Hemoglobinopathies in the Neonate

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EDUCATION GAPS

Neonatologists should know how to recognize and assess for both quantitative and qualitative hemoglobin disorders. Early diagnosis of moderate to severe hemoglobinopathies is crucial as it can prevent morbidity and mortality in patients affected by these conditions.

OBJECTIVES *After completing this article, readers should be able to:*

1. Describe the pathophysiology, typical presentation, and general complications associated with common quantitative and qualitative hemoglobin disorders.
2. Recognize the difference between α-globin and β-globin mutations and know when each of these related disorders present in the in utero or neonatal period.
3. Interpret newborn screening hemoglobinopathy results to provide early diagnosis and counseling to families.

ABSTRACT

Hemoglobinopathies in neonates constitute a group of disorders influenced by genetic mutations in the human globin genes. They are often broadly categorized into quantitative defects or qualitative defects, though they are not mutually exclusive. In quantitative defects, the mutation causes insufficient production of a normal globin chain, which can range from no production to mild deficiency. These are typically referred to as thalassemias. In qualitative defects, the structure of the hemoglobin is altered. The most common structural hemoglobinopathy is sickle cell disease. During fetal development, distinct globin chains are synthesized, which undergo a progressive switch to adult globin chains perinatally. This affects the timing of the clinical presentation of these disorders and thus, our ability to diagnose them. In this review, we focus on the epidemiology, genetic causes, clinical presentation, and general overview and management of common hemoglobin disorders that may be encountered in the neonatal period.

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ABBREVIATIONS

HPFH	hereditary persistence of fetal hemoglobin
NTDT	nontransfusion dependent
SCD	sickle cell disease
TDT	transfusion-dependent β-thalassemia

Hemoglobinopathies are disorders caused by abnormal production or structure of the hemoglobin protein. Many of these disorders are present in utero or during the neonatal period. In this review, we focus on the structure and

function of the hemoglobin molecule and then provide a comprehensive discussion of the more common types of hemoglobinopathies.

HEMOGLOBIN PRODUCTION

Hemoglobin is a heterotetrametric protein consisting of 2 polypeptide globin α subunits and 2 polypeptide globin β subunits. The globin subunits are encoded by multigene clusters on chromosome 16 for α-globin and chromosome 11 for β-globin (Fig 1). (1)(2)(3)(4) These globin polypeptides each contain a heme group that can reversibly bind oxygen, allowing it to be delivered to the tissues. Different α-like and β-like globin chains are synthesized during fetal development and neonatal development. The order in which different β-globins are expressed generally follows the order in which they are arranged along chromosome 11: 5′-ε-γ^G-γ^A-δ-β−3′. (2)(4) In the first 8 weeks of gestation, there is a brief period of embryonic globin gene expression. The embryonic chains ζ and ε are the first to be produced during early embryonic life, producing hemoglobin Gower 1, hemoglobin Gower 2, and hemoglobin Portland. After 8 weeks' gestation, the α-globin and γ-globin chains are predominantly expressed, which creates hemoglobin F ($\alpha_2\gamma_2$), termed fetal hemoglobin. Fetal hemoglobin is the most common hemoglobin at birth, accounting for 70% to 90% of hemoglobin in the neonatal period. After birth, the γ-globin chain of fetal hemoglobin is progressively replaced by the β-globin chain of adult hemoglobin termed hemoglobin A, or $\alpha_2\beta_2$, which occurs around 3 to 6 months of age. This is referred to as the hemoglobin switch (see Fig 2). (4)(5)(6) Due to the timing of globin chain switching during development, a premature infant will predominantly express hemoglobin F, which slowly decreases as the infant approaches term gestational age. In adults, hemoglobin F accounts for less than 1% of total hemoglobin, and the most common hemoglobin in adults is hemoglobin A ($\alpha_2\beta_2$) with a minimal amount of the minor hemoglobin A2 ($\alpha_2\delta_2$). (4)

HEMOGLOBINOPATHIES

Hemoglobinopathies are a heterogenous group of disorders caused by genetic mutations in the globin genes. They are often broadly categorized into quantitative defects or qualitative defects, but they are not mutually exclusive. (4) In quantitative defects, the mutation causes insufficient production of a normal globin chain, which can range from no production to mild deficiency. These are typically referred to as the thalassemias. In qualitative defects, the structure of the hemoglobin is altered. The most common structural hemoglobinopathy is sickle cell disease.

