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THERAPEUTIC OPTIONS AND MANAGEMENT APPROACH ON THALASSEMIA AN OVERVIEW

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ABSTRACT

People with thalassemia, the body produces an aberrant form of hemoglobin, a hereditary blood condition that runs in families. Anemia is caused by this disorder, which causes a significant number of red blood cells to be destroyed. Iron overload, cardiac arrhythmia, hepatitis, osteoporosis, and endocrine disorders are the primary problems that thalassemia patients confront; however, anemia can also present with conventional symptoms. Treatment options for thalassemia patients are based on how serious their condition is. The standard form of treatment for thalassemia is blood transfusion. The names of thalassemia syndromes are based on the defective hemoglobin produced or the globin chain that is impacted. Thus, Mutations in the β-globin gene result in β-thalassemia, while mutations in the α-globin gene cause α-thalassemia. This review covers the various forms of thalassemia, as well as its diagnosis, prevalence, complications, and management.

INTRODUCTION

Thalassemia can be defined as the most common hereditary red blood cell disorder that causes anemia due to defective genes that in turn code for the synthesis of globin proteins in the body. An individual with thalassemia may be a carrier or a patient depending on how their genotype is inherited. Alpha (α) and beta (β) are the two main types of thalassemiawhereby the former is the most prevalent type of thalassemia globally, particularly in the population of Southeast Asia (Goh et al., 2020).

The Greek words thalassa (sea) and haima (blood) are the source of the term Thalassemia and the globin chain impacted or the aberrant hemoglobin involved determines the name of the thalassaemia syndromes; β- thalassaemia can result from defects in the βglobin gene,

whereas α- thalassaemia can be caused by mutations in the α- globin gene. In individuals with β-thalassemia, the normal formation of α-globin chains remains, leading to the accumulation of α-globin that is mismatched in the erythroid precursors. The characteristic of all β-thalassemias is poor erythropoiesis because of the increased incapacity of free α-globin chains to form Hb tetramers. Rather, they precipitate and form inclusion bodies in the bone marrow, which lead to the intramedullary death of erythroid precursors. β-thalassemia Major patients always have iron overload from inadequate erythropoiesis and recurrent blood transfusions; these patients need repeated blood transfusions to maintain a normal quality of life. (Bashi and Fathi, 2022). Iron overload may have negative effects on the heart, kidneys, lungs, liver, and endocrine system, among other vital organs. (Fianza et al.,2021). Previous studies substantiate that HbA2 is lower if iron deficiency or the α-thalassemia trait is present; it is unaffected by gender, smoking, or tribal allegiance. (Zahraa et al., 2022). The predominant feature of the clinical picture of thalassemias is chronic anemia resulting from intra- and extramedullary hemolysis, ineffective erythropoesis, and iron overload after two events: first is increased intestinal iron absorption in patients who are not transfused and have thalassemics; and second is blood supply to patients who require transfusions ((Abd and Samarrai 2022). Additionally, some research has indicated a correlation between thalassemia patients and other diseases, including breast cancer, suggesting that thalassemia patients may get breast cancer. Due to an interaction of environmental and inherited factors, not just a coincidence. Recently published a report about a study on the many kinds of mammography. Among those with thalassemia (Picardo et al., 2015) and (Mahmoud, 2023)

TYPES OF THALASSEMIA

Is induced by a reduction in the synthesis of one or more globin chains. The kinds that impact either beta or alpha chain synthesis are the most significant ones.

α-thalassemia

There are many types of alpha thalassemia. Among these types, which are considered the majority typical, are silent carrier alpha thalassemia: there are two alpha-type genes present every chromosome 16. In silent carrier alpha thalassemia, one of the alpha genes is absent at the top of the chromosome, leaving three of the four genes. Patients in this type are healthy in terms of hematology, aside from occasional low values of red blood cells. The characteristic known as "alpha thalassemia" is typically brought about by the loss of one or two alpha α genes from chromosome 16 or from both chromosomes 16

The Indian subcontinent, Southeast Asia, and other regions of the Middle East have higher rates of the alpha thalassemia trait. Mild anemia and low red blood cell indices are characteristics of this trait. This variant is caused by three alpha globin genes being deleted or

rendered inactive, resulting in an excess of beta chains as well. Typically, patients arrive with icterus, splenomegaly, severe anemia, and abnormal red blood cell indices. Alpha thalassemia major: The severe form of homozygous alpha thalassemia is caused by the deletion of all alpha genes on both copies of chromosome 16 (Meri et al., 2022).

