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Subdivisions of Alpha Thalassemia

- Alpha thalassemia silent carrier
- Alpha thalassemia minor (trait)
- Hemoglobin H (HbH) disease
- Hemoglobin H-Constant Spring
- Hb Bart's hydrops fetalis

General Discussion

Summary

Alpha thalassemia is a general term for a group of inherited blood disorders characterized by reduced or absent production of alpha-globin subunits, resulting in low levels of hemoglobin that is otherwise fully functional. Hemoglobin is found in red blood cells; it is the red, iron-rich, oxygen-carrying pigment of the blood. A main function of red blood cells is to deliver oxygen throughout the body. There are two main forms of alpha thalassemia that are associated with significant health problems – hemoglobin (Hb) Bart's hydrops fetalis and hemoglobin H (HbH) disease. Hb Bart's hydrops fetalis is a severe syndrome that is usually fatal to the developing embryo during gestation or shortly after birth; however, recent advances have led to improved treatments for this condition. HbH disease is highly variable, and the specific symptoms and severity can vary greatly from one person to another. Some individuals will have only minor symptoms, while others will develop potentially serious complications. The characteristic finding of all forms of alpha thalassemia is anemia, with red blood cells that are small (microcytic), contain low levels of functional hemoglobin (hypochromic), and may break down in prematurely in both the bone marrow (ineffective erythropoiesis) and in the peripheral circulation (hemolysis). Consequently, severely affected individuals may not circulate sufficient oxygen-rich blood throughout the body. These individuals may experience fatigue, weakness, shortness of breath, dizziness or headaches. Severe anemia can cause serious, even life-threatening, complications if left untreated. Individuals with severe forms of HbH disease are usually treated with regular blood transfusions, which can result in the accumulation of excess iron in the body (iron overload). Although iron overload can damage numerous organs in the body, it can be effectively treated using several highly effective medications.

Alpha thalassemia is caused by mutations in two different genes, the *HBA1* and the *HBA2* genes. Most individuals inherit two copies of each gene (for a total of four genes); one of each from a person's father, and one of each gene from a person's mother. A mutation in any one of the four alpha genes results in a condition that has no symptoms (alpha thalassemia silent carrier), but individuals can pass the mutant gene on to their children. A mutation (or mutations) that affects two of the four alpha genes results in a condition that is asymptomatic or only very mild symptoms (alpha thalassemia minor). A mutation (or mutations) that affect three genes results in HbH disease, while defects that affect all four genes result in Hb Bart's hydrops fetalis.

Introduction

Thalassemia is a general term for a group of congenital, genetic disorders characterized by low levels of hemoglobin, decreased red blood cell production, and anemia. There are two main forms – alpha thalassemia and beta thalassemia – each with various subtypes. Alpha thalassemia is caused by reduced or absent production of alpha-globin subunits, while beta thalassemia is caused by reduced or absent production of beta-globin subunits. Alpha thalassemia minor and beta thalassemia minor, also known as alpha thalassemia trait or beta thalassemia trait, are common conditions in many demographics. Beta thalassemia major was first described in the medical literature in 1925 by an American physician named Thomas Cooley. Beta thalassemia major is also known as Cooley's anemia. These disorders are related, but distinct entities. The similar terminology and symptomology can cause confusion for affected individuals, their families, and physicians who are unfamiliar with these disorders or are not specialists in diagnosing and treating disorders of the blood and blood-forming organs (hematologists). NORD has a separate report on beta thalassemia.

Signs & Symptoms

The specific symptoms and severities of the alpha thalassemia conditions vary greatly from one person to another. Individuals with alpha thalassemia silent carrier do not develop symptoms, while individuals with alpha thalassemia minor do not develop any symptoms or are only mildly anemic. Many individuals with either form of alpha thalassemia go through life never knowing they carry an altered gene(s) for the disorder. In some cases, a diagnosis is made incidentally while they are being evaluated for another condition.

Two forms of alpha thalassemia are associated with significant symptoms, hemoglobin H disease and Hb Bart's hydrops fetalis.

HEMOGLOBIN H (HbH) DISEASE

The specific symptoms and severity of HbH disease can vary greatly from one person to another. Some individuals do not develop symptoms and only become aware of the disorder upon routine blood testing. In some cases, affected individuals do not develop symptoms until adulthood. Most individuals exhibit symptoms associated with minor to moderate anemia. However, some individuals will develop severe symptoms that can develop during childhood or even the first year of life. It is important to note that affected individuals may not have all the symptoms discussed below. Affected individuals or parents of affected children should talk to their physicians and medical teams about their specific case, associated symptoms and overall prognosis.

