vascular occlusion [19].

Although the association between SCD and the increased incidence of arterial events like stroke, has been well established, this association is less clear for venous thrombosis, and factors associated with venous TEE have not been well studied [20-23]. SCD is associated with significant morbidity and frequent hospitalizations making it difficult to distinguish if an increased risk of venous thrombosis is an indirect result of complications of SCD, or if the increased risk is a direct result of increased basal activation of the coagulation system related to the sickling process. Some studies have highlighted the association between race and the development of TEE among SCD patients [18,20], while other studies have suggested the role of reticulocytes in promoting thrombus formation and thus serve as a predisposing factor for TEE among SCD patients [22].

A careful search of the literature uncovered only few studies on the association of clinical and laboratory parameters with venous thrombosis and SCD. In the current study, we aimed to determine the prevalence of TEE and identify clinical and laboratory factors associated with the development of TEE in a cohort of SCD patients.

Patients and Methods

A retrospective medical chart review was conducted on patients diagnosed with SCD from January 1987 to December 2012, at the Hematology/Oncology department, King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia. KKUH is a tertiary care centre and Hematology service deals with a wide variety of benign and malignant hematological disorders. A major portion of the service is dedicated for the management of hemoglobinopathies, particularly SCA. Over the years, we have accumulated a large cohort of SCA patients who are regularly followed in the clinics and seen in the emergency for acute complications.

The study was approved by the institutional review board. Using a specially designed form, detailed demographic, clinical and laboratory data were recorded. Clinical parameters noted included age, gender, diagnosis, co-morbidities, type of SCD, treatment, splenomegaly, history of splenectomy, mortality and cause of death, and adverse events such as stroke, deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI) and peripheral vascular thromboembolism. Detailed history and risk factors associated with each episodes of TEE such as trauma, immobility, long travel, infections, etc were particularly noted. The laboratory data gathered included hemoglobin level, platelet count, white blood cell (WBC) count, blood group types, coagulation profile, serum ferritin, HbS, HbF and serum lactic dehydrogenase (LDH) level. All extracted data coincided with the time when the patients developed TEE, or at the time of visit to the Hematology clinics in steady state, if the patient did not develop TEE. Most of the patients with TEE presented to the emergency room and were admitted.

Venography was used to diagnose DVT during the early years of the study, which was replaced by Doppler ultrasound during 1990s, when it became available. Chest x-ray along with ventilation/perfusion scans was used to diagnose pulmonary embolism during the earlier years and this was replaced by spiral CT scans later. Pulmonary angiography and ventilation/perfusion scans were used occasionally along with CT scan in cases of diagnostic uncertainty.

Data were analyzed using Predictive Analysis Software version 18.0 (PASW, IBM, Chicago, IL, USA). Descriptive statistics were expressed as means ± standard deviation (SD) or percentages. Univariate analysis was performed to determine the significance and the differences in study parameters between the two groups. Additionally, the chi-square test for categorical variables and an independent t-test for continuous variables were also employed.

An age and gender adjusted regression model was constructed using all the factors reported in table 1 and was used to determine the significant variables associated with the development of TEE. A p value of < 0.05 was considered statistically significant. In order to identify potential predictors of TED, we constructed two logistic regression models, crude and age- and gender adjusted models, to calculate the odds ratio of TED development. We also calculated the corresponding 95% confidence intervals for each predictor.

Results

Of the 428 SCD patients, 207 (48.4%) were male and 221 (51.6%) were female, and the mean age of the whole group was 22.6 ± 11.7 years. Table 1 shows the demographic, clinical and laboratory characteristics of these patients.

Variables	Patients' values
Male/female, (%)	48.4/51.6
Age in years, mean ± SD	22.6 ± 11.7
Trauma, n (%)	19 (4.4)
Blood type groups, n (%)	
A	93 (21.7)
B	34 (7.9)
AB	4 (0.9)
O	297 (69.5)
Fracture, n (%)	8 (1.9)
Transient immobility, n (%)	34 (7.9)
Long travel >6 h, n (%)	86 (20.1)
Splenomegaly, n (%)	141 (32.9)
Infection, n (%)	85 (19.9)
Kidney disease, n (%)	12 (2.8)
Avascular necrosis, n (%)	35 (8.2)
Bronchial asthma, n (%)	31 (7.2)
Hypertension, n (%)	15 (3.5)
Diabetes mellitus, n (%)	8 (1.9)
Hemoglobin in g/dL, mean ± SD	9.7 ± 6.1
Platelet count in 10^9/L, mean ± SD	409.8 ± 187.0
WBC count in 10^9/L, mean ± SD	12.2 ± 5.9
Ferritin level in ng/mL, mean ± SD	1242.3 ± 2483.8
LDH in U/L, mean ± SD	369.1 ± 252.6
HbF, mean ± SD	10.6 ± 8.5
HbS, mean ± SD	82.1 ± 10.4

