WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 10, 1264-1277. Review Article ISSN 2277– 7105

REVIEW ARTICLE ON THALASSEMIA

Bhavani Bai Bhukya*, K. Malleswari and D. Rama Brahma Reddy

College Nalanda Institute of Pharmaceutical Sciences.

Article Received on
18 June 2021,

Revised on 08 July 2021,
Accepted on 28 July 2021

DOI: 10.20959/wjpr202110-21290

***Corresponding Author**
Bhavani Bai Bhukya
College: Nalanda Institute of Pharmaceutical Sciences.

ABSTRACT

Thalassemias are a heterogeneous grouping of genetic disorder that result from a decreased synthesis of alpha or beta chains of hemoglobulin (Hb).[1] Thalassemia is a blood disorder that is caused DNA mutations in cells that are responsible for producing hemoglobin. Hemoglobin made upof HEAM ring and 4 globin chains. 2 is alpha chains. and 2 beta chains. For most symptomatic patients with thalassemia, there is no definite cure only supportive management of the anemia is possible. A Very limited number of patients with thalassemia may be cured by bone marrow transplantation from HLA-identical donors.[2] The thalassemia are among the most common genetic disorder worldwide, occuring more frequently in the subcontinent, southeast Asia, and West Asia and West Africa. Ineffective bone marrow erythropoiesis and excessive red blood cells hemolysis together account for the anemia.[3] Alpha thalassemia depresses only the production of the alpha chains, and beta thalassemia depresses only production of beta chains. clinically both alpha and beta thalassemia may occur in major (homozygous), intermediate, and minor (heterozygous) genetic forms and also can interact with presence of abnormal hemoglobins in the same individual.[4]

KEYWORDS: Alpha thalassemia, Beta thalassemia, one mutated gene, two mutated genes, peripheral smear examination, reticulocyte count.

INTRODUCTION

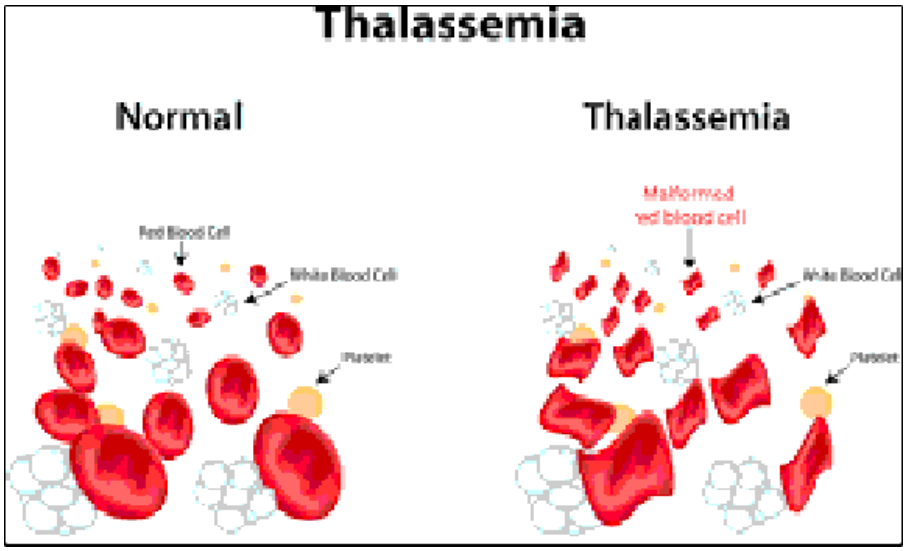
Thalassemia is an inherited autosomal recessive blood disorder. Which results in excessive destruction of red blood cells and further leads to anemia. It is caused by variant or missing genes that affects how the body make hemoglobin. people with thalassemia make less hemoglobin and fewr circulating red blood cells than normal results in mild or severe anemia.[5]

Globins chains structurally normal but have imbalance in production of two different types of

chains. May be either homozygous defect or heterozygous defects. Two major types of thalassemia;

Alpha: Caused by defect in rate of synthesis of alpha chains.

Beta: Caused by defects in rate of synthesis in beta chains.



Types of thalassemia

Alpha thalassemia

Alpha thalassemia is result of changes in genes for the alpha globin component of hemoglobin. Alpha globin has 4 alleles and disease severity ranges from mild to severe depending on the number of deletion of the alleles. Four allele deletion is the most severe form in which no alpha globins are produced and the excess gamma chains (presented during the fetal period) form tetramers. It is incompitable with life and results in hydrops fetalis.[6]

Condition	Genotype	Phenotype	MCV & MCH
Silent carrier	α c/ α -	Asymptomatic	Normal
Minor	α -/ α -; α c/ - -	Asymptomatic	Decreased
Hb H disease	α -/ - -	Moderate hemolytic anemia	Decreased
Hydrops fetalis	- -/ - -	Incompatible with postnatal life	Decreased

Etiology: Mutation in the DNA of cells that produce hemoglobin and inheritance.