Disease severity is influenced, in part, by the specific type of mutations present. HbH disease may be caused by deletional or nondeletional mutations, either alone or in combination. Deletional HbH disease occurs when a combination of deletion mutations remove three of the four genes that express the alpha-globin protein. This is the most common form of HbH disease. Nondeletional HbH disease occurs when a deletion mutation removes two alpha genes, and a nondeletional point mutation inactivates the third gene without physically removing it. Nondeletional mutations are generally associated with more severe anemia, are more likely to cause an enlargement of spleen and liver, and are more likely to require therapeutic blood transfusions.

HbH disease usually presents with anemia, which can be of varying degrees and severity. Anemia can be associated with fatigue, weakness, shortness of breath, lightheadedness, headaches, and yellowing of the skin, mucous membranes and whites of the eyes (jaundice). Severely affected infants often fail to grow and gain weight as expected based upon age and gender (failure to thrive). Some infants become progressively pale (pallor). Feeding problems, irritability or fussiness, abnormal enlargement of the liver (hepatomegaly), and the abnormal enlargement of the spleen (splenomegaly) may also occur. Growth deficiency can occur in some cases.

Splenomegaly may cause enlargement or swelling of the abdomen. Splenomegaly may be associated with an overactive spleen (hypersplenism), a condition that can develops because too many blood cells build up and are destroyed within the spleen. Hypersplenism can contribute to anemia in individuals with alpha thalassemia and

cause low levels of white blood cells, increasing the risk of infection, and low levels of platelets, which can predispose to bleeding.

Additional symptoms that may occur include masses that form because of blood cell production outside of the bone marrow (extramedullary hematopoiesis). These masses primarily form in the spleen, liver, chest, and spine. These masses can potentially cause compression of nearby structures and a variety of symptoms. Affected individuals may also exhibit leg ulcers, gallstones (cholelithiasis), and folic acid deficiency. Additionally, HbH disease tends to worsen when individuals take oxidant drugs, are exposed to certain chemicals, or have an infection because of the increased pace of destruction of red blood cells (hemolysis).

Some older adults with HbH disease, as well as individuals treated by regular blood transfusions, may develop iron overload, a condition characterized by the buildup of iron in various tissues of the body. Iron overload can cause tissue damage and impaired function of affected organs such as the heart, liver and endocrine glands. Iron overload can damage the heart and cause abnormal heart rhythms, inflammation of the membrane (pericardium) that lines the heart (pericarditis), and enlargement of the heart and disease of the heart muscle (dilated cardiomyopathy). Heart involvement can eventually progress to life-threatening complications such as heart failure. Involvement of the liver can cause scarring and inflammation of the liver (cirrhosis) and high blood pressure of the main vein of the liver (portal hypertension). Involvement of the endocrine glands can cause insufficiency of certain glands such as the thyroid (hypothyroidism) and pancreas (diabetes mellitus). Iron overload is a complication of repeated blood transfusions that may be used to treat some individuals with HbH disease. However, many adults who have never received a blood transfusion have developed iron overload, most likely due to increased absorption of iron from the gastrointestinal tract.

Hemoglobin H-Constant Spring is a variant of HbH disease and the most common nondeletional form of the disorder. Individuals with hemoglobin H-Constant Spring tend to have more severe anemia because red blood cell production is even less efficient than in nondeletional forms of HbH disease (ineffective erythropoiesis). Moderately severe splenomegaly is common in these individuals. Additional common symptoms include leg ulcers, gallstones, jaundice, and an increased risk for infection. Growth delays are more significant in affected children than in children with HbH disease. Affected individuals may be at particular risk of sudden, severe anemia that develops following an acute febrile illness, which is a nonspecific term for any illness, although it is usually one of rapid onset, accompanied by a fever.

