بسم الله الرحمن الرحيم

Thalassemia

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WORLD THALASSEMIA
DAY

Thalassemia

Thalassemia is a genetic disorder that is due to mutations of the genes that are responsible for the production of hemoglobin in the blood.

*Thalassemia are **a heterogeneous grouping of genetic disorders that result from a decreased synthesis of alpha or beta chains of hemoglobin (Hb).**

***Hemoglobin serves as the oxygen-carrying component of the red blood cells. It consists of two proteins, an alpha, & a beta.**

- **If the body does not manufacture enough of one or the other of these two proteins the red blood cells do not form correctly and cannot carry sufficient oxygen**

this causes anemia that begins in early childhood and lasts throughout life.

genetic mutation or a deletion

It is caused by either a genetic **mutation** or a **deletion** of certain key gene fragments**.**

Thalassemia is an inherited disease, meaning that at least **one of the parents** must be a **carrier** for the disease.

As thalassemia is an inherited condition, individuals with a family history of the condition are more likely to be affected.

If both parents possess **one gene** mutation, any children will have a 25% chance of inheriting a gene mutation, regardless of whether the parents are symptomatic.

If **one or both parents** possess **multiple gene** mutations, the risk of gene inheritance increases, and the child is more likely to experience symptoms.

Additionally, some particular ethnicities

Additionally, some particular ethnicities are associated with the condition more often, including people with **Italian, Greek, Middle Eastern, Asian and African** heritage.

The **genetic prevalence** of this condition varies greatly according to the region of the world, as well as the specific ancestry of an individual.

thalassemia is caused by mutations or deletions of the Hb genes, resulting in underproduction or absence of alpha or beta **chains.**

Alpha thalassemia is caused by deletions of alpha-globin genes, and beta thalassemia is caused by a point **mutation** in beta-globin gene on chromosome 11

Two new terminologies being used more often in clinical settings are transfusion requiring and non-transfusion requiring thalassemia and all the basic classification falls into these two types depending on the requirement of frequent blood transfusions or not

Risk factors

Factors that increase the risk of thalassemia include:

- **Family history of thalassemia.** Thalassemia is passed from parents to children through mutated hemoglobin genes.
- **Certain ancestry.** Thalassemia occurs most often in **African Americans** and in people of **Mediterranean** and **Southeast Asian** descent.

There are two broad types of thalassemia including

1-alpha-thalassemia and

2- beta-thalassemia

Each of which has a different prevalence among certain ethnicities or population groups.

Alpha-Thalassemia

Alpha-thalassemia is caused by alpha-globin gene **deletion** which results in reduced or absent production of alpha-globin chains.

Alpha-thalassemia arises due to **insufficient synthesis** of alpha-hemoglobin chains and an excess of beta chains.

There are four genes on chromosome **16** that are required to produce the alpha region of hemoglobin, two of which are **inherited** from each parent of an individual.

The number of gene mutations corresponds to the severity of the condition as follows:

Cont. … Alpha-Thalassemia

The number of gene mutations corresponds to the severity of the condition as follows:

1- One gene : no signs or symptoms but may pass the disease on to children as a silent carrier

2- Two gene: mild signs and symptoms, referred to as alpha-thalassemia minor or **alpha-thalassemia trait**

3- Three gene : moderate to severe symptoms, referred to as **alpha-thalassemia intermedia or hemoglobin H disease**

4-Four gene mutations: often fatal **before or shortly after childbirth,** referred to as **alpha-thalassemia major or** hydrops fetalis.

up to 20% of world population **are carries** to the α-thalassemia genes.

Deletion of one (-α) thalassemia gene **does not result** in notable health problem.

However, countries prevalent with both α-globin genes deletion (- -) from the same chromosome have more severe forms of thalassemia, either intermedia or sever

The region of the world and ethnicity of the individual is an important factor in the **prevalence** of the gene mutations alpha-thalassemia is more common in Southeast Asia than in other areas of the world, although anyone may be affected by the gene mutation that leads to this condition

The following list summarizes **which population groups are more** likely to be affected by **alpha-thalassemia**

	thalassemia trait Prevalence	suspected genetic carriers.
Southeast Asia	**1-30%**	**up to 40%**
Sub-Saharan Africa	**0%**	**to 50%**
Western Pacific	**0%**	**60%**
Eastern Mediterranean	**in 0-2%**	**60%**
Americas	**0-5%**	**40%**
Europe	**1-2%**	**12%**

Beta-Thalassemia

Beta-thalassemia occurs due to insufficient synthesis of beta-hemoglobin chains and an excess of alpha chains.