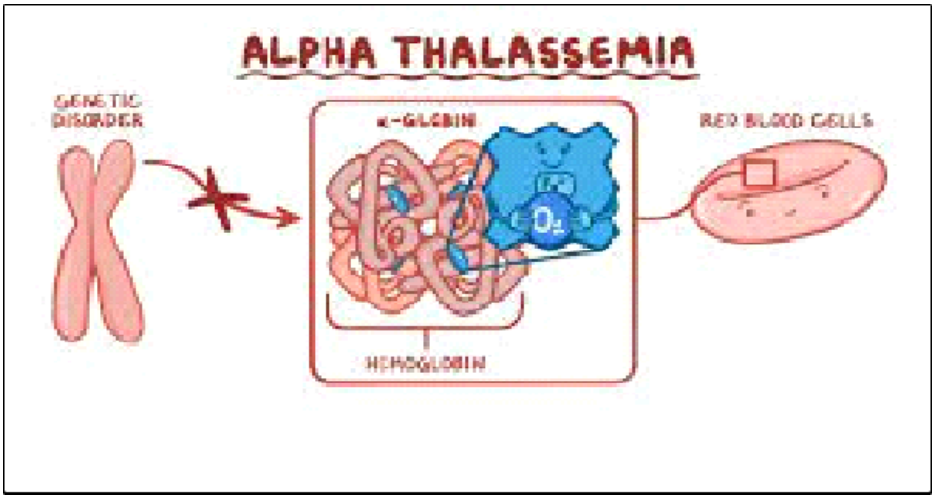
Epidemiology: Alpha thalassemia is prevalant in Asian and African populations while beta thalassemia is more prevelent in the mediterranean populations, although it is relatively common in southeast Asia and Africa too. Prevelence in these regions may be as high as 10%. The true numbers of thalassemia affected patients in the United States are unknown, as there is no effective screening method in place.[7]

Pathophysiology

Alpha thalssemia results when there is disturbance in production of alpha globin from any or all four of the alpha globin genes.

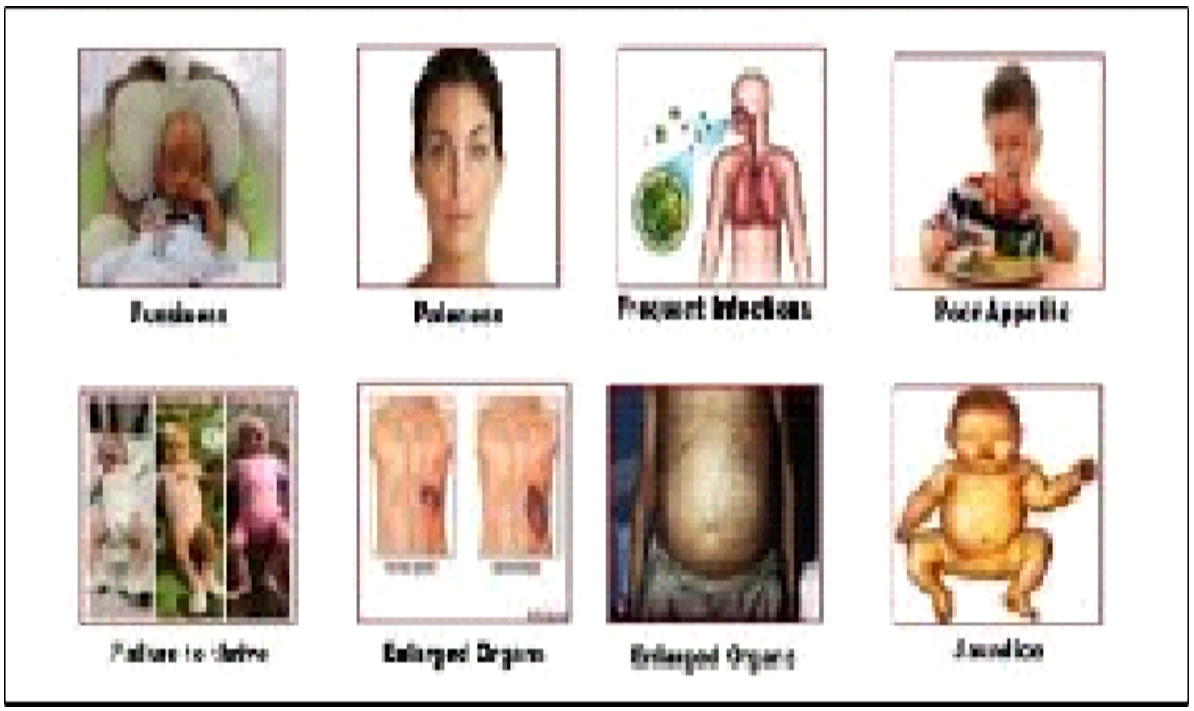
Genes are responsible for regulating the synthesis and structure of different globins which are divided into 2 clusters.

