

## Pathophysiology, Clinical Manifestations, and Carrier Detection in Thalassemia

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**Abstract:**Thalassemia's are genetic disorders inherited from a person's parents. Thalassemia's are prevalent worldwide with 25,000 deaths in 2013.Highest rates are in the Mediterranean, Italy, Greece, Turkey, West Asia, North Africa, South Asian, and Southeast Asia. Highest carriers(30% of the population) in the Maldives.Thalassemia's are classified into alpha-thalassemia, Beta-thalassemia, thalassemia intermedia, and beta thalassemia minor. The severity of alpha and beta thalassemia depends on how many of four genes for alpha or two genes for beta globin are missing. Hemoglobinopathies imply abnormalities in the globin proteins themselves. Health complications are mostly found in thalassemia major and intermediate patients. Signs and symptoms include severe anemia, poor growth and skeletal abnormalities during infancy. Untreated thalassemia major eventually leads to death, usually by heart failure.Diagnosis by hematologic tests, hemoglobin electrophoresis, and DNA analysis. Individuals with severe thalassemia require blood transfusion, drug therapy i.e.,deferoxamine,deferasirox, deferiprone,and bone marrow transplant. Most drugs have side effects. Prevention includespremarital screening,carrier detection, and genetic counselling.

**Keywords:** Carrier detection, Genetic disorder, Treatment, Thalassemia,

### I. Introduction

Thalassemia's are inherited blood disorder that can result in the abnormal formation of hemoglobin [1].Thalassemia's are genetic disorders inherited from a person's parents[2].There are two main types, alpha thalassemia and beta thalassemia[1].The severity of alpha and beta thalassemia depends on how many of four genes for alpha or two genes for beta globin are missing[2].As of 2013 thalassemia occurs in about 208 million people with 4.7 million having severe disease[3].The disease is more common among people of Italian, Greek, Middle Eastern, South Asian, and African descent[1].Males and females have similar rates of disease[4].It resulted in 25,000 deaths in 2013 down from 36,000 deaths in 1990[5].Those with minor degree of thalassemia similar to sickle-cell trait, have some protection against malaria explaining why they are more common in regions of the world where malaria exists[6].Clinical symptoms includes: mild to severe anemia, that results in feeling tired and pale skin. There also be bone marrow problems, and enlarged spleen, yellowish skin, dark urine, and among children slow growth [2].Diagnosis is typically by blood tests including a complete blood count, special hemoglobin tests, and genetic tests[7].Treatment for those with more severe disease often includes regular blood transfusions, iron chelation, and folic acid. Iron chelation may be done with deferoxamine or deferasirox. Occasionally a bone marrow transplant may be the option [8].Prevention primarily by premarital screening and carrier detection. The review describes the latest concepts in the diagnosis, treatment and carrier detection of thalassemia.

### II. Prevalence

The word *thalassemia* derives from Greek *thalassa* –“Sea”,and now Latin-*emia*(from Greek-“blood”. “Mediterranean anemia” was first described in people of Mediterranean ethnicities. “Mediterranean anemia” was renamed thalassemia major once the genetics were better understood. The word thalassemia was first used in 1932[9].The beta form of thalassemia is particularly prevalent among Mediterranean people, and this geographical association is responsible for its naming[9].Thalassemia resulted in 25,000 deaths in 2013 down from 36,000 in 1990[5].In Europe, the highest concentrations of the disease are found in Greece, coastal regions of Turkey(particularly the Aegean Region such as Izmir,Balikesir,Aydin,Mugala,and Mediterranean Regions such as Antalya,Adna,Mersin),in parts of Italy, particularly southern Italy and the lower Povalley. The major Mediterranean islands(except Balearics) such as Sicily,Sardinia,Malta,Corsica,Cyprus,and and Crete are heavily affected in particular. Other Mediterranean people, as well as those in the vicinity of the Mediterranean, also have high rates of thalassemia, including the people of West Asia and North Africa. Far from the Mediterranean, South Asian are also affected with World's highest concentrations of the carriers (30% of the population) being in the Maldives[10].