There are four categories to determine the severity of this disorder:

- Silent carrier: Of four possible alleles, those with silent carrier are one of who's damaged or absent (αα, oo). The RBC is lower than normal, but there are no additional complaints.
- Alpha-thalassemia trait/carrier: Of the four alleles, two are missing or have been taken off one chromosome (αα, oo) or both of them (αo and Ⅰ). He with this characteristic suffers from mild anemia.
- Hemoglobin H: With this kind of form, all three alleles are deleted, leaving only one functional allele. Individuals with hemoglobin H confront moderate to severe anemia, and occasionally exposure to specific chemicals or medications can make their condition worse, etc.
- Alpha-thalassemia major: This disorder results in hydrops fetalis syndrome or severe anemia when all four alleles (oo, oo) are absent. The patient has a noticeable hepatosplenomegaly, skeletal deformity, and a risk of inducing fetal death (Muskan,2020).

2-β-thalassemia

There is a single beta-globin gene within chromosome 11. Contrasting the duplication seen in alpha thalassemia. Beta thalassemia comes in different forms: Beta thalassemia minor or silent carrier: This type of thalassemia is caused by a very mild mutation. Typically, these patients exhibit no symptoms or signs, or they may experience slight variations in the quantity or size of red blood cells. This type of beta thalassemia is the most prevalent type. Intermediate beta thalassemia or beta thalassemia trait: In this state, there is a reduction in beta globin production (Putri et ai., 2022). It has been demonstrated that the b-thalassemia trait confers protection against myocardial infarctions, progressive coronary artery disease, and ischemic cerebrovascular accidents.9, 11 Patients with b-thalassemia trait have been linked to reduced blood pressure, blood viscosity, and serum cholesterol levels as a result of these protective characteristics. B-thalassemia Characteristic as a Preventive Factor for Alzheimer's disease (Mohammed et al., 2022).

There is only one type of gene in beta thalassemia, which is the beta globulin (HBB) gene on chromosome 11, and we can divide it into four types.

1. Thalassemia minor: Most people with thalassemia minor have low red blood cell counts and no symptoms. They can occasionally have mild 0 + anemia, which is represented as β/β or β/β thalassemia.
2. Thalassemia intermediate: People who have thalassemia intermedia + 0 + + lack one allele or have a mutated β /β or β /β allele. The various types of mutations present determine how severe the disease is. Although the majority of intermediate patients have mild anemia and don't require frequent blood transfusions, severe cases can necessitate blood transfusions for the duration of a patient's life. In children between the ages of six months and two years, symptoms may appear, even though they can receive fewer blood transfusions, their development and mental state have stagnated. Clinical complications, such as the formation of enucleate red blood cells (RBCs) this is because red blood cell multiplication has increased, It could be unable to further and cause premature death or suppression of production of red blood cells and anemia., can occur even though the patient receives low blood transfusions (Gupta R, 2018). Additional clinical variables include thrombophilia, leg ulcers, spleenectomy, iron overload, and infertility. Other; osteoporosis, joint, and cardiac bone pain are caused by deformities of the bones. One major cause of death is heart disease.
3. Thalassemia Major: Also referred to as Cooley's 0 0 anemia, Thalassemia Major, the beta globulin chain (β /β) is either deleted or not synthesized. Children who have thalassemia major may be identified in their first year of life if both of their parents have the disease or are carriers. In addition to producing paleness, jaundice, facial bone deformities, and occasionally failing to thrive during birth, they are unable to produce normal adult hemoglobin (A.D.A.M Inc, 2020).
4. Dominant β-thalassemia: It is an extremely rare condition in which a person have the same symptoms of thalassemia major even though they only have one mutated allele. The affected individuals have splenomegaly, jaundice, or mild to severe anemia (NORD).

Complications of thalassemia

The consequences of the disease itself or the side effects of the patient's treatment are what cause the patients' burden with thalassemia. Patients with transfusion-dependent thalassemia eventually develop iron overload, necessitating therapeutic intervention with iron chelation. Hematologists in particular should be the medical resource persons in charge of long-term monitoring and management (Hossain and Al Mosabbir, 2021).

For major cases of thalassemia, allogenic hematopoietic stem cell transplantation (HSCT) provides the most effective restorative course of action. However, for most thalassaemic cases, it is not practical due to donor obstacles or unavailability (HLA-matched donors),

insufficient resources and experience, Costly, and increased risk of HSCT-related death and diseases.

