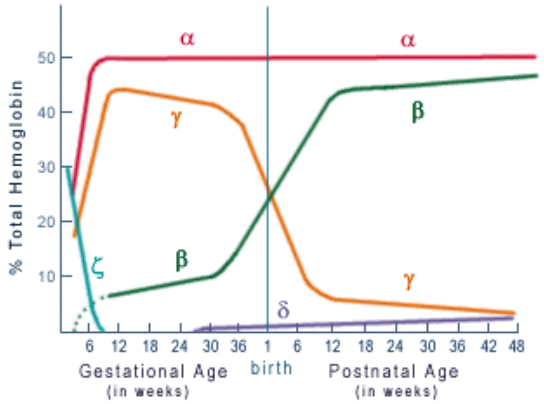
What is Thalassaemia?

Introduction

The thalassaemias are a diverse group of genetic blood diseases characterized by absent or decreased production of normal hemoglobin, resulting in a microcytic anemia of varying degree. The thalassemias have a distribution concomitant with areas where P. falciparum malaria is common.



In the normal adult, hemoglobin A, which is composed of two alpha and two beta globins (a2b2), is the most prevalent, comprising about 95% of all hemoglobin. Two minor hemoglobins also occur: hemoglobin A2, composed of two alpha and two delta globins (α2β2) comprises 2-3.5% of Hb, while Hb F, composed of two alpha and two gamma globins (α2γ2), comprises less than 2% of Hb.

The genes controlling globin production are on chromosome 16 (alpha a globin genes) and chromosome 11 (beta b, gamma g, and delta d genes). As seen in the diagram, the alpha globin molecule concentration is rather stable in fetal and adult life, because it is needed for both fetal and adult hemoglobin production. The beta globin appears early in fetal life at low levels and begins to rapidly increase after 30 weeks gestational age, reaching a maximum about 30 weeks postnataly. The gamma globin molecule reaches a high level early in fetal life at about 6 weeks and begins to decline about 30 weeks gestational age, reaching a low level about 48 weeks post gestational age. The delta globin appears at a low level at about 30 weeks gestational age and maintains a low profile throughout life.

Hemoglobin F, or fetal hemoglobin, is produced by the fetus in utero and until about 48 weeks after birth. Hb F has a high oxygen-affinity in order to attract oxygen from maternal blood and deliver it to the fetus. After birth, the production of adult hemoglobin rapidly increases and fetal hemoglobin production drops off.

Clinical Classification

Alpha Thalassaemia

The alpha thalassemias are caused by a decrease in production of alpha globin chains due to a deletion or mutation of one or more of the four alpha globin genes located on chromosome 16. Alpha gene mapping can be obtained to determine the specific mutation. Alpha thalassemia has four manifestations that correlate with the number of defective (lost) genes

(i) **Silent Carrier state**. This is the one-gene deletion alpha thalassemia condition. People with this condition are hematologically normal. They are detected only by sophisticated laboratory methods.

(ii) **Mild alpha-thalassemia**. These patients have lost two alpha globin genes. They have small red cells and a mild anemia. These people are usually asymptomatic. Often, physicians mistakenly diagnose people with mild alpha-thalassemia as having iron deficiency anemia. Iron therapy, of course, does not correct the anemia.

(iii) **Hemoglobin H disease** These patients have lost three alpha globin genes. The result is a severe anemia, with small, misshapen red cells and red cell fragments. The bone marrow works at an extraordinary pace in an attempt to compensate for the anemia. As a result, the marrow cavity within the bones is stuffed with red cell precursors. These cells gradually cause the bone to "mold" and flair out. Patients with hemoglobin H disease also develop large spleens. The spleen has blood forming cells, the same as the bone marrow. These cells become hyperactive and over expand, just as those of the bone marrow. The result is a spleen that is often ten times larger than normal. Large energy goes into the production of new red cells at an extremely accelerated pace.

(iv) **Hydrops fetalis**. This condition results from the loss of all four alpha globin genes. The affected individual usually succumbs to the severe anemia and complications before birth.