EPIDEMIOLOGY OVERVIEW

Historically, hemoglobinopathy variants have been naturally selected because of their protective advantage against severe malaria, resulting in the highest prevalence seen in tropical and subtropical regions affected by malaria. (7)(8)

THALASSEMIAS

Thalassemias are a group of disorders generally characterized by ineffective erythropoiesis and hemolysis. The disorders are often classified based on the type of globin

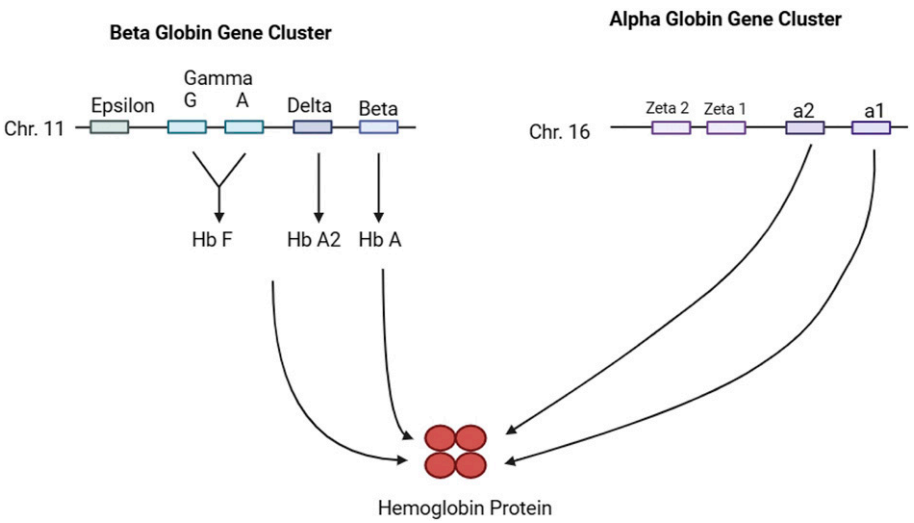

Figure 1. α- and β-globin gene clusters. Diagram of α- and β-globin gene clusters and their expression within the adult hemoglobin protein. The arrangement of genes corresponds with the order of their expression during development. Early fetal life is characterized by the expression of ζ α chains and ε β chains. In adults, hemoglobin chains are predominantly α chains combined with β chains and a smaller amount of γ and δ chains.

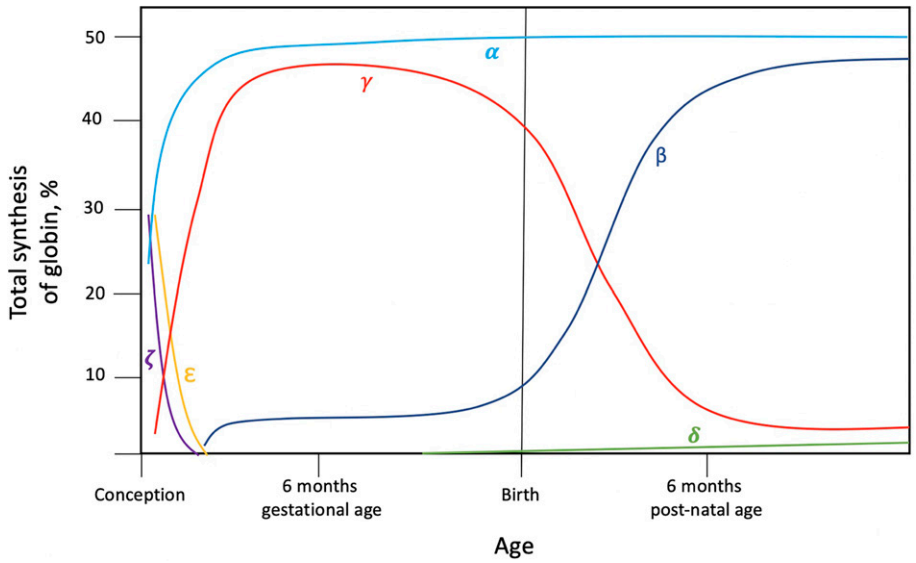

Figure 2. Hemoglobin switch. Schematic diagram depicting the change in hemoglobin chain expression through fetal and early postnatal life. By 6 months of age, γ chains drop precipitously and β chains increase, which corresponds to the time when clinical manifestations of β-thalassemias present.

chain that is affected: α-thalassemias are caused by decreased production of α chains, whereas β-thalassemias are caused by decreased production of β chains. Thalassemias have a wide range of clinical severities based on the number of genes affected, the types of mutations involved, and the subsequent effect on globin production.

