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Thromboembolic Events among Patients with Sickle Cell Disease: Risk Factors and Prevalence in a Tertiary Hospital in Saudi Arabia

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Abstract

Background: Sickle Cell Disease (SCD) can be complicated by thromboembolic disease. However, up-to-date there is no clarity on the risk factors associated with this complication. Here we report the prevalence of Thromboembolic Disease (TED) among SCD patients and find out factors associated with the development of these thromboembolic events in SCD.

Methods: Retrospective review of medical records of 477 patients diagnosed with SCD at King Khalid University Hospital, Riyadh, Saudi Arabia seen between 1982 and 2008. Review included demographic data, diagnosis, co-morbidities, type of SCD, laboratory and coagulation profiles, treatment, mortality, cause of death and adverse events including stroke, deep vein thrombosis, and infarction.

Results: TED was documented in 8.4% of our patients. Patients who developed TED had higher prevalence of trauma, transient immobility and chest infection and higher serum ferritin levels. The prevalence of TED was significantly associated with history of trauma, transient immobility, D-dimer level, serum ferritin level, presence of chest infection and HS.

Conclusion: The prevalence of TED among Saudi sickle cell disease patients is high considering the young age of our population. The presence of chest infection with and decreased D-dimer level with positive history of trauma and immobility in patients with SCD significantly increase the probability the patient will develop TED.

Keywords: Sickle cell anemia; Thrombosis; Deep vein thrombosis; Thromboembolic disease; Stroke

Introduction

Patients with SCD may suffer numerous complications including, stroke and cardiopulmonary complications, [1,2] bone diseases [3], kidney problems, [4] leg ulcers, [5] and pulmonary embolism and hypertension [6,7]. Pulmonary disease, including thromboembolic disease (TED) is a major cause of the morbidity of SCD [8].

It is has been reported that patients with SCD manifest laboratory evidence of a chronically activated coagulation system [6-8]. The association between SCD and the increased incidence of TED is not well established, nor is it clear, whether patients with SCD are at increased risk for TED [2,9-11].

A study in 2008 suggested that the predisposition to thrombosis among SCD patients is attributed to the role of reticulocytes in promoting thrombus formation [9]. Other studies suggested the role of race in the development of TED among SCD patients [10,11].

To clarify further the association between SCD as a risk factor for TED, the current study was conducted to determine the prevalence of TED in our SCD patients and compare the characteristics of patients who develop TED versus to those who did not develop TED.

Patients and Methods

This is a retrospective study of patients diagnosed with SCD who were seen at the Hematology unit of King Khalid University Hospital, King Saud University, Riyadh, Saudi Arabia between January 1982 and December 2008. The medical records of 477 patients were reviewed for demographic characteristics, medical history and laboratory results. These included: age, sex, diagnosis, co-morbidities, type of SCD, laboratory and coagulation profiles, treatment, mortality, and cause of death, adverse events including stroke, DVT, myocardial infarction, peripheral vascular thromboembolism and pulmonary embolism. Laboratory results including D-dimer, serum ferritin, hemoglobin, platelet count, white blood cell count and lactic dehydrogenase were taken at the time the patients developed TED or at the time of admission/clinic visits if they did not develop TED. Ethical approval was obtained from the Institution Review Board (IRB) of the College of Medicine, King Saud University, Riyadh, Saudi Arabia before the study was started.

Data were analyzed using Predictive Analysis Software version 18.0 (PASW, IBM, Chicago, IL, USA) Data were presented as mean ± standard deviation or as percentage distribution. Categorical variables were analyzed using Chi-square test and continuous variables were analyzed using independent t-test. To determine the strength of association, multivariate analysis was performed. A regression model was constructed to determine the significant variables associated with the development of TED. P-value of <0.05 was considered statistically

significant. TED was defined as any formation in any blood vessel of a clot that breaks loose and carried into the bloodstream. This includes areas like the coronaries, cerebral, peripheral vascular vessels, deep veins and the pulmonary vessels. The diagnosis was made through Doppler scans, high resolution CT scan, ventilation/perfusion scan or pulmonary angiography.