The Silent Carrier status is characterized by three functional genes that code for the production of alpha globins (-α/αα). Outside the newborn period, it is not possible to make this diagnosis by conventional methods. There is overlap between the red blood cell indices of these individuals and normal, although the MCV may be slightly lower. The silent carrier will experience no health problems in his/her lifetime. This carrier state is diagnosed by deduction when a 'normal' individual has a child with Hb H disease or with microcytic anemia consistent with alpha thalassemia trait. An unusual case of the silent carrier state is the individual who carries the Hemoglobin Constant Spring mutation [(αcsα/αα) or (ααcs/αα)]. This is an elongated a-globin due to a termination codon mutation. Individuals who have this mutation have normal red blood cell indices, but can have children who have Hb H-Constant Spring disease if the other parent has alpha thalassemia trait (--/αα). Generally, children with Hb H-Constant Spring are more affected clinically than children who have classic Hb H disease. Two Constant Spring

carriers can also pass on their genes to have a child with Homozygous Constant Spring, a condition that has similar clinical implications as Hemoglobin H disease.

Alpha thalassemia trait is characterized by two functional genes that code for the production of alpha globins [(-α/-α) or (--/αα)]. The two genes can either occur on the same chromosome (cis-type) or on each of the pair (trans-type). Cis-type a-thalassemia trait tends to be found in individuals of Asian descent, while trans-type tends to run in individuals of African descent. Cis-type can be co-inherited with another cis-type or hemoglobin H disease to result in alpha thalassemia major, or hydrops fetalis. Individuals who have alpha thalassemia trait are identified by microcytosis, erythrocytosis, hypochromia, and mild anemia. The diagnosis is made by a combination of family studies and the ruling out of both iron deficiency anemia and beta thalassemia trait. In the neonatal period, when hemoglobin Bart's (δ4) is present, the diagnosis can be strongly suspected. In children, there are no markers such as Hb A2 and Hb F to make the diagnosis. (One exception is the case where both of the deletions occur on the same chromosome and zeta [ε] globin is expressed in carriers. This is most common in Southeast Asians.) The diagnosis is one of exclusion. The clinician should be satisfied with the presumed diagnosis if the above criteria are met. During pregnancy, the microcytic anemia can be mistaken for anemia of pregnancy.

The individual with a thalassemia trait will experience no significant health problems except a possible slight anemia which cannot be treated with iron.

Hemoglobin H disease is characterized by one functional gene that codes for the production of alpha globins (--/-α). Hb H disease should be considered in the case of a neonate in whom all of the red blood cells are very hypochromic. These neonates have a high percentage of hemoglobin Bart's on the newborn screening results. In older children, this Hemoglobinopathy is characterized by moderate anemia with hemoglobin in the 8 to 10 gm/dL range, hypochromia, microcytosis, red cell fragmentation, and fast migrating hemoglobin (Hb H) on electrophoresis.

Hemoglobin H does not function as normal hemoglobin and has a high oxygen affinity (holds onto oxygen longer making it unviable for use by the body), so the measured hemoglobin in these children is misleading. Individuals who have Hb H generally have a persistent stable state of anemia, which may be accentuated by increased hemolysis during viral infections and by exposure to oxidant medications, chemicals and foods such as sulfa drugs, benzene, and fava beans (similar to individuals who have G6PD deficiency). As the red cells mature they loose their ability to withstand oxidant stress and Hb H precipitates, leading to hemolysis. Therapy for individuals who have Hb H disease includes folate, avoidance of oxidant drugs and foods, genetic counseling education and frequent medical care. Uncommon occurrences in a child with Hb H would be severe anemia, cholelithiasis, skin ulceration, and splenomegaly requiring splenectomy. Unlike individuals who have beta thalassemia, hemosiderosis is rare in Hb H disease.

Children with Hemoglobin H-Constant Spring (--/αcsα) have a more severe course than children who have Hb H. They have a more severe anemia, with steady state hemoglobin ranging between 7 and 8 gm/dl. They more frequently have splenomegaly and severe anemia with febrile illnesses and viral infections, often requiring transfusion. If anemia is chronically severe and the child has splenomegaly, a splenectomy may be performed. If splenectomy is anticipated, the complication of severe post-splenectomy thrombocytosis with hypercoagulability can occur, leading to thrombosis of the splenic vein or hepatic veins. This complication has also been reported as recurrent pulmonary emboli and clotting diathesis. At CHO, children who are scheduled to have surgery are treated pre-surgically with low molecular weight heparin, followed by low dose aspirin, continued indefinitely

The most severe form of alpha thalassemia is Alpha Thalassemia Major or **hydrops fetalis**, characterized by a deletion of all four genes that code for alpha globins (--/--). This diagnosis is frequently made in the last months of pregnancy when fetal ultrasound indicates a hydropic fetus. The mother frequently exhibits toxemia and can develop severe postpartum hemorrhage. These infants are usually stillborn. There can be other congenital anomalies, though none are pathognomonic for alpha thalassemia major. Since alpha globins are required for production of fetal and adult hemoglobin, the fetus suffers from significant in utero hypoxia. The only hemoglobins found in these infants are: Hb Portland (δ2γ2), Hb H (β4), and Hb Bart's (γ4), and no Hb A or A2. These babies can have other complications associated with hydrops, such as heart failure and pulmonary edema.

