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Review

Thalassemia

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ABSTRACT

Defects in protein structure or synthesis of hemoglobin are called hemoglobinopathies. Thalassemia is the most common hemoglobinopathy, and it is estimated that 5% of the world population carries at least one variant allele of thalassemia. The thalassemias can be classified as alpha or beta thalassemias. Beta thalassemia may present as silent carriers with normal hematological parameters, while beta thalassemia carriers have hypochromic microcytic anemia, associated with a high HbA2. However, patients with beta thalassemia intermedia and beta thalassemia major need transfusion intermittently or regularly and they are called non-transfusion dependent thalassemias or transfusion-dependent thalassemias, respectively. This review focuses on pathophysiology, clinical, laboratory features of thalassemias along with their treatment and follow-up.

INTRODUCTION

Hemoglobin is a tetrameric protein that contains two pairs of globin chains. The defects in protein structure or synthesis of hemoglobin are called hemoglobinopathies. To date, more than 800 hemoglobin variants have been identified.[1] Two gene clusters are responsible for hemoglobin production; the alpha (α) gene cluster consists of zeta (ζ), alpha 1 (α1), and alpha 2 (α2) genes located on chromosome 16.[2,3] The beta (β) gene cluster consists of epsilon (ε), gamma 1 (γ1), gamma 2 (γ2), delta (δ) and beta (β) genes located on chromosome 11.[2,3] The embryonic hemoglobins Gower-1 (2 ε2), Gower-2 (α2 ε2) and Portland (ζ2 γ2) are formed starting from the 8th week of fetal life. HbF (α2 γ2), which is the main Hb of fetal life, is noticed from the 9th week on, while HbA (α2 β2), which is the main Hb of adulthood, gradually prevails in comparison to HbF. HbA2 (α2 δ2) is synthesized in scant amounts after birth. The final Hb pattern is obtained at least six months after birth and consists of 95% HbA, 3.5% HbA2, and <2.5% HbF.[4]

The thalassemia comes from the Greek word “thalassa” which means sea, and –emia originates from a Latin word that means blood. The disease was first described in the Mediterranean population and was referred to as Mediterranean anemia. Thalassemia is the most common hemoglobinopathy, and it is estimated that 5% of the world population carries at least one variant allele of thalassemia.[5] Although thalassemias often show an autosomal recessive inheritance pattern, some types of thalassemias have rare dominant inheritance pattern.[5] The thalassemias can be classified as alpha

or beta thalassemias since the primary globin type of adults is HbA (α2 β2).

PATHOPHYSIOLOGY

Thalassemias are a group of diseases in which the the balance between alpha globin, and beta globin is impaired. This imbalance is caused by a decrease in the production of one or more globin genes. The reduced globin chain causes unpairing of the remaining globins, which are precipitated in erythrocyte precursors (ineffective erythropoiesis) or destroyed in the circulation (hemolysis) ultimately.[4] As a result, patients have varying degrees of anemia and extramedullary hematopoiesis. While beta thalassemias often develop with point mutations, alpha thalassemias mostly develop with deletional mutations.[6,7] If the mutation is a "missense" mutation in beta thalassemias, this causes decreased beta globin chain synthesis called β+. In "nonsense" mutations, β0 is a phenotype in which there is no beta globin synthesis. If one of the two beta globin genes carries a mutation, these individuals are called thalassemia carriers or thalassemia minors, who are usually clinically asymptomatic. Individuals with a homozygous or compound heterozygote thalassemia mutation in the beta globin gene may present with either thalassemia major or thalassemia intermedia phenotype. To distinguish between thalassemia major and intermedia, several clinical and laboratory findings should be considered (Table 1).

