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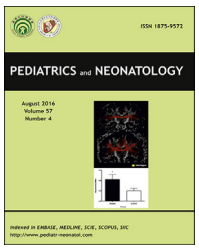

ORIGINAL ARTICLE

Coagulation Defects in Thalassemic Patients

Mostafa M. Abosdera*, **Alzahraa E. Almasry**, **Ehab S. Abdel-Moneim**

Pediatric Department, Sohag Faculty of Medicine, Sohag, Egypt

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Key Words
coagulation;
thalassemia;
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Background: Regular blood transfusion and compliance with iron chelation therapy has markedly improved life expectancy in thalassemia; however, this improvement is accompanied by several complications of this chronic disease including thromboembolic disorders. The objective of this work is to study natural coagulation inhibition as well as the fibrinolysis processes in thalassemic children who are otherwise in a steady state with no overt clinical manifestations of thromboembolism.
Methods: In a case–control study design conducted at Sohag University Hospital, Sohag, Egypt, 50 thalassemic children and 20 age- and sex-matched healthy controls were compared as regards prothrombin concentration, international normalized ratio, partial thromboplastin time, protein C, protein S, antithrombin III, D-dimers, and thrombin activatable fibrinolysis inhibitor (TAFI).
Results: When compared to healthy controls, natural coagulation inhibitors (protein C, protein S, and antithrombin-III) were significantly lower in thalassemic children ($p < 0.0001$). While D-dimers showed a significant increase in thalassemic children, TAFI was significantly lower ($p < 0.0001$). Splenectomized thalassemic children showed significantly lower levels of protein C, protein S and TAFI ($p < 0.001$, $p < 0.0001$, $p < 0.0001$, respectively) when compared to non-splenectomized thalassemic children.
Conclusion: Significant changes in natural coagulation inhibition and fibrinolysis processes favoring thromboembolism can be detected in otherwise healthy thalassemic children. Because these changes are more pronounced in splenectomized patients, study of primary prophylactic strategies in this subgroup is warranted.

* Corresponding author. Sohag University Hospital, Sohag, Egypt.
E-mail address: aabosdera@yahoo.com (M.M. Abosdera).

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1. Introduction

Prognosis of children with β-thalassemia has improved substantially in the last few decades. This was attributed to recent medical advances in optimizing transfusion therapy, iron chelation, and bone marrow transplantation. However, as life expectancy increases in such individuals, incidences of several serious complications increase as well; thromboembolic events (TEE) are one of such serious complications.[1] Borgna et al[2] surveyed nine Italian pediatric thalassemia centers, observing that 4% of the 683 patients with β-thalassemia major (TM) and 9.6% of the 52 patients with β-thalassemia intermediate (TI) experienced a TEE. Cappellini et al[3] followed 83 patients with TI over 10 years, 82 of whom where splenectomized, and they found that 29% had venous thrombotic events in the form of deep vein thrombosis, pulmonary embolism, or portal vein thrombosis. TEEs occur at a higher rate in patients with TI rather than in TM.[2,4] Clinically, the prevalence of thrombotic events in patients with TI can reach up to 20% compared to $<$ 1% in patients with TM. These events are mostly venous and primarily occur in splenectomized patients (22.5% vs. 3.5%).[5] This is due to the occurrence of hypercoaguability state which was found to be more common in TI than TM, which may be attributed to several factors, including procoagulant activity of hemolyzed circulating red blood cells, increased platelet activation, coagulation factor defects, depletion of antithrombotic factors and endothelial inflammation. These factors have been observed at a higher rate in splenectomized patients.[6]

The present work aims to study natural coagulation inhibition as well as the fibrinolysis processes in thalassemic children who are otherwise in a steady state with no overt clinical thromboembolic manifestations.

2. Patients and methods

This study included 50 children with TM (old and newly diagnosed cases) who were recruited during routine follow-up visit to thalassemia clinic, Sohag University Hospital, Sohag, Egypt. Their ages ranged from 6 months to 18 years; 58% were male. This study sample included 20 cases of nonsplenectomized TM, 10 cases of nonsplenectomized TI, 12 cases of splenectomized TM, and eight cases of splenectomized TI. Twenty age- and sex-matched healthy children with no evidence of previous blood disease or previous blood transfusion were recruited as a control group. Written informed consent was obtained from all caregivers of the studied children. Exclusion criteria were previous or current TEE, family history of coagulation disorder, children under anticoagulant, positive serology for hepatitis and evidence of liver cell failure or cardiomyopathy.

Background data were obtained by chart review. Venous blood (5 mL) in citrate was collected from each studied case and control. Separated plasma was frozen at −80°C. Plasma levels of protein C, protein S, and antithrombin III (AT-III), D-dimers, and thrombin activatable fibrinolysis inhibitor (TAFI) were measured using standard laboratory methods. Data were statistically described in terms of mean (± standard deviation) or number (%). Comparison of numerical variables between the cases and controls was made using the Student *t* test for independent samples. A *p*-value $<$ 0.05 was considered statistically significant. All statistical calculations were performed using SPSS (version 16 for Microsoft Windows; SPSS Inc., Illinois, USA).

3. Results

Natural coagulation inhibitors (protein C, protein S, and AT-III), D-dimers, and TAFI in cases and control groups are compared in Table 1. Significantly lower levels of protein C, protein S and AT- III were evident in thalassemic children. Protein C was low in 56% (28 out of 50) of patients, protein S in 60% (30 out of 50) of patients, and AT-III in 54% (27 out of 50) of patients. While D-dimers showed a significant increase in thalassemic children, TAFI was significantly lower in them. In Table 2 splenectomized and nonsplenectomized thalassemic children were compared as regards the studied parameters. Of the natural coagulation inhibitors, only protein C and protein S were significantly lower in splenectomized children. While D-dimers showed no differences between splenectomized and nonsplenectomized thalassemic children, TAFI was significantly lower in splenectomized thalassemic children.

4. Discussion

Profound hemostatic changes were observed in patients with thalassemia, so this study was conducted to investigate these hemostatic abnormalities. Protein C and protein S are instrumental in the regulation of blood clot formation. If their amount is inadequate or if either protein is not functioning properly, inappropriate or excessive clotting may occur with a resultant blockage of blood flow in the veins or, rarely, the arteries.[7]

In this study, the levels of protein C, protein S, and AT-III were statistically lower in cases in comparison to control group. Decreased levels of protein C and protein S in thalassemic patients have been reported elsewhere. Hassan et al[8] reported decreased levels of protein C and S in their study of 50 children with thalassemia in comparison to the control group.[9] Sipahi et al[10] reported that protein C,

Table 1 Natural coagulation inhibitors (protein C, protein S and AT- III), D-dimers, and TAFI in cases and controls.

Variables	Cases $n = 50$ *	Controls $n = 20$	p
Protein C	60.94 ± 7.16	105.57 ± 17.34	<0.0001
Protein S	56.55 ± 12.81	97.9 ± 11.06	<0.0001
AT-III	69.98 ± 11.66	114.23 ± 14.44	<0.0001
D-dimers	88.43 ± 11.2	50.93 ± 6.84	<0.0001
TAFI	97.1 ± 12.04	106.63 ± 9.86	<0.0001

AT-III = antithrombin III; NS-TI = nonsplenectomized thalassemia intermediate; NS-TM = nonsplenectomized thalassemia major; S-TI = splenectomized thalassemia intermediate; S-TM = splenectomized thalassemia major; TAFI = thrombin activatable fibrinolysis inhibitor.

* Twenty cases of NS-TM, 10 of NS-TI, 12 of S-TM, eight of S-TI.

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