HAEMOGLOBINOPATHIES

These diseases are caused by dysfunction of the genes encoding the globin chains of the hemoglobin molecule. Normal hemoglobin is comprised of two alpha and two non-alpha globin chains. Alpha globin chains are produced throughout life, so severe mutations may cause intrauterine death. Production of non-alpha chains varies with age; fetal hemoglobin (HbF-αα/γγ) has two gamma chains, while the predominant adult hemoglobin (HbA-αα/ββ) has two beta chains. Thus, disorders affecting the beta chains do not present until after 6 months of age. A constant small amount of hemoglobin A2 (HbA2-αα/δδ, usually < 2%) is made from birth.

THE THALASSEMIAS

Thalassemia are inherited blood disorders (autosomal recessive manner) in which there is partial or complete failure to synthesize a specific type of globin(chain alpha or beta chain). In alpha-thalassemia, disruption of one or both alleles on chromosome 16 may occur, with production of some or no alpha globin chains. In beta-thalassemia, defective production usually results from disabling point mutations on chromosome 11 causing no (β^0) or reduced (β^-) beta chain production. characterized by decreased hemoglobin production. Symptoms depend on the type of thalassemia from none to severe anemia . Individuals with thalassemia syndrome are most often of African, Asian, Mediterranean, or Middle Eastern descent.

Beta-thalassemia

Failure to synthesize beta chains (beta-thalassemia) is the most common type of thalassemia, most prevalent in the Mediterranean area. Heterozygotes have thalassemia minor or trait , a condition in which there is usually mild anemia and little or no clinical disability, which may be detected only when iron therapy for a mild microcytic anemia fails.
Homozygotes (thalassemia major) either are unable to synthesize hemoglobin A or at best produce very little; after the first 4-6 months of life they develop profound hypochromic microcytic anemia.

Clinical features :

Patients with the beta thalassemia trait generally have no physical findings. In patients with beta thalassemia major come with severe anemia, ineffective erythropoiesis, extramedullary hematopoiesis, and iron overload resulting from transfusion and increased iron absorption.

pallor from anemia and jaundice from hyperbilirubinemia, Bone deformities especially in the face and skull. Bone marrow expansion secondary to erythroid hyperplasia with intramedullary expansion and cortical bone thinning. maxillary enlargement, leading to an appearance known as chipmunk face, Xray findings include hair end appearance for the skull and thin cortex and wide medulla for long bones. Skin ulceration may be present on the extremities and dark color urine from hemolysis .
Cardiac examination may reveal heart failure and arrhythmia (eg, atrial fibrillation), related to either severe anemia or iron overload.
Abdominal examination may reveal palpable spleen , liver. Hepatomegaly related to significant extramedullary hematopoiesis is typically found. Patients who have received blood transfusions may have hepatomegaly or chronic hepatitis due to iron overload. Gall stone due to lifelong hemolytic state.

Endocrine dysfunction, especially affecting the pancreas(DM), testes Hypogonadism, and thyroid. Transfusion-associated viral hepatitis resulting in cirrhosis or portal hypertension also may occur.
Infection: People with thalassemia have an increased risk of infection. This is especially true if the spleen has been removed.

Growth retardation , anemia can cause the growth of a child to slow down. Puberty may also be delayed in children with thalassemia.
Thalassemia can be diagnosed via a complete blood count, hemoglobin electrophoresis, and DNA testing

Diagnostic features of beta-thalassemia major (homozygotes) : characterized by Failure to thrive, facial structure abnormalities, severe anemia, and splenomegaly.

- Profound hypochromic anemia
- Evidence of severe red cell dysplasia
- Erythroblastosis
- Absence or gross reduction of the amount of hemoglobin A
- Raised levels of hemoglobin F
- Evidence that both parents have thalassemia minor

Diagnostic features of Beta-thalassemia minor (heterozygotes)

- Mild anemia
- Microcytic hypochromic erythrocytes (not iron-deficient)
- Some target cells
- Punctate basophilia (Basophilic Stippling) : numerous basophilic granules in the cytoplasm of RBCs
- Raised hemoglobin A_2 fraction
- Evidence that one parent has thalassemia minor

Treatment of beta-thalassemia major

Patients require chronic **massive blood transfusion** therapy to maintain the patient's Hb at 9-10 g/dL, thus improving his or her sense of well-being while simultaneously suppressing erythropoiesis.**folic acid** treatment, Many patients develop endocrine deficiencies as a result of **iron overload**. Early endocrine evaluation is required for glucose intolerance, thyroid dysfunction, and delayed onset of puberty or secondary sexual characteristics
Iron chelation therapy with desferrioxamine and should be avoid iron therapy due to high risk of Iron overload
Splenectomy Splenomegaly causing mechanical problems, excessive transfusion needs
Vaccination with Pneumovax in splenectomy is advised, as is close monitoring for infection, leg ulcers, and biliary tract disease.
Allogeneic stem-cell transplants appears to be potentially curative.

