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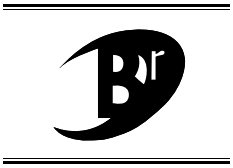

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REVIEW

Thalassemia and hypercoagulability

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KEYWORDS
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Summary Thalassemia is a congenital hemolytic disease caused by defective globin synthesis resulting in decreased quantity of globin chains. Although the life expectancy of β-thalassemia patients has markedly improved over the last few years, patients still suffer from many complications of this congenital disease. The presence of a high incidence of thromboembolic events, mainly in β-thalassemia intermedia, has led to the identification of a hypercoagulable state in these patients. In this paper, we review the molecular and cellular mechanisms leading to hypercoagulability in β-thalassemia, with a special focus on thalassemia intermedia being the group with the highest incidence of thrombotic events as compared to other types of thalassemias. We also discuss the recommendations for thrombosis prophylaxis in these patients.

Introduction

Thalassemia is a congenital hemolytic disease caused by defective globin synthesis resulting in decreased quantity of globin chains.[1] The severity of clinical course distinguishes this disease into two main subtypes: thalassemia major (TM) and thalassemia intermedia (TI). Patients with TI have, in general, a milder clinical phenotype than those with TM. The pathophysiology of TI is characterized by extravascular hemolysis, with the release into the peripheral circulation of damaged red blood cells and erythroid precursors because of a high degree of ineffective erythropoiesis.[1,2] The life expectancy of β-thalassemia patients has markedly improved over the last few years, as a result of regular blood transfusions and compliance with tight iron chelation therapies.[1] However, β-thalassemia patients still suffer from many complications

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Table 1 Prevalence of thromboembolic episodes in β-thalassemia in previous studies

Reference (year)	# of patients with thromboembolism (%)	Sites of thromboembolism
Michaeli et al. (1992)[3]	4 (TM) 4%	Recurrent arterial occlusion, recurrent PTE, venous thrombosis and one fatal stroke
Aessopos et al. (1997)[4]	6 (3 TM, 3 TI) 1%	Thrombotic strokes
Moratelli et al. (1998)[5]	26 (14 TM, 12 TI) 5.3% (overall) 3.3% (TM), 16.2% (TI)	–
Borgna Pignatti et al. (1998)[6]	32 (27 TM, 5 TI) 3.27% (TM + TI)	Thrombotic strokes-16, MT-1, PVT-2 DVT-6, intraatrial thrombosis-2, DIC in pregnancy-2, PTE-3
Akar et al. (1998)[7]	17 homozygous β-thalassemia	Nine had CNS involvement
Senanayake and Lamabadusuriya (2001)[8]	2 homozygous β-thalassemia (TM)	Cerebral thrombosis (hemiparesis)
Cappellini et al. (2000)[9]	24 TI 29%	PVT-9, DVT-3, STP-10, PTE-3, Priapism-1
Zalloua et al. (2003)[10]	4 TI 8%	Not specified
Taher et al. (2006)[11]	85 TI (3.9%) 61 TM (0.9%) Overall (1.65%)	DVT 32%, stroke 18%, PVT 16%, PE 13% and STP 4.7%

Abbreviations: PTE, pulmonary thromboembolism; PVT, portal vein thrombosis; DIC, disseminated intravascular coagulation; CNS, central nervous system; STP, superficial thrombophlebitis.

of their chronic disease, and a series of serious previously undescribed complications is now being acknowledged.

The presence of a high incidence of thromboembolic events, mainly in β-TI has led to the identification of a hypercoagulable state in thalassemic patients. Venous thromboembolic events, such as deep venous thrombosis (DVT), pulmonary embolism and portal vein thrombosis have been observed[3–11] (Table 1). However, there are relatively few epidemiological data on the overall frequency of these complications. A study by Taher et al. on 8860 thalassemia patients demonstrated that thromboembolic events occurred 4.38 times more frequently in TI than TM ($p < 0.001$), with more venous events occurring in TI and more arterial events occurring in TM.[11] Studies reported the incidence of stroke in β-TM to range from 2% to 20%.[6] In a study done to assess the rate of brain damage in patients with benign hemoglobinopathies, 37.5% of patients with TI showed asymptomatic brain damage on MR imaging.[12] In a series of β-TI patients, 24 patients (29%) developed either DVT, pulmonary embolism, or portal vein thrombosis during a 10-year follow up.[9] All patients except one had undergone splenectomy.

A study on survival and causes of death in TM, carried out in Italy at the end of the 1980s, indicated venous thromboembolism as the primary cause of death in four of 159 (2.5%) transfusion-dependent thalassemic patients.[13] In a recent survey involving nine Italian pediatric thalassemia centers, venous thromboembolism was observed in 4% of 683 patients with TM and in 9.6% of 52 patients with TI.[6] Even more recently, data from seven Italian centers on 720 patients with TM, 1.1% of the patients had thrombosis.[14]

Autopsy findings in thalassemia patients have definitely established hypercoagulability as a pathologic state. Autopsy series in patients with β-TM and β-TI describe the presence of DVT, pulmonary embolism and recurrent arterial occlusion, with thrombi in small and large pulmonary vessels.[3,9,15,16] Autopsies of a large series patients with β-thalassemia/hemoglobin E disease revealed thrombotic lesions in the pulmonary arteries.[17] These pulmonary arterial thromboembolism may have been due to circulating platelet aggregates. Similar findings of multiple microthrombi, which were composed mainly of platelets, were seen in the pulmonary arterioles and microcirculation in autopsies of two cases with splenectomized thalassemic disease.[18] As a result of multiple recent clinical studies and laboratory data, thalassemia has been referred to as a ''hypercoagulable state''.[19]

On the basis of the available data, there is evidence of increased hypercoagulability in thalassemia. This coagulation activation is attributed to many factors. Defining the contribution of the hypercoagulable state to the pathophysiology of