Epidemiology of Thalassemias

α-Thalassemia is seen in approximately 5% of the world's population. It is most prevalent in Southeast Asia, specifically Laos and Cambodia; however, it is also present in Africa and regions of the Mediterranean and Middle East. (9) The more severe cis-mutations are seen in Southeast Asia, whereas single gene mutations or trans mutations are more commonly seen in Africa. If both parents have a cis mutation, their offspring will have a 25% chance of having α-thalassemia major leading to hydrops fetalis. Hemoglobin constant spring, the most common type of nondeletional α-thalassemia, is predominantly seen in northeastern Thailand, southern China, and minority populations in Vietnam. (10)

β-thalassemias are less prevalent than α-thalassemias; however, they still affect 1.5% of the global population. Each year approximately 40,000 infants are born with the condition, and half will require regular blood transfusion therapy. Most people with β-thalassemias reside in a geographic region stretching from Africa, through southern Europe and the Middle East, to Southeast Asia. Hemoglobin E- β-thalassemia is most commonly found in Southeast Asia. (11)(12)

α-Thalassemia

α-Thalassemia is caused by mutations in 1 or more of the 4 α-globin genes. These can range in severity from 1 mutation causing a slightly decreased α-globin production, to a 4-gene mutation leading to no α-globin production. The majority of mutations are deletional, but point mutations have also been reported. When mutations occur on the same chromosome, they are considered to be in cis configuration. When mutations occur on opposite chromosomes, they are considered to be in trans configuration (see Table 1).

α-globin gene expression begins in utero, therefore severe mutations in these genes can be clinically apparent in utero and at birth. α-thalassemia carrier status occurs when 1 α-globin gene is mutated (-α/αα). This is clinically benign as there are 3 other normal-functioning α-globin genes. Mutations of 2 α-globin genes are classified as α-thalassemia trait, which causes low mean corpuscular volume, low mean corpuscular hemoglobin, and normal hemoglobin levels or very mild anemia. Affected individuals have normal growth and development.

Three α-globin deletions with only 1 active α-globin gene (- -/-α) is called deletional hemoglobin H disease. In hemoglobin H disease, the significant decrease in α-globin chains leads to an imbalance with the β-like chains. The excess γ chains (in utero) and β chains (neonatal) form tetramers called hemoglobin Bart (γ4) and hemoglobin H (β4), respectively. (10)(13) These tetramers are highly unstable, leading to precipitation of the hemoglobin in red blood cells, causing direct damage to the red cell membrane and leading

Table 1. Alpha Thalassemia Mutations

Nomenclature	Gene mutations	Presentation
α-thalassemia carrier	a1 a2 a1 a2	Asymptomatic Borderline low MCV Normal Hemoglobin
α-thalassemia trait Cis mutation	a2 a2 a1 a2	Asymptomatic Mild anemia Low MCV
Trans mutation	a1 a2 a1 a2	
Deletional Hemoglobin H disease	a1 a2 a2 a2	Mild to moderate microcytic anemia Chronic hemolysis Rarely require transfusions
Non-deletional Hemoglobin H – Constant Spring	a1 CS a2 a2	Moderate to severe microcytic anemia Chronic hemolysis Splenomegaly Often requires transfusions
α-thalassemia major	a2 a2 a2 a2	Hydrops fetalis Not compatible with life unless fetus receives intrauterine transfusions

A list of the common types of α-thalassemia with their corresponding genetic mutations and the resultant phenotypes. α-thalassemia carriers have 1 mutation. α-thalassemia trait refers to persons with 2 mutations, either in a cis or trans configuration. Deletional hemoglobin H disease is due to deletions of 3 of 4 genes. Nondeletional hemoglobin H disease is the result of 2 deletions and a third mutation such as hemoglobin constant spring, which leads to more severe anemia and chronic hemolysis. α-thalassemia major occurs when there are no α genes, which is not compatible with life unless the fetus receives intrauterine transfusions. MCV=mean corpuscular volume.

to chronic hemolysis. Patients often develop hyperbilirubinemia from the hemolysis and splenomegaly due to compensatory extramedullary hematopoiesis. Patients with deletional hemoglobin H often have mild to moderate anemia but do not usually require transfusions. (14)(15) There is a form of nondeletional hemoglobin H disease in which a cis mutation is inherited with a nondeletional mutation of a third α-globin gene. Examples include hemoglobin constant spring, Pakse, and Quong Sze mutations, which, if inherited with 2 α-gene deletions, can result in nondeletional hemoglobin H syndrome. (14) The constant spring mutation causes the production of an abnormally long α-globin protein, which is highly unstable, thus leading to more clinically significant symptoms compared with the deletional form of hemoglobin H disease. People with nondeletional hemoglobin H often require frequent transfusions. (14)(15) Almost all fetuses with hemoglobin Barts hydrops fetalis syndrome, because of a 4 α-globin gene deletion, die in utero or shortly after birth. (14)