- The alpha globin genes are encoded on chromosomes 16 and the gamma, sigma and beta globin genes are encoded on chromosome.[11]
- A normal person carriers a linked pair of alpha genes, 2 each from maternal and paternal chromosome.
- Therefore, alpha thalassemia occurs when there is a disturbance in production of alpha globin from any or all four of the alpha globin genes.
- When functional point mutations, frame shift mutations, nonsense mutations, and chain termination mutations occur within or around the coding sequences of the alpha globin gene cluster hemoglobin is impaired.
- When that occurs, protein synthesis may be inhibited.
- Normal production of alpha chains is absent which results in excess production of gamma globin chains in the fetus and newborn or beta globin chains in children andadults.
- The beta globin chains are capable of forming soluble tetramers (beta-4, or HbH)
- This form of hemoglobin is still unstable and precipitates within the cell, forming insoluble inclusions called Heinz bodies.
- These heinz bodies damage the red blood cells.
- This further results in damage to erythrocyte precursors and ineffective erythropoisis in the bone marrow, hypochromia and microcytosis of circulating red blood cells.[8]



Clinical presentations

- Shortage of red blood cells- Anemia
- Pale skin
- Weakness
- Fatigue
- Enlarged liver and spleen - hepatosplenomegaly
- Heart defects
- Abnormalities of the urinary system or genitalia
- Hb Bart syndrome can cause complications in pregnancy such as High blood pressure, premature delivery, Abnormal bleeding, Jaundice.[4]



Beta thalassemia

Beta thalassemia results from point mutations in the beta globin gene. It is divided into three categories basrd on the zygosity of the beta gene mutation. A heterozygous mutation (beta plus thalassemia) results in beta thalassemia minor in which beta chains are underproduced. It is mild and usually asymptomatic. Beta thalassemia major caused by a homozygous mutations (beta-zero thalassemia) of the beta globin gene, resulting in the total absence of beta chains. The condition in between these two types is called beta thalassemia intermedia with mild to moderate clinical symptoms.[9]

One mutated genes: Mild signs and symptoms. The condition is called Thalassemia minor.

