Journal of Medicine and Health Sciences Research 2025, 8: 1-9
https://doi.org/10.21839/jmhsr.2025.v8.9567

Review Article

Hemoglobinopathies & Types: Overview, Pathophysiology, and Epidemiology

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(Received: January 22, 2025; Revised: May 08, 2025; Accepted: May 09, 2025; Published: May 19, 2025)
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ABSTRACT

The hemoglobinopathies encompass all genetic diseases of hemoglobin. They fall into two main groups: thalassemia syndromes and structural hemoglobin variants (abnormal hemoglobins). α- and β-thalassemia are the main types of thalassemia; the main structural hemoglobin variants are HbS, HbE, and HbC. There are many subtypes and combined types in each group. The highly variable clinical manifestations of the hemoglobinopathies range from mild hypochromic anemia to moderate hematological disease to severe, lifelong, transfusion-dependent anemia with multiorgan involvement. According to the World Health Organization, about 5.2% of the world population and over 7% of pregnant women carry a significant variant, and 1.1% of couples worldwide are at risk of having children with a hemoglobin disorder. This review will explain the overview, pathophysiology, and epidemiologic scenarios of each hemoglobinopathy, the information of which will be useful for those who are working and interested in the following field.

Key words: Hemoglobinopathies, α-thalassemia, β-thalassemia, Anemia

INTRODUCTION

All hereditary hemoglobin diseases are referred to as "hemoglobinopathies". Hemoglobinopathies can be divided into two categories: structural hemoglobin variants, often known as aberrant hemoglobins, and thalassemia syndromes. The α- or β-globin genes are mutated or deleted in both cases. Thalassemia is the result of a malfunction in hemoglobin synthesis caused by a gene deficiency with normal hemoglobin structure. An aberrant hemoglobin variant results from a change in hemoglobin structure brought on by a gene deficiency (Kohne, 2011; Sabath, 2017). Certain hemoglobin variants are linked to clinical conditions like hemolysis from unstable hemoglobins (Teixeira *et al.,* 2017), hemoglobins with enhanced or decreased oxygen affinity (Jones & Shih, 1980), and sickle cell anemia and related sickling disorders (Piccin *et al.,* 2019). However, the majority of hemoglobin structural variants are clinically silent and are only found by chance, frequently while measuring HbA1c in diabetic patients (Sabath, 2017). Figure 1 illustrates the synthesis of hemoglobins with structural abnormalities (HbS, HbC, and HbSC) as well as hemoglobin deficiencies (α- and β-thalassemias).

Despite the extensive documentation of hemoglobinopathies' clinical and molecular causes, there is growing interest in their wider public health implications, particularly with regard to nutritionally vulnerable groups. Recent research has shown how micronutrient shortages affect a child's immune system and growth (Chowdhury *et al.,* 2019), which can make hemoglobinopathies more morbid in environments with low resources. Furthermore, studies have shown how crucial maternal nutrition, such as taking supplements of omega-3 fatty acids, is to improve pregnancy outcomes for women with long-term medical issues (Chowdhury *et al.,* 2020), such as blood disorders.

SICKLE CELL DISEASE (HEMOGLOBIN S DISEASE)

Overview

Sickle hemoglobin (HbS), a variant of the beta-globin gene, is the cause of sickle cell disease (SCD). Sickle hemoglobin is the predominant hemoglobin found in the red blood cells of people with sickle cell anemia, who have two copies of this variant (HbSS). Compound heterozygotes are people who have other forms of sickle cell disease. They have two copies of the β-globin gene variant, like HbC or Hb β-thalassemia, in addition to one copy of the HbS variant. These people generate a variety of different hemoglobins. A mixture of sickle and normal hemoglobin is produced by carriers, who have one copy of the sickle variant and one copy of the normal β-globin gene (HbAS). A common term used to describe the sickle cell disease carrier status is "sickle cell trait." According to one study, sickle cell trait may be a risk factor for unexpected death during physical exercise, even when those who have it do not exhibit sickle cell disease (Kark *et al.,* 1987). Furthermore, those who have sickle cell trait are immune to malaria (Aluoch, 1997). This protective action is thought to be the cause of the high frequency of the HbS variant.

Pathophysiology

Amino acid substitution in HbS β chains

Two normal α-globin chains and two mutant β-globin chains (β^S), in which valine has been substituted for glutamate

