

OVERVIEW ON THALASSEMIA: A REVIEW ARTICLE

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ABSTRACT

Thalassemia is a hereditary blood disorder which is passed down through families in which the body makes an abnormal form of hemoglobin. This disorder results in the destruction of red blood cell in large number, which leads to anemia. It is caused by mutation in the DNA of cells that make hemoglobin. Thalassemia should be prevented by premarital screening and prenatal diagnosis which is helpful in decreasing prevalence and future incidence of thalassemia. The most important problem in thalassemia patients are iron overload, cardiac arrhythmia, hepatitis, osteoporosis and endocrine disorder however there are typical signs and symptoms of anemia. People with thalassemia can get treatment as indicated by the degree of seriousness of their condition. Blood transfusion is the common treatment for thalassemia. This review presents the types, diagnosis, prevalence, complications and treatment of thalassemia. Thalassemias are a major public health issue in many populations which many health authorities fail to address. These requirements are not recognized by measures such as the Global Burden of Disease project, which ranks thalassemia very low in terms of disability-adjusted life years (DALYs), and fails to consider that it ranks highly in the one to four-year-old age group, making it an important contributor to under-5 mortality. Thalassemia does not fulfil the criteria to be accepted as a target disease for neonatal screening. Nevertheless, depending on the screening methodology, severe cases of thalassemia will be detected in most neonatal screening programs for sickle cell disease. This is very valuable because: (1) it helps to prepare the affected families for having a sick child and (2) it is an important measure of secondary prevention.

Keywords: Thalassemia; Hemoglobinopathies; Newborn Screening; Bone Marrow Transplant.

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INTRODUCTION

Thalassemia is a genetic disease that takes place in blood cells, is a major health problem all over the world where the value of hemoglobin (the main component of the red blood cells and oxygen transporter) is below normal (Patel S. and *et.al.*, 2018). Thalassemia results from a genetic defect affecting the hemoglobin production process, and this genetic defect is transmitted from parents to their children. Thalassemia depends upon the severity and type of the disease, as some children exhibit symptoms since birth, while others develop symptoms during the first two years of life. Symptoms may not be shown in people with the disorder i.e (those who have a single gene disorder) (Taher A. and *et.al.* 2009). More than 200 different mutations (defects) can be caused to the β -globin gene, which is present on chromosome 11. The majority of the mutations that cause β -thalassemia are point mutations i.e changing one letter of the genetic code. Various β -chain dysfunction mutations can happen in different ways (Vincenzo D and Christos K., 2017). Molecular DNA tests to detect mutations in patients. Allow prediction of disease severity. With the aid of

those molecular methods, the disease can be identified in the fetus during the earlier periods of pregnancy (Prenatal diagnosis) (Al-Allawi NK. and Hassan K., 2010).

What is thalassaemia?

The thalassaemias are a group of recessively autosomal inherited conditions characterised by decreased or absence of synthesis of one of the two polypeptide chains (α or β) that form the normal adult human haemoglobin molecule (haemoglobin A, $\alpha_2\beta_2$), which results in reduced haemoglobin in red cells and anaemia (Higgs DR, and et al., 2008). The term thalassaemia derives from the Greek words *thalassa* (sea) and *haima* (blood) and the thalassaemia syndromes are named according to the globin chain affected or the abnormal haemoglobin involved; β globin gene defects may give rise to β thalassaemia, while mutations of the α globin gene may cause α thalassaemia.

Which populations are at risk?

β thalassaemia is prevalent in areas around the Mediterranean, in the Middle East, in Central, South, and South East Asia, and in Southern China; α thalassaemia is prevalent in South East Asia, Africa, and India. Population cohort studies estimated that worldwide 1.5% (80-90 million people) are carriers of β thalassaemia and 5% are carriers of α thalassaemia (Flint J. and *et al.*, 1998). The high prevalence of α and β t thalassaemia genotypes in communities with endemic *Plasmodium falciparum* malaria has led to a theory that the thalassaemia gene mutations represent a mechanism of evolutionary protection (Weatherall D.J.,1997). Recent migrations of populations at risk to non-endemic countries has resulted in increasing prevalence of thalassaemia gene mutations in all parts of the world (Vichinsky E.P.,2005).

Classification of Thalassaemia:

Is due to decreased production of one or more globin chains. The most important types are those that affect either alpha or beta chain synthesis.