If the diagnosis is made early, intrauterine transfusions can be performed. There are reports of survival and chronic transfusion in these infants; CHO cares for one alpha thalassemia major baby with chronic transfusion therapy. Undoubtedly, more of these infants could be saved if the diagnosis is anticipated by prenatal diagnosis and treatment provided

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with the presumed diagnosis if the above criteria are met. During pregnancy, the microcytic anemia can be mistaken for anemia of pregnancy.

The individual with a thalassemia trait will experience no significant health problems except a possible slight anemia which cannot be treated with iron.

Clinical Classification

Beta Thalassaemia

There are more than 200 hundred of mutations within the beta globin gene, but approximately 20 different alleles comprise 80% of the mutations found world wide.

The beta thalassemia syndromes are much more diverse than the alpha thalassemia syndromes due to the diversity of the mutations that produce the defects in the beta globin gene. Unlike the deletions that constitute most of the alpha thalassemia syndromes, beta thalassemias are caused by mutations on chromosome 11 that affect all aspects of beta globin production: transcription, translation, and the stability of the beta globin product. Most hematologists feel there are three general categories of beta thalassemia:, Beta thalassemia trait, Beta thalassemia intermedia and Beta thalassemia major.

Hemoglobin E is very common abnormal hemoglobin in the Southeast Asian population, and when paired with a β0 thalassemia mutation, can produce severe transfusion-dependent (Eβ0) thalassemia.

i) Thalassemia minor, or thalassemia trait. These terms are used interchangeably for people who have small red cells and mild (or no) anemia due to thalassemia. These patients are clinically well, and are usually only detected through routine blood testing. Physicians often mistakenly diagnose iron deficiency in people with thalassemia trait. Iron replacement does not correct the condition. The primary caution for people with beta-thalassemia trait involves the possible problems that their children could inherit if their partner also has beta-thalassemia trait. Individuals who have Beta thalassemia trait have microcytosis and hypochromia; there may be targeting, elliptocytosis, though some individuals have an almost normal smear. Hemoglobins A2 and F will be elevated on hemogram results. These hematologic features can be accentuated in women with trait who are pregnant and in individuals who are folate or iron deficient. If iron deficiency is concurrent with beta thalassemia trait there may be a normal Hb A2. Iron deficiency causes decreased hemoglobin production, and folate or vitamin B12 deficiency can lead to megaloblastic anemia with increased Hb A2. Both of these deficiencies need to treated prior to evaluation for thalassemia trait. In iron, B12, and folate replete individuals, the Hb A2 can be as high as 3.5 to 8% and the Hb F as high as 1 to 5%. Generally, beta thalassemia trait is milder in African-Americans (who frequently have a promoter gene mutation) but has a similar presentation in individuals of Chinese, Southeast Asian, Greek, Italian, and Middle Eastern heritage.

Infants born in 42 of the 50 states in the United States with newborn screening programs will be diagnosed as having a hemoglobin disorder. In states without newborn screening

for hemoglobinopathies and in recent immigrants to this country, affected children are frequently identified outside the newborn period, and the evaluation of their microcytic anemia includes differentiation between iron deficiency and beta thalassemia trait. The red blood cell indices can be helpful in this differentiation, as the hemoglobin concentration and the red cell count will generally be lower in iron deficiency. The distinguishing finding in beta thalassemia is a hemoglobin electrophoresis with the finding of elevated Hb A2 and F. Both will be increased in beta thalassemia trait without iron deficiency, and will be normal or decreased in alpha thalassemia and isolated iron deficiency anemia. There are several formulas to help in office screening, but they are also based on the assumption that the child is not iron deficient. Usually iron deficiency can be ruled out using free erythrocyte protoporphyrin (FEP), transferrin saturation or ferritin as a screening test in children who have a hypochromic microcytic anemia. The least expensive test is a trial of iron and a repeated hemogram after a month. A lead level should be obtained if there is an index of suspicion for lead toxicity.