BETA THALASSEMIAS

Most commonly seen in the Mediterranean region, they are also found in Asia and Africa regions close to the equator. As with sickle cell anemia and erythrocyte G6PD enzyme deficiency, thalassemias are common in areas where malaria was once endemic.[8] Carriers of thalassemia are more resistant to malaria than normal individuals, and malaria infection has a milder clinical course in these carriers. Approximately 150 million people who are carriers of thallassemia live in the Mediterranean countries, the Arabian peninsula, the Middle East countries, the west of Africa, Iran, Pakistan, Afghanistan, India, and Southeast Asia. Today, due to global migration and ethnic interactions, β thalassemia can be encountered in all parts of the world. The frequency of β thalassemia carriers in Turkey is 2.1%, and this rate rises to 13% in some of the provinces in the Mediterranean region.[9,10]

Beta thalassemia patients may present as silent carriers with normal hematological parameters and normal Hb A2 levels with several mutations, such as -101 promoter mutation.[9,10] These individuals can not be distinguished by routine screening. Beta thalassemia carriers have hypochromic microcytic anemia, associated commonly with a high HbA2 (3.5-8%), HbA2 and HbF (5-20%) levels.[4] An erythrocytosis (RBC> $5x10^{12}$/L), microcytosis, normal RDW are common for beta thalassemia carriers, but also iron deficiency anemia, alpha thalassemia trait, and chronic disease anemia should be considered for differential diagnosis.

In beta thalassemia intermedia (BTI) patients do not need a regular transfusion regimen. They need less than five transfusions within a year and are called non-transfusion dependent thalassemias (NTDT). They show decreased hemoglobin, erythrocyte count, erythrocyte indices (MCV, MCH, MCHC), and increased RDW. In peripheral smear, severe

Table 1. Clinical and laboratory differences between thalassemia major and thalassemia intermedia

	β- thalassemia major	β- thalassemia intermedia
Onset (year)	<2	>2
Hemoglobin (gr/dL)	<7	8-10
Hepatosplenomegaly	Severe	Mild to moderate
HbF (%)	>50	10-50

HbF: Fetal hemoglobin

hypochromia, microcytosis, anisocytosis, poikilocytosis, target cells, polychromasia, basophilic stippling, and normoblasts are observed. A slight increase in reticulocyte level (2-4%) can be observed. In hemoglobin electrophoresis, HbA decreases (10-20%), HbF (70-80%) and HbA2 increases.[4] The mother and father should also be screened for thalassemia carrier state with complete blood count and hemoglobin electrophoresis, but in rare instances, molecular diagnosis may be required.

The patients with beta thalassemia major (BTM) are transfusion-dependent. Laboratory features of BTM are similar to BTI. However, since HbA synthesis is far less compared to BTI, HbA is not seen in hemoglobin electrophoresis, and HbF is more than 80% of total hemoglobin.

BETA THALASSEMIA MAJOR

Patients with homozygous β0-thalassemia often present with severe anemia due to inadequate HbA synthesis in the first 3 to 4th months of life. However, depending on the type of mutation and HbF production, the need for transfusion may be delayed up to 2 years of age. In patients who do not receive adequate transfusion therapy, growth retardation, hepatosplenomegaly, hypersplenism, bone changes due to bone marrow enlargement, thalassemic face (maxillary hyperplasia, frontal bossing, depressed nasal bridge) develop.[4] Transfusion therapy aims to prevent these changes due to ineffective erythropoiesis.

At the onset, to differentiate thalassemia major and intermedia transfusion should be deferred until Hb level drops below 7 gr/dL. However, in patients with growth retardation, thalassemic facial changes, and progressive splenomegaly, transfusion therapy should be initiated earlier. It is necessary to evaluate Hb electrophoresis, Rh and Kell subgroups, viral serology (CMV, HIV, Hepatitis B, HCV) tests before transfusion. Contemporary transfusion programs recommend that a lower hemoglobin limit of 9-9.5 gr/dL should be set before transfusions.[5]. Since a Hb decrease of 1 gr/dL per week is expected in patients, regular transfusions should be done every 3 to 4 weeks. A subgroup-appropriate, leucodepleted erythrocyte suspensions should be preferred. Alloimmunization, transfusion-related viral infections, transfusion reactions, and annual transfusion rates should be monitored in these patients.

