

#### THALASSEMIA INTERMEDIA



#### • Dr. A . EGHBALI

- Pediatric Hematologist & oncologist
- Iran University of Medical Sciences

- The term TI is clinically descriptive of beta-thalassemic patients whose clinical manifestations are not as mild as thalassemia minor or as severe as TM .
- The first description of TI was made by Rietti Greppi Micheli in 1955.
- Although TI is a nontransfusion-dependent thalassemia form, some patients occasionally need blood transfusions.
- They also require careful medical attention like TM to improve quality of life.

- Genetic heterogeneity of TI is associated with wide clinical spectrum presentations from mild to severe hemolytic anemia and can be divided into two subgroups:
- (1) Some patients are mildly affected leading to mild clinical problems until adult life.
- These patients maintain hemoglobin levels between 7 and 11 gr/dL and are usually transfusion independent or rarely require blood transfusions.

- (2)Patients with more severe anemia who generally present at ages 2–6 years old.
- Although they may not require regular transfusions like the first subgroup, without occasional transfusions and appropriate management, they frequently develop clinical symptoms such as skeletal deformities and growth retardation .

- While TI and TM have some overlap in their clinical presentations, differentiation of the two disorders is essential for optimal management and prevention of their later complications.
- TI can present with pallor, jaundice, anemia, splenomegaly or skeletal deformities during childhood or later.

- <u>Diagnosis of TI</u> is usually made after the age of 2 years with initial Hb levels of 7 gr/dL or more in patients with beta-thalassemia who are free of infection and have adequate folic acid.
- One of their parents is also atypical carrier of beta-thalassemia such as normal or borderline HbA2 or isolated increased HbF (usually up to 10%).

- The patients are usually referred with microcytic-hypochromic anemia and the peripheral smear shows mild to severe microcytosis and hypochromia, anisopoikilocytosis, polychromasia, target cell, basophilic stippling, and nucleated RBC (NRBC).
- Hb electrophoresis includes: HbA: 0-80%; HbA2: normal or up to 7%HbF: 10-100%.
- Serum iron, serum ferritin and transferrin saturation may be increased.

- Differential diagnosis between TI and TM is essential because :
- the first step for management of patients with TI is usually not transfusion;
- however, the first choice of TM management is blood transfusion.

	Thalassemia intermedia	Thalassemia major
Clinical manifestations		
Age of presentation (years)	>2	<2
Splenomegaly	Moderate to severe	Mild in case of optimal management
Transfusion	Nondependent or occasionally	Dependent
Pallor, jaundice	Usually yes	No or mild if optimal management
Skeletal deformities	Usually yes	No or mild if optimal management
Hematologic data		
Hb levels (g/dL)	$\geq 6-7$	<6-7
HbF (%)	10-50 (may be up to 100%)	>50 (may be less than 50%)
HbA2 (%)	>3.5	<3.5
Mean cell volume (MCV)	Decrease	Normal, if optimal management
Nucleated red blood cells (NRBC)	Increase	Normal, if optimal management
White blood cell (WBC)	Increase	Normal, if optimal management
Complications		
Thrombosis	Common	Less common
Pulmonary hypertension	Common	Rare
Right-sided heart failure	Common	Rare
Left-sided heart failure	Rare	Common
Legulcer	Common	Rare
Extramedullary hematopoiesis	Common	Rare
Endocrine complications	Uncommon	Common
Viral hepatitis	Rare	Common
Genetic and molecular charact	eristics	
Parents	One or both are atypical carriers of beta-thalassemia minor	Both are typical carriers of beta-thalassemia minor
Type of mutation	Silent to mild	Severe
Coinheritance of alpha-thalassemia, hereditary persistence of fetal hemoglobin,	Yes	No
polymorphism		

TABLE 1 Differentiation Between Thalassemia Intermedia and Thalassemia Major

#### Mutation Analysis and Molecular Definition of TI

- TI arises from gene mutations affecting beta-globin production.
- Most patients are homozygotes or compound heterozygotes for beta-thalassemia.
- The different phenotypes of patients with TI arise from different gene defects that cause a mild to severe alpha/beta-globin chains imbalance.