Results

SCD with thromboembolic disease

There were 40 (8.4%) patients who developed TED, 18 (45.0%) were males and 22 (55.0%) were females and 37 (92.5%) were Saudis. Mean age was 28.5 ± 11.7 years. Twenty-two (55.0%) were blood type O, 13 (32.5%) type A and 5 (12.5%) were of type B blood group. Among the 40 patients who had TED, 21 (52.5%) had CVA/stroke, 16 (40.0%) had Deep Vein Thrombosis (DVT) and 11 (27.5%) had pulmonary embolism (PE); Eight (20.0%) patients had either TED plus CVA and/or DVT and/or PE. There were 4 patients (10.0%) who had a family history of TED. There were 5 patients (12.5%) who had a history of trauma, 1 (2.5%) had history of cast, 1 (2.5%) had history of fracture, 8 (20.0%) had histories of transient immobility and 8 (20.5%) had history of long hours of travel (more than 6 hours). There were 11 (27.5%) patients who had splenomegaly and 2 (5.0%) had splenectomy. There were 11 (27.5%) reported cases of chest infection. Mean D-dimer level was 49.50 ± 212.50 mg/L, mean hemoglobin level was 9.30 ± 1.90 mg/L, mean platelet count was 435.10 ± 178.30 × 10^9/L, mean WBC count was 12.90 ± 5.90 × 10^9/L, mean ferritin was 2012.60 ± 2243.70 ng/mL and mean lactic dehydrogenase (LDH) was 346.70 ± 233.60 U/L. Mean 24-hour urine clearance was 0.69 ± 0.60, mean HA was 33.50 ± 21.0, mean HT was 8.80 ± 7.70, mean HA2 was 3.40 ± 0.80 and mean HS was 61.50 ± 19.00 (Table 1).

SCD without thromboembolic disease

The 437 patients (91.6%) had no TED, 216 (49.4%) males and 221 (50.6%) females, 418 (95.7%) were Saudis. Mean age was 21.8 ± 11.2 years. Three hundred and eight patients (70.5%) were blood type O, 89 (20.4%) were blood type A, 36 (8.2%) were blood type B and 4 (0.9%) were blood type AB. Fourteen patients (2.9%) had a history of trauma, 3 (0.6%) had a history of cast, 7 (1.5%) had a history of fracture, 30 (6.3%) had histories of transient immobility and 78 (16.4%) had history of long hours of travel (more than 6 hours). One hundred and sixty two patients (33.9%) had splenomegaly and 20 (4.2%) had splenectomy. There were 55 (11.5%) reported cases of chest infection.

Variables	With TED (n=40)	Without TED (n=437)	p values
Males/Females (%)	45.0/55.0	49.4/50.6	0.623
Age in years, mean ± SD	28.5 ± 11.7	21.8 ± 11.2	0.737
(+) history of trauma (%)	5 (12.5)	14 (2.9)	0.009
(+) history of cast (%)	1 (2.5)	3 (0.6)	0.227
(+) history of fracture (%)	1 (2.5)	7 (1.5)	0.669
(+) history of transient immobility (%)	8 (20.0)	30 (6.3)	0.003
(+) history of long travel (>6HR)	8 (20.0)	78 (16.4)	0.734
Had splenomegaly (%)	11 (27.5)	162 (33.9)	0.371
(+) chest infection (%)	11 (27.5)	55 (11.5)	0.008
Hemoglobin in g/dL, mean ± SD	9.3 ± 1.9	9.2 ± 1.8	0.757
Platelet count in 10^9/L, mean ± SD	435.1 ± 178.3	406.2 ± 186.9	0.356
WBC count in 10^9/L, mean ± SD	12.9 ± 5.9	12.2 ± 5.8	0.476
Ferritin level in ng/mL, mean ± SD	2012.6 ± 2243.7	969.5 ± 1295.5	0.001
LDH in U/L, mean ± SD	346.7 ± 233.6	381.2 ± 252.4	0.511
24-hour clearance, mean ± SD	0.69 ± 0.6	2.4 ± 16.2	0.63
HA, mean ± SD	33.5 ± 21.0	35.1 ± 28.9	0.864
HF, mean ± SD	8.8 ± 7.7	12.1 ± 8.7	0.17
HA_2, mean ± SD	3.4 ± 0.8	3.9 ± 1.7	0.195
HS, mean ± SD	61.5 ± 19.0	73.9 ± 20.1	0.03
Note: Correlations were done using Chi-square test and independent t-test where appropriate.			