HEMOGLOBIN (Hb) BART'S HYDROPS FETALIS

Hb Bart's hydrops fetalis, also known as alpha thalassemia major, is the most severe form of alpha thalassemia. The term hydrops fetalis describes the accumulation of large amounts of fluid (edema) in the tissues and organs of a developing fetus. Edema is widespread (diffuse). A developing fetus may also exhibit profound anemia, an abnormally enlarged liver (hepatomegaly), an abnormally enlarged spleen (splenomegaly), impaired brain development, and signs of heart failure. Abnormal accumulation of cerebrospinal fluid within the skull (hydrocephaly) may also occur. Hydrocephaly causes increased pressure on, and swelling of, the brain. A newborn infant may be pale and exhibit abnormalities of the skeleton and urinary (urogenital) tract. Hb Bart's hydrops fetalis is usually fatal before birth (stillbirth) or shortly after birth (neonatal period).

Causes

Alpha thalassemia is caused by alterations (mutations) in two adjacent genes, the *HBA1* and the *HBA2* genes. Every person has two copies of the *HBA1* gene (one from each parent) and two copies of the *HBA2* gene (also one from each parent). Affected individuals may have a mutation or combination of mutations in one gene, two genes, three genes, or all four copies of these genes. Genes provide instructions for creating proteins that play a critical role in many functions of the body. When a mutation of a gene occurs, the protein product may either function normally but be reduced in quantity, or function abnormally and be produced at normal levels. Depending upon the functions of the protein, this can affect many organ systems of the body.

Genetic diseases are determined by the combination of genes for a particular trait that are on the chromosomes received from the father and the mother. Investigators have determined that the *HBA1* and the *HBA2* genes are located on the short arm (p) of chromosome 16 (16p13.3). Chromosomes, which are present in the nucleus of human cells, carry the genetic information for each individual. Human cells normally have 46 chromosomes. Pairs of human chromosomes are numbered from 1 through 22, and the sex chromosomes are designated X and Y. Males have one X and one Y chromosome and females have two X chromosomes. Each chromosome has a short arm designated “p” and a long arm designated “q”. Chromosomes are further sub-divided into many bands that are numbered.

The *HBA1* and *HBA2* genes specify the production of (encode) alpha globin protein chains. There are three main types of hemoglobins: embryonic, fetal and adult. Embryonic hemoglobins are made during the first few months after conception. Fetal hemoglobins begin to express at eight weeks of gestation and rapidly replace embryonic hemoglobins. Starting at birth, fetal hemoglobins are replaced by adult hemoglobins in a process that is largely completed by ages 6-12 months. Normal hemoglobins are made up of specialized proteins called globins; fetal and adult hemoglobins comprise two alpha chains and two other protein chains, either gamma chains (in fetal hemoglobins) or beta chains (in adult hemoglobins).

A mutation in one alpha gene results in slightly lower production of functional alpha chains and does not cause any symptoms (silent alpha thalassemia carrier).

A mutation in two genes causes decreased production of functional alpha chains, but not enough to cause significant symptoms, although some individuals may have mild anemia (alpha thalassemia minor). When the two mutated genes are on the same chromosome 16, it is called a ‘cis’ deletion; when one mutated gene is from one chromosome 16 and the other mutated gene from the other chromosome 16, it is called a ‘trans’ deletion.

A mutation in three genes results in greatly reduced alpha chain production (hemoglobin H disease). The reduction or lack of alpha protein chains leads to an imbalance with the beta protein chains that are expressed in normal quantity. When the beta chains are present in vast excess (as occurs in Hb H disease), the excess chains bind together to create an abnormal type of hemoglobin called hemoglobin H. Hemoglobin H is unstable and causes red blood cells to break down faster than normal in the bone marrow (ineffective erythropoiesis) and in the peripheral circulation (hemolysis). Hemoglobin H-Constant Spring is an unusual form of HbH disease that is characterized by a significantly worse clinical course, and differs from the more common forms of Hb H disease insofar as one (of the three) affected alpha genes carries a non-deletional mutation.

A mutation in all four genes results in severely reduced or absent production of alpha chains (Hb Bart’s hydrops fetalis).

