Review Article *Iran J Ped Hematol Oncol. 2023, Vol 13, No 4, 269-276*

A review on thromboembolic events and neurological lesions in patients with β-thalassemia

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Received: 25 June 2022 **Accepted:** 19 September 2022

Abstract
B-thalassemia is the severe form of genetic illnesses which decreases the hemoglobin synthesis. One of the major complications in thalassemic syndromes, including β-thalassemia major and intermedia is thromboembolic events. In addition, thromboembolic events are more common in non-transfusion-dependent thalassemia than those in well-transfusion-dependent β-thalassemia. A combination of hypercoagulable states including, abnormalities in red blood cells, and platelet, antithrombin III, protein C, and protein S, and splenectomy are involved in thrombotic events, but thromboembolic events can be prevented and treated in these patients via blood transfusion, hydroxyurea, anticoagulants, and aspirin. Moreover, recent studies have demonstrated the involvement of the brain lesion in β-thalassemia patients. The involvement of vascular events of brain in patients with β-thalassemia intermedia is 29-83%, but the rate of asymptomatic brain lesions in the healthy people is 0-11%. In addition, neurological complications which have been attributed to various factors are chronic hypoxia, iron overload, bone marrow expansion, and desferrioxamine neurotoxicity. This review evaluated thromboembolic events and neurological lesions in patients with β-thalassemia and its probable curative therapy.
Keywords: Brain lesion, Thalassemia, Thromboembolic events

Introduction

Thalassemia is heterogeneous group of hereditary illnesses (1–12) caused by a reduction in the production of the hemoglobin's alpha or beta chains (1). Since our nation is situated in the thalassemia belt, it faces a public health issue. Iran has a rate of this gene of about 4%. The prevention program of thalassemia in Iran has been started in 1997, leading to a significant decrease of thalassemic newborn rate (2). B-thalassemia is the severe form of genetic illnesses which decreases the hemoglobin synthesis (4-8). In β–thalassemia disease, the beta gene cluster is placed on chromosome 11. The β –thalassemia can be divided into various varieties. There is no beta-chain production in β0 thalassemia.

A partial deficiency of beta-chain production is seen in β+ thalassemia. All forms of β–thalassemia are characterized by microcytosis and hypochromia. Given that β–thalassemia synthesis is nearly completely inhibited in patients with thalassemia major, severe anemia occur in the age of 3 to 6 months, when the synthesis of gamma-chain normally decreases. The anemia is associated with a stress situation in the bone marrow, leading the continuation of the synthesis of HbF, but at a much lower rate than is necessary to adequately compensate for anemia (7). Patients with β -thalassemia major from a very young age needed regular blood transfusion. Transfusion therapy improves survival, however the lack of iron elimination causes the metal to accumulate in various body organs. Iron

[DOI: 10.18502/ijpho.v13i4.13773]

accumulation mostly affects the liver, heart, and endocrine glands and causes mortality (9, 10). The second decade of life is when this pattern typically manifests (9). To remove extra iron from the body, which has negative effects on their hearts, these patients must undergo iron chelation therapy. Advances of therapy in patients with β-Thalassemia have caused longer life expectancy, increasing chances for education, and having a family (9-11).

These individuals' hypercoagulable status is caused by a number of variables (12). In addition, cerebral micro-thrombosis, and brain vascular involvement are other complications that may occur in dependent β-thalassemia and non-transfusion-dependent thalassemia (NTDT) (10).

Oxidative stress, and antioxidants in thalassemia

Hemichrome is formed in thalassemia patients due to oxidative stress, which is mostly brought on by the defects in their red blood cells. Hemichromes alter the protein band, ankyrin, and spectrin as well as other parts of the mature RBC membrane. Heme decomposes following the precipitation of hemichromes, releasing hazardous species of transferrin-bound iron (NTBI)(13).

Antioxidant defenses scavenge reactive oxygen species and free radicals. The remove of these oxygen metabolites is the function of antioxidant enzymes, including glutathione peroxidase and superoxide dismutase (SOD).

SOD exists in three forms, such as SOD1 (cytoplasm), SOD2 (mitochondria), and SOD3 (extracellular space). SODs play an important role in the hemolytic process. Glutathione and its redox enzyme system are important antioxidants against the accumulations of free radical. Moreover, it acts as detoxifying lipid peroxides and scavenging free radicals via glutathione peroxidase (14).