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

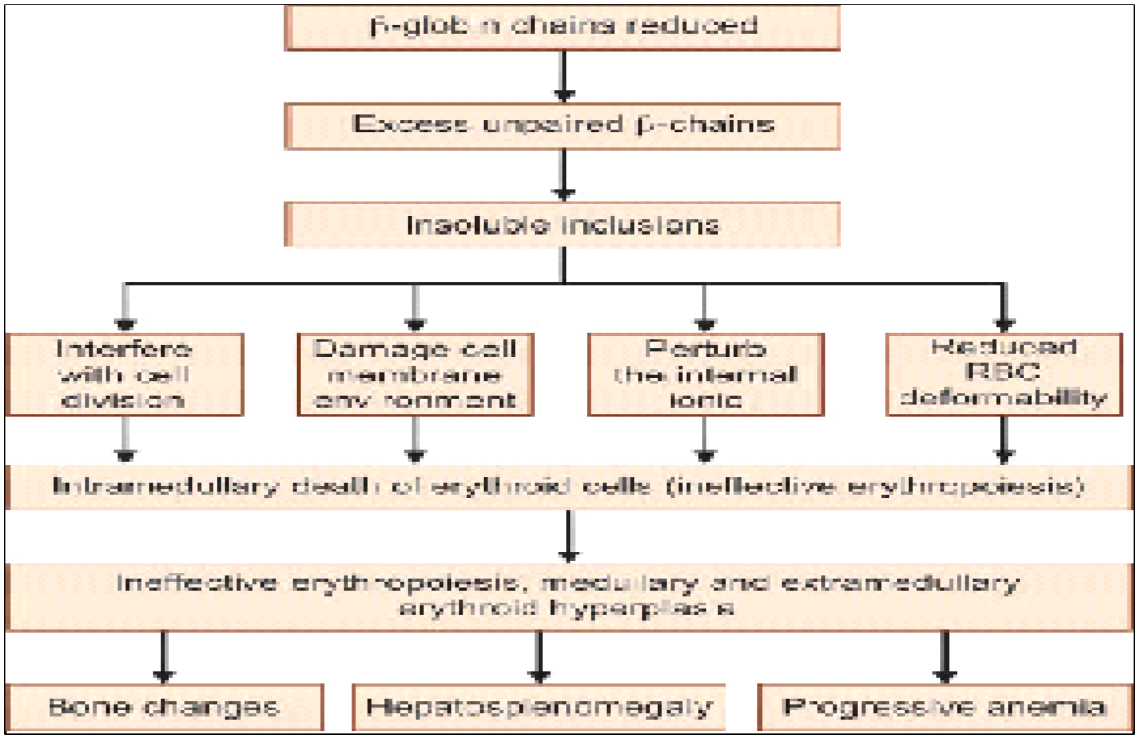
Etiology

- The HBB gene provides instructions for making a protein called beta-globin.
- When there is a mutation in the HBB gene, it prevents the production of any beta-globin.
- The absence of beta-globin is referred to as beta-zero thalassemia.
- Other HBB gene mutations allow some beta-globin to be produced but in reduced amounts. A reduced amount of beta globin is called beta plus thalassemia.
- A lack of beta-globin leads to a reduced amounts of functional hemoglobin. Without sufficient hemoglobin, red blood cells do not develop normally, causing a shortage of mature red blood cells.
- The low number of mature red blood cells leads to anemia and other associated health problems in people with beta thalassemia.[10]

Clinical presentation

- Jaundice
- Growth retardation
- Hepatosplenomegaly
- Endocrine abnormalities
- Severe anemia requiring life long blood transfusions

Pathophysiology



Complications

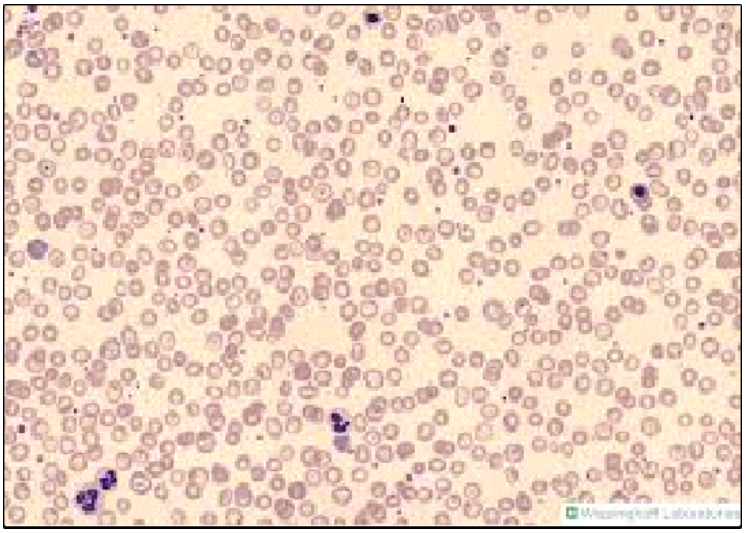
Untreated, thalassemia major leads to heart failure and liver failure problems. It also makes a person more likely to develop infections. Blood transfusion can help control some symptoms, but carry a risk of side effects from too much iron.[11]

Evaluation

Most children with moderate to severe thalassemia show signs and symptoms within theirfirst two years of life. Blood tests can reveal the number of red blood cells and abnormalities in size, shape or color. Blood tests can also be used for DNA analysis to look for mutated genes.

Chronic villus sampling: Usually done around the 11th week of pregnancy, this test involves removing a tiny piece of the placenta for evaluation.

Amniocentesis: Usually done around the 16th week of pregnacy, this test involves examining a sample of the fluid that surrounds the fetus.[12]



Complete Blood Count (CBC)

CBC is often the first investigation in a suspected case of thalassemia. A CBC showing low hemoglobin and low MCV is the first indication of thalassemia, after ruling out iron deficiency as the cause of anemia. The calculations of the Mentzer index (Mean corpuscular volume divided by red cell count) is useful. A Mentzer lower than 13 suggests that the patients has thalassemia, and an index of more than 13 suggests that the patients has anemia due to iron deficiency.