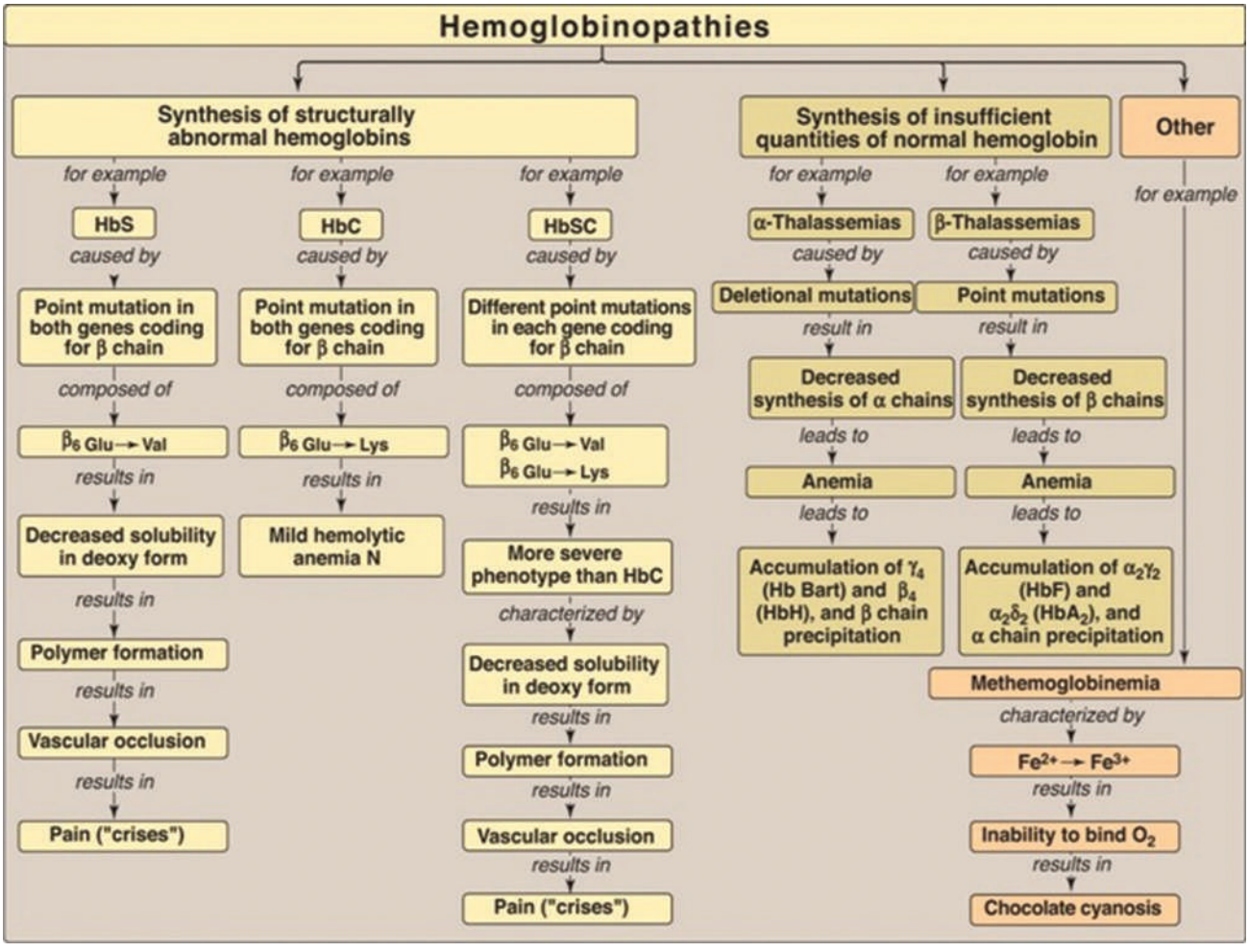

Figure 1: Synthesis of structurally abnormal hemoglobins (HbS, HbC, HbSC) and insufficient quantities of hemoglobin (α- and β-thalassemias) (Sabath, 2017)

at position six, are present in an HbS molecule (Figure 2). Consequently, HbS migrates toward the anode (positive electrode) more slowly than HbA does during electrophoresis at alkaline pH (Figure 3). HbS is less negative than HbA due to its decreased mobility, which is caused by the absence of negatively charged glutamate residues in the two β chains (Harvey & Ferrier, 2014).

Sickling and tissue anoxia

When the nonpolar valine is substituted for the charged glutamate, a protrusion on the β chain is created that fits into a complementary location on the β chain of another hemoglobin molecule within the cell (Figure 4). Deoxyhemoglobin S polymerizes inside the red blood cell (RBC) at low oxygen tension, creating a network of insoluble fibrous polymers that cause the cell to stiffen and distort, resulting in rigid, malformed RBC. These sickled cells often obstruct blood flow in the small capillaries. The tissue experiences localized anoxia, or oxygen deprivation, as a result of this disruption in the oxygen supply, which eventually causes pain and the death (infarction) of nearby cells. Deoxygenated HbS also rises as a result of anoxia (Harvey & Ferrier, 2014).

Variables that increase sickling

Any factor that raises the percentage of HbS in the deoxy state (i.e., lowers the affinity of HbS for O_2) increases the amount of sickling and, consequently, the severity of the disease. These factors include dehydration, elevated 2, 3-Bisphosphoglycerate in RBC, decreased pH, elevated pO_2, and elevated pCO_2 (Harvey & Ferrier, 2014).

Epidemiology

The disease is highly prevalent in the Middle East, Mediterranean, South Asia, and Sub-Saharan Africa. About 100,000 people in the US are thought to have sickle cell disease, and that number is only expected to rise (David *et al.,* 2018; Arigliani *et al.,* 2019; Ismail *et al.,* 2019).