- Like TM, three main factors are responsible for the clinical manifestations in untreated TI patients:
- ineffective erythropoiesis,
- chronic hemolytic anemia,
- iron overload.
- <u>Ineffective erythropoiesis</u> is responsible for erythroid marrow hyperplasia and skeletal deformities, hemolytic anemia and extramedullary hematopoiesis (EMH).
- <u>Hemolysis</u> is commonly associated with splenomegaly, hypercoagulable state, and pulmonary hypertension (PHT).

#### • <u>EMH:</u>

- Erythropoietic tissue masses occur as a compensatory mechanism to overcome chronic hemolysis, EMH is most commonly found in the liver, spleen, and lymph nodes.
- Paraspinal masses can cause cord compression and neurological damage .
- Paraspinal EMH mainly presents as pseudotumors, which may possibly cause a variety of neurological symptoms due to spinal compression.

- EMH has also been reported in
- pleura,
- pericardium,
- chest ,
- intracranial cavity,
- adrenal glands,
- and some other organs .

- Hydroxyurea (HU) therapy, blood transfusion, and radiation therapy are therapeutic options for EMH in these patients.
- The dosage of HU should be higher (20–30 mg/kg/d) compared to the dosage that it is usually used for TI for enhancement of gamma globin chain synthesis (8–15 mg/kg/d).
- The other treatment modalities should be considered if the patient does not respond to HU therapy.
- Surgery is not recommended as it has been related to bleeding in these patients.

#### • Thrombosis:

- In a cohort study that was done it was demonstrated that thromboembolic event (TEE) occurred 4.38 times more frequently in TI than TM patients .
- The most important factor involved in hypercoagulability is exposure of negatively charged phospholipids on the RBCs membrane remnants as a result of oxidative stress and subsequent activation of the prothrombinase complex and enhanced thrombin generation.

- However, some other factors like decreased levels of the antithrombotic proteins C and S,
- endothelial exposure to inflammation,
- and oxidative effects of hemolysis
- and increased number of activated platelets in splenectomized patients are also involved in TEEs in these patients.

- Splenectomized TI patients have a higher incidence of TEE compared to non splenectomized TI patients .
- These patients who develop TEE are <u>characterized</u> by high NRBC and platelet counts, and are more likely to have evidence of PHT and be transfusion naive.
- Furthermore, <u>high NRBC and platelet counts as well as transfusion</u> <u>naivety are associated with earlier development of TEE after</u> <u>splenectomy</u>.

- Deep and portal vein thrombosis, pulmonary embolism, and brain ischemia and infarction resulting in stroke are the main thromboembolic complications in TI patients .
- Overt stroke is much more common in TM than TI due to higher stroke related risk factors such as diabetic mellitus, heart failure and arrhythmia in these patients but silent ischemic brain lesions are more common in TI.
- studies in Iran and Lebanon showed the frequency of silent ischemic brain lesions in 26% and 60%, respectively.

- (CVA) and silent ischemic lesions are reported especially frequently in TI patients in the subgroup of patients who are :
- adults, transfusion-independent, splenectomized, and have a platelet count >500 ×10 9/L.
- It is highly recommended that patients with silent infarcts be treated with antiplatelet drugs.
- Blood transfusion on a regular basis should be strongly considered in such patients and definitely initiated for patients with symptomatic CNS disease.

- Prophylactic anticoagulation therapy is also recommended in TI patients who are undergoing some types of surgery
- Low molecular weight heparin can be used for a period of 7–14 days postoperatively to prevent postsurgery thrombosis.
- However, in patients with TEE life-long anticoagulation seems to be rational and effective in prevention of recurrent TEE.