Hypercoagulable state in thalassemia

According to studies, a hypercoagulable state has been observed in the patients with thalassemia. Several abnormalities in red blood cells, and platelet, antithrombin III, protein C, and protein S, and splenectomy are involved in the pathogenesis of a hypercoagulable state in thalassemia (10, 15), which are explained as follow.

Red Blood Cells

Hemichromes are produced as a result of the oxidation of the globin subunits in thalassemia patients' red blood cells. By attaching to RBC membranes, this substance induces hem to disintegrate and releases harmful iron into the bloodstream (16). The free iron causes the formation of RBC antigens and the oxidation of the membrane proteins.

Adhesion Molecules

Endothelial adhesion proteins, such as E-selectin, von Willebrand factor, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1, have been shown to be elevated in thalassemia patients, indicating endothelial damage (17).

Platelet

Activated platelets have been seen in patients with TM**.** Low survival of platelets in these patients particularly splenectomized subjects have reported. Additionally, these patients' platelets exhibit a higher expression of CD26p and CD63. The result is an increase in platelet activation and aggregation (16).

Coagulation Factors

Reduced levels of protein C, S and antithrombin III are seen in patients with thalassemia (16, 17-19). Liver dysfunction caused by a variety of factors is one of the common morbidities in thalassemia patients. These factors are vitamin and protein deficiency, hepatic hemosiderosis, and viral infections (16).

[DOI: 10.18502/ijpho.v13i4.13773]

Splenectomy

The risk of thromboembolic events in splenectomized patients with thalassemia intermedia is much higher than non-splenectomized patients (16, 20). High platelet numbers and their aggregation are the cause of thrombosis in people who have had their spleens removed.

Thromboembolic events in patients with *β*-Thalassemia

Due to increased activated platelets and hemolyzed red blood cells, which result in the production of thrombin, the hypercoagulable state is a substantial risk factor for thrombotic stroke in people with -thalassemia intermedia and -thalassemia major. Recent studies have revealed thromboembolic events in both populations with thalassemia major, and thalassemia intermedia.

According to a clinical investigation, thromboembolic events occur 4.38 times more frequently in people with thalassemia intermedia than in people with thalassemia major(21). The thromboembolic events can occur in every part of the body. Portal vein thrombosis, pulmonary embolism, and recurrent arterial occlusions are the most serious thromboembolic events in thalassemia patients (10).

In addition, thromboembolic events in non-transfusion dependent thalassemia are more common than those in well-transfusion-dependent thalassemia (10, 22). Furthermore, thromboembolic events are more prevalent in β-TI than those in β-TM.

In addition, the combination of these abnormalities involved in the pathogenesis of a hypercoagulable state in thalassemia has contributed in thromboembolic events. Moreover, independent risk factors for the development of thromboembolic events included a hemoglobin level of < 9 gr/dl, plenectomy, a serum ferritin level of > 1000 ng/ ml, and age of > 35 years.

Brain vascular lesions in patients with β-Thalassemia

Involvement of brain vascular happens in 29-83% of patients with β-thalassemia intermedia (10). Another study showed asymptomatic brain damage in 37.5% of patients with thalassemia intermedia on magnetic resonance imaging (21). But the rate of asymptomatic brain lesions in the control group or healthy people is between 0-11%. Additionally, patients with thalassemia have had a variety of thromboembolic events, including major and intermedia -thalassemia (with incidence rates of 0.9-4% and 3.9-29%, respectively) (10, 23). In individuals with -thalassemia, ischemic cerebrovascular events fall into two categories: overt strokes and quiet cerebral infarcts, which involved varied degrees of deep cerebral white matter and sub-cortical areas (11). Patients with -thalassemia major and thalassemia intermedia, respectively, frequently have overt strokes and quiet brain infarcts (10).

Pathophysiology of ischemic cerebral infarcts lesions

The exact pathophysiology of ischemic cerebral infarcts is not known. However probable underlying causes are including large vessel involvement, microangiopathy, and venous thrombosis (23); but, a hypercoagulable condition is the most significant contributing factor in the pathogenesis of silent cerebral infarcts in β-TM and particularly β-thalassemia intermedia (10).

Abnormal RBC in patients with thalassemia has a tendency to aggregation, thrombin generation and the increase of thromboembolic presentations, thus transfusion may decrease thromboembolic events via reducing RBC (24). Moreover, the presence of silent cerebral infarcts on brain imaging is related to an enhanced risk of overt stroke, transient ischemic

[DOI: 10.18502/ijpho.v13i4.13773]

attack, and reduction in cognitive function (25).