For patients with α-thalassemia, management depends on the severity of the phenotype. Most people with hemoglobin H are not transfusion-dependent. However, during acute infections, particularly with parvovirus, that can trigger an aplastic crisis, they may require support with transfusions. Folic acid supplementation can be recommended because of the rapid cell turnover and thus higher folic acid consumption. (16) In patients with severe phenotypes, additional complications, such as iron overload, growth delay, splenomegaly, and cholelithiasis, should be monitored. (15)(16)

Diagnosis of α-thalassemia cannot be determined based on hemoglobin electrophoresis. Genetic testing is required and often done based on family history or clinical suspicion in a patient with microcytic anemia. Preconception counseling is extremely important for those with α-thalassemia. If

both parents are carriers of a cis mutation, there is a 25% risk in each pregnancy that the fetus will inherit all 4 mutations and therefore lack all α-globin genes. When all α chains are deleted (–/–) the lack of α-globin production is not compatible with life. Affected fetuses may survive the first and second trimesters because of the persistence of embryonic ζ-globin chains, but unless given transfusions, they will go on to develop hydrops fetalis. In addition to hydrops fetalis of the fetus, placentomegaly can occur, as well as potentially life-threatening complications in the pregnant patient (eg, preeclampsia, hemorrhage, and disseminated intravascular coagulation). In utero transfusions have been an effective treatment of these fetuses if detected early enough in pregnancy followed by life-long transfusions in the surviving infants. (16) These couples should receive genetic counseling with prenatal diagnosis in future pregnancies. Prenatal diagnosis can be performed using DNA-based diagnosis via amniocentesis. (15)(16)(17)

β-Thalassemia

β-Thalassemias are most commonly caused by point mutations in 1 of the 2 β-globin genes. These mutations can affect transcription, translation, or post-translation modifications, hence leading to a wide array of clinical severities because of the varying effects on β-globin production. Mutations that lead to mild reductions in β-globin synthesis are denoted as β^+ whereas mutations leading to the complete absence of β-globin synthesis are denoted as β°. Homozygous β° mutations lead to no detectable β-chain synthesis. As a result of excess α chains, red cell precursors are prematurely destroyed, resulting in chronic hemolysis. (2)(3)

Classification of β-thalassemia was previously based on the symptoms of the patient as well as the degree of anemia. Individuals were classified as having β-thalassemia major, intermedia, or minor. More recently, classification has focused on whether the patient requires transfusions or not, a treatment that is initiated based on the severity of an individual's anemia and/or symptoms. Transfusion-dependent β-thalassemia (TDT) is usually caused by homozygous β° mutations or compound heterozygous $\beta^+/\beta°$ mutations. Individuals with only 1 β-globin mutation, or homozygous β^+ mutations, generally do not require transfusions and are classified as non–transfusion-dependent β-thalassemia (NTDT). Phenotypes can be influenced by 3 primary factors:

1. the quantity of *β*-globin chain synthesized by the individual
2. the concurrent inheritance of α-thalassemia, which alters the ratio of α- to *β*-globin chains, thereby alleviating certain hemolytic effects
3. the presence of a mutation that enhances hemoglobin F production, offering partial compensation for the deficiency in *β*-globin chains. (11)(14)

Children with TDT will clinically present around 6 to 12 months of age, coinciding with the time of hemoglobin switch and subsequent drop in hemoglobin F levels with minimal to no hemoglobin A production. Children with NTDT present later in childhood, usually during routine examinations which reveal a microcytic anemia. (2) Diagnosis of β-thalassemia is based on hemoglobin electrophoresis showing elevations in hemoglobin F and hemoglobin A2 with a reduction or absence of hemoglobin A. Genetic sequencing of the β-globin gene can confirm the diagnosis.