#### • **PHT**:

- PHT, defined as systolic pulmonary artery pressure >35 mmHg, may be a common complication in TI patients with a frequency that has been reported to be as high as 60%.
- However, other studies found a frequency of 10–12%.
- *PHT is the primary cause of right sided congestive heart failure* in these patients,.
- Hemolysis has a key role in the development of PH in TI patients.
- It was shown that chronic hemolysis leads to nitric oxide depletion due to nitric oxide scavenging, arginine catabolism, and endogenous nitric oxide synthesis inhibition.

- It also contributes to enhanced platelet activation and increased endothelin-1 release ,and thus, endothelial dysfunction, increased vascular tone, inflammation, hypercoagulability, vascular remodeling, and destruction of pulmonary vasculature, which ultimately results in hemolytic anemia-associated PH.
- Blood transfusion and sildenafil (in some cases) are recommended as an optimal therapy in *β*-TI patients with PAH.
- Some studies have shown that HU therapy alone or in combination with I-carnitine or magnesium can be effective in improving hematologic parameters and cardiac status in patients with TI.

- Iron overload and Endocrine complications:
- increased iron absorption due to chronic hemolytic anemia can cause iron overload and serious iron-related organ complications like cardiac dysfunction and endocrine dysfunction including diabetic mellitus, hypogonadism, infertility, and hypoparathyroidism .
- Endocrine complications are less common in TI patients in comparison with TM patients because of fewer blood transfusions and therefore less severe overload.

#### • Leg ulcer:

- Leg ulcer is a serious complication in TI patients occurring in almost one third of patients with poorly controlled disease .
- They usually appear in the second decade of life and are generally located on the medial or lateral malleoli.
- The ulcers can develop after minor trauma and tend to expand rapidly.
- Chronic anemia, reduced oxygen delivery to the distal regions and venous stasis in TI patients may cause leg ulcers in older patients.





- Also, increased rigidity of erythrocytes cellular membrane,
- local edema due to venous stasis,
- right sided heart failure,
- repetitive local trauma,
- skin infections,
- hypercoagulablility, and prothrombotic tendency are other contributing factors to ulcer formation.
- **Blood transfusion** (in some cases), **local wound care**, and **HU** therapy are the major strategies in these cases.

- Other complications:
- Cachexia and hyperuricemia due to the hypercatabolism of erythroid hyperplastic tissue (more prevalent in TI in comparison to TM)
- and cholelithiasis induced by hyperbillirubinemia are some other metabolic complications in TI.
- Alloporinol therapy is recommended in cases with hyperuricemia.

#### TREATMENT OF TI

- Treatment of TI is essential for prevention of clinical complications.
- The limited options available for management of TI include :
- transfusion therapy,
- iron chelation,
- splenectomy,
- modulation of gamma-globulin chain production,
- stem cell transplantation.

# **Transfusion Therapy**

TABLE 4 Indications of Blood Transfusion in Thalassemia Intermedia		
Regular transfusion	Occasional transfusion	
Pulmonary hypertension (PHT)	Decrease exercise tolerance	
Congestive heart failure (CHF)	Cord compression	
Persistent symptomatic severe anemia (Hb <	Thrombosis	
6-7 gr/dL) leading to persistent growth retardation	Pregnancy	
Progressive skeletal deformities	Growth failure	
Progressive pathologic fracture	Legulcer	
	Priapism	
	Severe anemia (Hb < 6-7 gr/dL)	

- Iron overload in TI is frequently derived from transfusion therapy.
- In addition, chronic hemolysis, ineffective erythropoiesis, and hypoxia may lead to increased intestinal iron absorption through suppression of the regulatory protein hepcidin.
- Until recently, the cutoff for starting chelation was an LIC of 7 and above.

 The (TIF) recommends to initiate iron chelation therapy corresponding to a ferritin level of above 800 ng/mL and an LIC of 5 mg Fe/g dry weight or above.

