Chapter

Thromboembolism in Beta-Thalassemia Disease

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Abstract

Thalassemia disease is a common inherited hemolytic anemia frequently found in several parts of the world, especially in the Mediterranean and some Asian countries. Besides the complications of secondary hemochromatosis from regular red blood cell (RBC) transfusion and increased gastrointestinal absorption of iron, thromboembolism (TE) is one of the common long-term complications of beta-thalassemia disease, particularly in patients with non-transfusion-dependent thalassemia (NTDT), which is commonly seen after the second decade of life. The risk factors of TE in beta-thalassemia disease including exposure of phosphatidylserine of abnormal RBCs, increase of platelet activation and aggregation, elevation of endothelial microparticles and increased endothelial activation, decreased nitric oxide (NO) secondary to hemolysis, rise of platelet count and nucleated RBCs after splenectomy, organ dysfunction caused by hemochromatosis, and thrombophilia such as natural anticoagulant deficiencies leading to hypercoagulable state. The understanding of the pathophysiology would result in effective prevention of this complication of beta-thalassemia disease.

Keywords: thromboembolism, beta-thalassemia, NTDT

1. Introduction

Beta-thalassemia disease is one of the most common congenital hemolytic anemia commonly found in the malarial belt areas including the Mediterranean, the Middle East, Transcaucasus, Africa, South and Southeast Asian countries, and China [1]. It is inherited by autosomal recessive manner [1, 2]. Beta-thalassemia disease is the result from the mutation of beta-globin genes causing decrease of beta-globin leading to imbalance of alpha-globin and beta-globin and subsequently causing ineffective erythropoiesis. According to the Thalassemia International Federation (TIF), patients with thalassemia disease can be categorized into two groups, transfusion-dependent thalassemia (TDT) and non-transfusion-dependent thalassemia (NTDT), based on their phenotypes and genotypes [1–3]. The major long-term complication of TDT is hemochromatosis-induced organ failures secondary to red blood cell (RBC) transfusion [1, 2], while the complications of NTDT are hemochromatosis secondary to increased iron absorption from gastrointestinal tract, pulmonary hypertension, leg ulcer, and thromboembolism (TE) [3–5].

The incidence of thromboembolism is between 0.8 and 2.7 per 1000 population [6] which has been increasing over the decades in both adult and pediatric population [6, 7] patients with thalassemia disease are at risk of hypercoagulable state and thromboembolism [8, 9]. The studies of thromboembolism in thalassemia disease

have been increasingly published recently. Understanding the pathophysiology of thromboembolism in thalassemia diseases is the key for the management to prevent this complication.

2. Incidence

The incidence of thromboembolism in patients with thalassemia diseases is between 1.7 and 9.2% [4, 10, 11]; therefore, the incidence of thromboembolism in patients with thalassemia diseases is approximately 10 times higher than normal population [6]. The incidence is 4.4 times more prevalent in patients with NTDT than ones with TDT [10]. However, this complication could be seen in both patients alpha- and beta-thalassemia diseases [4].

3. Pathophysiology

The pathophysiology of thromboembolism in beta-thalassemia disease is the combinations of abnormalities in several parts of hemostatic system including [9, 12]:

1. Exposure of phosphatidylserine (PS) to external membrane of abnormal RBCs called "flip-flop phenomenon" which is caused by the decrease of normal asymmetrical dissemination of RBC membrane phospholipids [9]. In addition, free iron secondary to hemochromatosis induces lipid oxidation and elevates the level of membrane-bounded hemichromes and immunoglobulin causing alteration of the structures of spectrin and band 3 protein of RBC membrane and consequently resulting in aggregation and adhesion of abnormal RBCs to endothelial cells [9].

2. Increased number of circulating activated and aggregated platelets which are especially found in splenectomized patients [13, 14]. The activated and aggregated platelets of splenectomized patients with thalassemia usually have shorter platelet lifespan [14], higher response to several agonists, i.e., adenosine diphosphate (ADP), epinephrine, and collagen [15], and more elevated level of plasma beta-thromboglobulin [16] than the platelets of normal population. All findings reflect hyperaggregation of platelets which result in increased thrombin generation [15].

3. Increased endothelial activation caused by the activation of monocytes and granulocytes leads to endothelial injury and increased level of endothelial adhesion proteins and tissue factor contributing to hypercoaguable state. Moreover, the elevation of endothelial cell, platelet and white blood cell (WBC) and RBC microparticles, which are the shedded fragments containing high PS with the size of 0.1–2 μm from activated and apoptotic cells, leads to increased activation of hemostatic system [17–19].

4. Decreased nitric oxide (NO), secondary to hemolysis caused by the decreased level of arginine leads to pulmonary vasoconstriction and subsequently results in chronic pulmonary thromboembolism [12, 20].

