

Sickle Cell Beta Thalassemia Disease

Information for Physicians and Other Health Care Professionals

Definition Sickling hemoglobinopathies are inherited disorders that result in production of an abnormal form of hemoglobin. Beta thalassemias are inherited disorders that result in the decreased synthesis or complete absence of the beta globin chains of hemoglobin. Sickle cell beta thalassemia (Hb S/ β Th) is an inherited form of sickle cell disease that affects red blood cells both in the production of abnormal hemoglobin, as well as the decreased synthesis of beta globin chains. Individuals with sickle cell beta thalassemia have one abnormal beta chain, β^S , and a defective beta-globin gene, either in decreased synthesis, β^+ , or complete absence of synthesis, β^0 .

Clinical Symptoms The severity of the disease varies because the beta thalassemia gene may still produce a small amount of normal hemoglobin. If a small amount of normal hemoglobin, β^+ , is produced, an individual may have milder symptoms of sickle cell disease. However, if no normal hemoglobin, β^0 , is produced, an individual is almost clinically identical to sickle cell anemia.

Newborn infants are usually well. Hemolytic anemia and vaso-occlusive complications develop during infancy or early childhood.

Any sign of illness in an infant with sickling disease is a potential medical emergency. Acute and chronic tissue injury can occur when sickled cells cause vascular occlusion. Sickling diseases can cause severe pain anywhere in the body, but most often in the hands, arms, chest, legs and feet. Complications may include, but are not limited to, the following:

- **Sepsis** – The first sign of infection may be a fever of 101 F or greater. These children require immediate medical attention. Children with sickle cell diseases are susceptible to pneumococcal infections.
- **Acute chest syndrome** – A serious condition caused by infection and/or trapped sickled red blood cells in the lungs. Symptoms may include dyspnea, coughing and chest pain.
- **Hand-and-foot syndrome** – This painful swelling of the hands and feet is due to severe vascular occlusion.
- **Splenic sequestration crisis** – Early signs include pallor, enlarged spleen and pain in the abdomen due to accumulation of sickled cells within the spleen. This complication can result in circulatory collapse and shock, with sudden death, if not recognized and treated immediately.
- **Aplastic crisis** – The bone marrow temporarily stops producing red blood cells, resulting in severe anemia. The child may appear pale, tired and less active than usual.
- **Stroke** – Cerebral vascular occlusion due to sickled cells can affect even very young children. Any loss of consciousness or weakness in an extremity should be evaluated promptly.
- **Painful episodes** – The pain of sickling disorders is acute and can be quite severe; even very young children may require prescription medications for pain relief.

Newborn Screening and Definitive Diagnosis In Illinois, newborn screening for any sickle cell disease is performed by high performance liquid chromatography (HPLC) testing to determine the presence of abnormal hemoglobins (Hgb) in whole blood. Unaffected infants will have mostly fetal hemoglobin (Hgb F) and some adult hemoglobin (Hgb A). HPLC has been shown effective in detecting hemoglobinopathies characterized by synthesis of an abnormal hemoglobin molecule immediately after birth. A baby testing positive for sickle cell beta thalassemia will have higher than normal fetal hemoglobin Hgb F with Hgb S and little to no presence of adult hemoglobin (Hgb A). **All abnormal newborn screening test results indicating a sickle cell disorder require appropriate confirmatory blood tests, sometimes including testing of parents and siblings for actual diagnosis. Even small transfusions may cause false negative screening test results and any results indicating that the baby was transfused require repeat testing 90 days after the last transfusion. Referral to a pediatric hematologist for evaluation and diagnostic testing is recommended within the first month of life and should not be delayed until the infant is older.**

There are several recommended testing methods for diagnosis of hemoglobinopathies and thalassemias: **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 infants diagnosed with a hemoglobinopathy or thalassemia should be tested; genetic counseling services should be offered to parents.

Treatment The National Institutes of Health clinical guidelines for management of sickle cell diseases state, **"Penicillin prophylaxis should begin by 2 months of age for infants with suspected sickle cell anemia, whether or not the**

definitive diagnosis has been established.” Antibiotic therapy should continue until at least 5 years of age. Normal dosage for an infant is 125 mg of penicillin twice a day until 3 years of age, when dosage is increased to 250 mg twice a day. An alternative antibiotic is available for children who are allergic to penicillin therapy. Prescription pain medication also may be indicated during sickling crises. Health care monitoring and maintenance with appropriate immunizations is imperative to the health of the baby, and pneumococcal conjugate vaccine immunizations also are recommended, beginning at 2 months of age. Chronic blood transfusion therapy, followed by chelation therapy later in life to remove excess iron, may be necessary in severe cases.

Incidence Combined sickle cell beta thalassemia disease is the most common form of sickle cell disease in people of Mediterranean descent, including people of Italian, Greek or Turkish heritage. This is because beta thalassemia is fairly common in the Mediterranean region, and people with the sickle cell gene inhabit some parts of these regions. Illinois started universal newborn screening for sickle cell diseases in 1989; each year approximately 100 infants are diagnosed with a form of sickle cell disease.