In transfusion-dependent thalassemias, iron overload inevitably will develop due to iron gained from transfusions and increased gastrointestinal iron absorption, which is responsible for morbidity and mortality. Iron accumulates primarily in the liver, followed by endocrine organs and the heart. Hypothyroidism, hypogonadotropic hypogonadism, growth hormone deficiency, hypoparathyroidism, and diabetes mellitus may develop due to iron overload.[11] Besides, iron overload in the heart, causing arrhythmias and heart failure, can be fatal. Chelation therapy is necessary to prevent these complications, and iron overload should be regularly monitored for adequate chelation. Monitoring of serum ferritin, measured at least 3- month intervals, facilitates chelation management, but it does not reflect tissue iron status properly. Today, T2* and R2* MR imaging has become the standard for indirect, quantitative measurement of iron accumulation in heart and liver.[12] It is recommended to start the follow-up with MRIs after the age of 8-10 and once a year henceforth.

Iron chelation should be initiated after 10 to 15 transfusions or when serum ferritin rises above 1,000 ng/mL.[13] However, iron chelators are not approved for use under two years of age. Information on three different iron chelators is shown in Table 2. These drugs can be used alone or together with deferiprone to reduce cardiac iron load. Ideally, serum ferritin level is desired to be between 500-1000 ng/mL. When the serum ferritin level decreases below 500 ng/mL in transfusion dependent patients, it is recommended to suspend chelator therapy.[13-15]

Splenectomy should be recommended in cases of hypersplenism, with signs such as the mass effect of the spleen, also in cytopenias or increased annual

Table 2. Iron chelators

	Deferoxamine	Deferiprone	Deferasirox
Administration	iv, sc, 8-12 h/day, 5-7 day/week	Oral tablets, suspension 3 times daily	Oral dispersible and film-coated tablet, Once daily
Dose	25-60 mg/kg/d	75-100 mg/kg/d	20-40 mg/kg/d (dispersible) 14-28 mg/kg/d (film-coated)
Excretion	Urine, feces	Urine	Feces
Adverse reactions	Local reactions, retinal toxicity, ototoxicity, bone toxicity	Agranulocytosis, arthralgia	Gastrointestinal disturbances, increase in hepatic transaminase levels , rash, mild creatinine increase, ophthalmologic toxicity, ototoxicity
Monitoring parameters	Eye examination and hearing test once a year	Complete blood count, ALT monitoring	Serum creatinine, ALT, total and direct bilirubin once a month
Specifications	Low adherence	Effective in reducing cardiac iron	High adherence

iv: Intravenous, sc: Subcutaneous, ALT: Alanine aminotransferase

need for blood transfusion (> 200 mL/kg) in patients with thalassemia.[5,16] Splenectomy is often not recommended before the age of 5, as the risk of sepsis is high. Apart from the risk of infection after splenectomy, the risk of thrombosis and pulmonary hypertension also increases.[16] Because of the possibility of pneumococcal sepsis, polyvalent pneumococcal vaccine and then lifelong prophylactic penicillin is recommended for at least 3-4 weeks before splenectomy.

It has been 30 years since the first hematopoietic stem cell trasplantation (HSCT) performed for thalassemia major patients. Today, allogeneic transplantation is a curative method and standard clinical practice in patients with thalassemia major. Therefore, all patients with thalassemia major should be screened for family donors, and HSCT should be recommended before organ damage due to development of iron overload. In Turkey, a study conducted with 245 children with thalassemia major, disease-free survival was 68%, overall survival 85%, and transplant-related mortality 7.7%.[17] According to Pesaro experience, hepatomegaly, portal fibrosis, and insufficient iron chelation are independent adverse risk factors for transplantation.[18]

Gene therapy seems to be an alternative, curative treatment option in patients with thalassemia major who do not have suitable HSCT donors. Autologous HSCT is performed after correction of beta-globin mutation mediated by lentiviral vectors or gene editing.[19] In addition, activation of HbF synthesis by these methods alleviates the clinical signs of beta thalassemia. Initial results are exciting, and permanent increase in Hb, decrease in the need for transfusion, and improvement in quality of life have been reported.