Nowadays, it is found in populations living in Africa, the Americas, and Tharu people in the Terai region of Nepal and India [10]. It is believed to account for much lower malaria sickness and deaths [11], accounting for the historic ability of Tharus to survive in areas heavy malaria infestation, where other could not. Thalassemia's are particularly associated with people of Mediterranean origin, Arabs (especially Palestinian and people of Palestinian descent), and Asians [12]. Maldives has the highest incidence of thalassemia in the world with carriers rate of 18% of the population. The estimated prevalence is 16% in people from Cyprus, 1% in Thailand, and 5-10% in Iran, and 3-8% from Bangladesh. China, India, Malaysia, and Pakistan [13,14,15,16]. Thalassemia also occur in descendants of people from Latin America, Mediterranean countries (e.g. Greece, Italy, Spain, and others), and Portugal [13].

### **III. Pathophysiology**

Normally, the majority of adult hemoglobin (HbA) is composed of four protein chains, two  $\alpha$  and two  $\beta$  globin chains arranged into a heterotetramer. In thalassemia, patients have defects in either in  $\alpha$  or  $\beta$  globin chain, causing production of abnormal red blood cells (In Sickle-cell disease, the mutations is specific to beta globin). The thalassemia's are classified according to which chain of hemoglobin molecule is affected. In  $\alpha$ -thalassemia, production of the  $\alpha$  chain is affected, while in  $\beta$ -thalassemia, production of  $\beta$  chain is affected. The beta globin chains are encoded by a single gene on chromosome 11,  $\alpha$  globin chains are encoded by two closely linked genes on chromosome 16 [17].

In a normal person two copies of each chromosome, two loci encode the  $\beta$  chain and four loci encode the  $\alpha$  chain. Deletion of one of the  $\alpha$  loci has a high prevalence in people of African or Asian descent, making them more likely to develop  $\alpha$ -thalassemia.  $\beta$ -thalassemia are not only common in Africans, but also in Greeks and Italians [15]

#### **Alpha-thalassemia**

The alpha-thalassemia involve the genes *HBA 1* and *HBA2* [18,19], inherited in a Mendelian recessive fashion. Two gene loci and four alleles exist. It is also connected to the deletion of 16p chromosome  $\alpha$ . Thalassemia result in decreased alpha-globin production, therefore fewer alpha-globin chains are produced, resulting in an excess  $\gamma$  chains in newborns. The excess  $\beta$  chains form unstable tetramers (called hemoglobin H or HbH of 4  $\beta$  chains), which have abnormal oxygen dissociation curves.

#### **Beta-thalassemia**

Beta-thalassemia's are due to mutations in the HBB gene on chromosome 11 [20], also inherited in an autosomal, recessive fashion. The severity of the disease depends on the nature of the mutation and on the presence of mutation in one or both alleles. Mutated alleles are called  $\beta^+$  when partial function is conserved (either the protein has reduced function, or it functions normally but is produced in reduced quantity) or  $\beta^0$  when no functioning protein is produced. The situation of both alleles determines the clinical picture:

a).  $\beta$ -thalassemia major (Mediterranean anemia or Cooley anemia) is caused by a  $\beta^0/\beta^0$  genotype. No functional beta chains are produced, and thus no hemoglobin A can be assembled. This is the most severe type form of  $\beta$ -thalassemia.

b).  $\beta$ -thalassemia intermedia is caused by a  $\beta^+/\beta^0$  or  $\beta^+/\beta^+$  genotype. In this form, some hemoglobin A produced.

c).  $\beta$ -thalassemia minor is caused by a  $\beta/\beta^0$  or  $\beta/\beta^+$ . Only one of two beta globin alleles contains a mutation, so beta chain production is not terribly compromised and patients may be relatively asymptomatic.

#### **Hemoglobinopathy**

Hemoglobinopathy is a kind of genetic defect that results in abnormal structure of one of the globin chains of the hemoglobin molecule [21]. Hemoglobinopathies are inherited single-gene disorders, in most cases, they are inherited as autosomal co-dominant traits [22]. Common hemoglobinopathies include sickle-cell disease. It is estimated that 7% of the world population (420 million) are carriers, with 60% of total and 70% of pathological being in Africa. Hemoglobinopathies are most common in ethnic population from Africa, the Mediterranean basin and Southeast Asia [22].

Hemoglobinopathies imply structural abnormalities in the globin proteins themselves [23]. Thalassemia in contrast, usually result in underproduction of normal proteins, often though mutations in regulatory genes. The two conditions may overlap, however, since some conditions which cause abnormalities in globin proteins (hemoglobinopathy) also affect their production (thalassemia). Thus, some hemoglobinopathies are also thalassemia's, but most are not [23].