1- α thalassemia:

There are several forms of alpha thalassemia. The most common forms are: Silent carrier alpha thalassemia: There are two alpha genes located on each chromosome 16. (Pintail A . and Liver M., 1996). In the silent carrier state, one of the alpha genes is absent, leaving three of four genes (aa/ao). Patients are hematological healthy, except for occasional low red blood cell indices. Alpha thalassemia trait: This form is usually caused by the deletion of two alpha (a) genes on one chromosome 16 (aa/oo) or the deletion of one gene from each chromosome 16. Alpha thalassemia trait is more common in Southeast Asia, the Indian subcontinent, and some parts of the Middle East. This trait is characterized by mild anemia and low red blood cell indices. Hb H disease: This form results from the deletion or inactivation of three alpha globin genes (oo/ao), resulting also in an excess of beta chains. Patients usually present with severe anemia, splenomegaly, icterus, and abnormal red blood cell indices. Alpha thalassemia major: This condition results from the deletion of all alpha genes on both copies of chromosome 16 (oo/oo), leading to the severe form of homozygous alpha thalassemia (Pintail A . and Liver M., 1996).

2- β thalassemia:

In contrast to the duplication found in alpha thalassemia, there is only one beta-globin gene on chromosome 11. There are several forms of beta thalassemia: Silent carrier beta thalassemia or beta thalassemia minor: The mutation that causes this form of thalassemia is very mild. These patients usually have no signs or symptoms, or have some minor changes in number or size of the red blood cell. This is the most common form of beta thalassemia. Beta thalassemia trait or beta thalassemia intermediate: In this condition, the production of beta globin is decreased. Patients have mild anemia, abnormal red blood cell indices, and abnormal hemoglobin electrophoresis results with elevated levels of Hb A2, Hb F, or both. Thalassaemia major (Cooley's anemia): In this

condition, the patient can't produce beta globin. To compensate, the marrow produces gamma globin and more alpha globin. This condition is characterized by transfusion-dependent anemia, massive splenomegaly, bone deformities, growth retardation, and peculiar facies in untreated individuals. Hemoglobin electrophoresis shows high level of Hb A₂, Hb F, and no Hb A. Happens as a result of a deficiency or defect in two beta type series (Akhavan H, and *et.al.* 2011). Which consists of hemoglobin and divided into a) thalassemia minor, results from a defect in a single chain and the patient is asymptomatic, but shows a simple anemia during routine blood tests (Martin A, and Thompson AA. , 2013). and intermediate thalassemia, which is an intermediate condition between minor and major types, where patients may live a normal life, but need occasional blood transfusion in times of illness and pregnancy (May C. and *et.al.*, 2018). In thalassemia major type, patients suffer from severe anemia, bone marrow and hypertrophic swelling and need regular blood transfusions to live normally, and the symptoms do not occur at child's birth, but appear during the first two years of the child's life (Martin, A., & Thompson, A.A., 2013). Phenotypically β -thalassemia is of three types. β -thalassemia minor is a heterozygous state in which there is around 50% decrease in synthesis of β -globin protein, causing mild to moderate microcytic anemia. Affected individuals are usually asymptomatic. β -thalassemia intermedia shows mild to moderate anemia, (Mohssin MY, and *et.al.* 2015).

Associated Disorders:

Multiple blood transfusions result in iron overload, which can cause secondary hemosiderosis. Cardiac involvement is a major cause of death in patients with thalassemia. Transfusion hemosiderosis has been classified into 3 stages based on the number of blood units given. The higher the number of packed red blood cells units given, the more advanced the stage. Advanced stage is associated with more severe clinical symptoms and more abnormal cardiac functions. Patients who have received regular blood transfusions sometimes develop liver enlargement due to swelling of the phagocytic and parenchymal cells from the

deposition of hemosiderin. Calcified bilirubin stones are common in patients with beta thalassemia major. People with thalassemia major frequently exhibit features of diabetes mellitus. This could be due to defective pancreatic production of insulin, but insulin resistance has also been implicated. Adult patients with thalassemia major are known to have low fertility; this is attributed to the commonly encountered hypogonadotropic hypogonadism. People with thalassemia, especially with thalassemia intermedia, have higher risk of thromboembolism event as compared to the general population (Sirachainan, 2013). Children or young adults with thalassemia usually present with osteopenia or osteoporosis despite adequate transfusion and iron chelation therapy. The mechanism for osteopathy in thalassemia patient is complex. Osteoporosis reduces bone strength and increases risk of skeletal abnormalities, fractures, spinal deformities, nerve compression, and growth failure (Sanctis. D. *et al.*, 2013).