There are two genes on chromosome 11 that are required to produce the beta region of the hemoglobin chain
each of which is inherited from one parent.

The **number of gene mutations corresponds to the severity** of the condition as follows
1-*One gene mutation: mild signs or symptoms, referred to as beta-thalassemia minor or thalassemia trait
2-•Two gene mutations: moderate to severe symptoms, referred to as beta-thalassemia major or Cooley's anemia

One mutated gene: Mild signs and symptoms.
The condition is called thalassemia minor.

- Two mutated genes: Signs and symptoms will be moderate to severe.

This condition is called thalassemia major, or Cooley anemia. **Babies born** with two mutated beta hemoglobin genes are usually healthy **at birth**, but disease starts to manifest after 6 months of life when fetal hemoglobin(Hb-gamma) disappears and is replaced by adult Hb.

People with origins in the Mediterranean, as well as both African and South Asian areas, are **more likely to be affected** by beta-thalassemia.

estimated prevalence

The estimated prevalence of those affected by the genetic mutations responsible for **beta-thalassemia** throughout the world includes

	Prevalence
Eastern Mediterranean	: 2-18%
Europe:	0-19%
Western Pacific	0-13%
Sub-Saharan Africa	0-12%
Southeast Asia	0-11%
Americas:	0-3%

Thalassemia presentation

Thalassemia presentation varies widely depending on the type and severity.

A complete history and physical examination can give several clues that are sometimes not obvious to the patient themselves.

The following findings can be noted:

Skin

pallor due to anemia and jaundice due to hyperbilirubinemia resulting from intravascular hemolysis. fatigue due to anemia as the first presenting symptom.

Extremities examination can show ulcerations. Chronic **iron deposition** due to multiple transfusions can result in **bronze skin**.

Musculoskeletal

Extramedullary expansion results in **deformed facial** and other skeletal bones and an appearance known as chipmunk face.

Cardiac; Iron deposition can disrupt the cardiac rhythm, and the result is various arrhythmias. Due to chronic anemia, overt heart failure can also result.

Abdominal

Chronic hyperbilirubinemia can lead to precipitation of bilirubin gall stones and manifest as typical colicky pain of cholelithiasis. Hepatosplenomegaly can result from chronic iron deposition

Hepatic

Hepatic involvement is a common finding in thalassemia, particularly due to chronic iron deposition. **Chronic liver failure** or cirrhosis or transfusion-related viral hepatitis.

Slow Growth Rates

Anemia can inhibit a child's growth rate, and thalassemia can **cause a delay in puberty**. Particular attention should focus on the child's growth and development according to age.

Endocrinopathies; The deposition of iron in the pancreas can lead to diabetes mellitus; in the thyroid or parathyroid glands can lead to hypothyroidism and hypoparathyroidism, respectively. The deposition in joints leads to chronic arthropathies. In the brain, iron prefers to accumulate in the substantia nigra and manifests as early-onset Parkinson's disease and various other physiatry problems. These symptoms fall in the vast kingdom of hemochromatosis

Screening and diagnosis of thalassemia

Several laboratory tests have been developed to screen and diagnose thalassemia

a) Complete blood count (CBC): CBC is often the first investigation in a suspected case of thalassemia

CBC showing **low Hb** and **low MCV** is the first indication of thalassemia, after ruling out iron deficiency as the cause of anemia.

b) The calculation of the *Mentzer index* (mean corpuscular volume divided by red cell count) is useful.