Mutations in the alpha genes are inherited in an autosomal recessive manner. Recessive genetic disorders become manifest when an individual inherits a mutation of the corresponding gene from each parent. If an individual receives one normal gene and one gene for the disease, the person will be a carrier for the disease, but usually will not show symptoms. The risk that two carrier parents both pass a defective gene to an offspring and producing an affected child, therefore, is 25% for each pregnancy. The risk of bearing a child who is also a carrier (like each parent) is 50% for each pregnancy. The chance that a child will receive a normal gene from both parents and be genetically normal for that particular trait is 25% for each pregnancy. For genes carries on chromosomes 1-22, risk is the same for males and females. The inheritance of alpha thalassemia is somewhat more complicated insofar as each parent contributes two alpha genes to an offspring, rather than only one. The *HBA1* and *HBA2* genes are inherited in pairs, meaning that both genes from one chromosome are passed on from a parent to a child. Consultation with a genetic counselor is recommended for families or parents who are known or suspected of carrying an alpha thalassemia mutation, even if it does not cause symptoms. Additionally, the organizations listed in the Resources section of this report have more detailed information on the genetics of alpha thalassemia.

Researchers have determined that the progression and severity of alpha thalassemia tend to vary based upon the

specific type of mutation present in a gene(s) as well as the specific location of the mutation on the gene(s). This is known as genotype-phenotype correlation and allows physicians to predict individuals who are at risk of developing more severe symptoms (e.g. individuals with HbH-Constant Spring). However, because of the number of genes involved, the expression of genotype and phenotypes in alpha thalassemia is diverse and varied, and the specific genotype-phenotype correlations are not completely understood. More research is necessary to fully clarify genotype-phenotype correlations in alpha thalassemia.

Researchers also believe that additional factors influence the severity of HbH disease and Hb Bart's hydrops fetalis, including modifier genes and environmental factors. Modifier genes, unlike the gene that causes alpha thalassemia, can affect the clinical severity of the disorder. More research is necessary to discover the various genetic and environmental factors associated with alpha thalassemia and their exact role in the development of the disorder.

Affected Populations

Alpha thalassemia is one of the most common autosomal recessive disorders in the world. Increased immigration of people from areas with a higher incidence of alpha thalassemia has led to an increased incidence of the alpha-globin disorders in the US and other Western nations. Although the incidence and prevalence is increasing in United States and Northern Europe, the exact incidence or prevalence remains unknown. Severe forms of alpha thalassemia (HbH disease and Hb Bart's hydrops fetalis) have been estimated to occur in approximately 1 in 1,000,000 individuals in the general population in Northern Europe and North America. However, some studies have shown that alpha thalassemia may be under-recognized and underdiagnosed in these countries, making it difficult to determine their true frequency.

Alpha thalassemia is found in most populations worldwide, but is most common in the Middle East, Southeast Asia, and certain Mediterranean countries. Hb Bart's hydrops fetalis and HbH disease are primarily recognized in Southeast Asia. The estimated incidence of Hb Bart's hydrops fetalis in Southeast Asia is 1 in 200-2,000 births; its incidence in other parts of the world is unknown. The incidence of HbH disease in these countries is approximately 4-20 individuals per every 1,000 births.

Some studies have estimated that as much as 5% of the world's population carries an alpha-thalassemia variant (i.e., a mutation in one of the two pairs of genes associated with alpha thalassemia).

Related Disorders

Symptoms of the following disorders can be similar to those of alpha thalassemia. Comparisons may be useful for a differential diagnosis.

Hydrops fetalis can occur in association with other conditions including various chromosomal disorders, numerous genetic disorders, fetal cardiac abnormalities, fetal infections, and maternal and placental disorders. The combination of hydrops fetalis and the presence of a high proportion of Hb Bart's (an assembly excess fetal gamma chains) is unique to alpha thalassemia conditions. Hemolytic anemia, which occurs in HbH disease, can be associated with numerous other disorders.

ATR-16 syndrome is an extremely rare genetic disorder in which affected individuals lose a large amount of genetic material (monosomy) on chromosome 16 that includes both the alpha globin genes as well as several important adjacent genes. The condition typically results in either alpha thalassemia trait or a mild form of hemoglobin H disease. A variety of additional symptoms may occur including intellectual disability, microcephaly, clubfoot, and distinctive facial features that include widely spaced eyes (hypertelorism), a broad, prominent bridge of the nose, small ears, and a short neck. In males, certain genital abnormalities may be present such as failure of the testes to descend (cryptorchidism) and the abnormal placement of the urinary opening on the underside of the penis (hypospadias). ATR-16 syndrome occurs as a spontaneous (*de novo*) event with no previous family history or in parents with a balanced chromosomal translocation that is inherited in an unbalanced manner. ATR-16 syndrome is

a contiguous gene syndrome, in which the loss of genetic material on a chromosome causes the loss of function of several adjacent genes. In ATR-16 syndrome both the *HBA1* and the *HBA2* genes are affected.