- Suspension of therapy should be initiated when serum ferritin level is 300ng/ml corresponding to an LIC level of 3 mg Fe/g dry weight or less.
- The TIF also recommends that all patients above the age of 10 be frequently evaluated for iron overload by LIC at 1–2 year intervals along with serial measurements of serum ferritin every 3 months.
- It can be said that *serum ferritin alone is not a reliable measure of iron overload* in these patients because it underestimates the iron load,
- and annual assessment of LIC by biopsy or preferably by noninvasive imaging methods like R2 and T2\* MRI sequences have more reliable and reproducible results.

- There are few clinical studies of chelation therapy in TI patients, but all three licensed chelators including deferoxamine (Desferal), deferiprone (Ferriprox), and deferasirox (Exjade) achieve a good response.
- Compliance may be better with deferasirox than with deferoxamine or deferiprone because it requires only one oral dose daily.

# Modulation of Gamma-Globin Chain Production

- Enhanced gamma-globin chain production might address some of the major clinical manifestations in TI patients by <u>increasing</u> the production of HbF and <u>reducing</u> the alpha/beta-globin chain imbalance.
- One of the best known drugs to enhance gamma-globin chain production is <u>HU</u>.

# Modulation of Gamma-Globin Chain Production

- The results show that a significant number of transfusion-dependent TI patients became transfusion free or needed only occasional transfusions.
- Significant increases of Hb levels in not transfused patients were also reported .
- <u>A recent study showed that combination therapy of HU (8–15 mg/kg/d) with L-carnitine or magnesium chloride could be more effective in improving hematologic parameters and cardiac status in patients with TI than HU alone .</u>

# Modulation of Gamma-Globin Chain Production

- predictors of a good response to HU:
- Co-inheritance of alpha- thalassemia, Hb E/B thalassemia,
- younger age,
- higher Hb levels,
- higher age at the first transfusion before HU therapy
- history of splenectomy

# Modulation of Gamma-Globin Chain Production

- During 10 years of observation, HU had no significant adverse effects in these patients such as
- malignancy,
- infertility,
- or bone marrow suppression when used at a dose of 8–15 mg/kg/d .

# Modulation of Gamma-Globin Chain Production

- Recombinant human erythropoietin (rHuEPO) is another erythropoiesis and HbF inducer that was shown to ameliorate the thalassemia clinical symptoms by increasing HbF cells and HbF induction.
- A recent study also showed that rHuEPO combined with HU has a superior therapeutic effect in the clinical and hematological responses and improved quality of life in TI patients in comparison with HU therapy alone .

ullet

# Splenectomy

- Removal of the spleen may be a useful treatment strategy in severe forms of TI increasing the Hb levels by 1–2 g/dL and improving growth and development.
- Indications for splenectomy in TI are numerous, however, splenectomized patients are at greater risk of thrombosis, infection, and PHT, therefore, the decision to remove the spleen should be made with considerable caution.

ullet

# Splenectomy

- TIF guidelines on splenectomy indicate that splenectomy should be avoided in nontransfusion dependent thalassemia patients younger than 5 years of age.
- Furthermore, patients should undergo splenectomy in case of
- worsening anemia leading to poor growth and development,
- hypersplenism
- massive splenomegaly with concern of splenic rupture

# Splenectomy

 Moreover, it is very important to keep in mind that abdominal sonography is mandatory before surgery because the gallbladder and accessory spleen should be inspected during splenectomy and removed in case of cholethiasis or accessory spleen.

#### Stemcelltransplantation:

- <u>It is not usually recommended in not transfused or irregularly</u> <u>transfused patients with TI,</u>
- <u>although if these patients are transfusion dependent, it may be</u> <u>considered.</u>

#### Other treatment considerations:

- These include:
- daily folic acid supplementation,
- antioxidant,
- anticaogulation in the perioperative period,
- and adequate dietary or supplemental vitamin D and calcium for prevention of osteoporosis .

#### Survival and Health-Related Quality of Life in TI

- In conclusion, although the clinical manifestations of TI are usually milder that TM, the prognosis and the rate of complications are often worse.
- Right sided heart failure due to long-standing PHT, thrombosis and brain ischemia, EMH in some vital regions like spinal cord, and iron overload are major and life-threatening complications of TI.