Hb- reduced (3-9mg/dl)

RBC Count- increased

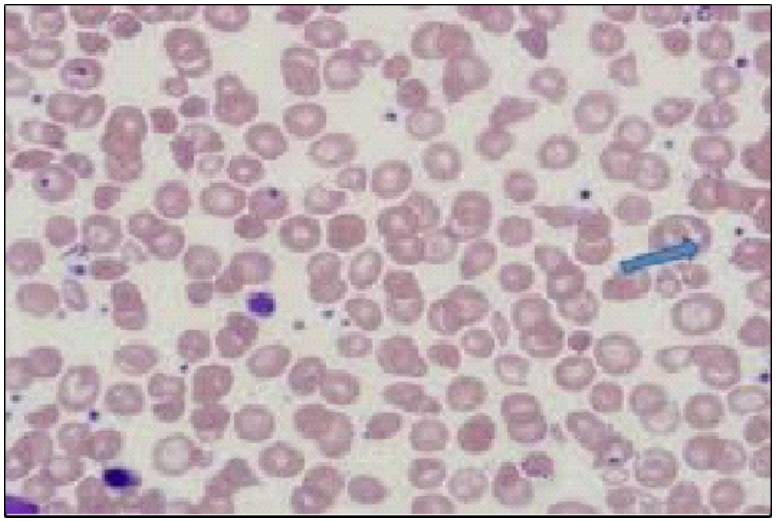
WBC, PLATELETS- normal

RBC indices- MCV&MCH, MCHC-normal, RDW-normal.

Peripheral blood smear

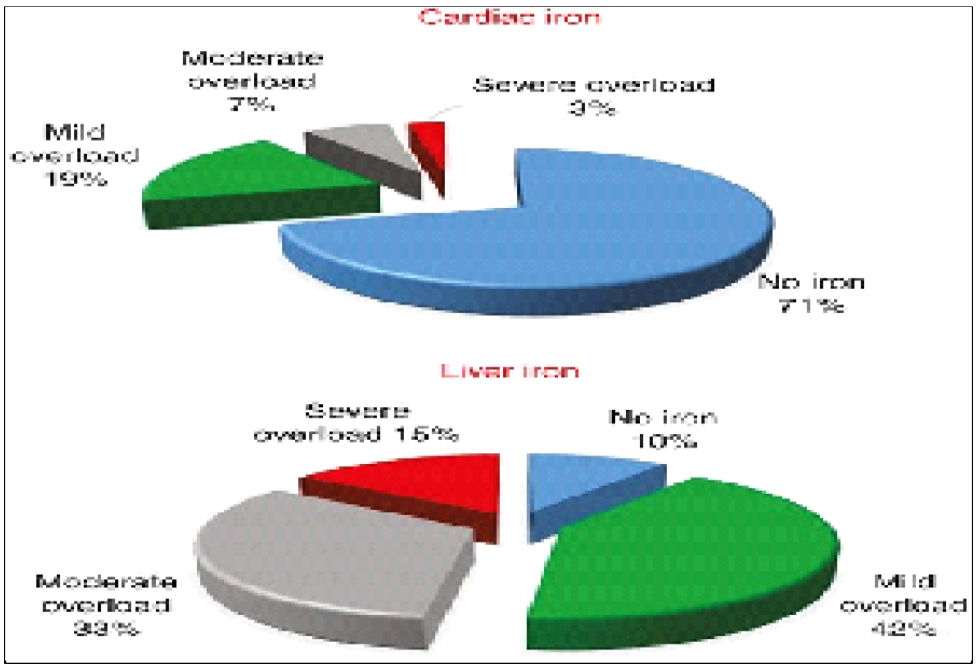
A blood smear (also called peripheral smear and manual differential) is next, to asses additional red cell properties. Thalassemia can present with the following finding on the peripheral blood smear:

- Microcytic cells (Low MCV)
- Hypochromic cells
- Variation in size and shape (Anisocytosis and Poikilocytosis)
- Increased percentage of reticulocytes
- Target cells
- Heinz bodies



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.