Without treatment, children with TDT will develop hepatosplenomegaly and marrow expansion from ineffective erythropoiesis and will suffer from growth and developmental delays, complications of iron overload, and a shortened lifespan. Treatment of TDT consists of red cell transfusions typically made every 3 to 4 weeks. Transfusions are given to target a goal hemoglobin nadir of greater than 9 to 9.5 g/dL (90–95 g/L) to suppress innate erythropoiesis and support oxygen-carrying capacity. Transfusion therapy results in improved growth, decreased skeletal abnormalities, reduced hypersplenism, and decreased gut iron absorption. Generally, children with NTDT do not require transfusions except during special circumstances such as surgeries, acute infections, or to support growth during childhood. (18)

In 2019, the US Food and Drug Administration approved the medication luspatercept for adults older than 18 years with TDT. The medication improves late-stage erythroid maturation, and thus increases hemoglobin levels, leading to a reduction in transfusion requirements. (19) In 2022, gene therapy for thalassemia was approved, the first transformative therapy that allows individuals with TDT to become transfusion-independent. (20)(21)

COMMON STRUCTURAL HEMOGLOBIN VARIANTS

Epidemiology of Structural Variants

Structural hemoglobin variants arise from genetic mutations that cause an abnormal globin chain structure in the hemoglobin. Hemoglobin S, the most prevalent, is seen in high frequencies across sub-Saharan Africa, the Mediterranean, the Middle East, and India, regions with a significant malaria burden. (8)(22) Hemoglobin C is prevalent in West Africa and Southeast Asia and within diverse populations in Africa, South and Central America, and Southern Europe. (23) Hemoglobin E predominantly affects individuals from the

Indian subcontinent and Southeast Asia, with Thailand, Laos, and Cambodia exhibiting frequencies approaching 60%. (9)

Hemoglobin S Syndromes

Hemoglobin S is caused by a point mutation in codon 6 of the β-globin gene on chromosome 11, resulting in an amino acid substitution in which glutamic acid is replaced by valine. Upon deoxygenation inside the red cell, hemoglobin S will polymerize, leading to a conformational change in the red cell shape into a "sickle." Individuals who inherit 1 hemoglobin S gene have sickle cell trait. These individuals are generally asymptomatic. Sickle cell disease (SCD) is an autosomal recessive group of disorders caused by either the homozygous inheritance of the hemoglobin S gene or a compound heterozygous mutation involving hemoglobin S and another β-globin mutation that can influence sickling. Homozygous inheritance, termed hemoglobin SS, causes the more severe form of the disease. If a patient coinherits a sickle mutation and a hemoglobin C allele, they will have hemoglobin SC disease, which is typically milder than hemoglobin SS. When a sickle mutation is inherited with β-thalassemia, the severity of the resulting sickling disorder depends on the severity of the coinherited β-thalassemia mutation. Coinheritance of a β^0 mutation, which produces no hemoglobin A, results in severe SCD similar to hemoglobin SS. (24)(25)(26)

Children with SCD typically do not present with symptoms until 6 to 12 months of age when fetal hemoglobin levels begin to decrease and hemoglobin S production increases. Sickling of the red cells leads to a combination of intermittent vaso-occlusion in the vasculature as well as chronic hemolysis. This leads to acute complications and chronic organ damage. Common complications include strokes, retinopathy, acute chest syndrome, nephropathy, functional asplenia, and subsequent increased risk for infections, avascular necrosis, and episodes of acute vaso-occlusive pain crises. (22)(24)

Early diagnosis of SCDs is important because early initiation of prophylactic penicillin, usually by the age of 2 months, has been shown to decrease mortality from bacteremia. (27) Disease-modifying therapies such as hydroxyurea and blood transfusions have been shown to decrease complications. Curative therapy includes stem cell transplantation. In 2023, gene therapy for SCD was approved. Through ex-vivo genetic modification, these treatments offer patients a transformative opportunity to drastically ameliorate their disease. Results from ongoing clinical trials have shown drastic improvement in hemoglobin levels and a reduction of vaso-occlusive crises. (28)

Hemoglobin C

Hemoglobin C results from a single amino acid mutation leading to glutamic acid being replaced by lysine in the sixth position of the β-globin chain. Individuals with the hemoglobin C trait (hemoglobin AC) are phenotypically normal whereas individuals who inherit 2 copies of the hemoglobin C allele (hemoglobin CC disease) often have mild chronic hemolytic anemia. Because of chronic hemolysis, individuals have an increased risk of gallstones. Folic acid is often provided to prevent folate deficiency. Typically, transfusions are not needed. (23)

Hemoglobin E

Hemoglobin E is caused by a mutation in the β-globin gene that creates an alternate splice site leading to decreased production of an abnormal β chain. Individuals with hemoglobin E trait can have mild microcytosis and are asymptomatic. Individuals with coinheritance of hemoglobin E and a β-thalassemia mutation can present with an array of phenotypes ranging from mild anemia to severe anemia requiring transfusion support. Modifiers such as the type of β-thalassemia mutation, and whether the individual coinherited α-thalassemia, can affect the phenotype. (2) Individuals who coinherit hemoglobin S and hemoglobin E (hemoglobin SE) exhibit a mild sickle cell phenotype similar to hemoglobin S/β^+ thalassemia.