Alpha thalassemia X-linked intellectual disability (ATR-X) syndrome is a rare genetic disorder that affects multiple organ systems of the body. ATR-X syndrome is characterized by intellectual disability, characteristic facial features, abnormalities of the genitourinary tract, and alpha thalassemia. Alpha thalassemia is not seen in every case. Additional abnormalities are usually present in most cases. ATR-X syndrome is inherited as an X-linked recessive genetic condition. Some researchers have suggested the name XLID-hypotonic face syndrome be used to designate several disorders formerly considered separate entities including ATR-X syndrome, Carpenter-Waziri syndrome, Chudley-Lowry syndrome, Holmes-Gang syndrome and X-linked intellectual disability-arch fingerprints-hypotonia syndrome. These syndromes occur due to mutations of the same gene on the X chromosome. Some researchers prefer use of the name ATR-X syndrome because it is the most widely-recognized term for this disorder. (For more information on this disorder, choose “ATR-X syndrome” as your search term in the Rare Disease Database.)

An acquired form of alpha thalassemia, sometimes known as alpha thalassemia-myelodysplastic syndrome or ATMDS, has been identified that occurs in certain individuals with myelodysplasia. Myelodysplastic syndromes is a general term for a group of blood disorders that occur as a result of disordered development of blood cells within the bone marrow. ATMDS involves acquired mutations in the same gene that causes ATR-X syndrome, but most likely involves additional genetic and environmental factors.

Diagnosis

A diagnosis of alpha thalassemia is based upon identification of characteristic symptoms, a detailed patient history, a thorough clinical evaluation and a variety of specialized tests. Hb Bart’s hydrops fetalis can be diagnosed before birth in most cases.

In the United States, infants may be diagnosed with alpha thalassemia through newborn screening. Newborn screening is a public health program that mandates the evaluation of newborn infants for a variety of disorders that are treatable, but not readily apparent at birth. Each state’s newborn screening program (and the specific disorders tested) is different. Further testing is required to determine the exact type of alpha thalassemia present.

Clinical Testing and Workup
Physicians will take a blood sample from individuals suspected of having one of the alpha thalassemia conditions. Several different tests can be performed on a single blood sample. Individuals suspected of having alpha thalassemia will undergo blood tests such as a complete blood count (CBC). A CBC measures several components and aspects of blood including the number, concentration, size, shape, and maturity of blood cells. A specialized blood test known as hemoglobin electrophoresis measures the different types of hemoglobin found in blood.

With alpha thalassemia, a CBC is required to measure the amount of hemoglobin and the number and the size and shape of red blood cells, which are fewer in number and smaller in size (microcytic) than in individuals without alpha thalassemia. Red blood cells may also be pale in color (hypochromic) and of varying shapes. A blood sample can also be tested to measure the amount of iron in the blood, which can be elevated in certain individuals with alpha thalassemia.

Molecular genetic testing can confirm a diagnosis of alpha thalassemia. Molecular genetic testing can detect mutations in the *HBA1* and *HBA2* genes known to cause the disorder, but is available only as a diagnostic service through specialized laboratories.

Prenatal diagnosis in pregnancies with an increased risk of Hb Bart’s hydrops fetalis is possible by Doppler ultrasonography, a non-invasive procedure in which reflected sound waves are used to create an image of the developing fetus that allows physicians to see how blood flows through blood vessels. Specifically, this test is used to measure the rate of blood flow through the cerebral arteries of the fetus, which correlates strongly with anemia in the

fetus. In at-risk pregnancies, Hb Bart's hydrops fetalis can be diagnosed as early as the 13th to 14th week of gestation

Testing of immediate family members such as other children or an affected parent's siblings is recommended because, even in the absence of symptoms, these individuals may be carriers for alpha thalassemia silent carrier or alpha thalassemia minor.

Standard Therapies

Treatment
Alpha-thalassemia pregnancies are rising in North America and require prenatal counseling, overall community education, and well-developed intrauterine management plans. Individuals with alpha thalassemia, particular the intermediate or severe forms, will benefit from referral to a thalassemia treatment center. These specialized centers can provide comprehensive care for individuals with alpha thalassemia including the development of specific treatment plans, monitoring and follow up of affected individuals, and state-of-the-art medical care. Treatment at such a center ensures that individuals and their family members will be cared for by a professional healthcare team (physicians, nurses, physical therapists, social workers and genetic counselors) experienced in the treatment of individuals with alpha thalassemia. Genetic counseling will be of benefit for affected individuals and their families. Psychosocial support for the entire family is essential as well.