HEMOGLOBIN C DISEASE

Overview

One of the most prevalent structural hemoglobin variants in the human population is hemoglobin C (HbC). The

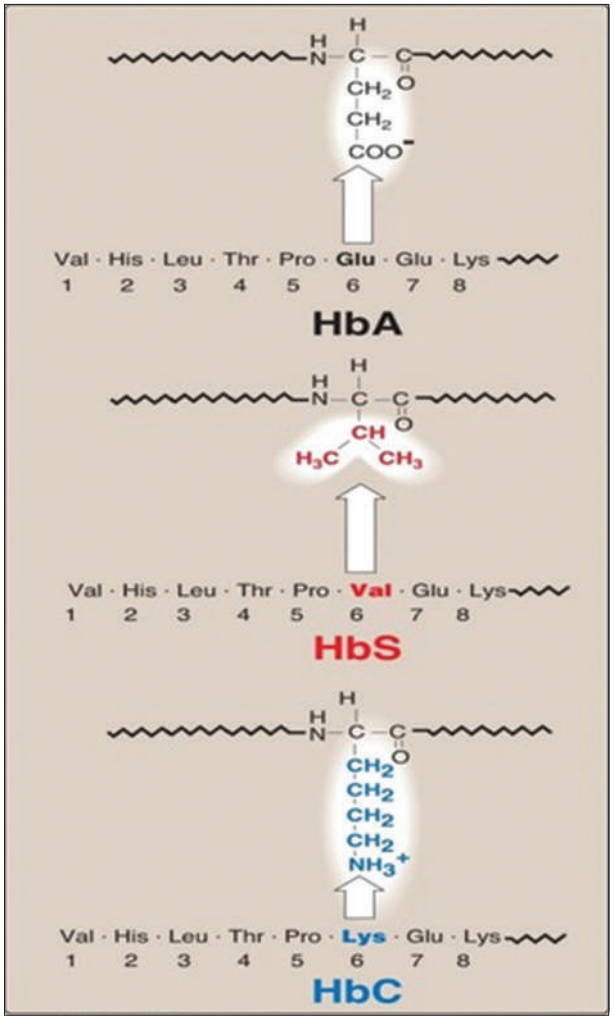

Figure 2: Amino acid substitutions in hemoglobin S (HbS) and hemoglobin C (HbC) (Harvey & Ferrier, 2014)

biparental inheritance of the allele encoding hemoglobin C causes this autosomal recessive disease. If both parents have hemoglobin C, the child has a 25% probability of having hemoglobin C disease, a 50% chance of having a carrier child, and a 25% chance of neither having hemoglobin C disease nor being a carrier (Karna *et al.,* 2020). While people with hemoglobin C disease (HbCC) may have mild hemolytic anemia, splenomegaly, and borderline anemia, people with hemoglobin C trait (HbAC) are phenotypically normal and show no clinically noticeable restrictions or symptoms. Genetic counseling and anticipatory guidance are crucial in the treatment of individuals with hemoglobin C disease, even though the clinical complications are not severe. However, inheritance with other hemoglobinopathies, such as hemoglobin S, can have serious consequences (Medscape, 2017).

Pathophysiology

The amino acid substitution of lysine for glutamic acid at position six of the beta hemoglobin chain (β6Glu-Lys) results in hemoglobin C (HbC), a structural variants of normal

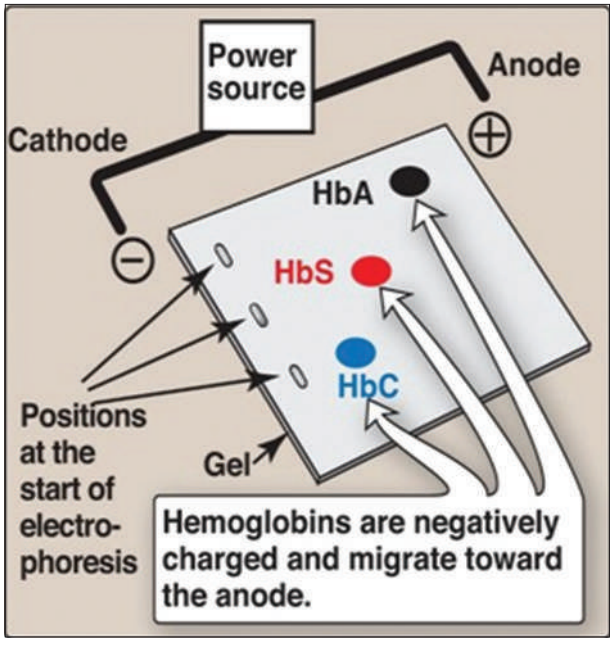

Figure 3: Hemoglobins (HbA), (HbS), and (HbC) after electrophoresis (Harvey & Ferrier, 2014)

hemoglobin A (HbA) (Figure 2). Because of electrostatic interactions between positively charged β6-lysyl groups and negatively charged groups on nearby molecules, HbC is less soluble than HbA in red blood cells. Red cell survival may be shortened and blood viscosity and cellular rigidity may increase as a result of crystal formation (Figure 5) (Medscape, 2017).