OTHER VARIANTS

Unstable Hemoglobins

Unstable hemoglobins can result from a mutation in any of the globin chains. Mutations are often inherited in an autosomal dominant pattern. These mutations cause changes in the solubility of the hemoglobin, thus leading to instability and hemoglobin precipitation referred to as Heinz bodies. These precipitates can bind to the red cell membrane causing a change in the membrane leading to breakdown and clearance of the affected cells in the spleen. The red cell lifespan can be severely shortened leading to anemia. (29)

Clinical presentation of unstable hemoglobins is variable, and the severity is linked to the causative variant and its influence on hemoglobin stability. As a result, the spectrum of clinical manifestations can be broad, ranging from no symptoms to severe chronic hemolytic anemia. Of particular importance to the neonatologist, unstable γ-globin mutations can cause transient neonatal hemolytic anemia, which resolves between 6 and 9 months of age because of the transition from fetal to adult hemoglobin. Generally, unstable hemoglobinopathies manifest as mild phenotypes and patients may exhibit mild chronic hemolytic anemia.

Patients should be educated about prevention, including avoidance of oxidant drugs and prompt evaluation during hemolytic episodes. Infections can often precipitate hemolysis. In patients with severe hemolysis, transfusion support may be required. Others only require transfusions during hemolytic crises, often prompted by infections. Splenectomy can be considered in severe cases, but not as the preferred option because it can cause a hypercoagulable state in some people. (29)

Methemoglobins: Hemoglobin M

Some types of hemoglobin variants, termed hemoglobin M, can result in methemoglobin. Methemoglobin is a condition in which heme iron becomes oxidized. As a result, the oxygen-carrying capacity of blood decreases because oxidized iron cannot reversibly bind oxygen. In most cases, a tyrosine is substituted for a histidine in the proximal and distal sites of the α or β chains, leading to an iron-phenolate complex. (30)

Inheritance of hemoglobin M is autosomal dominant. Affected individuals often have chronic methemoglobinemia. As a result, they typically present with cyanosis. Patients can also have hemolysis and may present with neonatal jaundice. Depending on which chain is mutated, individuals will present at different time points. In the case of α-globin variants, the dusky color of affected infants will be noted at birth. When there is a β-globin variant, the symptoms become apparent only after β chains have replaced the fetal γ chains at 6 to 9 months of age. (31)

Hemoglobin M can be diagnosed with electrophoresis. No effective treatment exists for cyanosis in patients with hemoglobin M, however, individuals are often otherwise asymptomatic.

Hereditary Persistence of Fetal Hemoglobin and *δβ*-Thalassemia

Hereditary persistence of fetal hemoglobin (HPFH) and δβ-thalassemia are benign conditions in which individuals exhibit markedly elevated levels of hemoglobin F into adulthood. δβ-Thalassemia results from a large deletion encompassing both the δ- and β-globin genes. (32) Heterozygotes often are characterized by hemoglobin F levels between 5% and 20% and mild microcytic anemia. HPFH mutations are caused by a large deletion in the region between the γ- and β-globin genes or a point mutation in the γ-globin gene promoter. (32) Deletional HPFH is characterized by hemoglobin F levels of 10% to 20% with no effect on red blood cell indices. (32)

HPFH and δβ-thalassemia are clinically important because elevated hemoglobin F levels can attenuate the disease severity of coinherited β-chain hemoglobinopathies, such as in patients with combined hemoglobin S and HPFH.

NEWBORN SCREENING

Newborn screening programs have the ability to diagnose hemoglobinopathies at birth, thus allowing for early implementation of preventive care. The US newborn screening program began screening for SCD in 1975. Since 2006, all 50 states have adopted universal screening for SCD. However, screening for α- and β-thalassemia is not yet universal in all states. (33)(34)

Advancements in diagnostic technology have led to the adoption of isoelectric focusing or high-performance liquid chromatography for detecting hemoglobinopathy in newborn screening programs. Both technologies have high sensitivity and specificity for the diagnosis of SCD and severe thalassemia. (35)

Interpretation of newborn screening results is based on the order in which the hemoglobin types are reported (Table 2). The diagnostic report lists the primary hemoglobin type detected with the highest concentration, followed by subsequent variants in descending order based on the amount present. For example, a child with a normal hemoglobin phenotype would have the results "FA," signifying the predominant hemoglobin at birth first, hemoglobin F, followed by the smaller amount of hemoglobin A that is detected.