Diagnostic challenges can still arise: if both alpha and beta thalassemia coexist, the changes in Hb A2 and F will not be apparent, and as noted above, there are instances of normal or elevated levels of Hb A2 and F in beta thalassemia trait. Family studies and, if warranted, DNA analysis can be used to make a definitive diagnosis

(ii) Thalassemia intermedia. Thalassemia intermedia are a confusing concept. The most important fact to remember is that a thalassemia intermedia is a description, and not a pathological or genetic diagnosis. Patients with thalassemia intermedia have significant anemia, but are able to survive without blood transfusions. The factors that go into the diagnosis are:

The degree to which the patient tolerates the anemia.

The threshold of the physician to transfuse patients with thalassemia.

Children who are diagnosed with Thalassemia Intermedia have a homozygous or heterozygous beta globin mutation that causes a decrease in beta chain production, but not to the degree that chronic transfusion therapy is required. The phenotype can also occur in children who have a mutation that increases production of γ -globin, in children who have co-inherited alpha thalassemia and beta thalassemia, and in other rarer mutations. Children who have thalassemia intermedia are able to maintain a hemoglobin of 7 gm/dl or slightly higher with a greatly expanded erythron and may manifest bony deformities, pathologic fractures and growth retardation. Children who have thalassemia intermedia can also have delayed pubescence, exercise intolerance, leg ulcers, inflammatory arthritis and extra medullary hematopoiesis causing spinal cord compression, a medical emergency requiring radiation therapy and transfusion. They can also have iron overload due to increased absorption of iron from the gastrointestinal tract and intermittent transfusion. They are at risk for the cardiac and endocrine complications of hemosiderosis, but usually at an older age than chronically transfused children. Chelation therapy is indicated for increasing ferritin and elevated liver iron.

Children who can not maintain hemoglobin between 6 and 7 gm/dl should have an alternative diagnosis considered. If thalassemia is the cause of the anemia, transfusion and/or splenectomy should be considered. Frequently, adolescents and adults are unable to tolerate the degree of anemia that is seen in thalassemia intermedia. Hypersplenism, splenic pain, congestive heart failure secondary to anemia, severe exercise intolerance, thrombocytopenia and leukopenia should be considered indications for beginning transfusion therapy or for splenectomy in the child who has severe hemolytic anemia

(iii) Thalassemia major. This is the condition of severe thalassemia in which chronic blood transfusions are needed. In some patients the anemia is so severe, that death occurs without transfusions. Other patients could survive without transfusions, for a while, but would have terrible deformities. While transfusions are life-saving in patients with thalassemia major, transfusions ultimately produce iron overload. Chelation therapy, usually with the iron-binding agent, desferrioxamine, deferiprone or defrasirox, is needed to prevent death from iron-mediated organ injury

Beta thalassemia major was first described by a Detroit pediatrician, Thomas Cooley, in 1925. The clinical picture he described is prevalent today in countries without the necessary resources to provide patients with chronic transfusions and iron chelation therapy. Children who have untreated thalassemia major have ineffective erythropoiesis, decreased red cell deformability, and enhanced clearance of defective red cells by macrophages (immune system cells). The result is a very hyper metabolic bone marrow with thrombocytosis, leukocytosis and microcytic anemia in the young child prior to the enlargement of their spleen. At presentation they have almost 100% percent Hgb F (these cells have a longer life span due to a balanced globin ratio, as γ rather than β, globin is present Hgb F). These children have little or no Hgb A2 and a low reticulocyte count. The diagnosis can be confirmed by demonstrating thalassemia trait in both parents, by globin biosynthetic ratios, or by beta gene screening. Beta gene screening identifies the most common and some uncommon mutations, but not all mutations. An electrophoresis showing only Hgb F, a complete blood count and a smear will generally be diagnostic. In most states, these children will be discovered by state screening or occasionally by the obstetrician who makes a diagnosis of thalassemia trait in the mother and obtains a family history of thalassemia or anemia in both parents prior to the birth of the baby.