The nature of arthritis in patients with beta-thalassaemia trait (b-thal trait) is still unknown. Some studies suggest it may be a mild form of seronegative rheumatoid arthritis, particularly in Mediterranean populations (Montecucco et al., 1999) and (Al-Karawi et al., 2023).

Nowadays, the mortality rate for thalassemia patients in Western countries has decreased, between 1980 and 1999, there were 12.7 fatalities per 1000 patients; in the years that followed, there were 1.65 deaths per 1000 patients due to notable breakthroughs in iron chelation treatment and blood transfusion. However, due to exposure to disease and side effects of treatment, such as exposure to hepatitis C, complications from iron overload, bone diseases, endocrine diseases, and many other complications, as well as premature death of the individual, there are still significant morbidities associated with progression. Age. (Taher and Cappellini, 2018).

These results imply that those with β-thalassemia minor are more susceptible to H. pylori infection than healthy individuals. But there is still a lot to learn about just how this increased susceptibility operates (Zamani et al., 2018 and Kadhim et al., 2023).

Compared to non-thalassemia patients, transfusion-dependent patients were found to have a lower health-related quality of life because of underlying complications like splenectomy, small build, malnourishment, and extended hospital stays (Mettananda et al., 2019) . They were reported to exhibit social restraint, low IQ, hopelessness, and subpar academic performance (Tarım, 2022). Patients experience severe physical, psychological, and social trauma, as do members of their families, particularly mothers.

Epidemiology of thalassemia

An evaluation of the prevalence of thalassemia major in the populations in the Middle East and North Africa (MENA region) "a significant indicator of risk in the case of major thalassemia" found that Saudi Arabia (KSA) had a higher rate of β-thalassemia, with 1–15% of the overall population carrying β-thalassemia and 5–10% carrying α-thalassemia, given the prevalence of consanguineous unions "Kim and Tridane (2017)" In Jordan, the prevalence of β-thalassemia carriers was 3 to 5.9%, whereas the same area showed a prevalence of 2 to 3.5% for α-thalassemia carriers. In Egypt, 4.5% of β thalassemia carriers were found, but Kuwait reported a 5–10% incidence of α thalassemia carriers. Compared to Bahrain, the UAE exhibited a greater prevalence of carriers of both β and α thalassemia. In Bahrain and the United Arab Emirates, the prevalence of β- and α-thalassemia is 49.2% and 2.9%, respectively (Kim and Tridane, 2017).

According to a study by Modell and Darlison (2008), of the 850 million people living in the US, the projected rate of thalassemia per 1000 individuals was 0.06%. 0.07% of the 585 million people living in Africa, 0.13 % of the 879 million people living in Europe, 0.66% of the 1564 million people living in South East Asia, and 0.76% of the 1.761 million people living in the Western Pacific. It was subsequently discovered, however, that the frequency of beta thalassemia gene is lower than that for alpha thalassemia; moreover, its incidence in Southeast Asia can be up to about 25 % at some places. (Abu-Shaheen et al., 2020). The regions of the Middle East and North Africa, specifically the Gulf Cooperation Council countries such as the United Arab Emirates, Saudi Arabia, and Iraq, have a low prevalence of alpha thalassemia compared to the prevalence of the other type of disease beta-thalassemia. (Kim and Tridane, 2017) and (Kready et al., 2023).

According to various studies, the vast majority of patients with transfusion-dependent thalassemia contract mild or asymptomatic COVID-19. In addition, these patients also produce a statistically equivalent IgG antibody response to COVID-19 as do controls. But the serological response, with a more rapid fall in antibody titers than that of the control group after three to six months is only transient. This underlines the need to protect this vulnerable group through immunization (Kumari et al., 2023) and (Al-Jandeel et al., 2023).

Laboratory Diagnosis of Thalassemia

A variety of laboratory tests are necessary for the diagnosis of thalassemia and abnormal hemoglobin in humans. Notably, these tests include the assessment of red blood cell characteristics using an automatic hematology analyzer, the identification of Hb A2, and the study of Hb and Hb F. Capillaries, area electrophoresis, and high-performance liquid chromatography (HPLC).