Old age is another risk factor for the development of silent cerebral infarcts in thalassemic patients; thus numerous risk factors are needed to accumulate these lesions (26).

Neurological complications

Various studies have shown the involvement of nervous system in patients with β -thalassemia.

Neurological complications are attributed to several factors, including iron overload, chronic hypoxia, bone marrow expansion, and desferrioxamine neurotoxicity.

Hypoxia

The deficiency of oxygen amount in the tissues of the body is defined as hypoxia. It is prevalent in patients with hemoglobinopathies. Chronic hypoxia is a sign of disease severity in hemoglobinopathies and is associated with increased morbidity and mortality (27).

Erythropoietin expression rises as a result of tissue hypoxia. Despite increased tissue hypoxia and erythropoietin levels, there is a persistent imbalance between erythrocyte supply and demand in thalassemia illness due to inefficient erythropoiesis. Erythropoietin levels are high as a result, and the bone marrow becomes hypercellular. A vicious loop created by tissue hypoxia, increased erythropoietin, and inefficient erythropoiesis may eventually lead to a significant expansion of erythroblasts (13).

Hemosiderosis

Hemosiderosis in thalassemia is due to frequent transfusions and enhanced iron absorption. One unit of packed red cells involves approximately 250 mg of iron, and some individuals take more than 100 units of packed red blood cells. Iron deposition occurs in tissue, including spleen, heart, endocrine organs, liver, and skin. Pump failure and cardiac toxicity is a frequent reason of death. Therefore, iron overload leads to mortality and morbidity associated with thalassemia (7).

The sensorineural hearing loss caused by cochlear siderosis was related to the effect of iron on neuronal pathways in thalassemia patients (9). The discovery of subclinical neurological issues that were partially ascribed to the toxic effect of iron excess was made possible by the use of modern neurophysiologic techniques, such as evoked potentials. The cortex, putamen, and caudate nucleus were among the brain areas where iron was found, according to magnetic resonance imaging (9).

Chelation therapy

Iron can be regulated by chelation therapy via preventing the formation of hemosiderin in the vital organs and increases the quality of life among patients with thalassemia (28).

Deferoxamine (DFO)

DFO is commonly used in the treatment of patients with β-thalassemia. Consistent chelation therapy with DFO results in a negative iron balance, reduces tissue iron stores, prevents iron-induced organ damage, and enhances overall survival. Despite the benefit of DFO therapy in β-thalassemic patients, there are concerns considering its safety. Intravenous administration of DFO is associated with various organ toxicity, including bone, pulmonary, renal, and growth abnormalities (12).

Toxicity

Several studies have shown that DFO lead to neurotoxicity via the generation of oxygen free radical and by inhibition of the function essential enzymes. But this effect in different individuals was different. DFO negatively aggravates and intervenes the auditory way of patients with thalassemia disrupting their sensory-neural answer (28).

DFO induced optic neuropathy

According to studies, there is an association between the losses of optic

[DOI: 10.18502/ijpho.v13i4.13773]

perception with DFO toxicity among patients with thalassemia. Moreover, the stop of chelation therapy lead to a slight visual loss; but, severe vision loss in 51 one eye was observed in one of the children (28).

DFO associated peripheral neuropathy

Peripheral neuropathy in contrast to neurotoxicity may be due to the result of DFO therapy. The characteristics of clinical manifestation of these conditions are paresthesia, myalgias, and attenuate muscle power (28).

Nutrition deficiency

There is conflicting reports regarding the levels of trace metals, and vitamins in the blood of patients with thalassemia and their deficiency status is known to associate with nervous system pathology. Vitamin B12-related neuropathy has seen in patients with thalassemia. Vitamin B12 deficiency may affect optic nerves, spinal cord, brain, and peripheral nerves. Folic acid deficiency is less frequently observed in well-transfused thalassemic patients; however it is still a significant problem in patients with intermediate forms of this disease.

Iron chelation treatment is associated with increased copper and zinc fecal and/or urinary excretion. Furthermore, there is a minimally association between trace element depletion with neurological complications (9)

Inhibition and therapy of thromboembolic events

Blood Transfusion

In these with symptomatic CNS thrombosis, it is recommended regular blood transfusion. In patients with B-TI who underwent surgery, the beneficial effects are hydroxyurea regular blood transfusions, aspirin and anticoagulants (16, 29).