When HbC encounters intravascular regions of low oxygen tension, it does not result in linear intracellular polymerization, in contrast to sickle cell disease (Charache *et al.,* 1967). Vaso-occlusion does not develop, despite evidence of decreased red cell deformability linked to the HbC variant. A higher mean corpuscular hemoglobin concentration (MCHC) on a complete blood count may be observed in both the heterozygous (HbSC, HbAC) and homozygous (HbCC) states, which might cause red cell dehydration (xerocytosis) (Medscape, 2017).

Epidemiology

In South East Asia and Atlantic West Africa, this mutation is highly prevalent. Although its precise allelic distribution among these diverse communities is still unknown, HbC is present in a variety of populations in Africa, southern Europe, and South and Central America.

The western region of Burkina Faso has the highest anticipated frequency of HbC, with an allele frequency of 24%, according to a global database of population surveys (Modell & Darlison, 2008; Piel *et al.,* 2013). About 1 in 5000 African Americans in the US are homozygotes for HbC, while 2-3% are heterozygotes (Schneider *et al.,* 1976). Additionally, people without documented African heritage have been shown to have HbC (Galbraith & Green, 1960).

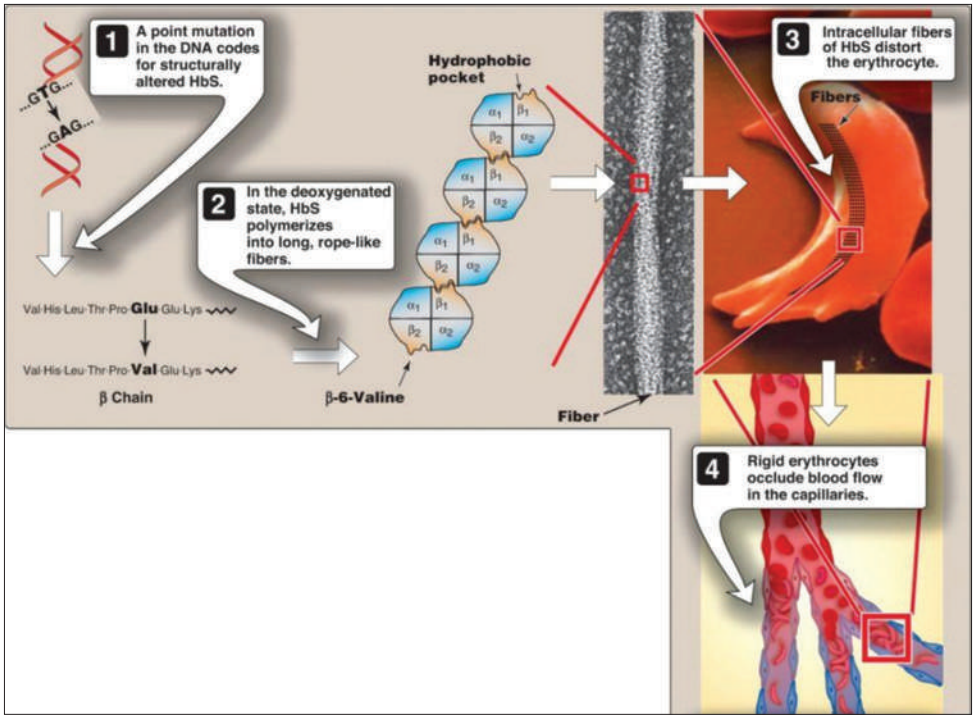

Figure 4: Molecular and cellular events leading to sickle cell crisis. HbS=hemoglobin S (Harvey & Ferrier, 2014)

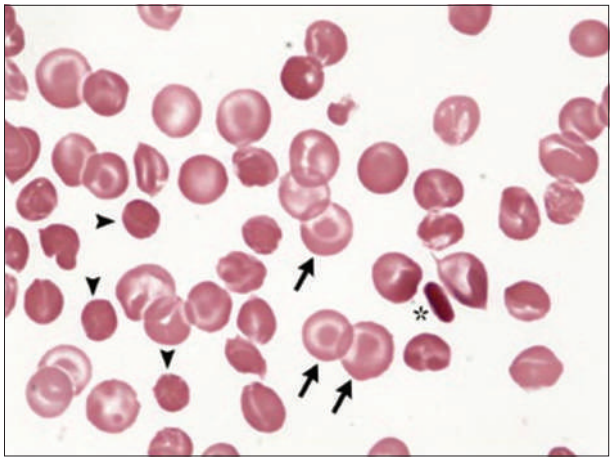

Figure 5: This peripheral blood smear shows target cells (arrows) and crystals (star), typically seen in hemoglobin C disease

HEMOGLOBIN SC DISEASE

Overview

Another RBC sickling illness is HbSC disease. Haemoglobin SC (HbSC) disease is caused by co-inheritance of mutations in the beta globin gene (HBB) for hemoglobin S (HbS) and hemoglobin C (HbC) (Steinberg & Nagel, 2009; Nagel *et al.,* 2003). Compared to sickle cell anemia, hemoglobin levels in HbSC illness are often greater and may potentially be below normal. Adults with HbSC anemia experience less frequent and milder symptoms, such as excruciating crises, than those with sickle cell anemia. Clinical variability is substantial, nevertheless (Harvey & Ferrier, 2014).