### **IV. Clinical Manifestations**

Three main forms have been described thalassemia major, thalassemia intermediate and thalassemia minor. All people with thalassemia are susceptible to health complications that involve the spleen (which is

often enlarged and frequently removed) and gallstones [24]. These complications are mostly found in thalassemia major and intermediate patients. Individuals with  $\beta$  thalassemia major usually present within the first two years of life with severe anemia, poor growth and skeletal abnormalities during infancy. Untreated thalassemia major eventually leads to death, usually by heart failure, therefore, birth screening is very important [25]. Excess iron causes serious complications within the liver, heart and endocrine glands. Severe symptoms include liver cirrhosis, liver fibrosis and in extreme cases, liver cancer [26]. Heart-failure, growth impairment, diabetes and osteoporosis are life threatening contributions brought upon by  $\beta$  thalassemia (TM) [27]. The main cardiac abnormalities seen to have resulted from thalassemia and iron overload include left ventricular systolic and diastolic dysfunction, pulmonary hypertension, valvulopathies, arrhythmias and pericarditis. Increased gastrointestinal iron absorption is seen in all grades of beta thalassemia and increased red blood cell destruction by the spleen due to ineffective erythropoiesis further releases additional iron into the bloodstream [28].

People with thalassemia have an increased risk of infection. This is especially true if the spleen has been removed. Thalassemia can make the bone marrow expand, which causes bones to widen. This can result in abnormal bone structure, especially in the face and skull. Bone marrow expansion also makes bones thin and brittle, increasing the risk of broken bones [29].

### **V. Diagnosis**

Abdominal pain due to hypersplenism and splenic infarction and right- upper quadrant pain caused by gallstones are major clinical manifestations. However, diagnosing thalassemia from symptoms alone is inadequate. Physicians note these associative due to this disease's complexity [30], The associated signs can attest to the severity of the phenotype: pallor, poor growth, inadequate food intake, splenomegaly, jaundice, maxillary hyperplasia, dental malocclusion, cholelithiasis, systolic ejection murmur in the presence of severe anemia and pathological features. Based on symptoms, tests are ordered for a differential diagnosis. These tests include complete blood count; hemoglobin electrophoresis, serum transferrin, ferritin, total iron-binding capacity; urine urobilin and urobilinogen, peripheral blood smear, which may show codocytes, or target cells [31], hematocrit, and serum bilirubin [32,33].

### **Molecular analysis**

All beta thalassemia's may exhibit abnormal red blood cells, a family history is followed by molecular –DNA analysis [34]. This test is used to investigate deletions and mutations in the alpha and beta globin producing genes. Family studies can be done to evaluate carrier status and the types of mutations present in other family members. Molecular or DNA testing is not routine, but can help diagnose the thalassemia and determine carrier status. In most cases in treating physician uses a clinical pre-diagnosis assessing anemia symptoms: fatigue, breathlessness and poor exercise tolerance [35]. Further genetic analysis may include HPLC should routine electrophoresis prove difficult [32].

### **VI. Therapy**

People with mild thalassemia traits do not require medical of follow-up care after the initial diagnosis in made [30]. People with  $\beta$  –thalassemia trait should be warned that their condition can be misdiagnosed as more common iron deficiency anemia. They should avoid routine use of iron supplements; iron deficiency can develop, though, during pregnancy or from chronic bleeding [36]. Counseling is indicated in all persons with genetic disorders, especially when the family is at risk of a severe form of disease that may be prevented [37]. *People with severe thalassemia require medical treatment. A blood transfusion regimen was the first measure effective in prolonging life* [36].

### **Drug therapy**

Multiple blood transfusions can result in iron overload. The iron overload related to thalassemia may be treated with chelation therapy with the frequently used medications that include deferoxamine, deferiprone or deferasirox [38]. These treatments have resulted in improving life expectancy in those with thalassemia major [38].

**Deferoxamine** is only effective via daily injections which make its long-term use more difficult. It has the benefit of being inexpensive and decent long term safety [38].

**Deferasirox** has the benefit of being an oral medication. Common side effects include: nausea, vomiting and diarrhea. It however is not effective in everyone and is probably not suitable in those with significant cardiac issues related to iron overload. The cost is also significant [38].