Hydroxyurea

Hydroxyurea has the capacity to decrease the production of plasma biomarkers associated with thrombin and coagulation activation factors in patients with β-thalassemia intermedia. This effect is attributed to the diminished expression of phospholipids on the surface of red blood cells (16, 30).

Anticoagulants

Low-molecular-weight heparins are routinely applied for preventing of post-surgery thrombosis. The selection of anticoagulant is dependent to the site of thromboembolic event. Aspirin is proposed mostly for arterial thrombosis, but heparins and warfarin are usually used for venous thromboembolism (16).

Aspirin

Aspirin can block the synthesis of thromboxane A_2 and decrease the aggregation of platelet. It reduces the conversion of arachidonic acid to thromboxane β_2, leading the inactivation of platelet (31). Moreover, the protective effect of aspirin on thromboembolic events in splenectomized β-talassemia intermedia with thrombocytosis has shown in some studies (15). Another study was conducted a study on patients with β-thalassemia intermedia and patients with β-thalassemia major and divided them into two groups based on aspirin consumption and recommended low-dose aspirin for patients with high-risk thalassemia for preventing new lesions or progression of brain lesions. Patients with splenectomy, older age, and severe iron overload are considered as high-risk groups (16).

Treatment of neuropathy

Gene therapy

In this method, a mutated gene can be replaced using nucleic acid therapy delivered through viral vectors. This therapy aims to restore the disrupted equilibrium caused by the abnormal products of the mutated protein. In cases of β-thalassemia, the BCL11A gene encodes the transcription factor BCL11a, which plays a pivotal role in regulating the

[DOI: 10.18502/ijpho.v13i4.13773]

transition from fetal hemoglobin to hemoglobin A in adult red blood cells. Adjusting the levels of fetal hemoglobin can rectify the aberrant beta-globulin chains in hemoglobin. This procedure involves the preparation of autologous cells and the correction of the genetic mutation. Additionally, alternative techniques include the reintroduction of stem cells and the repopulation of recombinant stem cells to an optimal level. This comprehensive approach not only restores the normal integrity of red blood cells but also mitigates neurological abnormalities that may be exacerbated by these genetic conditions (28).

Diagnostic procedures

Magnetic Resonance Imaging (MRI) of the brain is a valuable diagnostic tool for identifying subclinical or asymptomatic lesions in the central nervous system of thalassemia patients. In a study by Karimi et al., conducted on splenectomized patients with β-thalassemia intermedia, pathological findings were observed in the MRI scans of 28% of these patients. Furthermore, the study reported that splenectomized patients with β-thalassemia intermedia, a history of thrombocytosis, and irregular transfusions are at a significantly higher risk of developing vascular brain damage (32). For diagnostic purposes, MRI of the brain should be considered when these patients reach 20 years of age or even earlier to detect asymptomatic or subclinical vascular damage. Additionally, it is recommended to repeat brain MRI every 3-5 years thereafter because microvascular injury may not be adequately assessed with a single MRI study. Consequently, further research employing various imaging procedures may be necessary to assess the extent of ischemic damage (31). On the other hand, brain computed tomography (CT) scans are not effective for detecting cerebral venous sinus thrombosis in these patients. In the early stages, diffusion-weighted magnetic resonance imaging (DW-MRI) is the preferred procedure for screening asymptomatic brain vascular damage (23). Positron Emission Tomography-Computed Tomography (PET-CT), unlike MRI, is not useful for detecting silent cerebral infarcts in patients with β-thalassemia intermedia. However, PET-CT is highly beneficial for identifying neuronal dysfunction, a common occurrence in thalassemia patients due to iron overload. Therefore, combining procedures such as MRI and PET-CT can be a more comprehensive approach for recognizing functional neurological deficits and strokes in thalassemia intermedia patients (33).

Biomarkers of CNS injury and Brain Ischemia

S100 calcium-binding protein β (S100β), and neuron-specific enolase are two biomarkers for the identification of CNS injury, and brain ischemia. The levels of S100β, and NSE increases in situations, including brain hypoxia, ischemic stroke, or head trauma (34).

Conclusion

In conclusion, patients with *B*-thalassemia are at high risk for thromboembolic events and neurological lesions.

Conflict of interest

None

Funding

None

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[DOI: 10.18502/ijpho.v13i4.13773]

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