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Review Article

Thalassemia and the hypercoagulable state

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ABSTRACT

Thalassemia, an inherited hemolytic disorder, is associated with a high incidence of thrombosis. The major mechanisms underlying thromboembolism (TE) are an abnormal red blood cell surface, platelet activation and endothelial cell activation. A higher risk of TE is found in splenectomized patients due to thrombocytosis and increased abnormal RBCs in the circulation. Regular RBC transfusions can reduce the proportion of abnormal RBCs and suppress erythropoiesis. Regular transfusion may also reduce levels of circulating coagulation markers and reduce elevated pulmonary artery pressure. To prevent thromboembolic events, aspirin is now recommended for splenectomized patients with thrombocytosis.

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Introduction

Thalassemia is an inherited hemolytic disorder which is common in the Mediterranean region, the Far East and South America but more prevalent in the Southeast Asian countries. The prevalence of gene

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carriers in these regions is between 5% and 70% [1]. The annual world incidence of thalassemia is estimated to be approximately 1 in 100,000 [2]. Thalassemia is characterized by decreased or abnormal synthesis of α or β globin chains resulting in α and β-thalassemia disease respectively. Its severity is divided into three categories. Thalassemia major (TM), such as hemoglobin Bart's hydrops fetalis, β^0/β^0 and β^0/β^+, is a transfusion dependent form. Thalassemia intermedia (TI), such as hemoglobin H (HbH) and HbE/$\beta^{0/+}$, is a non-transfusion dependent thalassemia. Thalassemia minor, such as β/β^0, β/β^+, α-thal 1 and α-thal 2 traits, is a carrier state that is not associated with symptoms of anemia [3]. The characteristic features of thalassemia are anemia, jaundice, bone changes and hepatosplenomegaly from extramedullary hematopoiesis. Major complications include osteopenia/osteoporosis, immune dysfunction (especially in splenectomized patients), endocrine dysfunction and heart failure that results from chronic anemia, iron overload, pulmonary hypertension and thromboembolism (TE). TE may occur in both venous circulations, including deep vein thrombosis (DVT), portal vein thrombosis (PVT) and pulmonary embolism (PE), and in arterial vessels, such as ischemic stroke including the moyamoya syndrome [4–8].

Incidence of Thromboembolism

In a study of 8,860 TM and TI patients with a mean age of 30 ± 13 years from 8 Mediterranean countries, the overall incidence of TE was 1.65%. Venous TE (57%) was more common than arterial TE (40%) with simultaneous arterial and venous TE recorded in 3% of patients (Table 1) [8]. A systematic review of 11,791 TM and TI patients demonstrated the incidence of cerebral TE events, including ischemic stroke, transient ischemic attack and silent cerebral infarction, to be 1.13%. The mean age at which patients started to experience this complication was at 15.9 years for TM and 24.7 years for TI [9].

Thalassemia Major

The incidence rate of TE in TM has been estimated at 0.9% to 4%, which is less than the incidence reported in TI. Ischemic stroke is a relatively common event. In addition, similar incidence rates for VTE have also been reported in TM [8].

Thalassemia Intermedia

The incidence of TE in TI has been reported to be higher than in TM. The reported range is 3.9% to 29%. The most common site of TE is venous TE including DVT, PE and portal vein thrombosis. However, one pediatric study demonstrated the incidence of silent ischemic stroke in TI to be around 18% [10]. The postulated etiologies for TE in TI include ineffective erythropoiesis, chronic anemia from non-regular blood transfusion and iron overload from increased gastrointestinal absorption [11]. The OPTIMAL CARE study demonstrated that the risks for TE in TI were splenectomy, age over 35 years old, and serum ferritin levels more than 1,000 ng/mL [12].

Table 1
Type of thromboembolism. *From: Taher A et al. Thromb Haemost 2006; 96:488–491.*

Site of thromboembolism	Overall (%)	Thalassemia major (%)	Thalassemia intermedia (%)
Deep vein thrombosis	32	23	39
Ischemic stroke	18	28	9
Portal vein thrombosis	16	11	19
Pulmonary embolism	13	8	12
Superficial thrombophlebitis	4.7	0	8

Evidence of Coagulation Hyperactivation in Thalassemia

Coagulation hyperactivation is common in thalassemia as evidenced by increased plasma markers such as thrombin-antithrombin complex (TAT), prothrombin fragment (F1 + 2) and global thrombin generation, especially in splenectomized patients [13–15]. The reported low levels of protein C and protein S have been related to a consumptive process [15,16].

Disturbed hemostasis in thalassemia has also been demonstrated by thromboelastrometry in whole blood; abnormalities included shortened clotting and clot formation times, and increased maximum clot firmness, especially in splenectomized patients [17]. These findings are compatible with a clinical hypercoagulable state.

Mechanism of Thromboembolism in Thalassemia

Platelet Activation

The evidence for platelet activation in thalassemia includes elevated urinary metabolites of prostacyclin (PGI2) and thromboxane A2 (TXA2) [18]. In addition, increased platelet expression of CD62P (P-selectin) and CD 63, which are markers of platelet activation, have been shown [19,20]. Abnormal platelet aggregation has been demonstrated in TM, HbH and HbEE [21,22]. Furthermore, chronic platelet activation results in a shortened platelet survival. In addition, the lifespan of platelets has been reported to be shorter in splenectomized β-thalassemia patients than the splenectomized controls (Fig. 1) [23].

Abnormal RBC Surface

Exposure of negatively charged phosphatidylserine on red cells in TM has been demonstrated by increased binding of annexin V [13,20]. Membrane perturbation in thalassemia is explained by the excess α or β-hemoglobin chains causing denatured hemoglobin, such as hemichrome, which together with free iron result in oxidative damage to proteins on the RBC membranes including protein band 3, ankyrin and spectrin [24,25]. Following the precipitation of hemichrome, heme disintegrates and non-transferrin bound iron is released. The exposed phosphatidylserine then activates coagulation resulting in coagulation hyperactivation (Fig. 1).

Endothelial Cell Activation

Elevated plasma levels of soluble endothelial activation/injury markers, such as ICAM1, VCAM1, von Willebrand factor and thrombomodulin, have been demonstrated in thalassemia. Moreover, increased numbers of endothelial-derived microparticles has been shown in thalassemia [26]. Abnormal thalassemic RBCs adhere more avidly to endothelial cells [27]. In addition, decreased nitric oxide (NO) during hemolysis contributes to vasoconstriction, diminishes blood flow, and increases both platelet activation and endothelin-1 levels (Fig. 1) [16].

Splenectomy

Most TM and TI patients who develop TE have previously undergone splenectomy. Following splenectomy, thrombocytosis occurs in concert with increased platelet activation and aggregation. In addition, increased numbers of circulating abnormal RBCs that express phosphatidylserine are found in the circulation. Thrombin generation potential is increased, especially in patients who have not received regular transfusions when compared to the level in non-splenectomized patients [16]. The previous study reported that high NRBC count $\geq 300x10^9$/L, platelet count $\geq 500x10^9$/L and non-transfused splenectomized TI contributed to the shortened time to development of TE in TI (Fig. 1) [28].