A child with hemoglobin SS would have the results "FS," again signifying the predominant hemoglobin at birth, hemoglobin F, followed by the lesser amount of hemoglobin S that is being produced, and *no* hemoglobin A.

Table 2. Newborn Screen Hemoglobinopathy Interpretation

NEWBORN SCREEN RESULT	PRESUMED DIAGNOSIS
FA	Normal
FAS	Sickle cell trait
FS	Sickle cell anemia: Hemoglobin SS or hemoglobin S/β^0 thalassemia
FSA	Hemoglobin S/β^+ thalassemia
FSC	Hemoglobin SC disease
F	Transfusion-dependent β-thalassemia (β-thalassemia major)
FA Barts	Hemoglobin H disease

Newborn screening results for hemoglobinopathy. The diagnostic newborn screening report lists the primary hemoglobin type detected with the highest concentration, followed by subsequent variants in descending order based on the amount present. F=hemoglobin, A=hemoglobin A, S=hemoglobin S, C=hemoglobin C, Barts=tetramer of γ-globin chains.

Carriers of hemoglobin S will have the result "FAS," signifying the higher production of normal adult hemoglobin A compared with the amount of hemoglobin S being produced.

Newborn screening results for a child with severe β-thalassemia (ie, Cooley anemia) would show only hemoglobin F and no hemoglobin A, thus signifying the complete lack of normal adult hemoglobin production. Newborns with the β-thalassemia trait often go undetected. Severe α-thalassemia (hemoglobin H disease) can be detected, as the screening methods can detect the fast migrating hemoglobin Barts bands. However, α-thalassemia trait and α-thalassemia carriers often go undetected as the small amount of hemoglobin Barts produced is often below the level of detection. (35)

Universal newborn screening in the United States is an important public health advancement; however, states often have limited capacity to implement systems to ensure access to comprehensive follow-up care. Therefore, it is imperative that neonatologists and general pediatricians are equipped at interpreting the results and appropriately counseling patients on the diagnoses.

CONCLUSIONS

Hemoglobinopathies in neonates encompass a broad range of hemoglobin disorders with a wide array of phenotypes. Children can present perinatally, around 6 to 12 months of age, or later in life, depending on the specific mutations inherited. As a result, neonatologists often have the opportunity to diagnose these disorders. Understanding the physiology of hemoglobin development, having an awareness of the clinical spectrum of hemoglobinopathies, along with the ability to accurately interpret newborn screening results, can lead to early diagnoses and better outcomes in children with more severe phenotypes. As novel treatments such as gene therapy continue to arrive on the scene, prompt diagnosis will be paramount to providing children with early access to these transformative therapies.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the developmental biology of hemoglobin types.
- Know the clinical and laboratory features of neonatal hemoglobinopathies, including the thalassemias.
- Know the indications for and approaches to screening for hemoglobinopathies in the newborn population.