Pathophysiology

HbSC red blood cells (RBCs) have low (1-3%) levels of HbF and almost equal numbers of HbC and HbS (Nagel *et al.,* 2003; Gualandro *et al.,* 2015). HbS-HbC interactions and RBC dehydration due to altered membrane transporter activity both influence the pathophysiology of HbSC illness. The concentration of HbS rises when RBCs are dehydrated (Mozzarelli *et al.,* 1987). HbS subunits polymerize at moderate to high intra-erythrocyte concentrations, resulting in lengthy, stiff molecules that impede the microcirculation as RBCs enter (Nagel *et al.,* 2003). Tetragon crystals develop at high oxygenated HbC concentrations, but they disintegrate quickly in the deoxygenated condition (Nagel *et al.,* 2003). According to Nagel *et al.* (2003), HbF prevents HbC crystallization and HbS polymerization. Similar to the hemoglobin SS (HbSS) condition, increasing HbF has therapeutic value in HbSC. The three processes that result in RBC dehydration and cation loss are additional possible targets for therapeutic intervention: (1) nonselective, deoxy-dependent calcium ion permeability in the P-sickle pathway (Gallagher, 2015) (2) enhanced K-Cl cotransport that causes water, potassium, and chloride loss; and (3) calcium-activated Gardos potassium channels (Nagel *et al.,* 2003; Gallagher, 2015; Rees *et al.,* 2015). The transfer of erythrocyte water and solutes is not thoroughly understood and has not yet been effectively used therapeutically (Gallagher, 2015). Magnesium, a K-Cl cotransport modulator, had unsatisfactory first results in HbSS and HbSC studies (Wang *et al.,* 2011; Rees *et al.,* 2015; Nottage *et al.,* 2016).

Epidemiology

About 30% of SCD cases in the US and the UK are caused by HbSC. SCD affects 1 in 2000 newborns born in the UK, and HbSC affects 1 in 7174 (Streetly *et al.,* 2008). Likewise, in the United States, 1 in 941 neonates have sickle cell disease (SCD), and 1 in 6173 have hemoglobin S disease (HbSC) (Therrell Jr *et al.,* 2015). More than 50% of SCD is caused by HbSC in regions of West Africa, where HbC first appeared (Saraf *et al.,* 2014). Because one *HBB* (beta globin gene) mutation confers a survival benefit against severe malaria, the allelic frequency of HbC results (Modiano *et al.,* 2001; Piel *et al.,* 2013). Both voluntary and involuntary emigration from West Africa brought HbC to Europe and the Americas. At least 55,000 babies are born with HbSC every year throughout the world (Weatherall, 2010).

METHEMOGLOBINEMIA

Overview

Methemoglobinemia is a potentially fatal disorder when the heme iron in hemoglobin oxidizes to the ferric [Fe^{3+}] state, reducing the hemoglobin's ability to carry oxygen. This results in methemoglobin that is unable to bind oxygen. Oxygen cannot be bound or transported by ferric iron. Functional anemia is caused by elevated methemoglobin levels (Figure 6) (Kane *et al.,* 2007). Methemoglobin concentrations in healthy persons are less than 3.0% of total hemoglobin (multiply by 0.01) to convert methemoglobin concentration to proportion of total hemoglobin (Ashurst & Wasson, 2011). Beyond this threshold, the concentration determines the severity of symptoms and the course of treatment for methemoglobinemia (Ashurst & Wasson, 2011; Skold *et al.,* 2011).

Pathophysiology

When hemoglobin is oxidized to contain iron in the ferric [Fe^{3+}] state instead of the typical ferrous [Fe^{2+}] state, methemoglobin is created. When a hemoglobin molecule is in the ferric form, any one of the four iron species inside it cannot bind oxygen. The molecule undergoes allosteric modifications when iron is present in the ferric [Fe^{3+}] state, which causes the oxygen-dissociation curve to move to the left. This change causes the ferrous iron to have a higher affinity for oxygen, which impairs the tissue's ability to release oxygen (Wright *et al.,* 1999). These alterations ultimately result in tissue hypoxia due to reduced oxygen delivery.

Tyrosine is typically substituted for an amino acid in hemoglobin M illness due to a mutation in the gene encoding one of the globin proteins. Iron can be stabilized in the ferric [Fe^{3}□] form thanks to this mutation. According to Curry (1982),

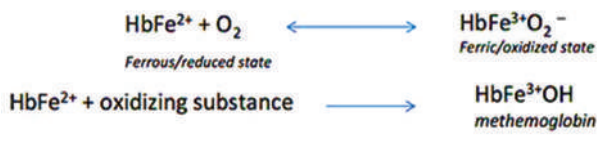

Figure 6: Formation of methemoglobin

patients with hemoglobin M illness often have methemoglobin levels between 15 and 30% and show no symptoms.

Normally, when oxygen is routinely delivered to tissue, a tiny quantity of iron oxidizes to the ferric [Fe^{3}□] state. The enzyme cytochrome-b5 reductase is responsible for maintaining methemoglobin levels below 1%. Methemoglobin is converted back to functional hemoglobin by cytochrome-b5 reductase using NADH produced during glycolysis (Skold *et al.,* 2011).