Table 1: *Demographic characteristics of 428 patients with SCD.*

Table 2 shows the comparative analyses between the SCD patients with and without TEE. Forty-nine (11.4%) patients developed TEE; of these, 27 (55.1%) had arterial events, 20 (40.8%) had venous events and 2 (4.1%) patients had both arterial and venous events. Out of 49 patients with TEE, 22 (44.9%) patients experienced cerebrovascular accident (CVA), 11 (22.4%) had DVT alone, 6 (12.2%) had PE alone, 3 (6.1%) had both DVT and PE, 3 (6.1%) had myocardial infarction, 2 (4%) had peripheral ischemia, 1 (2%) had both CVA and PE, and 1 (2%) had CVA, DVT, and PE (Table 3). Compared with SCD patients who did not have TEE, those who developed TEE had a higher incidence of trauma or injury to the body (12.3% vs. 3.4%, p = 0.003), transient immobility (18.7% vs. 6.6%, p = 0.003), hypertension (12.3% vs. 2.4%, p = 0.003), diabetes mellitus (8.2% vs. 1.0%, p = 0.006), and a positive family history of TEE (8.2% vs. 2.6%, p = 0.033). Also, the mean HbS level was significantly higher among patients with TEE than those without (86.2 ± 7.1 vs. 78.6 ± 10.2, p = 0.037) (Table 2).

Variables	With TEE (n = 49)	Without TEE (n = 379)	p value
Males/females, n Age, mean ± SD	25/24 28.97± 14.6	186/193 21.7 ± 11.9	0.561 0.001
Family history of TEE, n (%)	4 (8.2)	10 (2.6)	0.033
Trauma, n (%)	6 (12.3)	13 (3.4)	0.003
Blood groups, n (%)			
A	14 (28.6)	79 (20.7)	0.424
B	5 (10.2)	29 (7.6)	
AB	—	4 (1.0)	
O	28 (57.2)	269 (70.6)	
Transient immobility, n (%)	9 (18.7)	25 (6.6)	0.003
Long travel >6 h, n (%)	8 (16.3)	78 (20.4)	0.560
Splenomegaly, n (%)	15 (30.6)	126 (33.1)	0.093
Kidney disease, n (%)	1 (2.0)	11 (2.9)	0.766
Avascular necrosis, n (%)	4 (8.2)	31 (8.1)	0.933
Hypertension, n (%)	6 (12.3)	9 (2.4)	0.003
Diabetes mellitus, n (%)	4 (8.2)	4 (1.0)	0.006
Hemoglobin in g/dL, mean ± SD	10.4 ± 3.2	9.5 ± 3.7	0.084
Platelet count in 10^9/L, mean ± SD	424.6 ± 178.6	408.0 ± 188.2	0.575
WBC count in 10^9/L, mean ± SD	12.4 ± 5.7	12.2 ± 5.9	0.809
Ferritin level in ng/mL, mean ± SD	1529.5 ± 2072.9	1180.7 ± 2565.0	0.466
LDH in U/L, mean ± SD	378.6 ± 256.1	327.9 ± 236.7	0.331
HbF, mean ± SD	9.0 ± 7.7	13.0 ± 9.4	0.134
HbS, mean ± SD	86.2 ± 7.1	78.6 ± 10.2	0.037

Table 2: *Comparative analysis of variables among SCD patients with and without thromboembolic events (TEE).*
Note: Correlations were studied using chi-square test and independent t-test, where appropriate.

Type of event (Number is 49)	Arterial events	Venous events	Both arterial and venous events
Number	27	20	2
CVA	22		
MI	3		
PI	2		
DVT		11	
PE		6	
DVT + PE		3	
CVA+PE			1
CVA+DVT+PE			1

Table 3: *Details of arterial and venous thrombosis.*

Out of 49 patients with TEE, 22 (44.9%) patients experienced cerebrovascular accident (CVA), 11 (22.4%) had DVT alone, 6 (12.2%) had PE alone, 3 (6.1%) had both DVT and PE, 3 (6.1%) had myocardial infarction, 2 (4%) had peripheral ischemia, 1 (2%) had both CVA and PE, and 1 (2%) had CVA, DVT, and PE.

Patients with TEE had a higher total Hb, platelet count, ferritin level and LDH levels, and a lower HbF level, but these associations did not reach statistical significance. There was no significant association between the development of TEE and gender, splenomegaly, splenectomy, blood group type or avascular necrosis (Table 2). In multiple regression analysis, the development of TEE was significantly associated with age ($r = 0.199$, $p < 0.001$), hypertension ($r = 0.177$, $p < 0.001$), trauma ($r = 0.143$, $p = 0.03$), transient immobility ($r = 0.147$, $p = 0.003$), family history of TEE ($r = 0.014$, $p = 0.033$) and HbS level ($r = -0.309$, $p = 0.037$).

Trauma, immobility, and chest infection were found to be statistically significant predictors for TED development in our sample. The unadjusted odds ratio (OR) for trauma was 5.6 (95% CI: 1.9 - 16.7), for immobility was 4.3 (95% CI: 1.7 - 10.7) and for chest infection was 2.3 (95% CI: 1.1 - 5.1). After adjustment for age and gender, the resulting ORs didn't change (Table 4).