Children who have untreated thalassemia generally die in the first decade of life from anemia and septicemia, and may suffer from pathologic fractures. When palliative transfusions are introduced, children live into their late teens, but eventually succumb to heart failure if iron overload is not treated. But with the introduction of frequent chronic transfusion therapy and adequate iron chelation, children are now enjoyin a near normal life. The longevity of patients who are compliant with chelation therapy or who have received bone marrow transplantation is now well established. Many patients are in their 5^{th} or 6^{th} decade of life well-educated, employed/earning and enjoying happy married life.

Causes

A baby inherits one gene of each pair from both parents to have his own set of pairs. Thus each child gets half his genes from each parent.

Beta thalassaemia trait is passed from parents to children in autosomal recessive pattern of inheritance. Child inherits one beta globin gene from each parent. When both parents carry normal beta globin gene, child will inherit two normal beta globin genes .When one of the parent carries an affected beta globin gene (beta thalassaemia carrier) and the other parent carries a healthy beta globin gene, then each child has 50% chance of inheriting affected gene from carrier parent.

Symptoms

Alpha Thalassaemia

Silent Carrier State: No symptoms

Minor: Hematological normal. Benign condition with mild or no anaemia Symptom free and no abnormal physical findings
Haemoglobin levels are not reduced below 10g/dl

Mild Alpha Thalassaemia:
May fall under stress such as puberty, pregnancy, infection or nutritional deficiency
Patient has small RBCs. Suffers from a mild anemia.

Intermediate: Is usually asymptomatic.
Mistakenly diagnosed as alpha-thalassemia having iron deficiency anemia.
No clear cut distinction with major
In mild cases, growth and development of the child may be relatively normal
Severe cases may present with the clinical picture similar to transfusion dependent beta thalassaemia major

Hydrops fetalis:
Complications before birth. Invariably stillborn

Beta Thalassemia

Silent Carrier State: No symptoms

Minor: Microscopic, hypochromic anaemia. Symptom free and no abnormal physical findings.

Intermedia: Palor and splenomegaly are prominent. Growth and development often get affected if the anaemia persists for a long time in the absence of blood transfusions
Many borderline patients with severe anaemia manage to survive without transfusions Most of them present late in life (four to seven years or even later). Maintain Hb between 6-9 g/dl. Often are small and appear malnourished. Anaemia is persistent, progressive and does not respond to any form of therapy. Marrow cavity within the bones is stuffed with red cell precursors causing bone to flair out. Puberty may be delayed by 2-3 years.

Major Bony abnormalities particularly involving the cheeks and forehead. Infants well at birth but develop anaemia between 3-18 months of age. Have poor appetite, fail to thrive and become weak and lethargic. Enlarged spleens become irritable and cry excessively. Development e.g. sitting, standing is delayed. Their growth - i.e. gain in weight, height, head and chest circumference are affected. Bone marrow expansion to compensate for excessive ineffective erythropoiesis which results in marked skeletal deformities. Hypertrophy of the skull may produce deafness Upper respiratory infections are common Excessive erythropoiesis also occurs in liver and spleen resulting in the enlargement of organs. Iron absorption is proportional to erythropoiesis. This adds to iron overload

Diagnosis

Alpha Thalassaemia

There are four genes coding for alpha chain production. These genes are located on chromosome 6. As a result there are at least five forms of alpha thalassemia depending on the number and location of the abnormal genes. Frequently, the diagnosis of alpha thalassemia trait in a parent is discovered after the birth of an affected child.

i. Hydrops Fetalis (Homozygous Alpha Thalassemia)

All genes are abnormal. There is no alpha chain production hence no Hgb F production and death in utero.

Laboratory diagnosis of Hydrops Fetalis

At autopsy the cord blood shows severe anemia, less than 6g/dl. There is no Hgb A or Hgb F on electrophoresis, most of the hemoglobin is hemoglobin Bart's which consists of 4 gamma chains.

ii. Hemoglobin H Disease

Three genes are abnormal and one gene is coding for alpha chains. As a result there is limited production of Hgb F in utero and Hgb A after birth. The excess gamma chains form Hgb Bart's and the excess beta chains form Hgb H both of which are unstable and precipitate in the cell resulting in the premature destruction in the marrow and spleen with splenomegaly.

Laboratory diagnosis of Hemoglobin H Disease

In the adult steady state Hb levels vary from 8.9 to 12.7 g/dl and the red cell indices are decreased. There is a reticulocytosis of approximately 5%, but the reticulocyte response is inadequate for the degree of anemia, a consistent finding in Chronic anemia.