Alpha-thalassemia

The alpha thalassemia (α-thalassemia) syndromes are a group of hereditary anemias of varying clinical severity. They are characterized by reduced or absent production of 1 or more of the globin.It is common in Southeast Asia. There are two alpha gene loci on chromosome 16 and therefore each individual carries four alpha gene alleles.

Signs and symptoms of alpha thalassemia:

These include the following:

- **Silent carrier** - If one is deleted .Persons who inherit 3 normal alpha-globin genes (-α/αα) are essentially asymptomatic, there is no clinical effect.
- **Alpha thalassemia trait** - Individuals with alpha thalassemia trait are also asymptomatic. there may be a mild hypochromic anemia. Alpha thalassemia trait Inheritance of 2 normal alpha-globin genes through either heterozygosity for alpha(0) thalassemia (αα/--) or homozygosity for alpha(+) thalassemia (-α/-α).
- **Hemoglobin H (HbH) disease** - the patient has hemoglobin H disease. Inheritance of 1 normal alpha-globin HbH disease (--/-α) Symptoms of include episodes of severe pallor and anemia.
- **Hydrops fetalis (alpha thalassemia major)** If all four are deleted, the baby is stillborn (hydrops fetalis). Individuals with hydrops fetalis (--/--) usually die in utero or shortly after birth; infants who survive to be born have massive total body edema with high-output congestive heart failure due to the severe anemia; they also have massive hepatomegaly due to heart failure and extramedullary hematopoiesis.

Hemoglobin H is a beta-chain tetramer, formed from the excess of beta chains, which is functionally useless, so that patients depend on their low levels of HbA for oxygen transport.

Diagnostic features of HbH disease (-α/--) have moderate to severe anemia.

- Hemoglobin level - 7-10 g/dL
- Reticulocyte count - 5-10% (the higher the reticulocyte count, the more severe the hemolysis)
- MCV - 55-65 fL
- Peripheral blood smear - hypochromia, microcytosis, Poikilocytosis and target cells .

Management of alpha thalassemia

Mild forms of alpha thalassemia may not require treatment except as needed for management . In some cases folic acid may be useful. Patients with more severe anemia may require lifelong transfusion therapy. splenectomy may be beneficial for some patients with HbH disease. In very severe cases, allogeneic hematopoietic stem cell transplantation may be considered.

Sickle-Cell Anemias

It is inherited as an autosomal recessive trait, a single glutamic acid to valine substitution at position 6 of the beta globin polypeptide chain. Homozygotes only produce abnormal beta chains that make hemoglobin S (HbS, termed SS), and this results in the clinical syndrome of sickle-cell disease. Heterozygotes produce a mixture of normal and abnormal beta chains that make normal HbA and HbS (termed AS), and this results in the clinically asymptomatic sickle-cell trait.

Epidemiology in Mediterranean, southeast Asia and tropical Africa the heterozygote frequency is over 20%, Individuals with sickle-cell trait are relatively resistant to the lethal effects of falciparum malaria in early childhood; the high prevalence in equatorial Africa can be explained by the selective survival advantage it confers in areas where falciparum malaria is endemic. However, homozygous patients with sickle-cell anemia do not have correspondingly greater resistance to falciparum malaria.

Pathogenesis: When haemoglobin S is deoxygenated, the molecules of hemoglobin polymerize to form pseudo crystalline structures known as 'tactoids'. These distort the red cell membrane and produce characteristic sickle-shaped cells). The polymerisation is reversible when reoxygenation occurs. The distortion of the red cell membrane, however, may become permanent and the red cell 'irreversibly sickled'. The greater the concentration of sickle-cell hemoglobin in the individual cell, the more easily tactoids are formed, but this process may be enhanced or retarded by the presence of other hemoglobins. Thus, the abnormal hemoglobin C variant participates in the polymerisation more readily than hemoglobin A, whereas hemoglobin F strongly inhibits polymerisation.