**Deferiprone** is a medication that is given by mouth. Nausea, vomiting, and diarrhea are relatively common with its use [38]. It is available in both Europe and the United States [39,40]. It appears to be the most effective agent when heart is significantly involved [38]. There is no evidence from randomized controlled trials to support zinc supplementation in thalassemia [40].

### **Adverse drug effects**

**Deferoxamine** could lead to toxic side effects if doses greater than 50mg/kg body weight are administered. These side effects may include auditory and ocular abnormalities, pulmonary toxicity, sensorimotor neurotoxicity, as well as changes in renal function [41]. Another toxic effect of deferoxamine mostly in observed children in children is the failure of linear growth. This reduction in height may occur as a result of deferoxamine chelating metals other than iron which are required for normal growth. The toxic effect of deferoxamine on linear growth could also be due to excess deferoxamine accumulating in tissues and interfering with iron- dependent enzymes which are involved in the post-translational modification of collagen [42].

**Deferiprone**(DFP) can be subjected to glucuronidation in the liver, which may expel as much as 85% of drug from the body before it has had chance to chelate iron .DFP also has a well-known safety profile, with agranulocytosis being the most serious side effect [43]. While agranulocytosis has been reported in less than 2% of patients treated, it is potentially life-threatening and requires close monitoring of the white cell count[44]. Less serious side effects include gastrointestinal symptoms, which were found in 33% of patients in the first year of administration, but fell to 3% in following years, arthralgia, and zinc deficiency, with the latter being a problem especially for individuals with diabetes[43].

**Deferasirox**; however have a wide variety of side effects. These may include headaches, nausea, vomiting, and joint pains [45]. Some evidence has been shown of a link to gastrointestinal disorders experienced by some people who have received the treatment [46]. Indicanthrin has high bioavailability and minimal side effects, like vomiting or diarrhea [47].

### **Bone marrow transplant**

It is possible to be cured, with no more need of blood transfusions, thanks to Bone Marrow Transplantation(BMT) from compatible donor, invented in 1980s by Prof.Guido Lucarelli. In low –risk young patients, the thalassemia-free survival is 87%, the mortality is 3 %. The drawback is that this curative method required an HLA(Human leucocyte Antigen)-matched compatible donor[48]. If the patient does not have an HLA-matched donor such as the first curative method requires, there is another curative method called Bone Marrow Transplantation(BMT) from haploidentical mother to child(mismatched donor), in which donor is the mother. It was invented in 2002 by Doctor Pietro Sodani. The results are these: thalassemia free survival rate 70%, rejection 23 %, and mortality 7%. The best results are with very young patients [49].

## **VII. Carrier detection**

A screening policy exists in Cyprus to reduce the incidence of thalassemia, which since the program's implementation in the 1970s (which also includes pre-natal screening and abortion) has reduced the number of children born with the hereditary blood disease from 1 out of every 158 births to almost zero[50].

In Iran as a premarital screening, the man's red cell indices are checked first, if he has microcytosis (mean cell hemoglobin <pg or mean red cell volume < 80fl), the woman is tested . Women is tested. When both are microcytic their hemoglobin A2 concentrations are measured. If both have a concentration above 3% (diagnostic of thalassemia trait) they are referred to the local designated health post for genetic counseling [15]. Iran is a country with high prevalence of about 5-10% of *beta*-thalassemia trait[51]. Iran's experience shows that genetic screening can be successful in lower resource countries and also provides some lessons for high resource nations[15].

In 2008, in Spain, a baby was selectively implanted in order to be a cure for his brother's thalassemia. The child was born from an embryo screened to be free of the disease before implantation with In vitro fertilization. The baby's supply of immunologically compatible blood was saved from implantation to his brother. The implantation was considered successful [52]. In 2009, in India, a group of doctors and specialists in Chennai and Coimbatore registered the successful treatment of thalassemia in a child using a sibling's umbilical cord blood[53].

## **VIII. Conclusion**

Thalassemia's are inherited disorder, beta thalassemia has high severity. Signs and symptoms include mild to severe anemia. Diagnosis by detailed blood tests and genetic analysis. Treatment for individuals with severe disease, blood transfusion, iron chelation, deferoxamine genetic analysis or deferasirox, and bone marrow transplant. Prevention by premarital screening, and carrier detection.

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