Nicotinamide adenine dinucleotide phosphate hydrogen methemoglobin (NADPH-MetHb) reductase is another mechanism by which methemoglobin can be reduced. For its reducing power, NADPH-MetHb reductase uses NADPH that is produced in the hexose monophosphate shunt by glucose-6-phosphate dehydrogenase (G6PD) (Curry, 1982). NADPH-MetHb reductase plays a very little role in the reduction of methemoglobin under normal physiological conditions, but exogenous electron donors, like methylene blue, can improve the activity of this alternate reduction pathway during oxidative stress. This connection to G6PD frequently causes people to believe that G6PD deficiency is a risk factor for methemoglobinemia in and of itself.

Epidemiology

Although it is extremely uncommon, the true incidence of congenital methemoglobinemia caused by cytochrome b5 reductase deficiency is unknown. Siberian Yakuts, Athabaskans, Eskimos, and Navajo have been reported to have higher rates of disease (Burtseva *et al.,* 2017). Although it is also an uncommon condition, acquired methemoglobinemia is far more common than the congenital variant. The majority of instances are brought on by topical or local anesthetic usage or unintentional chemical exposure.

THALASSEMIAS

Overview

Hereditary hemolytic disorders known as thalassemias are caused by an imbalance in the production of globin chains. Collectively, they are the most prevalent single-gene disorders in people. Each α-globin chain has a β-globin chain partner because the synthesis of the two chains is typically coordinated. Owing to this, $\alpha_2\beta_2$ (HbA) is formed. Either the α- or β-globin chain's synthesis is flawed in thalassemias. Numerous mutations, such as deletions of entire genes or changes to one or more nucleotides in the DNA, can result in thalassemia. Depending on which globin type is mutated, there are two forms of thalassemia: beta- (β-) thalassemia and alpha- (α-) thalassemia (Harvey & Ferrier, 2014).

α-Thalassemias

Overview

The synthesis of α-globin chains is either absent or reduced in many illnesses, usually due to deletional mutations. There are multiple levels of α-globin chain deficits since each person's

genome contains four copies of the α-globin gene, two on each chromosome 16 (Figure 7). Since there are no outward signs of α-thalassemia, a person is referred to as a silent carrier if one of the four genes is faulty. A person is diagnosed with α-thalassemia trait if two α-globin genes are faulty. A person has hemoglobin H (β4) disease, a hemolytic anemia of varying severity, if three α-globin genes are faulty. While some people will only experience mild symptoms, others may experience more severe side effects. Since α-globin chains are necessary for the synthesis of HbF, hemoglobin Bart (γ4) disease with hydrops fetalis and fetal death comes from the deficiency of all four α-globin genes; nevertheless, new developments have led to better treatments for this ailment (Harvey & Ferrier, 2014).

All types of alpha thalassemia are characterized by anemia, which includes small (microcytic) red blood cells with low levels of functional hemoglobin (hypochromic) and the potential for premature breakdown in the bone marrow (ineffective erythropoiesis) and peripheral circulation (hemolysis). As a result, those who are badly impacted

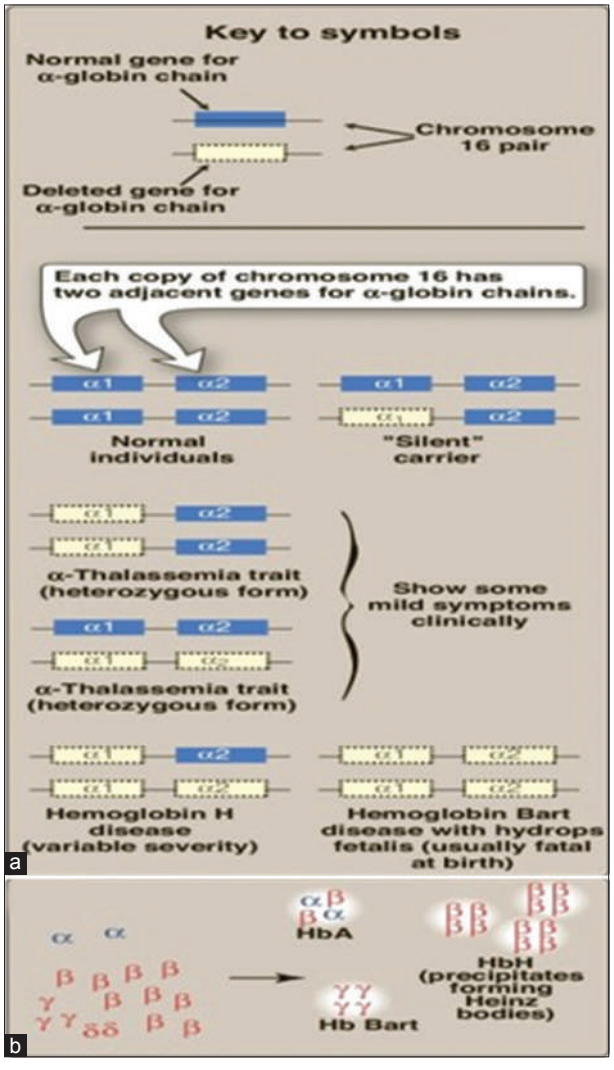

Figure 7: a) α-Globin gene deletions in the α-thalassemias and b) Hemoglobin (Hb) tetramers formed in α-thalassemias (Harvey & Ferrier, 2014)