	Unadjusted OR (95% CI)	Age - and Gender - Adjusted OR (95% CI)
Trauma		
No	1.00 (reference)	1.00 (reference)
Yes	5.6 (1.9 - 16.7)*	5.6 (1.9 - 16.7)*
Cast		
No	1.00 (reference)	1.00 (reference)
Yes	4.7 (0.5 - 46.4)	4.6 (0.5 - 45.8)
Fracture		
No	1.00 (reference)	1.00 (reference)
Yes	1.7 (0.2 - 14.3)	1.8 (0.2 - 14.6)
Immobility		
No	1.00 (reference)	1.00 (reference)
Yes	4.3 (1.7 - 10.7)*	4.3 (1.7 - 10.8)*
Travel		
No	1.00 (reference)	1.00 (reference)
Yes	1.4 (0.6 - 3.1)	1.3 (0.6 - 3.1)
Chest infection		
No	1.00 (reference)	1.00 (reference)
Yes	2.3 (1.1 - 5.1)*	2.3 (1.1 - 5.2)*

Table 4: *Logistic regression models, crude and age - and gender adjusted models.*

Discussion

Substantial evidence supports a high prevalence of hypercoagulability and increased incidence of thromboembolic events (TEE) in patients with SCD [24,25]. In the present study, we tried to identify the prevalence of TEE and factors that may help predict TEE in SCD patients. We found that 11.4% of patients developed TEE while venous TEE developed in 5.1% of patients. This appears high considering the younger age of our patient population. Naik., et al. found venous TEE in 11.3% and 25% of patients in 2 different cohorts, although the median age was higher at the time of development of TEE [25,26]. This suggests that thrombosis risk may increase with advancing age in these patients, as found in our study.

In our attempt to identify risk factors associated with the development of TEE, we found that older patients with a family history of TEE, history of trauma, transient immobility or hypertension were more at risk of developing TEE. Furthermore, this study indicated that SCD patients who develop TEE were more likely to have an elevated HbS levels. None of the other laboratory markers such as WBC count, platelet count, total Hb, HbF or LDH were associated with the development of TEE. More specific markers and tests of hypercoagulability were not performed in most of our patients and merit further evaluation.

Our age- and gender-adjusted regression analysis shows that patients with positive history of trauma and immobility had five and four more odds of developing TED, respectively. Additionally, patients with previous history of chest infection had 2.3 more odds of developing TED.

SCD patients are known to be at a higher risk of premature death due to cardiopulmonary complications and arterial and venous TEE may significantly contribute to that [23]. Therefore, older patients with SCD should be carefully monitored for these complications. Furthermore, presence of diabetes mellitus, hypertension, family history of TEE, a high HbS with a recent history of trauma and immobility should alert the physicians for a higher risk of developing thrombosis. Although patients with trauma and immobility usually receive prophylactic anticoagulation routinely, this is not clear for patients with other risk factors described above. Patients belonging to this high risk group may be candidates for prophylactic anticoagulation. Prospective studies are needed before such an intervention can be recommended routinely.

There are only few published studies on the association of clinical and laboratory parameters with venous thrombosis and SCD, leaving the door open for exploration of this association and whether a cause-and-effect relationship can be established between the risk factors identified in this study and their role in SCD and development of TEE. The age- and gender-adjusted regression analysis showed that patients with positive history of trauma and immobility had five and four more odds of developing TEE, respectively.

This study investigated the clinical and laboratory factors associated with the development of thrombosis, particularly venous thrombosis, among SCD patients. The overall incidence of TEE was 11.4% in this cohort and venous thrombosis occurred in 5.1% patients, suggesting a direct link between SCD and TEE. The prevalence of TEE in this cohort of SCD patients appears high considering the younger age of the study population. This study further suggests that SCD patients may have identifiable clinical and laboratory features that can indicate whether a patient has an elevated risk of developing TEE.

Our study population consists of patients mainly from the South-Western province of Saudi Arabia. SCD from this area is known to be of intermediate severity as compared to the milder Arab-Indian haplotype of Eastern province and the more severe African type [3-5]. It remains to be determined whether our study population is representative of other populations of SCD patients, although previous literature indicates that patients with SCD as well as SCD carriers may be at a higher risk of TEE, particularly venous thrombosis [22,24-26].

We acknowledge certain limitations of this study. Apart from the retrospective design, patients with TEE may have been over represented due to referral bias. It is also possible that there was an underestimate of TEE because it was not clinically suspected and investigated

in some patients. Further prospective studies are warranted to confirm our findings and to determine whether similar associations exist within other populations of SCD patients.

Conclusion

In conclusion, the prevalence of TEE, particularly venous thrombosis, was high among our SCD patient population. Older age, hypertension, history of trauma, transient immobility, family history of TEE and a higher HbS were significantly associated with thromboembolic development. Further prospective studies are needed to confirm the results of this study. We plan to focus on, and study venous TEE in SCA patients, in the near future.

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