



**NEWBORN SCREENING
OFFICE OF HEALTH PROMOTION**
535 W. Jefferson St., 2nd Floor
Springfield, IL 62761
Phone: 217-785-8101
Fax: 217-557-5396

Hemoglobin H Disease (Alpha Thalassemia) Information for Physicians and Other Health Care Providers

Definition Hemoglobin H disease is an inherited hemoglobin disorder in which three of the four alpha globin genes normally present are deleted or have a mutation which impairs alpha globin chain production. This leads to an excess of beta globin chains, which are unstable, precipitate within the cell and lead to destruction of the red blood cells. Hemoglobin H is a thalassemia-like syndrome characterized by hemolysis as well as ineffective red cell production. Co-inheritance of HbH with other globin gene defects can affect the severity of the condition.

Clinical Symptoms Infants with hemoglobin H disease are normal at birth and generally remain so. Some children with HbH disease, however, will have poor growth. Signs of hemoglobin H disease include a moderate anemia in the range of 7-10 g/dL with marked microcytosis, jaundice and hepatosplenomegaly. Some may develop the facial and other skeletal deformities more commonly associated with beta-thalassemia. Others may experience gallstones and leg ulcers. Episodes of hemolysis may be brought on by drugs or infections. Co-inheritance of HbH with other globin defects can result in a more severe chronic anemia for which monthly transfusions are needed. Severe iron overload can occur over time with HbH disease, even in minimally or non-transfused patients.

Newborn Screening and Definitive Diagnosis In Illinois, newborn screening for Hemoglobin H disease is performed by high performance liquid chromatography (HPLC) testing to determine the amount of Bart's hemoglobin present. Samples with 25 percent or greater of Bart's hemoglobin (gamma tetramers) are considered suggestive of Hemoglobin H disease. HPLC has been shown to be effective for detecting hemoglobinopathies characterized by synthesis of an abnormal hemoglobin molecule immediately after birth. **All abnormal newborn screening test results indicating Hemoglobin H disease require appropriate confirmatory blood tests which may include testing of the parents. Referral to a pediatric hematologist for diagnosis within the first month of life is recommended and should not be delayed until the infant is older.** Transfusions may alter the newborn screening test results for Hemoglobin H disease. Neonates who are transfused after birth should have their newborn screening repeated post-transfusion in the time frame recommended by IDPH.

There are several recommended testing methods for diagnosis of hemoglobinopathies such as Hemoglobin H disease. **Hemoglobin electrophoresis including both cellulose acetate and citrate agars (one is not sufficient), isoelectric focusing and high performance liquid chromatography** are considered proven, reliable and accurate methods for defining an infant's hemoglobin phenotype. All siblings of an infant diagnosed with a Hemoglobin H disease should be tested. Genetic counseling services should be offered to parents.

Treatment Hemoglobin H disease has a wide spectrum of clinical severity in patients, therefore, early diagnosis is important so patients can be followed. Hemoglobin levels and the patient's growth and development should be regularly monitored. Complications related to chronic hemolysis also need to be assessed. Infections should be monitored closely so any severe drop in hemoglobin can be recognized and treated. Health care monitoring and maintenance with appropriate immunizations are important as well.

Incidence Hemoglobin H disease affects as many as one in 15,000 births in some U.S. states with ethnic populations similar to Illinois. The prevalence of HbH disease is highest in Laotian and Cambodian newborns, but is also seen in infants of Chinese, Vietnamese, Thai, Filipino and, to a lesser degree, Middle Eastern ancestry. The greatest incidences of heterozygotes (carriers) are found in African Blacks (one in 30 births) and Southeast Asians (one in 20 births). People of southern Chinese, Mediterranean, Asian Indian, and Middle Eastern ancestry are also commonly found to be carriers.

Inheritance Pattern The genes for alpha globin are on chromosome 16. There are two genes for alpha globin production on each chromosome. Some alpha globin deletions remove one gene (silent carrier state). Some alpha globin gene deletions remove both alpha globin genes (alpha thalassemia trait). The deletions can occur in both the *cis* and *trans* orientations. In the *trans* orientation one alpha globin gene is deleted on both chromosome 16s. The *cis* orientation is more common in Asians while the *trans* orientation is more common among people of African ancestry. Point mutations also may occur in the alpha thalassemia genes which reduce or stop alpha globin production as well.

Hemoglobin H disease is inherited in an autosomal recessive manner. Hemoglobin H disease results from mutations in three of the four alpha globin genes normally present. In hemoglobin H disease one parent carries one alpha globin gene mutation (deletion or point mutation), while the other parent carries a double deletion in the *cis* orientation. The parents are unaffected healthy carriers, although alpha thalassemia trait carriers may be anemic and microcytic on a CBC. With each pregnancy there is a 25 percent chance that a child will be born with Hemoglobin H disease. There is a 25 percent chance that a child will inherit one alpha globin gene mutation and a 25 percent chance a child will inherit the double alpha globin deletion. There is also a 25 percent chance the child will inherit two normal hemoglobin genes. These risks hold true for each pregnancy. Genetic counseling services are recommended for individuals who carry alpha thalassemia or have hemoglobin H disease.

Physiology Reduced production of alpha globin chains results in an accumulation of excess beta chains which aggregate to form nonfunctional hemoglobin H and a reduced amount of hemoglobin A. The reduced amount of hemoglobin A produces hypochromic, microcytic red blood cells. Additionally, the production of hemoglobin H creates red blood cells which are sensitive to oxidative stress and results in increased red blood cell destruction. Hemoglobin H disease is mainly a hemolytic disorder. Hemolysis can worsen with exposure to oxidant drugs, moth balls and infections.

Key Points for Parents Avoid overly alarming the child's parents if the diagnosis has not yet been confirmed. If the child needs additional testing or diagnostic evaluation, make certain the parents understand the importance of following the pediatrician's and/or specialist's recommendations for additional testing and referrals.

Follow-up After Confirmation of Diagnosis These guidelines should be followed after a diagnosis of Hemoglobin H disease has been confirmed:

1. Regular visits to a pediatric hematologist.
2. Parents should understand that Hemoglobin H disease is a lifelong illness which will require continued monitoring of hemoglobin level, growth and development.
3. Provide a list of support services such as the local health department, early intervention service providers, and the Comprehensive Thalassemia Program at Lurie Children's Hospital.
4. Genetic counseling services are recommended to help the parents understand the complexity surrounding the carrier state and inheritance of this disease.
5. Additional information about newborn screening can be found at:
 - Baby's First Test: <http://www.babysfirsttest.org/>
Health Resource and Service Administration (HRSA), Grant no. U36MC16509, Quality Assessment of the Newborn Screening System.
 - National Center for Biotechnology Information: <http://www.ncbi.nlm.nih.gov/gtr/>
National Center for Biotechnology Information, U.S. National Library of Medicine 8600 Rockville Pike, Bethesda MD, 20894 USA.