could not have enough blood that is rich in oxygen flowing throughout their bodies. These people may suffer from headaches, dizziness, exhaustion, weakness, or shortness of breath. If severe anemia is not treated, it can lead to major problems, including death. Regular blood transfusions for those with severe forms of HbH illness can lead to iron overload, which is an accumulation of extra iron in the body. Although iron overload can damage numerous organs in the body, it can be effectively treated using several highly effective medications (National Organization for Rare Disorders, 2017). Several very effective drugs can be used to treat iron overload, despite the fact that it can harm several organs in the body (National Organization for Rare Disorders, 2017).

Pathophysiology

Hemoglobin H can lead to hemolytic anemia and chronic hypochromic microcytic anemia, both of which can get worse during times of oxidative stress. Increased hemolysis and inefficient erythropoiesis are good ways to describe this. Reduced alpha chain synthesis and cell hyperhydration result in poor hemoglobin production, which causes microcytic hypochromic anemia. It's unclear what causes the hyperhydration in alpha thalassemia. According to one theory, the typical loss of K-Cl and water that occurs during the remodeling process of red blood cells is prevented by the K-Cl cotransporter stopping early (Harewood & Azevedo, 2020).

The survival time for hemoglobin H has also been reduced to half of normal, from 28 to 37 days to 12 to 19 days. Two primary factors have been explained by this: an aberrant red blood cell membrane that is stiffer and has more inclusion bodies. The inclusions were believed to be beta chain tetramer aggregates, which form in the red blood cell and harm it, causing the spleen to remove them. It has also been suggested that these inclusion bodies make people more vulnerable to oxidative stress (Harewood & Azevedo, 2020).

Epidemiology

α-thalassemia is primarily found in tropical and sub-tropical regions, where 80–90% of the population may be carriers, similar to sickle cell and β-thalassemia traits (Weatherall & Clegg, 2001; Piel *et al.,* 2014; Piel & Weatherall, 2014). Although the exact process is yet unknown, it is thought that α-thalassemia is selected because carriers are more resistant to the effects of malaria falciparum, just like the other hemoglobin-related diseases. People from places where malaria has been endemic for centuries frequently have sickle cell, β-thalassemia, and α-thalassemia features that interact. The Middle East, the Mediterranean region, and South East Asia are where the most severe types, such as HbH illness and Hb Bart's Hydrops Foetalis, are found. Over the past three decades, there has been a significant shift in the endemicity of thalassemia due to population mobility. Previously considered non-endemic for hemoglobinopathies, regions such as North America and North Europe now face significant challenges in diagnosing and treating sickle cell disease in general

and α-thalassemia in particular due to its complexity and prevalence (Farashi & Harteveld, 2018).

β- Thalassemias

Overview

The synthesis of β-globin chains is either absent or reduced in many illnesses, usually due to point mutations that impact the generation of functional mRNA. α-globin chain production, however, is typical. Excess α-globin chains precipitate because they are unable to form stable tetramers, which results in the early demise of cells that were originally intended to mature into red blood cells. There is also an increase in $\alpha_2\delta_2$ (HbA_2) and $\alpha_2\gamma_2$ (HbF). The β-globin gene is found in only two copies in each cell, one on each chromosome 11. If only one β-globin gene is faulty, people with β-globin gene deficiencies have β-thalassemia trait (β-thalassemia minor); if both genes are faulty, they have β-thalassemia major (Cooley anemia) (Figure 8). Physical signs of β-thalassemias don't show up until a few months after delivery since the β-globin gene isn't produced until late in fetal gestation. People with β-thalassemia minor typically don't need special therapy because they make some β chains. However, because of inefficient erythropoiesis, newborns with β-thalassemia major appear healthy at birth but develop severe anemia, usually in the first or second year of life. Extramedullary hematopoiesis also causes skeletal alterations (Harvey & Ferrier, 2014).

Pathophysiology

Two alpha and two non-alpha globin chains unite to form the tetramer known as hemoglobin. Up to six months of age, fetal hemoglobin (HbF), which is made up of two alpha and two gamma chains, serves as the main hemoglobin. The main component of adult hemoglobin is hemoglobin A (HbA), which is made up of two alpha and two beta chains. Hemoglobin A_2 (HbA_2), which is made up of two alpha and two delta chains, is a smaller form of adult hemoglobin (Needs *et al.,* 2020).

