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Epistaxis in Thalassemia: Study of the Hemorrhagic Profile

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ABSTRACT

Introduction: Significant alterations in the hemostatic system already exist in polytransfused children with beta thalassemia that make it a high risk condition for both hemorrhagic manifestations and future development of thromboembolic events. The pathophysiologic defects may result from platelets abnormalities, inherent red cell defects, coagulation inhibitors deficiency or additional acquired abnormalities like cardiac or liver dysfunction and hormonal deficiencies.

Objective: To assess the hemostatic defect underlying epistaxis in thalassemic children and to compare results with matched controls having epistaxis as the presenting symptom but not due to a hematological disorder.

Patients and Methods: Twenty one thalassemic patients (19 thalassemia major & 2 thalassemia intermedia) attending the hematology clinic of the New Children's Hospital, Cairo University were included in the study together with ten age and sex matched controls. All patients were subjected to full clinical examination, complete blood count, serum ferritin, alanine transaminase (ALT), aspartate transaminase (AST), total and direct bilirubin, alkaline phosphatase, prothrombin time (PT), prothrombin concentration (PC) and activated partial thromboplastin time (aPTT).

Results: A highly significant decrease was observed in platelet aggregation to ADP and ristocetin in patients than control (p=0.000, 0.000 respectively). PC and PT were significantly affected in patients than control (p=0.000, 0.001 respectively). PTT was non significantly prolonged in patients. AST and ALT were increased in patients with only significant increase in ALT (p=0.000). Platelet aggregation was increased in splenectomized versus non-splenectomized thalassemics.

Conclusion: Bleeding tendency in thalassemia can be attributed to a defect in platelet aggregation. Hepatic dysfunction associated with the disease can be a contributing factor.

Key Words: *Epistaxis - Thalassemia - Hemorrhagic profile.*

INTRODUCTION

Standards of care for thalassemic patients have improved in recent years, resulting in almost doubling of the average life expectancy. As a consequence, additional previously undescribed complications are now being recognized. In particular, profound hemostatic changes which can present either as thrombotic or hemorrhagic events are being observed in patients with ß-thalassemia major and intermedia.

Many thalassemic patients suffer from bleeding tendency, notably epistaxis and easy bruising, possibly attributed to defective platelet aggregation in response to ADP, collagen and ristocetin **[1]**.

Minor abnormalities in the coagulation mechanism of these patients were reported as prolonged prothrombin time and reduction in the plasma levels of clotting factors I, II, V, VI, IX and XI.

Reduced levels of prothrombin in different age groups of thalassemic were reported suggesting that this anomaly is related to the thalassemia rather than to hepatic dysfunction due to hemosiderosis which is a rare occurrence in children **[2]**.

Spontaneous intracranial hemorrhage is one of the cerebrovascular complications in ß thalassemia major which is most probably multifactorial in origin, the predisposing factors included recent blood transfusion, prolonged prothrombin time and partial thromboplastin time as well as decreased platelets **[3]**.

We conducted this study to assess the hemostatic defect underlying epistaxis in thalassemia children and to compare results with matched control suffering from epistaxis without any hematological disorder.

PATIENTS AND METHODS

Patients:

Twenty one thalassemic patients (12 males and 9 females) attending the Hematology Clinic of the New Children's Hospital, Cairo University were included in this study together with ten age and sex matched control.

The patients were composed of 19 ß - thalassemia major (TM) and 2 thalassemia intermedia (TI) with a mean age of 11.0±4.5 years.

Ten patients (47%) were splenectomized and 11 (52.4%) had splenomegaly. All patients were presenting with epistaxis as a frequent symptom and were assessed for the underlying cause of bleeding together with 10 age and sex matched control.

All patients were on regular 3-4 weeks blood transfusion therapy of 10-15ml/kg except the 2 thalassemia intermedia. Eighteen patients were on chelation therapy (subcutaneous desferroxamine, 25-50mg/kg 5 days a week) but only 7 were compliant.

None of our patients were on anti-platelet therapy.

All patients and control were subjected to full history taking and thorough clinical examination and laboratory investigations.

- Complete blood count (CBC).
- Serum ferritin.
- Alanine transaminase (ALT), aspartate transaminase (AST), total and direct bilirubin and alkaline phosphatase.
- Prothrombin time (PT), prothrombin concentration (PC) and activated partial thromboplastin time (aPTT).
- Platelet aggregation was tested using adenosine 5-diphosphate (ADP) and ristocetin as in vitro aggregating agents.

Methods:

Blood samples were taken 3-4 weeks after blood transfusion and were sent for routine biochemical and hematological tests.

CBC including platelet count by electronic counters (Coulter, Advia 120).