There is an increase in GDF11 production as a result of intramedullary apoptosis and ineffective erythropoiesis. GDF11 is a “transforming growth factor β ligand” and inhibits the differentiation of erythroid precursors. More effective erythropoiesis can be achieved with new treatment strategies based on the principle of binding to GDF11. For this purpose, there are two molecules developed as luspatercept (ACE-536) and sotatercept (ACE-011). Luspatercept prevents GDF11 from binding to its receptor. Its subcutaneous administration every three weeks has been recommended. According to the results of the Phase II study, in the thalassemia major group, a reduction of more than 33% in need

for blood transfusion was observed in 83% of the patients. On the other hand, in the non-transfusion dependent thalassemia group, Hb levels increased by more than 1 gr/dL in 78% and 1.5 gr/dL in 56% of the patients. The results are similar in the Luspatercept Phase III study (BELIEVE study).[20]

BETA THALASSEMIA INTERMEDIA

Patients with BTI are not transfusion dependent; however, they may need a transfusion during infections, inflammation, and pregnancy due to increased hemolysis. Hypochromia and microcytic anemia are present, and Hb levels are between 6-10 gr/dL. Medullary expansion in bone marrow, hepatosplenomegaly, hypersplenism, extramedullary hematopoiesis, pulmonary hypertension, leg ulcers, thrombosis, and growth retardation can be seen in patients with beta thalassemia intermedia.[21] Hemosiderosis may develop due to increased gastrointestinal iron absorption, especially in the liver. In these patients, it is more challenging to monitor iron overload by serum ferritin since iron accumulation is mainly in hepatocytes compared to macrophages. On the other hand, with or without hepatitis C infection, the risk of hepatocellular cancer is higher in patients with beta thalassemia intermedia than patients with thalassemia major. Regular transfusion may also be required in patients with TI when growth retardation, exercise intolerance, hypersplenism, bone changes, and extramedullary hematopoiesis develop.[21]

ALPHA (α) THALASSEMIAS

Alpha thalassemias are more common, especially in Southern China, Malaysia, and Thailand. The milder phenotypes are also found in people with African origin. The risk of hydrops fetalis is higher in Asians since alpha thalassemia-1 carriership (i.e., presence of 2 alpha globin gene deletions in the αα/- in cis position) are more prevalent in Asians.

In silent alpha carrier state (alpha thalassemia-2), Hb Barts is detected at a rate of 2-5% in the cord blood in the neonatal period, which disappears after the first three months. Detection of these individuals outside the neonatal period is only possible by performing in vitro Hb chain synthesis or molecular tests.

In severe alpha carrier state or alpha thalassemia-1, hematological features are similar to beta thalassemia carriers. MCV is low, and RBC is often high. However, HbA2 levels are normal or lower than normal. In peripheral blood smear, erythrocytes have hypochromia, microcytosis, anisocytosis, poikilocytosis, polychromasia, and basophilic stippling. Hb Barts is seen in 5 to 10% of newborns which disappears after six months of life. A definitive diagnosis is made by in vitro Hb chain synthesis and DNA studies.[22-24]

Patients with HbH disease may present with hemoglobin between 8-10 gr/dL and hypochromia, microcytosis, anisocytosis, poikilocytosis, polychromasia, and target cells in peripheral blood smears. Inclusion bodies are seen on the erythrocytes after incubation of erythrocytes with bright cresyl blue.[25] In 20-40% newborns Hb Barts is detected in Hb electrophoresis, replaced by HbH in 5-30% of the cases in time. A definitive diagnosis should be made based on a decrease in α chain synthesis and DNA studies. Acquired HbH disease has also been reported secondary to myeloproliferative and myelodysplastic diseases.[26]

HbH disease presents with hypochromia and microcytic moderate to severe anemia. Splenomegaly, scleral icterus, and gallstones can be observed in patients. Since they do not show symptoms except during infection, inflammation, or pregnancy, It may not be diagnosed until the second decade. HbH patients should be monitored for growth, osteopenia, and iron accumulation. Also, folic acid supplementation should be initiated.[23,24]

ERADICATION AND PRENATAL DIAGNOSIS

In Turkey, pre-marital screening has been carried out since the 2000s, and as of November 2018, pre-marital screening was extended to all over the country. Prenatal diagnosis was made for the first

time in 1975 by fetal blood sampling between 18-22 weeks of gestation by in vitro hemoglobin chain synthesis and measurement of α/β globin ratio. Today, thalassemia mutations are analyzed by isolating DNA from fetal chorionic villus samples.

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