Etiology:

Thalassemia is due to decreased production of at least one globin polypeptide chain (beta, alpha, gamma and delta) which results in unbalanced hemoglobin synthesis. Inheritance of thalassemia is autosomal recessive. Beta Thalassemia results from decreased production of beta-polypeptide chains. Heterozygotes are carriers and have asymptomatic mild to moderate microcytic anemia (thalassemia minor). Homozygotes (beta-thalassemia major or Cooley's anemia) develop severe anemia and bone marrow hyperactivity. Alpha thalassemia is a result of decreased production of alpha globins. Heterozygotes for a single gene defect results in silent alpha thalassemia state. Heterozygotes with defects in two of the four genes result in alpha thalassemia trait, and tend to develop mild to moderate microcytic anemia but with no symptoms. Defects in three of the four genes more severely impair alpha-chain production, resulting in the formation of tetramers of excess beta chains (HbH) or, in infancy, gamma chains (Bart's Hb). Defects in all four genes are a lethal condition unless given blood transfusions in utero, because hemoglobin that lacks alpha chains does not

transport oxygen. Another thalassemia form is hemoglobin E (Hb E) related. Hb E, one of the most common hemoglobinopathies, is due to missense mutation in codon 26, which belongs to splicing sequence of Beta globin gene. This mutation not only affects structure but also reduces the production rate of beta globin. As consequence, Hb E trait and disease usually present with mild Beta thalassemia phenotype. Co-inheritance of Hb E and thalassemia is commonly found in Southeast Asia, India and Bangladesh (Sharma et al., 2013). This compound heterozygote state of Hb E/Thalassemia results in a variable phenotype ranging from mild anemia to transfusion dependency (Olivieri et al., 2010). The most significant genotype is Hb E/Beta thalassemia, which accounts for 50% of severe beta thalassemia worldwide (Fucharoen and Weatherall, 2012). Patients with Hb E/Beta thalassemia have a higher risk of pulmonary hypertension or vitamin D deficiency (Atichartakarn. and *et al.*, 2014).

Signs and symptoms of thalassemia:

Iron overload: Regular blood transfusion results in the iron overload in the patient's body and it is the most common complications related to thalassemia and the excess of iron can damage liver, heart and endocrine system (Greer, J. P. and *et al.*, 2018). **Infection:** Individuals with thalassemia have high risk of infection and this is harmful for body organs. **Bone deformities:** In this disease, development of body is influenced. Subsequently, it might be seen in patients with thalassemia. In most of the cases, skull bone is seen. The bones of the face and the skull become thicker, and also results in skeletal abnormalities (Sharma, D. C., and *et al.*, 2017). **Enlarged spleen:** Spleen enlargement has many infectious, viral and bacterial causes, and is incidental due to bugs in the blood flow and liver failures. When liver becomes inflamed, it will squeeze the spleen. Thalassemia is one of the diseases that lead to spleen enlargement. **Symptoms like anemia:** For example, Shortness of breath, Cold hands and feet, pale skin, Irritability, Dark urine and Fatigue (Kumar, R. and *et al.*, 2012).

Prevalence:

In Pakistan, prevalence of thalassemia is increasing each year. About 5,000 child births are affected with β -thalassemia and its prevalence is about 6% and about 50,000 patients are registered all over the country. According to WHO (world health organization) around 8000 pregnancies are at risk each year in Iran and is most prevalent in the region of Mediterranean basin, Greek, Italian, Middle Eastern, Africa and Asia. The significant Mediterranean islands are heavily influenced specifically (Angelucci, E. and *et al.*, 2014). Other Mediterranean individuals, just as those in the region of the Mediterranean, additionally have high rates of thalassemia, including the people of West Asia and North Africa. A long way from the Mediterranean, South Asian are additionally influenced with World's most elevated groupings of the transporters (30% of the population) being in the Maldives (Cazzola, M. and *et al.*, 1995). **Diagnosis:**