Mentzer lower than 13 suggests that the patient has thalassemia, **more than 13** suggests that the patient has anemia due to **iron deficiency.**

the MCV is usually less than 75 fl with thalassemia and rarely less than 80 fl in iron deficiency until the hematocrit is less than 30 percent. For children, the Mentzer index (MCV/red blood cell count) can help distinguish between iron deficiency and thalassemia

in MCV test measures the size and volume of red blood cells. A normal MCV range is roughly 80–100 fl . If someone's MCV level is below 80 fl, th will likely develop or have microcytic anemia. Alternatively, if their MCV levels are greater than 100 fl, they could experience macrocytic anemia.

c) Peripheral blood smear: A blood smear (also called peripheral smear and manual

c) Peripheral blood smear: A blood smear is next, to assess additional red cell properties. Thalassemia can present with the following findings on the peripheral blood smear :Microcytic cells (low MCV), Hypochromic cells, Variation in size and shape (anisocytosis and poikilocytosis)Increased percentage of reticulocytes,Target cells,Heinz bodies

d) Iron studies (*serum iron, ferritin, unsaturated iron-binding capacity (UIBC), total iron-binding capacity (TIBC), and percent saturation of transferrin)* are also done to rule out iron deficiency anemia as the underlying cause.

e) Erythrocyte porphyrin levels may be checked to distinguish an unclear beta-thalassemia minor diagnosis from iron deficiency or lead poisoning. Individuals with **beta-thalassemia** will have normal porphyrin levels, but those with the latter conditions will have elevated porphyrin levels.

f) Hemoglobin electrophoresis: Hemoglobinopathy (Hb) evaluation assesses the **type and relative amounts of hemoglobin present in red blood cells**.

i-Hemoglobin A (HbA); Composed of both alpha and beta-globin chains, is the type of Hb that typically makes up 95% to 98% **of hemoglobin for adults.**

Ii-Hemoglobin A2 (HbA2) is normally 2% to 3% of Hb while

Iii-hemoglobin F usually makes up less than 2% of Hb in adults

- **Beta thalassemia** disturbs the balance of beta and alpha hemoglobin chain formation.
- **Patients with the beta-thalassemia major** usually have **larger percentages of HbF and HbA2 and**
- **absent or very low HbA.**

Those with beta-thalassemia **minor** usually have a **mild elevation of HbA2 and mild decrease of HbA**.

HbH is a less common form of hemoglobin that may be seen in some cases of alpha thalassemia. HbS

HbH is a less common form of hemoglobin that may be seen in some cases of alpha thalassemia.

Hemoglobinopathy (Hb) assessment is **used for prenatal screening** when parents are at **high risk for hemoglobin** abnormalities and state-mandated newborn hemoglobin screening.

g) DNA analysis:

help to confirm mutations in the alpha and beta globin- producing genes **DNA testing is not a routine procedure but can be used to help diagnose thalassemia and to determine carrier status if needed.**

Since having relatives carrying mutations for thalassemia increases a person's risk of carrying the same mutant gene, **family studies may be necessary to assess carrier status and the types of mutations present in other family members.**

h). Genetic testing of amniotic fluid

is useful in those rare instances where a **fetus has an increased risk** for thalassemia. This is particularly important **if both parents likely carry** a mutation because that increases the risk that their child may inherit a combination of abnormal genes, causing a more severe form of thalassemi

Prenatal diagnosis with **chorionic villi** sampling at 8 to 10 weeks or by amniocentesis at 14 to 20 weeks' gestation can be carried out in high-risk families

I. Multisystem evaluation:

Evaluation of all related systems should be done on a regular basis due to their frequent involvement in the disease progression. Biliary tract and gall bladder imaging, abdominal ultrasonography, cardiac MRI, serum hormone measurements are a few examples that can be done or repeated depending on the clinical suspicion and case description.

Treatment / Management

Thalassemia treatment depends on the type and severity of the disease.

❑ **Mild thalassemia (Hb: 6 to 10g/dl):**

Signs and symptoms are generally mild with thalassemia minor and little if any, treatment is needed. Occasionally, patients may need a blood transfusion, particularly after surgery, following childbirth, or to help manage thalassemia complications.

❑ **Moderate to severe thalassemia (Hb less than 5 to 6g/dl):**

❖ **Frequent blood transfusions: More severe forms of thalassemia often require regular blood transfusions, possibly every few weeks.**

❖ **The goal is to maintain Hb at around 9-10 mg/dl to give the patients**

❖ **a sense of** well being and also to **keep a check on erythropoiesis** and suppress extra medullary hematopoiesis. **To limit transfusion-related complications, washed, packed red blood cells (RBCs)** at approximately

8 to 15 mL cells per kilogram (kg) of body weight over 1 to 2 hours are recommended.