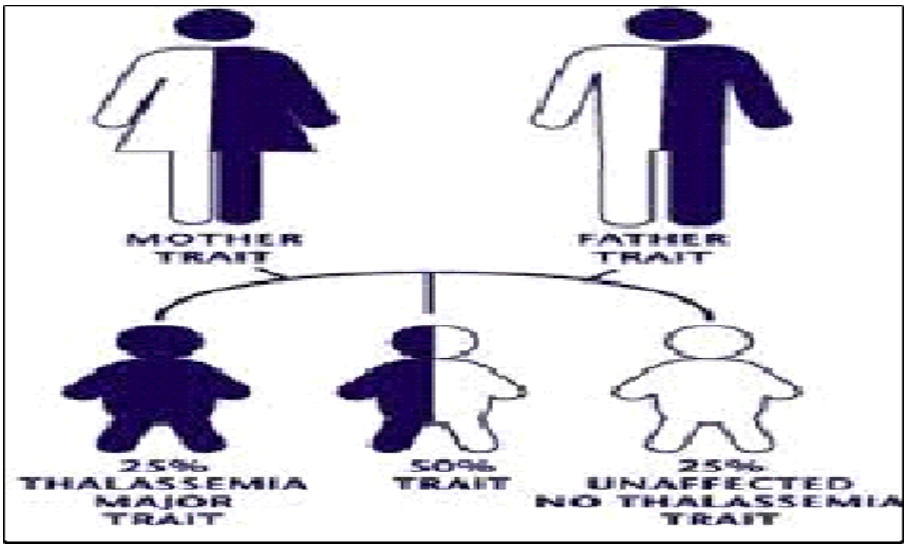


DNA analysis

These tests are serves to help confirm mutations in the alpha and beta globin producing genes. DNA testing is not a routine procedure but can be used to help diagnosis thalassemia and to determine carrier status if needed.

Since having relative carrying mutations for thalassemia increases a persons risk of carrying

the same mutant gene, family studies may be necessary to asses carrier status and the types of mutations present in other family members.



Reticulocyte count

Reticulocyte count (A measure of young red blood cells) may indicate that your bone marrow is not producing an adequate number of red blood cells. Studies of iron will indicate whether the cause of anemia is iron deficiency or thalassemia (Iron deficiency is not the cause of anemia in people with thalassemias).

Routine chemistry tests

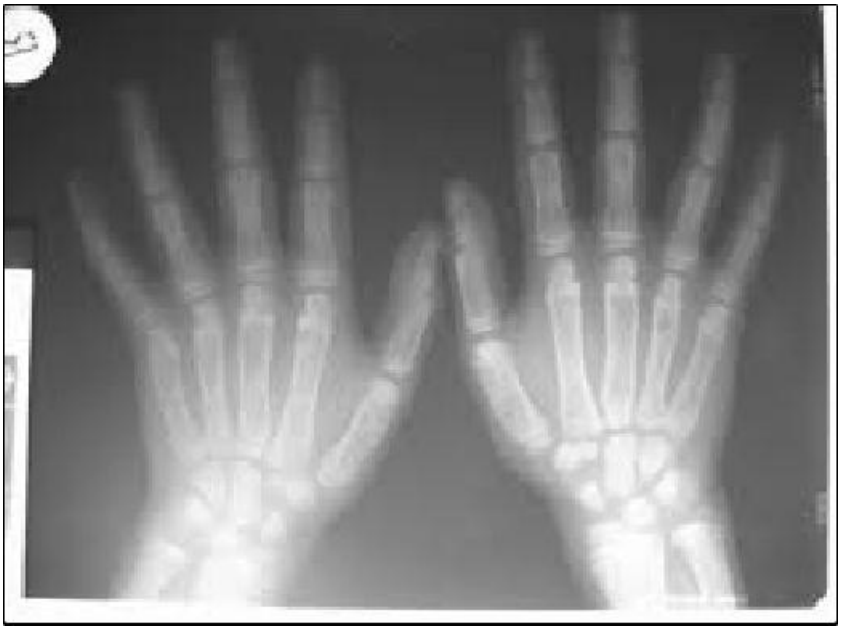
- Indirect bilirubin elevated in thalassemia major.
- Assessment of iron status, total iron binding capacity, and ferritin level important in defferentiating thalassemia from iron deficiency anemia.

Hemoglobin electrophoresis

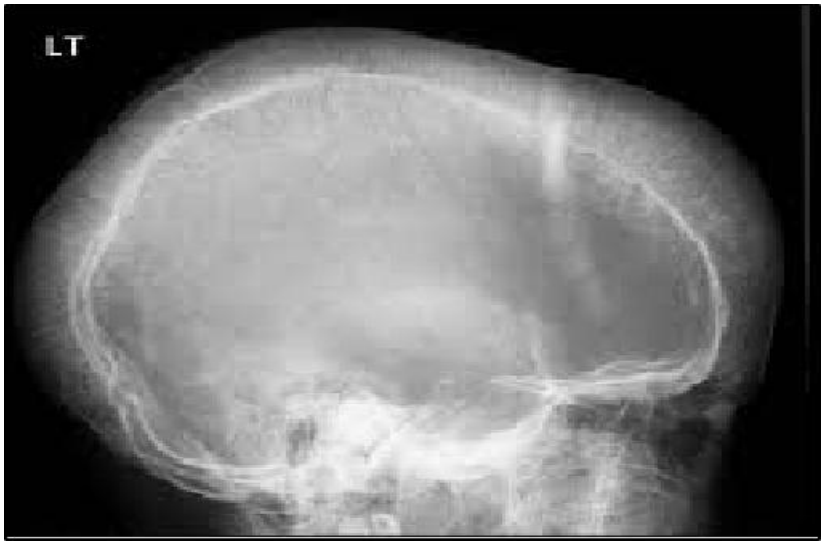
Important role in diagnosing and differentiating various forms of thalassemias. It can differentiate among Hb A, Hb A2, and Hb F, as well as detect presence of abnormal hemoglobins such as hemoglobin Bart's.