Table 1: Comparative analysis of variables among SCD patients who develop TED versus SCD patients who did not develop TED.

Mean D-dimer level was 508.7 ± 987.8 mg/L, mean hemoglobin level was 9.2 ± 1.8 mg/L, mean platelet count was 406.2 ± 186.9 × 10^9/L, mean WBC count was 12.2 ± 5.8 × 10^9/L, mean ferritin was 969.5 ± 1295.5 ng/mL and mean LDH was 381.2 ± 252.4 U/L. Mean 24-hour urine clearance was 2.4 ± 16.2, mean HA was 35.1 ± 28.9, mean HF was 12.1 ± 8.7, mean HA_2 was 3.9 ± 1.7 and mean HS was 73.9 ± 20.1 (Table 1).

Correlations between patients who developed TED versus those who did not develop TED

The prevalence of trauma was significantly more seen among those who developed TED than those who did not developed TED (12.5% *vs.* 3.2%, p=0.004). History of transient immobility was also significantly more frequent among those who had TED than those who did not have TED (20.0% *vs.* 6.8%, p=0.003). The presence of chest infection was also significantly more prevalent among those who had TED than those who did not have TED (27.5% *vs.* 12.6%), p=0.008. Serum ferritin level was significantly higher among those who had TED than those who did not have TED. HS was significantly lower among patients who had TED than those who did not have TED (Table 1).

The prevalence of TED was significantly associated with history of trauma (p=0.004), history of transient immobility (p=0.003, serum ferritin level (p=0.001), presence of chest infection (p=0.008) and HS (p=0.030) There were no significant correlations between development of TED and gender, age, splenectomy, blood type, history of cast, history of fracture, family history of TED, splenomegaly, LDH level, 24-hour urine clearance, HF and HA_2 (Table 1).

Discussion

In this study, we report an 8.2% of TED among patients with SCD seen at our institution. Assuming the homogeneity of our population, the assumption of a direct link between SCD as a risk factor itself in the development of TED remains vague, in the sense that there has been no literature that can provide as evidence on how much of SCD patients will eventually develop TED. However, based on our results, it is clear that SCD patients who develop TED have a chronically activated coagulation system as previously suggested by Austin in 2007, [11] making them more at risk to development of thromboembolic events. Another thing is whether or not our Saudi population is more at risk to development of TED remains to be known.

In our attempt to identify the risk factors associated with the development of TED, the results obtained indicated that high WBC count, history of immobility, history of trauma, and high platelet count. Fitzhugh et al. [2] suggested the greater association of premature deaths among SCD patients with cardiopulmonary complications. However, they also suggested that acute complications such as infection can no longer be the leading cause of death, instead they suggested that there is already a shift from infections to the more chronic cardiopulmonary complications such as arrhythmia and pulmonary hypertension leading to premature death [2]. Our study showed that the presence of infection is still prevalent among our SCD patients (Table 1). Probably this explains why in some cases, specifically SCD patients who are above 50 years old, die mostly of infectious causes rather than from other problems [2]. Therefore, and on this basis older patients with SCD should be carefully monitored for their WBC count, especially when it reaches more than 20,000 cells/mm^3, and for high platelet counts, long hours of immobility, and trauma. A careful search of the literature uncovered very few studies on the association between SCD and TED, leaves the door open for the future exploration of this connection and whether or not a "cause-and-effect" could be established between these risk factors and their role in the association between SCD and prevalence of TED.

Conclusion

The prevalence of TED in SCD patients in our cohort is high considering the young age of our population. SCD itself may not be a risk factor for TED. However, in the presence of infection with a high WBC count, a high platelet count, and positive histories of trauma and immobility, patients with SCD have a significantly increased probability of developing TED.

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