5. Rise of platelet count and nucleated RBCs (NRBCs) after splenectomy which was firstly reported in 1966 [21]. This phenomenon is a strong associated factor of thromboembolism in patients with thalassemia disease particularly

when the platelet count is higher than 600,000/mm^3 and the NRBCs count is more than 300/mm^3 after splenectomy [22].

6. Organ dysfunction resulting from hemochromatosis particularly cardiac hemochromatosis causes cardiomyopathy and cardiac arrhythmia [12] which is found in beta-thalassemic patients who TDT for 42% [23].

7. Thrombophilia, i.e., natural anticoagulant deficiencies, leads to hypercoagulable state. Deficiencies of protein C and protein S, the natural anticoagulant proteins, have been reported as a risk factor of thromboembolism in patients with beta-thalassemia disease [12, 24, 25]. In addition, increased incidence of antiphospholipid antibodies, i.e., lupus anticoagulant, anticardiolipin, and anti-beta 2-glycoprotein 1, is commonly found in patients with beta-thalassemia disease. Those antibodies are considered as strong thrombophilic risk factors causing thromboembolism [12, 26].

4. Presentations of thromboembolism in beta-thalassemia

Thromboembolism in patients with beta-thalassemia diseases could be found in both arterial and venous sites. However, venous thromboembolism is more commonly found in patients with thalassemia intermedia or NTDT, while arterial thromboembolism is more frequently seen in patients with thalassemia major or TDT [10].

4.1 Venous thromboembolism

Although patients with beta-thalassemia disease are at risk of venous thromboembolism, deep vein thrombosis and pulmonary thromboembolism, the two common types of venous thromboembolism in normal population, are not generally observed. Pulmonary thromboembolism was found in lung biopsy to 41% of patients with beta-thalassemia/hemoglobin E. However, higher incidence was found in the older and splenectomized patients [27]. Simplified, revised Geneva score, based on several clinical variables, i.e., hemoptysis, old age of more than 65 years, history of venous thromboembolism, tachycardia, unilateral lower limb pain with or without deep palpation and edema, active malignancy, and surgery or fracture of lower limb within 1 month prior to the suspected symptoms and signs, has been published to use for diagnosing pulmonary thromboembolism. The more scores patients get, the higher chance of pulmonary embolism patients have [28]. Computed tomography pulmonary angiography, magnetic resonance pulmonary angiography, and ventilation/perfusion scan could be used to diagnose pulmonary thromboembolism even though conventional pulmonary angiography is the gold standard [29].

Portal vein thrombosis, which is considered as venous thrombosis of an unusual site, is more commonly reported in patients with beta-thalassemia disease [30–34] with the odds ratio of 3.5 [31]. Patients with acute portal vein thrombosis usually present with symptoms and signs of portal hypertension of bowel ischemia, i.e., abdominal pain and distension, fever, nausea/vomiting, rectal hemorrhage, and splenomegaly. If patients were not diagnosed, they might turn to sepsis-like symptoms, e.g., shock, signs of peritonitis, and even death [35]. Unlike acute portal vein thrombosis, patients with chronic portal vein thrombosis are usually asymptomatic until the presence of first symptoms and signs, i.e., upper gastrointestinal hemorrhage, splenomegaly, and ascites [35]. Doppler ultrasound, computed tomography, and magnetic resonance imaging could be used for diagnosis of portal vein thrombosis [35]. Apart from splenectomy, higher splenic weight and thalassemia

intermedia are major risk factors of portal vein thrombosis in patients with beta-thalassemia disease [30, 33]. Laparoscopic splenectomy was reported about the higher incidence of portal vein thrombosis even though this technique provided the better other surgical outcomes than the conventional technique [30].

4.2 Arterial ischemic stroke

Beta-thalassemia disease has been reported as a risk factor of arterial ischemic stroke since 1972 [36]. Compared to venous thromboembolism, arterial ischemic stroke is more common in patients with beta-thalassemia major [11]. Moyamoya syndrome, a cerebral vasculopathy caused by spontaneous occlusion of the arteries at the circle of Willis [37], was also reported in pediatric patients with beta-thalassemia disease and caused arterial ischemic stroke [38, 39]. Symptom and signs of acute ischemic stroke are based on the involved cerebral areas ranging from nonspecific symptoms, i.e., headache, nausea and vomiting, seizure, and impaired consciousness to specific neurological deficits, i.e., abnormal speech and spatial perception, hemiparesis, hemianesthesia, blurred vision, and poor coordination or walking, and cranial nerve palsies [40]. Though computed tomography of the head with or without angiography is the standard for diagnosing arterial ischemic stroke, magnetic resonance imaging of head with or without angiography could provide more details of the affected parts of the brain with higher sensitivity [40].