On the peripheral blood film, red cells are microcytic, Hypochromic with anisopoikilocytosis. The electronically measured red cells distribution width [RDW] is increased. Almost all red cells have HbH inclusions, visible microscopically when erythrocytes are incubated and stained with brilliant Cresyl Blue (BCB). However HbH inclusions generally occur in multiples and cover the cell surface, producing a golf ball

like appearance, whereas Heinz bodies are usually eccentrically located and are relatively few per cell.

Serum iron - increased
Ferritin - increased
TIBC - decreased

Hemoglobin electrophoresis – Hb electrophoresis (alkaline PH) in affected neonates shows about 25% to 40% Hb Barts (γ_4) but as β chain synthesis replaces γ during the first few months of life, Hb Barts is gradually replaced by Hb H (β_4). Electrophoresis of adult specimens shows Hbs A, H and A_2, with a trace amount of Hb Barts in 10% of patients. The Hb F level is normal whereas the Hb A_2 levels are nearly always reduced HbH levels can vary widely from 2% to 40%.

iii. Heterozygous alpha Thalassemia (minor)-The clinical picture varies somewhat depending upon whether or not the two deleted genes are on the same chromosome or not. In alpha thalassemia^0 both genes are absent from the same chromosome. In alpha thalassemia$^+$ one gene is missing from each chromosome. The + form tends to be slightly more severe with slightly lower hemoglobin levels.

Laboratory diagnosis of alpha thalassemia minor
In both forms however, there are only minor changes with perhaps a mild anemia. The MCV and MCH are usually boarder-line low with the MCH being depressed more often than the MCV. The RDW tends to increase if an anemia develops as a result of pregnancy etc. Hemoglobin electrophoresis is normal with increased levels of Hgb Bart's if the cord blood is electrophoresed.

Alpha Thalassemia Silent - Only one of the four genes is abnormal. As a result there is a near normal production of alpha chains with very few if any clinical or laboratory changes.

Beta Thalassaemia

The genes controlling beta chain production are located on chromosome 11. If both genes fail then the patient is said to have beta thalassemia major. If only one gene fails then the patient has beta thalassemia minor.

BETA THALASSEMIA MINOR (HETEROZYGOUS) (B+) this is the most common of the thalassemias. These patients are clinically well, and are usually only detected through routine blood testing. Physicians often mistakenly diagnose iron deficiency in people with thalassemia trait.

Individuals who have Beta thalassemia trait have microcytosis and hypochromia; there may be targeting, elliptocytosis, though some individuals have an almost normal smear. Hemoglobins A2 and F will be elevated on hemogram results.

Beta chain production is less than normal due to the failure of one of the genes coding for beta chains. Alpha chain production continues at a near normal rate. The alpha chains combine with the available beta chains resulting in decreased levels of hemoglobin A. There still remains an excess alpha chain and this stimulates the increased production of delta chains. The alpha and delta chains combine to form increased amounts of hemoglobin A2. If there is still an excess of alpha chains the normal mechanism which switches off gamma chain production does not function correctly and the rate of gamma chain production is greater than in a normal adult. This results in the formation of increased amounts of hemoglobin F.

Laboratory diagnosis of beta thalassemia minor

These patients are not severely anemic. The importance of identifying heterozygous beta thalassemia is to prevent the investigation and expense caused by confusion with iron deficiency. As well these patients can then be provided appropriate genetic counseling. Hemoglobin, Hematocrit is decreased. The RBC count is not as low as the hemoglobin and hematocrit; in fact it is usually normal. This is due to the fact that the marrow can still produce the cells but cannot fill them with hemoglobin. Hence the Hgb is low and the empty cells occupy less space thus lowering the Hct relative to the erythrocyte count. Hemoglobin is very seldom, if ever, below 95 g/L. If the Hgb is less than 93 g/L it is unlikely the patient has beta thalassemia minor. Morphology is microcytic and hypochromic. Anisocytosis is only slight and not near as marked as in iron deficiency. This is reflected in a near normal RDW and red cell histogram which is shifted to the left but of near normal dimensions. There is slight poik with an occasional target cell. A moderate basophilic stippling is common. Indecies show a characteristic discordance. The MCV is slightly decreased and the MCH is decreased. The MCHC is normal. The RBC number is usually normal. The discriminant factor (DF) is a mathematic manipulation of the indices and generates a number which can be used to help differentiate between thalassemia minor and iron deficiency. At least three formulas are in use. The England-Frazer formula is the most often used.