Serum ferritin by microparticle immunoassay (IMX).

Platelet aggregation test was done using aggregometer by method of Born **[4]**.

The patients and control were tested using platelet rich plasma (PRP) which was obtained by adding one-tenth volume of 3.2% trisodium citrate to collected blood. Aggregation test was done by addition of aggregating agents (ADP, Ristocetin sulphate).

The results were quantitated by measuring the percentage fall in the optical density of PRP, 3 minutes after the addition of the aggregating agent. Normal range for ADP and ristocetin is 50-90%.

Statistical analysis:

All data were summarized as mean ± standard deviation (SD) for numerical data and as percentage and ratio for categorical data.

Appropriate statistical tests of significance (unpaired student *t*-test) was used to compare results in different groups.

RESULTS

A significant decrease was found in platelet aggregation to ADP and ristocetin in patients than control (p=0.000, 0.000 respectively) (Table 1 & Fig. 1). PC and PT were significantly affected in cases than control (p=0.000, 0.001 respectively). PTT was prolonged in patients but with no statistical significance. Platelet count, AST and ALT were also increased in patients than control with only ALT of significance (p=0.000) (Table 1).

Further splitting of the patients was done based on the splenic status. Platelet count was significantly increased in splenectomized patients (p=0.008) versus non-splenectomized while platelet aggregation markers showed a non-significant increase in splenectomized patients (Table 2).

Table (1): Clinical and laboratory data of patients and control.

	Patients (n=21) Mean ± SD	Control (n=10) Mean ± SD	*p*-value
Age	11.0±4.5	8.4±2.7	
Gender	12 M, 9 F	5 M 5 F	
Type of thalassemia:	19 TM, 2 TI		
Splenic	10 splenectomized		
Status	11 splenomegaly		
Hb (g/dl)	6.8±1.4	11.3±1	0.000
Hct (%)	21.1±4.4	33.4±2.7	0.000
Platelet (X 10^9/L)	393.34±296.6	302.1±100	NS
Plt. Aggreg:			
ADP (%)	28.3±27.5	88.6±12.13	0.000
Ris (%)	43.9±28.4	91.1±9.70	0.000
PC (%)	72.7±17.2	98.0±3.39	0.000
PT (Sec)	15.29±3.0	12.6±0.2	0.001
PTT (Sec)	42.5±10.54	38.0±17.0	NS
AST (IU/L)	102.57±90.1	52.35±40.4	NS
ALT (IU/L)	114.47±79.4	27.0±24.2	0.000

M : Male.
F : Female.
TM : Thalassemia major.
TI : Thalassemia intermedia
Hb : Hemoglobin.
Ht : Hematocrite
ADP : Adenosine diphosphate.
Ris : Ristocetin.
PC : Prothrombin concentration.
PT : Prothrombin time.
PTT : Partial thromboplastin time.
ALT : Alanine transaminase.
AST : Aspartate transaminase.
p.value <0.05 = Significant.
>0.05 = Insignificant.

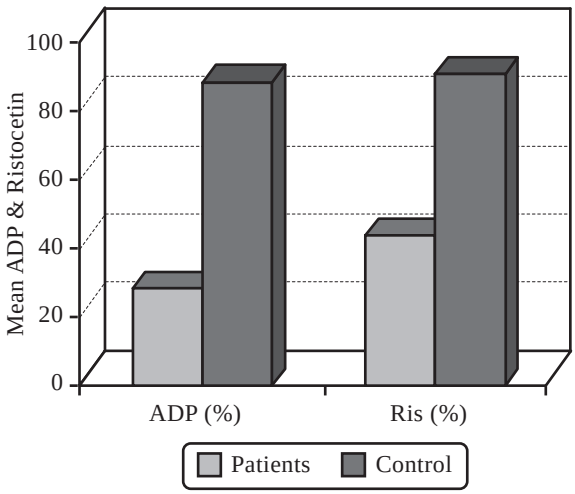

Fig. (1): ADP and Ristocetin levels in patients and control.

Table (2): Platelet changes in patients, splenectomized Vs non-splenectomized.

	Splenectomized (n=10)	Non-splenectomized (n=11)	*p*-value
Platelet (X 10^9/L)	583.4±304	197.7±115.7	0.008
Plt. Aggreg:			
ADP (%)	34.3±34.1	23.9±22.3	NS
Ris (%)	47.7±31.4	39.4±27.8	NS

DISCUSSION

The currently used therapeutic strategies in ß-thalassemia major and intermedia have prolonged the survival for many patients. This longer survival has been accompanied by the appearance of a number of previously underscribed complications, in particular hemostatic derangements.

A previous study evaluating the hemostatic changes in a group of 50 thalassemics reported 32% of cases having minor bleeding tendency and one with ecchymotic patch while none of the patients had thrombo-embolic episodes **[5]**.