Clinical features: Sickling is precipitated by hypoxia, acidosis, dehydration and infection. Irreversibly sickled cells have a shortened survival and plug vessels in the microcirculation. This results in a number of acute syndromes, termed 'crises', and chronic organ damage. The lungs are particularly susceptible in individuals with sickle cell disease and may be involved in pulmonary hypertension.

- *Vaso-occlusive crisis*. Plugging of small vessels in the bone produces acute severe bone pain. This affects areas of active marrow: the hands and feet in children (so-called dactylitis) or the femora, humeri, ribs, pelvis and vertebrae in adults. Patients usually have a systemic response with tachycardia, sweating and a fever. This is the most common crisis.
- *Sickle chest syndrome*. This may follow on from a vaso-occlusive crisis and is the most common cause of death in adult sickle disease. Bone marrow infarction results in fat emboli to the lungs which cause further sickling and infarction, leading to ventilatory failure if not treated.
- *Sequestration crisis*. Thrombosis of the venous outflow from an organ causes loss of function and acute painful enlargement. In children the spleen is the most common site. Massive splenic enlargement may result in severe anemia, circulatory collapse and death. Recurrent sickling in the spleen in childhood results in infarction and adults may have no functional spleen. In adults the liver may undergo sequestration with severe pain due to capsular stretching.

- *Aplastic crisis*. Infection of adult sicklers with human erythrovirus 19 results in a severe but self-limiting red cell aplasia. This produces a very low hemoglobin which may cause heart failure. Unlike in all other sickle crises, the reticulocyte count is low.

Investigations: Patients with sickle-cell disease have a compensated anemia, usually around 60-80 g/L. The blood film shows sickle cells, target cells and features of hyposplenism. A reticulocytosis is present.
The definitive diagnosis requires hemoglobin electrophoresis to demonstrate the absence of HbA, 2-20% HbF and the predominance of HbS. Both parents of the affected individual will have sickle-cell trait. Sickle cell disease is best differentiated from sickle cell trait by hemoglobin electrophoresis.

Management: All patients with sickle-cell disease should receive prophylaxis with daily folic acid, penicillin V to protect against pneumococcal infection which may be lethal in the presence of hyposplenism. vaccinated against pneumococcus, Hemophilus influenzae B, hepatitis B
Vaso-occlusive crises are managed by aggressive rehydration, oxygen therapy, adequate analgesia (which often requires opiates) and antibiotics.
Blood Transfusion may be used in a sequestration or aplastic crisis. A regular blood transfusion programme to suppress HbS production and maintain the HbS level below 30% may be indicated in patients with recurrent severe complications such as cerebrovascular accidents in children or chest syndromes in adults.
Exchange blood transfusion, in which a patient is simultaneously venesected and transfused to replace HbS with HbA, may be used in life-threatening crises or to prepare patients for surgery.
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approximately 15% die by the age of 20 years and 50% by the age of 40 years.

Management of the patient with splenectomy

- Vaccinate with pneumococcal, *Haemophilus influenzae* type B, meningococcal group C and influenza vaccines at least 2-3 weeks before elective splenectomy. Vaccination should be given after emergency surgery, but may be less effective
- Pneumococcal re-immunisation should be given at least 5-yearly and influenza annually. Vaccination status must be documented
- Life-long prophylactic penicillin V 500 mg 12-hourly is recommended. In penicillin-allergic patients, consider erythromycin
- A card or bracelet should be carried by splenectomised patients to alert health professionals to the risk of overwhelming sepsis
- In septicaemia, splenectomised patients should be resuscitated and given intravenous antibiotics to cover pneumococcus, *Haemophilus* and meningococcus
- The risk of malaria is increased
- Animal bites should be promptly treated with local disinfection and antibiotics, to prevent serious soft tissue infection and septicaemia

Medical indication for splenectomy : hereditary spherocytosis, thalassemia major, and certain forms of immune thrombocytopenic purpura (ITP) unresponsive to medical management. Myeloproliferative disorders may lead to massive splenomegaly and can cause symptoms that are best relieved by splenectomy, primarily for symptomatic relief, Thrombotic thrombocytopenic purpura (TTP) and hairy-cell leukemia unresponsive to other treatment, lymphoma, autoimmune hemolytic anemia . splenic abscesses, cysts, or splenic mass.

There is a trial of novel possibilities for treating of beta thalassemia and sickle cell anemias by a genome engineering technique CRISPR-Cas9, (CTX001) is a medication that indirectly increases the production of hemoglobin F, which substitutes the type of hemoglobin in the red blood cells of affected patients.