England-Frazer: MCV - (HgbX5) - RBC - 3.4 = if negative Thalassemia minor positive iron def

White cell count and differential - normal
Reticulocytes - relative increase
Platelets - decreased

Bone marrow - normal to slight erythroid hyperplasia.

Serum iron - normal
TIBC - normal
Ferritin - normal
Bilirubin - slight increase due to intramedullary hemolysis
FEP - normal

Hemoglobin studies:
Hgb A - decreased
Hgb A2 - increased
Hgb F - Slight increase to normal

BETA THALASSAEMIA INTERMEDIA

Variants of Beta Thalassaemia

Delta/Beta Thalassemia

The gene controlling delta chain production is located very close to the beta gene on chromosome 11. If one gene is deleted then the other may be affected. Homozygous Delta/Beta Thalassemia is similar to beta thalassemia, but symptoms are milder. Most patients survive to adult life with minimal transfusion requirements. Laboratory diagnosis of homozygous delta/beta thalassemia

Anemia - variable 40 to 100g/L. Morphology - hypochromic microcytic with marked anisocytosis and poikilocytosis. Erythrocyte inclusions are common. Hemoglobin electrophoresis shows 90 to 100% Hgb F. Heterozygous Delta/Beta Thalassemia is similar to beta thalassemia minor but symptoms tend to be less severe.

Laboratory diagnosis of heterozygous delta/beta thalassemia
Anemia - mild Morphology - hypochromic microcytic with slight anisocytosis and poikilocytosis. The indices are discordant.

Hemoglobin electrophoresis -
Hgb A - decreased
Hgb F - 5 to 15%
Hgb A2 – normal

Hemoglobin Lepore

This is a mix-up in the production of the non-alpha chain. The carbon end is the amino acid sequence of the delta chain while the N-terminal end is the amino acid sequence of the beta chain.
There are at least three variants depending on the length of the mixed up segments:
1. Washington
2. Hollandia
3. Baltimore

Laboratory diagnosis of homozygous Hgb Lepore
Homozygous Hgb Lepore There is no normal beta or delta chain production. The clinical and laboratory findings are identical to Beta thalassemia major except on electrophoresis.
Hemoglobin electrophoresis:

Hgb F 80 to 90%
Hgb A absent
Hgb A2 absent

Hgb Lepore 10%
Hgb Lepore moves in the same position as Hgb S

Laboratory diagnosis of heterozygous Hgb Lepore
The clinical and laboratory findings are identical to beta thalassemia minor except on electrophoresis.

Hemoglobin electrophoresis:
Hgb A decreased
Hgb A2 decreased
Hgb Lepore 10%

Hemoglobin E

Hemoglobin E is not a thalassemia but is, rather a Hemoglobinopathy. Thalassemia is characterized by the inability to produce sufficient numbers of globin chains. Hemoglobinopathies are characterized by the production of abnormal globin chains. Hemoglobin E is a beta chain variant in which lysine is substituted for glutamic acid in position 26. It is believed to be the most common Hemoglobinopathy in the world. Hemoglobin E occurs in Southeast Asia, especially in Cambodia, Laos and Thailand.

The importance of Hemoglobin E lies in the fact that: Patients with hemoglobin E have microcytic blood pictures which may be confused with thalassemia or initial stages of iron deficiency. Patients who inherit both genes for Hemoglobin E and beta-thalassemia have severe anemia.

Laboratory diagnosis of Hemoglobin E

Patients who are homozygotes are mildly anemic - Hgb 9 to 10 g/dL. Hematocrit and RBC count are also decreased hence the indices are uniformly depressed. The RDW is increased. The RBC histogram is slightly shifted to the right. The morphology is microcytic with anisocytosis and poikilocytosis with many target cells. The presence of these cells may make it difficult to recognize the microcytosis. The WBC and differential is usually normal.

Retic count - slight increase 5 to 10%
Serum iron - increased/normal
TIBC - decreased/normal
Ferritin - increased/normal
Percent saturation - increased
Hemoglobin electrophoresis
Hgb A - decreased
Hgb E - increased
Hgb A2 - variable
Patients who are heterozygotes are not anemic but have an elevated RBC count and target cells are present.