References

1. Higgs DR. The molecular basis of α-thalassemia. *Cold Spring Harb Perspect Med*. 2013;3(1):a011718
2. Taher AT, Musallam KM, Cappellini MD. β-Thalassemias. *N Engl J Med*. 2021;384(8):727–743
3. Thein SL. The molecular basis of β-thalassemia. *Cold Spring Harb Perspect Med*. 2013;3(5):a011700
4. Harteveld CL, Achour A, Arkesteijn SJG, et al. The hemoglobinopathies, molecular disease mechanisms and diagnostics. *Int J Laboratory Hematol*. 2022;44(suppl 1): 28–36
5. Wang X, Thein SL. Switching from fetal to adult hemoglobin. *Nat Genet*. 2018;50(4):478–480
6. Forget BG. Progress in understanding the hemoglobin switch. *N Engl J Med*. 2011;365(9):852–854
7. Taylor SM, Parobek CM, Fairhurst RM. Haemoglobinopathies and the clinical epidemiology of malaria: a systematic review and meta-analysis. *Lancet Infect Dis*. 2012;12(6):457–468
8. Aidoo M, Terlouw DJ, Kolczak MS, et al. Protective effects of the sickle cell gene against malaria morbidity and mortality. *Lancet*. 2002;359(9314):1311–1312
9. Vichinsky EP. Changing patterns of thalassemia worldwide. *Ann N Y Acad Sci*. 2005;1054:18–24
10. Fucharoen S, Viprakasit V. Hb H disease: clinical course and disease modifiers. *Hematology Am Soc Hematol Educ Program*. 2009:26–34
11. Weatherall DJ. The definition and epidemiology of non-transfusion-dependent thalassemia. *Blood Rev*. 2012;26 Suppl 1:S3–6
12. Angastiniotis M, Modell B, Englezos P, Boulyjenkov V. Prevention and control of haemoglobinopathies. *Bull World Health Organ*. 1995;73(3):375–386
13. Chui DH. Alpha-thalassemia: Hb H disease and Hb Barts hydrops fetalis. *Ann N Y Acad Sci*. 2005;1054:25–32
14. Lal A, Vichinsky E. The clinical phenotypes of alpha thalassemia. *Hematol Oncol Clin North Am*. 2023;37(2):327–339
15. Vichinsky EP. Alpha thalassemia major–new mutations, intrauterine management, and outcomes. *Hematology Am Soc Hematol Educ Program*. 2009:35–41
16. Carr S, Rubin L, Dixon D, Star J, Dailey J. Intrauterine therapy for homozygous alpha-thalassemia. *Obstet Gynecol*. 1995;85(5 Pt 2):876–879
17. Pongtanakul B, Sanpakit K, Chongkolwatana V, Viprakasit V. Normal cognitive functioning in a patient with Hb Bart's hydrops successfully cured by hematopoietic SCT. *Bone Marrow Transplant*. 2014;49(1):155–156
18. Rachmilewitz EA, Giardina PJ. How I treat thalassemia. *Blood*. 2011;118(13):3479–3488
19. Cappellini MD, Taher AT. The use of luspatercept for thalassemia in adults. *Blood Adv*. 2021;5(1):326–333
20. Leonard A, Tisdale JF, Bonner M. Gene therapy for hemoglobinopathies: beta-thalassemia, sickle cell disease. *Hematol Oncol Clin North Am*. 2022;36(4):769–795
21. Locatelli F, Lang P, Wall D, et al. CLIMB THAL-111 Study Group. Exagamglogene autotemcel for transfusion-dependent β-thalassemia. *N Engl J Med*. 2024;390(18):1663–1676
22. CDC. Sickle Cell Disease: Data and Statistics. https://www.cdc.gov/sickle-cell/data/?CDC_AAref_Val=https://www.cdc.gov/ncbddd/sicklecell/data.html. Published 2024. Accessed May 4, 2024.

23. Bibek Karna SKJ, Al Zaabi E. Hemoglobin C disease. In: Island T, ed.: StatPearls; 2024: https://www.ncbi.nlm.nih.gov/books/NBK559043/. Accessed May 1, 2024.
24. Serjeant GR. The natural history of sickle cell disease. *Cold Spring Harb Perspect Med*. 2013;3(10):a011783
25. Frenette PS, Atweh GF. Sickle cell disease: old discoveries, new concepts, and future promise. *J Clin Invest*. 2007;117(4):850–858
26. Bainbridge R, Higgs DR, Maude GH, Serjeant GR. Clinical presentation of homozygous sickle cell disease. *J Pediatr*. 1985;106(6):881–885
27. Gaston MH, Verter JI, Woods G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia. A randomized trial. *N Engl J Med*. 1986;314(25):1593–1599
28. Sharma A, Boelens JJ, Cancio M, et al. CRISPR-Cas9 Editing of the HBG1 and HBG2 Promoters to Treat Sickle Cell Disease. *N Engl J Med*. 2023;389(9):820–832
29. Gallagher PG. Diagnosis and management of rare congenital nonimmune hemolytic disease. *Hematology Am Soc Hematol Educ Program*. 2015;2015:392–399
30. Mansouri A, Lurie AA. Concise review: methemoglobinemia. *Am J Hematol*. 1993;42(1):7–12
31. Alonso-Ojembarrena A, Lubián-López SP. Hemoglobin M disease as a cause of cyanosis in a newborn. *J Pediatr Hematol Oncol*. 2016;38(3):173–175
32. Bollekens JA, Forget BG. Delta beta thalassemia and hereditary persistence of fetal hemoglobin. *Hematol Oncol Clin North Am*. 1991;5(3):399–422
33. Consensus conference. Newborn screening for sickle cell disease and other hemoglobinopathies. *JAMA*. 1987;258(9):1205–1209
34. US Preventive Services Task Force. Screening for sickle cell disease in newborns: recommendation statement. *Am Fam Physician*. 2008;77(9):1300–1302
35. Hoppe CC. Newborn screening for non-sickling hemoglobinopathies. *Hematology Am Soc Hematol Educ Program*. 2009:19–25