Radiological changes

Small bones (hand)- earliestbony changes, rectangular appearence, medullary portion of bone is widened& bony cortex thinned out with coarse trabecular pattern in medulla.



- Skull- widened diploid spaces- interrupted porosity gives hair on end appearence
- Delayed pneumatization of sinuses- maxilla appears avergrow with prominent malar eminences.[13]



Management

Non pharmacological treatment

Nutritional supplements, in the form of folic acid supplements, and monitoring of B12 levels are important, as these nutrients are key components to making healthy blood cells. Bone marrow and stem cell transplant from a comptible related donor is the only treatment that can cure thalassemia.[14]

Pharmacological treatment

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

Mild thalassemia: (Hb: 6-10g/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 childchild, or to help manage thalassemia complications.

Moderate to severe thalassemia: (Hb less than 5- 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 9-10mg/dl to give the patients a sense of well and also keep a check on erythropoiesis and supress extramedullary hematopoiesis. To limit transfusion related complications, washed, packed red blood cells (RBCs) at approximately 8-15ml cells per kilogram (kg) of body weight over 1-2 hours are recommended.[15]

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, (Bonemarrow transplant), is a potential option in selected cases, such as children born with severe thalassemia. It can eliminate the need for lifelong blood transfusion. However, this procedure has its own complications, and the clinician must weigh these against the benefits. Risks includes graft vs. host disease, chronic immunosuppressive therapy, graft failure, and transplantation-related mortality.[16]

Gene therapy

It is the latest advancement in severe thalassemia management. It involves harvesting the autologous hematopoietic stem cells (HSCs) from the patients and genetically modifying them with vectors expressing the normal genes.

These are then reinfused to the patients after they have undergone the required conditioning to destroy the existing HSCs. The genetically modified HSCs produce normal hemoglobin chains, and normal erythropoiesis ensues.

Splenectomy

Patients with thalassemia major often undergo splenectomy to limit the number of required transfusion. Splenectomy is the usual recommandation when the annual transfusion requirement increases to or more than 200-220mL RBCs/kg/year with a hemotocrit value of 70%.[17]

Medications

- Folic acid oral:- 250-1000mcg/day with or without food once a day 1-5 mg/day administration IM, IV OR SC once a day

Side effects: Serious allergic reactions, including Rash, itching, swelling, dizziness, trouble breathing.

- **Deferoxamine:-** 1000 mg initial dose and followed by 500mg every 4 hrs for two doses.

1000-2000mg/day should administered over 8-24 hrs, should administred by subcutaneous.

Side effects: Fast heartbeat, blue lips, skin or fingernails, severe blood diarrhea with cramping

- **Defoxamine:-** 500mg/ vial or 2 mg/vial.
- **Deferasirox:-** 125mg, 250mg, 500mg.[18]

Prevention

- Blood tests and family genetics studies can show wheather an individual has thalassemia or is a carrier.
- A Genetic counselor can detail the family background, discuss risks, and give you information on available testing.[19]

CONCLUSION

- Imbalance og globin chains cause hemolysis, impair erythropoiesis
- Alpha thalassemia intermedia or hemoglobin H disease, causes hemolytic anemia
- Alpha thalassemia major with hemoglobin barts usually results in fatal hydrops fetalis
- Affected children will require regular lifelong blood transfusions.
- Bone marrow transplantation can be curative for some children with beta thalassemia major
- Peson with thalassemia trait have a normal life expectancy.[20]

REFERENCES

1. LHe N, Chen W, Yang Y, Xie YJ, Xiong ZY, Chen DY, Lu D, Liu NQ, Yang YH, Sun

XF, Elevated Prevalence of Abnormal Glucose Metabolism and Other Endocrine Disorders in Patients with β-Thalassemia Major: A Meta-Analysis. BioMed research international, 2019; [PubMed PMID: 31119181]