Specific therapeutic procedures and interventions may vary, depending upon numerous factors, such as the specific type of alpha thalassemia; the progression of the disease; the presence or absence of certain symptoms; severity of the disease upon diagnosis; an individual's age and general health; and/or other elements. Decisions concerning the use of particular drug regimens and/or other treatments should be made by physicians and other members of the health care team in careful consultation with the patient based upon the specifics of his or her case; a thorough discussion of the potential benefits and risks, including possible side effects and long-term effects; patient preference; and other appropriate factors.

Individuals with alpha thalassemia silent carrier and alpha thalassemia minor usually do not develop symptoms and do not require treatment. It is important that individuals with alpha thalassemia minor be correctly diagnosed, however, in order to avoid unnecessary treatments for similarly appearing conditions such as iron deficiency anemia.

Many individuals with HbH disease do not require treatment. Physicians may recommend folic acid and vitamin (minus iron) supplementation in some cases. Supplementation with folic acid, a B vitamin, may facilitate the production of red blood cells in certain individuals. Folic acid may be given at the same time as blood transfusions, and does not interfere with the effectiveness of medications that are given to lower iron levels. Vitamin supplementation is given because of the risk for vitamin D or calcium deficiency. Individuals with HbH disease should avoid oxidative medications, fava beans, and mothballs, all of which can contribute to the rapid, premature destruction of red blood cells (hemolytic crisis) and potentially an episode of acute, severe anemia. Affected individuals should also receive prompt treatment for infection, which can also trigger hemolytic crisis.

Some individuals with HbH disease may require blood transfusions. A blood transfusion is a common procedure in which affected individuals receive donated blood in order to restore the levels of healthy, functioning hemoglobin to their blood. During this procedure, donated blood is delivered to the body through a small, plastic tube inserted into a blood vessel (intravenously). The procedure may take anywhere from 1-4 hours. Individuals with HbH disease occasionally require blood transfusions such as when suffering from an illness or infection or when planning to undergo surgery. Repeated transfusions may be required, particularly during early infancy or later adulthood.

Less often, specific individuals with HbH disease require blood transfusions on a regular basis. Such individuals include those with severe anemia affecting the function of the heart or those with expansion of the bone marrow. The decision to undergo regular blood transfusions in HbH disease is difficult and is best made after close consultation with an experienced treatment team. Regular blood transfusions may contribute to the accumulation of excess iron in

the body (iron overload). Iron overload can result in excess amounts of iron accumulating in various tissues of the body and can potentially cause a variety of symptoms depending on the specific organ systems involved. Iron overload is treated by medications that remove excess iron from the body (chelation) such as deferoxamine. Deferoxamine is an iron chelator, a drug that binds to iron in the body allowing it to be dissolved in water and excreted from the body through the kidneys. Other oral iron chelators, such as deferiprone and deferasirox, are also been used to lower excess levels of iron.

The surgical removal of the spleen (splenectomy) may be recommended in certain cases of nondeletional HbH or HbH-Constant Spring, specifically in children with massive splenic enlargement (splenomegaly) or overactivity of the spleen (hypersplenism). An abnormally enlarged spleen can cause severe pain and contribute to anemia. Removal the spleen may be considered if other forms of therapy fail or cannot be tolerated. Splenectomy has led to improvement in certain cases. However, this surgical procedure carries risks such as blood clot formation within a vein (venous thrombosis), which are weighed against the benefits in each individual case. Because of advances in treatment in the past several years, splenectomy is performed less often for individuals with HbH disease.

Treatment of additional complications sometimes associated with alpha thalassemia or iron overload is symptomatic and supportive and often follows standard guidelines. For example, the repeated occurrence of gallstones may necessitate the surgical removal of the gall bladder (cholecystectomy). Special attention is recommended for the early diagnosis and prompt treatment of heart (cardiac) disease potentially associated with iron overload.

PREGNANCY
Women with HbH disease who are pregnant are at risk of complications such as preeclampsia, excessive bleeding just before childbirth (antepartum hemorrhage), congestive heart failure, miscarriage, and premature delivery. Preeclampsia is a condition characterized by high blood pressure and the presence of protein in the urine; it can be associated with swelling, vision changes, headaches, and sudden weight gain. Women with HbH disease require high-risk perinatal care.