Moreover, the focal foci in the cerebral white matter on the magnetic resonance imaging of the brain called "silent cerebral infarction" could be found at 24–61% of patients with beta-thalassemia disease [41, 42]. However, a recent study in adult patients with beta-thalassemia disease who were asymptomatic showed that the abnormal findings on the magnetic resonance imaging of the brain were not different from the adult controls [43].

4.3 Diagnosis

Making a diagnosis of thromboembolism in patients with beta-thalassemia does not differ from diagnosing this condition in normal population which is usually based on the imaging of the suspected area of thromboembolism, e.g., computed tomography with angiography of the brain in a patient who is suspicious for having an arterial ischemic stroke. Several studies have demonstrated derangement of proteins hemostatic system in patients with beta-thalassemia diseases including increased platelet aggregation and coagulation proteins (factor VIII and von Willebrand factor) and decreased natural anticoagulants (protein C, protein S, and antithrombin) [24, 25] which encourage hypercoagulable state [44]. Besides diagnosing a symptomatic patient, the novel investigations, i.e., thrombin generation assay and rotatory thromboelastometry (ROTEM®), are able to demonstrate patients with hypercoagulable state in patients with beta-thalassemia disease who are at risk of developing thromboembolism [45, 46]. In addition, yearly monitoring of thrombin generation markers, e.g., D-dimer and thrombin-antithrombin (TAT) complex, is recommended by TIF in patients with thalassemia who are splenectomized [47].

5. Treatment

1. Regular RBC transfusion is recommended to treat patients with beta-thalassemia disease, particularly NTDT, who are at risk of thromboembolism or have developed thromboembolic events by keeping hemoglobin level higher

than 9 g/dL [3] to correct hypercoagulable state as transfusion naïve patients are prone to have thromboembolism [12, 22, 48].

2. Hematopoietic stem cell transplantation (HSCT) has been reported as the management that could normalize the abnormal hemostatic derangement in patients with beta-thalassemia disease by increasing natural anticoagulant proteins and decreasing microparticles and RBC-expressing PS and activating platelets in the circulation [49, 50].

3. Antithrombotic agents in patients with beta-thalassemia disease who have thromboembolism are recommended as per the standard local or international guidelines to treat patients with thromboembolism [3, 12].

    a. Anti-platelets: acetyl salicylic acid (ASA)

ASA 2–5 mg/kg/day is the mainstream management for the prevention and treatment of thromboembolism in patients in beta-thalassemia especially in splenectomized patients who have platelet count higher than 500,000/mm^3 [3]. However, ASA resistance has been reported in patients with thalassemia who were splenectomized, and increase dose of ASA could overcome this resistance [51].

    b. Anticoagulants consist of conventional anticoagulants, i.e., unfractionated heparin, low-molecular-weight heparin, vitamin K antagonist (VKA), and direct oral anticoagulants (DOAC) including direct oral anti-activated factor X (Xa), e.g., rivaroxaban, and direct oral antithrombin (IIa), i.e. dabigratan. Those medications are used to treat thromboembolism in patients with beta-thalassemia disease. Unlike sickle cell disease, the evidences of using DOAC in patients with thalassemia disease who develop thromboembolism are limited [52]. However, the recent study showed that using rivaroxaban in patients with hemoglobinopathies including thalassemia was effective and did not increase risk of bleeding or thrombosis [53].

4. Hydroxyurea, a hemoglobin F stimulating agent, was reported about the favorable effects not only increased hemoglobin F, hemoglobin level and improved the clinical symptoms of beta-thalassemia disease but also decreased hypercoagulable state due to the diminished exposure of PS on RBC membrane [54, 55]. Moreover, Iqbal et al. recently reported the change of metabolites, i.e., glycerol, triethanolamine, linoleic acid, palmitic acid, and stearic acid to the healthy pattern of metabolic pathway in pediatric patients with beta-thalassemia disease after treating with hydroxyurea [56].

Since patients with beta-thalassemia disease are at risk of thromboembolism as the same as other medical inpatients, the current approach is to stratify patients with the optimal risk assessment model (RAM) by using the available approaches, e.g., Padua Prediction Score and the Caprini Risk Assessment Model, to guide thromboprophylaxis [57]. However, the systematic review showed that there was not any specific risk assessment model which was superior to the others [58]. Moreover, thalassemia-specific risk assessment model for thromboprophylaxis may need to be developed due to distinctive pathophysiology of thromboembolism in patients with beta-thalassemia disease.

In conclusion, the hypercoagulable state in beta-thalassemia disease is the result of several risk factors, a combination of which is often the drive behind a clinical thromboembolism. Splenectomy and transfusion naivety are increasingly

highlighted as important risk factors for thromboembolism, especially in patients with NTDT. An individualized approach is recommended to establish an optimal strategy for preventing the occurrence of this complication in patients with beta-thalassemia disease.

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