Inheritance Patterns Sickle cell beta thalassemia is inherited in an autosomal recessive pattern. Sickle cell beta thalassemia occurs when one abnormal gene for the production of hemoglobin S is inherited from one parent and one abnormal gene for the production of beta thalassemia is inherited from the other parent. The genes for both hemoglobin and beta thalassemia are both located on chromosome 11. There is one gene for each on each chromosome 11, for a total of two. In hemoglobin S carriers, only one hemoglobin gene is abnormal. In beta thalassemia carriers, only one beta globin chain gene is abnormal. In sickle cell beta thalassemia disease, an individual has one abnormal hemoglobin gene and one abnormal beta thalassemia gene.

As an autosomal recessive disorder, the parents of a child with a sickle cell beta thalassemia disease are usually unaffected, healthy carriers of one of the conditions; having one normal gene and one abnormal gene for either sickle cell trait or beta thalassemia. Beta thalassemia carriers have a 50/50 chance to pass on the abnormal gene to their children. Sickle cell trait carriers have a 50/50 chance to pass on the abnormal gene to their children. A child of two carriers has a 25 percent chance of receiving two abnormal genes and developing the disease, and a 50 percent chance of being an unaffected carrier of either of the abnormal genes; either carrying the abnormal hemoglobin S gene only, or carrying the abnormal beta thalassemia gene only. There is also a 25 percent chance a child would receive two normal genes and is therefore unaffected and is not a carrier for either condition. These risks hold true for each and every pregnancy between a sickle cell carrier and a beta thalassemia carrier.

Genetic counseling services are recommended for individuals with sickle cell beta thalassemia and for those who carry either of the abnormal genes (sickle cell carrier or beta thalassemia carrier), particularly concerning future pregnancies. These individuals may have questions about the disorders that are best answered by hematology specialists and genetic counselors.

Physiology Normal blood contains mostly hemoglobin A. Hemoglobin A is comprised of equal quantities of alpha-globin chains and beta-globin chains of hemoglobin. Hemoglobin A requires these globin chains in equal proportions to function and transport oxygen properly.

While beta thalassemia is caused by a defect in the beta-globin gene, controlling the production of the beta-globin chains of hemoglobin, sickle cell disease is caused by a defect in hemoglobin itself with the presence of abnormal hemoglobin S. In a person affected with sickle cell beta thalassemia, some of the red blood cells sickle in shape, subsequently hemolyzing resulting in anemia, which is a hallmark of sickling diseases. And because of the reduced production of beta-globin chains prevents the development of normal red blood cells, the production of both quantity and quality of red blood cells is affected. As a result, the sickled cells do not live as long as normal red blood cells, tend to get stuck in blood vessels and block flow of blood to certain parts of the body. These consequences can lead to poor growth, impaired physical activity, bone deformities, fragile bones and enlargement of the liver and spleen.

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. If results indicate the presence of sickle cell beta thalassemia disease, make certain the parents understand the importance of following the pediatrician's and/or pediatric hematologist's recommendations for additional testing and referrals.

Follow-up After Confirmation of Diagnosis These guidelines should be followed after a diagnosis of sickle cell beta thalassemia disease has been confirmed:

1. Regular visits to a comprehensive sickle cell program or a pediatric hematologist and strict compliance in antibiotic administration are crucial to the health and future well-being of the baby. Parents should understand the importance of twice-daily doses of prophylactic penicillin as an effective measure to reduce both morbidity and mortality from pneumococcal infections in infants with sickle cell beta thalassemia disease.
2. Parents of infants with sickle cell beta thalassemia disease should be instructed in all aspects of routine child care. They should be able to accurately check the infant's temperature. They must be able to recognize early symptoms of complications, including the warning signs of inactivity, fever, pallor and respiratory distress. Parents should be taught to palpate the infant's spleen and to recognize splenic enlargement. Parents must understand the importance of prompt assessment of the infant by a pediatric hematologist when fever, pallor, unexplained irritability, diarrhea, vomiting or other signs of illness are present. Fever of 101 F or greater requires immediate medical evaluation.
3. Provide a list of support services available in the community, such as the local health department and early intervention services. **The Sickle Cell Disease Association of Illinois offers family support and educational services to the families of children and adults with sickle cell diseases. The association may be contacted at 312-345-1100.**

For more information about newborn screening in general and about sickle cell diseases specifically, contact the National Newborn Screening and Genetics Resource Center, 1912 W. Anderson Lane, Suite 210, Austin, TX 78757; telephone 512-454-6419; fax 512-454-6509; website <<http://genes-r-us.uthscsa.edu>>. Other resources include: <<http://www.genetests.org>> and Online Mendelian Inheritance in Man <<http://www.ncbi.nlm.nih.gov/omim/>>.