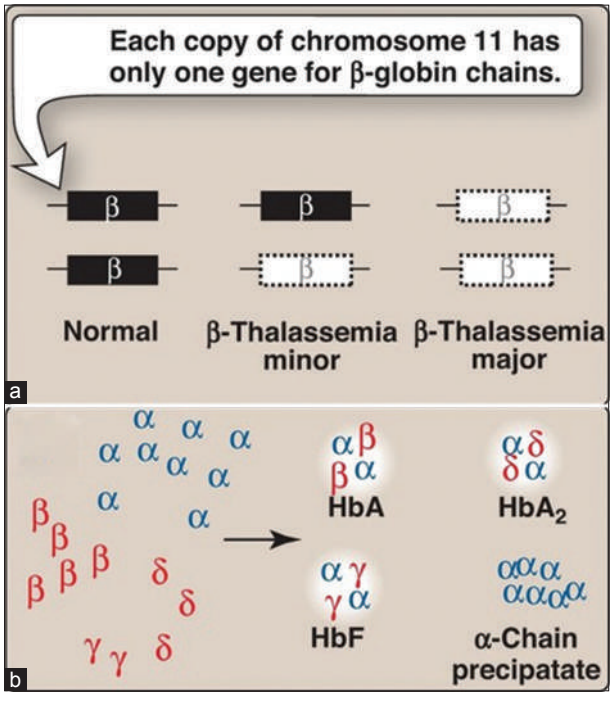

Figure 8: a) β-Globin gene mutations in the β-thalassemias and b) Hemoglobin (Hb) tetramers formed in β-thalassemias (Harvey & Ferrier, 2014)

There are two distinct pathophysiologies for beta-thalassemia. First, anemia results from decreased hemoglobin synthesis, and as beta chains for HbA production are reduced, HbF and HbA_2 rise. The second, and most pathologically significant, is that the relative excess alpha chains create insoluble alpha chain inclusions that result in significant intramedullary hemolysis in beta-thalassemia major and intermedia. In addition to bone marrow growth and extramedullary hematopoiesis, this inefficient erythropoiesis causes severe anemia and erythroid hyperplasia. Bony abnormalities resulting from bone marrow enlargement include maxillary projection and frontal bossing, which are typical of the facial bones. Iron hyperabsorption results from biochemical signaling from bone marrow enlargement that involves the bone morphogenetic protein (BMP) pathway and inhibits hepcidin synthesis (Frazer *et al.,* 2012). Patients who receive inadequate treatment or who are transfusion-dependent run the risk of developing end-organ damage from iron excess. Thrombocytopenia and hepatic dysfunction are also brought on by hepatosplenomegaly by extramedullary hematopoiesis and continuous hemolysis (Needs *et al.,* 2020).

Due to decreased HbA production, beta-thalassemia minor results in microcytosis and, at most, moderate anemia. Because they have one intact beta-globin gene, people with beta-thalassemia minor can still manufacture enough hemoglobin to meet their body's normal needs without developing severe erythroid hyperplasia. Additionally, an increase in other hemoglobin types, most often HbA_2, makes up for the hemoglobin deficiency (Needs *et al.,* 2020).

Additionally, beta-thalassemia can produce a variety of clinically significant anemias in the heterozygous beta-thalassemia carrier and coexist with other hemoglobinopathies (such as hemoglobin S, C, and E). When the nearby delta and beta genes are deleted, delta-beta-thalassemia develops, which has clinical characteristics with beta-thalassemia. The pathophysiology of delta-beta-thalassemia is similar to that of beta-thalassemia; however, because the delta chain is also impacted, there isn't an elevated HbA_2 (Needs *et al.,* 2020).

Epidemiology

In addition to countries along the north coast of Africa and South America, beta-thalassemia is common throughout the Mediterranean region, the Middle East, Central Asia, India, Southern China, and the Far East. Southeast Asia, Sardinia (10.3%), and Cyprus (14%), according to reports, have the highest carrier frequencies (Flint *et al.,* 1998). Plasmodium falciparum malaria selective pressure is probably the cause of the high gene frequency of beta-thalassemia in these

areas (Flint *et al.,* 1998). In practically every nation in the world, including Northern Europe, where thalassemia was formerly nonexistent, it has been brought about by population migration and interethnic marriage. According to estimates, between 80 and 90 million people worldwide—roughly 1.5% of the total population—carry beta-thalassemia, and 60,000 symptomatic individuals are born each year, the vast majority of whom are in developing nations. It is believed that 1 in 10,000 people in the European Union and 1 in 100,000 people worldwide experience symptoms each year. However, there is a dearth of reliable information on carrier rates in many populations, especially in regions of the world that are known or anticipated to be severely impacted (Vichinsky, 2005). Only roughly 200,000 people with thalassemia major are still alive and listed as receiving regular treatment worldwide, according to the Thalassemia International Federation (Cappellini *et al.,* 2008). HbE/beta-thalassemia, which is most common in Southeast Asia, where the carrier frequency is approximately 50%, is the most common combination of beta-thalassemia with aberrant Hb or structural Hb variation with thalassemic features (Galanello & Origa, 2010).

CONCLUSION

To sum up, hemoglobinopathies are the most prevalent hereditary illnesses worldwide. Only a small number of the many hemoglobin variations have therapeutic importance. The severity can be decreased by raising awareness of the illness through public media and medical community education. In order to eradicate the prevalence of hemoglobinopathies, further supplementary control initiatives such as genetic counseling and prenatal diagnosis will be crucial.

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