Chelation therapy: Due to chronic transfusions, iron

Chelation therapy: **Due to chronic transfusions, iron starts to get deposited in various organs of the body.**
Iron chelators (deferasirox, deferoxamine, deferiprone) are given concomitantly to remove extra iron from the body.

Stem cell transplant: **Stem cell transplant, (bone marrow transplant), is a potential option in selected cases, such as children born with** severe thalassemia. **It can eliminate the need for lifelong blood transfusions.**

However, this procedure has its own **complications,** and the clinician must weigh these against the benefits. Risks include including graft vs. host disease, chronic immunosuppressive therapy, graft failure, and transplantation-related mortality.

Gene therapy: It is the latest advancement in severe thalassemia management.

❑ Lifestyle modifications

❑ **Initially, particularly for mild cases of thalassemia**, individuals should make small **modifications to their diet** and lifestyle to help in the management of the co cases of thalassemia,

- It is important **to eat a balanced diet** with **fresh nutritious foods**, as this can help patients to feel more energized.
- In some instances, **supplementation of folic acid** may be recommended to **encourage red blood cell growth** and
- **calcium and vitamin D for** added bone strength.

❑ Due to the increased risk of individuals with thalassemia experiencing an overload of iron,

- it is **recommended to avoid excess iron**. For this reason, vitamins or supplements that contain iron
- .

Di Reports exist that drinking tea aids in reducing iron absorption from the intestinal tract. So, in thalassemia patients tea might be a healthy drink to use routinely.

Vitamin C helps in iron excretion from the gut, especially when used with deferoxamine. But using vitamin C in large quantities and without concomitant deferoxamine use, there is a higher risk for fatal arrhythmias. So, the recommendation is to use low quantities of vitamin C along with iron chelators (deferoxamine). and exercise

- **Additionally,** taking measures to **reduce the risk of infections** **can** be beneficial.
- This includes **washing hands** frequently and **avoiding contact** with people that are sick.
- **Immunizations** to protect from influenza, meningitis, pneumococcal disease and hepatitis B are also recommended.

Prevention

In most cases, we can't prevent thalassemia.

If there is a case of thalassemia, or carry of thalassemia gene, genetic counselor is recommended for guidance for having children in a future .

Prenatal diagnosis and genetic counselling

Prenatal diagnosis and therapeutic abortion is the most effective way to prevent severe thalassemia. In some countries,

Premarital Screening and Genetic Counselling (PMSGC) has been implemented Cyprus, Greece and Italy have demonstrated successful prevention of new cases of thalassemia major. **However,** studies showed that the effect **of mandatory PMSGC is less satisfactory in the Middle East countries** PMSGC programme aims to reduce β-thalassaemia births

- There is a form of assisted reproductive technology diagnosis,
- which **screens an embryo in its early stages** for genetic mutations combined with in vitro fertilization.
- This might help parents who have thalassemia or who are carriers of a defective hemoglobin gene have healthy babies.

Gene Carriers

It is important for individuals who are known to carry gene mutations that may lead to thalassemia to **seek medical advice before** deciding to have children. This is because it is possible for future children to inherit the defective gene, particularly if both parents are carriers, regardless regardless of the presence of symptoms.

-thalassemia **in Jordan**

β-thalassemia is a common hereditary disorder, especially in the Middle East and is the most common hemoglobinopathy in Jordan with

The carrier prevalence rate of thalassemia in Jordan is currently reported as around 2–4%.

in Jordan there were about 1500 thalassaemia patients with a prevalence rate of about 4 to 6% of Beta Thalassemia Major (BTM)

(Hamamy, et al., 2007).

Jordan was among the nations that took special care in preventative measures in the form of premarital screenings. These **screenings helped prevent the marriage of carriers** of the illness which were around 3.5 percent of the population.

It was made clear that this measure had decreased the incidence of the disease by 40 percent and that medical professionals hoped the rate to be halved, similar to other Mediterranean countries.


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thank you