CE systems are capable of differentiating between carriers and patients with thalassemia. It has been frequently employed to take the role of physical labor. These devices offer accurate and repeatable qualitative and quantitative analyses of Hb componentsThis has enabled us to identify thalassemia in prenatal and postnatal patients more quickly. Many modern and advanced techniques have been used to detect the point mutation, and DNA analysis is able to identify the specific thalassemia mutation. In addition, genotyping for thalassemia can be performed by using melting curve analysis and real-time polymerase chain reaction (PCR). But when previous molecular analysis methods fail to identify the mutation, DNA sequencing will be used. In recent years, thalassemia has also been identified using genome sequencing by NGS. (Munkongdee et al., 2020).

Therapeutic options for thalassemia

Aside from conventional treatments such as frequent blood transfusions and iron-chelating medications, one potential treatment for thalassemia is pharmacological stimulation of the gamma globin gene. Regular blood transfusion overloads the body with iron, which is bad for the heart and liver (de Montalembert et al.,2017). Several pharmaceutical drugs that raise the level of HbF are used to adjust the degree of thalassemia. Examples of such drugs: Hydroxyurea is an effective and affordable drug that normalizes the activity of several signaling pathways, increasing HbF synthesis and, therefore, reducing the need for regularly blood transfusions (Iqbal etal.,2018).

Despite being a potential therapy for thalassemia, allogenic (hemopoietic cell) transplantation has several challenges in its implementation. The scarcity of donors who match the human leukocyte antigen (HLA), the possibility of graft rejection in specific situations, and the impact of iron toxicity on the rejection or failure of hematopoietic stem cell transplantation (HSCT) (Pilo and Angelucci 2019). The most recent treatment option that eliminates clonal dominance, graft rejection, and mortality is lentiglobin gene therapy. Nonetheless, some patients have been documented to experience delayed platelet engraftment. (Anurathapan et al.,2019).

Blood transfusion

A build-up of α-globin chains and insufficient production of normal haemoglobin lead to severe anemia, which in turn causes ineffective erythropoiesis. (Al-Sharifi et al.,2019). Patients with thalassemia major or intermediate need blood transfusions on a regular basis; the frequency of transfusions varies from person to person. (Mettananda et al.,2019). Regular blood transfusions prolong the life expectancy of patients while maintaining organ function, often adding several years to their survival. Additionally, a perfect blood transfusion reduces weariness, lethargy, and laziness. (Sharma et al.,2011).

Furthermore, blood gives afflicted individuals the power they need to live properly and boldly handle stress and other circumstances (Roberts et al.,2016). Transfusions of unscreened blood frequently result in transfusion-transmitted infections in patients. (Mahmoud et al.,2016). Some recipients of incompatible blood transfusions also experience potentially fatal allergic reactions.

For thalassemic people, the immunological reactions that arise between the donor and the recipient as a result of incompatible blood can be fatal. The most frequent infections that arise from using unscreened blood are syphilis, dengue virus, HIV, hepatitis B, hepatitis C, malaria, and HIV. (Bird et al.,2016). Bacterial contamination of blood iron accumulation may also cause harm to the patients. Iron overload is the most hazardous and worrisome health condition

that thalassemia major patients deal with throughout the blood transfusion phase of their therapy. (Amjad et al.,2020).

Iron overload

It is the main cause of death in thalassemia patients, and receiving blood transfusions leads the patient's body into excess iron overload, making it difficult to prevent., which becomes deadly when it builds up around vital organs like the heart, liver, and kidneys, resulting in heart problems and renal failure. (Origa 2017). An increase in the removal of erythrocytes from the peripheral circulation or intramedullary cell death are the results of imbalanced, overabundant globin chains that tend to precipitate close to the red blood cell membrane. The precipitated globin chains (inclusion bodies) cause damage that is partly attributed to hemochromes, heme (protoporphyrin), and liberated iron. The liver is where most of the proteins needed to keep the iron balance in the body are produced. It also serves as a place to store excess iron. Additionally, it is crucial for the release of iron from hepatocytes into the bloodstream to fulfill the body's metabolic needs. (Hasan and Mahmoud 2018).

Hemorrhages and blood spots on the skin can also develop from repeated transfusions. medications for the augmentation of Hb The γ-globin gene is activated by hydroxyurea, which also increases HbF production. One inexpensive and efficient medication that helps some thalassemia patients reduce the frequency of blood transfusions needed is hydroxyurea. (Ansari et al.,2019) . When two α chains join with γ-globin chains, they form HbF, which replaces the damaged haemoglobin (Ansari et al., 2017).

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