2. Vichinsky E, Cohen A, Thompson AA, Giardina PJ, Lal A, Paley C, Cheng WY, McCormick N, Sasane M, Qiu Y, Kwiatkowski JL, Epidemiologic and clinical characteristics of nontransfusion-dependent thalassemia in the United States. Pediatric blood [PubMed PMID: 29637688]
3. Ahmadpanah M, Asadi Y, Haghighi M, Ghasemibasir H, Khanlarzadeh E, Brand S, {b}In Patients with{/b} Minor Beta-Thalassemia, Cognitive Performance Is Related to Length of Education, But Not to Minor Beta-Thalassemia or Hemoglobin Levels. Iranian journal of psychiatry, 2019 Jan; [PubMed PMID: 31114617]
4. Modell B, Khan M, Darlison M. Survival in beta-thalassaemia major in the UK: data from the UK Thalassaemia Register. Lancet, 2000; 355(9220): 2051—2052. [PubMed]
5. Cunningham MJ, Macklin EA, Neufeld EJ, Cohen AR. Thalassemia Clinical Research Network. Complications of beta-thalassemia major in North America. Blood, 2004; 104(1): 34—39. [PubMed]
6. Rachmilewitz EA, Schrier S. Pathophysiology of β thalassemia. In: Steinberg MH, Forget BG, Higgs DR, Nagel RL, editors. Disorders of Hemoglobin: Genetics, Pathophysiology, and Clinical Management. Cambridge, UK: Cambridge University Press, 2001; 233—251.
7. Ager JA, Lehmann H. Observations on some fast haemoglobins: K, J, N, and Bart's. Br Med J, 1958; 1(5076): 929—931. [PMC free article] [PubMed] [Google Scholar]
8. Benites BD, Cisneiros IS, Bastos SO, Lino APBL, Costa FF, Gilli SCO, Saad STO, Echocardiografic abnormalities in patients with sickle cell/β-thalassemia do not depend on the β-thalassemia phenotype. Hematology, transfusion and cell therapy. 2019 Apr - Jun;[PubMed PMID: 310
9. Manzoor I, Zakar R, Sociodemographic determinants associated with parental knowledge of screening services for thalassemia major in Lahore. Pakistan journal of medical sciences, 2019. [PubMed PMID: 31086537]
10. Pootrakul P, Sirankapracha P, Hemsorach S, Moungsub W, Kumbunlue R, Piangitjagum A, Wasi P, Ma L, Schrier SL. A correlation of erythrokinetics, ineffective erythropoiesis, and erythroid precursor apoptosis in Thai patients with thalassemia. Blood, 2000; 96(7): 2606—2612. [PubMed]
11. Cunningham MJ, Macklin EA, Neufeld EJ, Cohen AR. Thalassemia Clinical Research

Network. Complications of beta-thalassemia major in North America. Blood, 2004; 104(1): 34—39. [PubMed]

12. Cazzola M, Borgna-Pignatti C, Locatelli F, Ponchio L, Beguin Y, De Stefano P Transfusion, 1997; 37(2): 135-40.
13. Singha K, Taweenan W, Fucharoen G, Fucharoen S, Erythrocyte indices in a large cohort of β-thalassemia carrier: Implication for population screening in an area with high prevalence and heterogeneity of thalassemia. International journal of laboratory hematology, 2019; 17. [PubMed PMID: 31099487]
14. Jariwala K, Mishra K, Ghosh K, Comparative study of alloimmunization against red cell antigens in sickle cell disease [PubMed PMID: 31115372]
15. Olivieri NF, Brittenham GM. Iron-chelating therapy and the treatment of thalassemia. Blood, 1997; 89(3): 739—761. [PubMed]
16. Hoffbrand AV, Cohen A, Hershko C. Role of deferiprone in chelation therapy for transfusional iron overload. Blood, 2003; 102(1): 17—24. [PubMed] [Google Scholar.
17. Weatherall DG, Clegg JB. The Thalassemia Syndromes Oxford, UK: Blackwell, 2000; 4. [Goole]
18. Weatherall DG, Clegg JB. The Thalassemia Syndromes. Oxford, UK: Blackwell, 2000; 4.
19. Hoffbrand AV, Cohen A, Hershko C. Role of deferiprone in chelation therapy for transfusional iron overload. Blood, 2003; 102(1): 17—24. [PubMed]
20. Argiolu F, Sanna MA, Addari MC, et al. Bone marrow transplantation in thalassemia. The significance of Cagliari. Bone Transplant, 1997; 19(2): 65.
21. Weatherall DJ. The thalassemias. In: Beutler B, Lichtman MA, Coller BS, Kipps TJ, Seligsohn S, editors. Williams Hematology. New York: McGraw-Hill, 2001; 6: 562—564.