For diagnosis of thalassemia, different modalities are being used at different stages. In prenatal life diagnosis could be made with the help of Chorionic Villous Sampling at 10-12 weeks of gestation, to decide accordingly and on parent's wish to continue pregnancy or to abort pregnancy of a thalassemic child (Singer, S. T. , 2009). Most of the patient's shows signs and symptoms after birth like anemia e.g. fatigue, paleness, weakness, slowness in growth, dark urine, abdominal swelling, and facial bone deformities within first 2 years of life. Laboratory test like complete peripheral film and blood count is very helpful in diagnosis of thalassemia but Hb-electrophoresis and genetic test could also be done for diagnosis (Pearson, H. and *et al.*, 1996).

Complications:

Possible complications that occur in thalassemic patients are iron overload which is due to frequent blood transfusions which may also damage heart, liver and glands. Bone deformities also occur due to marrow hyperplasia, especially face and skull bones which in result make bones thin and brittle

(Sharma, D. and *et al.*, 2017). Splenomegaly may also occur due to the excess destruction of RBCs which results in the removal of spleen. Slow growth is due to affected endocrine glands and hormones. In many examinations, bone density is notably diminished (cause osteoporosis) in patients with β -thalassemia, especially those with hypogonadism (Nang, M. 2012).

Prevention:

Thalassemia should be prevented by premarital screening and prenatal diagnosis which is helpful in decreasing prevalence and future incidence of thalassemia. Prenatal diagnosis includes Chorionic villus sampling, this test is usually done around the 11th week of pregnancy and involves removing a tiny piece of the placenta for evaluation (Sharma, D. and *et al.*, 2017). Health education awareness is the only way to reduce the rate of hereditary disorders in our society like in European Countries.

Treatment:

Beta thalassemia major includes following Treatments: Blood transfusions: during this procedure, blood will be given to a patient intravenously. The type of thalassemia will determine the frequency of the blood transfusions. More-severe forms of thalassemia often require frequent blood transfusions, possibly every 3-4 weeks (Terrenato, L. and *et al.*, 1988). Bone marrow transplant: is the curative treatment for this disease. If a patient is young and has a suitable donor, he may be recommended bone marrow transplant. During the treatment, high-dose chemotherapy is given to the patient to eliminate the defective thalassemia-producing cells in the marrow and replace them with healthy donor cells (MoafiA, V. , 2010 ; Singer, S. , 2009).

Conclusions:

The thalassemia syndromes are hereditary disorders with a complex pathophysiology and serious multi-organ involvement. Current treatment may lead to long survival and a good quality of life. This includes benefitting from a full education, marriage, and parenthood, as well

as contributing to the society as ordinary citizens do. In contrast, for the majority of patients, access to quality and holistic care is not possible. For these patients, thalassemia is a tragic disease with life-threatening complications which imply death in adolescence or early adulthood and result in a life of disability. Even in well-organized and well-resourced health services the provision of adequate supplies of safe blood and iron chelation are thought to meet patient needs, often ignoring the role of endocrine, cardiac, and liver monitoring by specialized teams which can deal with emerging vital organ dysfunction. The need for at least one expert reference center supporting secondary centers within each country in an organized network must be part of a policy directed and supported at the central level. This is in accordance with the concept of European Reference Networks (ERNs) for rare disorders; thalassemia falls into this category of disease in most countries. Emerging new therapies, such as genetic interventions aiming to reduce globin chain imbalance, are likely to benefit those able to afford current management modalities leaving the “silent majority” to struggle with what basic treatments that they can afford. The solution is for health authorities to meet their obligations to those born with these conditions and persuade society and economists that investment in their health is meeting an obligation to human rights. In this picture the question is whether neonatal screening programs can effectively contribute to achieve the desired outcomes. In areas where effective pre-conceptual or premarital prevention programs are fully applied, few cases will be picked up postnatally. In such a setting, newborn affected infants are often in families which have been informed and have chosen to give birth to an affected child. Even where there is no prevention policy, infants generally present clinically at a very young age and require immediate intervention due to severe anemia. To develop a policy solely for the early detection of thalassemia does not seem necessary. However, where there is a program for the detection of sickle cell disease,

some thalassemia syndromes and most variants may be identified. This can be beneficial for secondary prevention but also in some settings for the early detection of new cases.

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