Many thalassemics experience epistaxis as well as easy bruising. To study hemorrhagic events in our patients we assessed platelet aggregation to ADP and ristocetin in thalassemic children presenting with epistaxis and compared them to their matched control.

Our patients showed significant Platelets hypoaggregation with ADP and ristocetin. It was reported that there are several platelet abnormalities in thalassemia as impaired aggregation, increased circulating aggregates and shortened platelet survival **[2]**. Diminished plate-

let aggregation response to ADP, epinephrine, collagen and ristocetin may be due to an intrinsic defect of thalassemic platelets e.g., membrane abnormality which can be due to the release of some substances by hemolysed red cells inducing a platelet defect directly or at the membrane level **[6]**. On resuspension of these platelets in normal plasma, their diminished aggregation didn't correct.

Impaired aggregation can also be attributed to the presence of plasmatic isoantibodies resulting from previous blood transfusion **[7]**.

Mild hemorrhagic tendency in the form of bruising and epistaxis was observed in a group of ß-thalassemia patients. A consistent platelet anomaly manifested by diminished platelet aggregation to ADP, collagen and ristocetin was found and could be responsible in part for the hemorrhagic phenomena **[1]**.

Some studies showed that not only hypoaggregation can occur in thalassemics but also hyper-or normal aggregation **[8]**. This is in contrast to our results where only 9% showed normal aggregation and none showed hyperaggregation.

In our study, splenectomized patients had increased platelet count and better aggregation with ADP and ristocetin than those with intact spleen which agrees with the results of Opartkiattikul and Colleagues, 1992) **[9]**.

Thrombocytosis, increased platelet aggregation and decreased natural coagulation inhibitors (protein C and antithrombin III) in splenectomized patients may be significant in thrombotic complications in such cases while defective platelet aggregation and prothrombin activity in non-splenectomized thalassemics may give rise to hemorrhagic tendencies **[10]**. In splenectomized thalassemics, platelet aggregation to ADP, ristocetin, adrenalin and collagen showed better results than non-splenectomized cases. Splenectomy is recommended to improve preexisting hemostatic defects especially with regards to platelet function **[6]**.

In addition to increased platelet number in splenectomized patients, chronic platelet activation is present in ß-thalassmia major and intermedia. This may explain the weak response of thalassmic platelets to aggregation agonists as the activated platelets become refractory to additional stimulation **[11]**. The presence of morphological platelet abnormalities in splenectomized patients with ß-thalassmia may also contribute to an enhanced risk of vascular complications **[12]**.

Our results showed that PT and PTT were prolonged in patients than control which agrees with the results of a study reporting a 33.3% and 40.7% prolongation of PT and PTT in 30% of a group of poorly chelated thalassemia major patients exhibiting bleeding manifestations. **[13]**. ALT and PT showed significant elevation in patients than control (p=0.00, 0.001 respectively). Furthermore our patients were iron overloaded with a mean serum ferritin of 2855.9± 1906.2ng/ml which correlated positively with liver function **[14]**. Therefore, epistaxis in our patients may be partly related to hepatic dysfunction.

Despite that none of our patients suffered from thromboembolic problems, splenectomized patients are at high risk of developing thrombosis due to the existence of a low grade consumptive coagulopathy **[15]**.

Thalassemics have a chronic hypercoagulable state with increased incidence of thromboembolic episodes. The pathophysiologic defects include inherent red cell defects, platelet abnormalities, deficiency of coagulation inhibitors and additional acquired abnormalities like cardiac and liver dysfunction and hormonal deficiencies **[16]**.

Venous thrombosis is more prevalent in B-thalassemia intermedia patients who are not receiving regular transfusions and who have undergone splenectomy. Thalassemia intermedia occurred 4.38 times more frequently in thalassemia intermedia than thalassemia major with more arterial events occurring in thalassemia major **[17]**.

Thalassemia Intermedia patients have high plasma levels of coagulation and fibrinolysis activation. Furthermore, thalassemic red cells and erythroid precursors from splenectomized patients had an enhanced capacity to generate thrombin.

The addition of prophylactic antithrombotic therapy has only recently been suggested for high-risk patients with ß-TI who are exposed

to transient thrombotic risk factors. Thalassemia major patients who had developed an acute thrombotic event should be considered for prolonged antithrombotic therapy **[18]**.

In conclusion, bleeding tendency in our thalassemic patients can be attributed to a defect in platelet hemostasis namely platelet hypoaggregation. Hepatic dysfunction associated with the disease can be a contributing factor as well.

Vitamin K supplementation to compensate for hepatic synthesis defects can be of benefit.

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