Women who are carrying a fetus with Hb Bart’s hydrops fetalis are at risk for potentially serious complications during the pregnancy including abnormally low amniotic fluid levels (oligohydramnios), preeclampsia, excessive bleeding (hemorrhage), anemia, kidney failure, congestive heart failure, infections, tearing away of the placenta from the inner wall of the uterus (placental abruption), and premature labor. Women who are carrying a fetus with Hb Bart’s hydrops fetalis require high-risk perinatal care. Early therapeutic termination of such at-risk pregnancies may be discussed as an option because of the potentially serious complications to the mother and because of the severity of the syndrome.

Investigational Therapies

For many years, there were no effective treatments for Hb Bart’s hydrops fetalis. Most pregnancies resulted in stillbirth or in severely ill newborns who pass away shortly after birth. However, recent medical advances have allowed physicians to attempt to improve treatment of the disorder. Such treatment includes administering blood transfusions before birth to the developing fetus (intrauterine or “within the uterus”) and immediately after birth. In extremely rare cases, affected infants have survived the newborn period, but require regular blood transfusions and medication to prevent iron overload. These infants may be at an increased risk for other congenital complications.

Some developing fetuses have also been treated by hematopoietic stem cell transplantation (HSCT). Hematopoietic stem cells are special cells found in the bone marrow that manufacture different types of blood cells (e.g., red blood cells and platelets). During this type of transplant, an affected individual’s bone marrow cells are eradicated by chemotherapy or radiation and replaced with healthy marrow from a donor, usually from a closely matched family member such as a sibling. A hematopoietic stem cell transplant has the potential to correct the underlying abnormality that causes alpha thalassemia. Some researchers are studying the potential of intrauterine HSCT, which would take advantage of the unique fetal immune system, potentially allowing the fetus to become more tolerant of the transplant cells.

The advances in treating infants with Hb Bart's hydrops fetalis before and immediately following birth have resulted in ethical issues and questions for parents and physicians. It is extremely important that affected families receive counseling from experienced qualified professionals on the medical, psychological, economic and ethical issues they will face in dealing with a Hb Bart's hydrops fetalis pregnancy.

Gene therapy is being studied as another approach to therapy for individuals with HbH disease and Hb Bart's hydrops fetalis. In gene therapy, the defective gene present in a patient is replaced with a normal gene to enable the production of the active enzyme and prevent the development and progression of the disease in question. Given the permanent transfer of the normal gene, which can produce high levels of the missing alpha globin protein, this therapy can, theoretically, lead to a "cure." However, at this time, there remain some technical difficulties to resolve before gene therapy can be advocated as a viable alternative approach.

Information on current clinical trials is posted on the Internet at www.clinicaltrials.gov. All studies receiving U.S. government funding, and some supported by private industry, are posted on this government web site.

For information about clinical trials being conducted at the NIH Clinical Center in Bethesda, MD, contact the NIH Patient Recruitment Office:

Toll-free: (800) 411-1222
TTY: (866) 411-1010
Email: prpl@cc.nih.gov

For information about clinical trials sponsored by private sources, in the main, contact: www.centerwatch.com

For more information about clinical trials conducted in Europe, contact: https://www.clinicaltrialsregister.eu/

Supporting Organizations

- Cooley's Anemia Foundation, Inc.
  330 7th Ave
  Suite 900
  New York, NY 10001 USA
  Phone: (212) 279-8090
  Toll-free: (800) 522-7222
  Email: info@cooleysanemia.org
  Website: http://www.cooleysanemia.org

- March of Dimes
  1275 Mamaroneck Avenue
  White Plains, NY 10605
  Phone: (914) 997-4488
  Email: AskUs@marchofdimes.org or preguntas@nacersano.org
  Website: http://www.marchofdimes.org and nacersano.org

- NIH/National Heart, Lung and Blood Institute
  P.O. Box 30105
  Bethesda, MD 20892-0105
  Phone: (301) 592-8573
  Email: nhlbiinfo@rover.nhlbi.nih.gov
  Website: http://www.nhlbi.nih.gov/

- Thalassemia Support Foundation

PO Box 26398
Santa Ana, CA 92799
Email: tsf@helpthals.org
Website: http://www.helpthals.org

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