

**The New Jersey Department of Health and Senior Services
Newborn Screening and Genetic Services**

Sickle Cell Disorders

Information for Health Professionals

Description

In general, sickle cell disease is a term that describes a group of genetic disorders characterized by the predominance of HbS. The three most common are HbSS disease, the combination of HbS with another beta chain variant, Hb C (Hb SC), and sickle beta thalassemia (HbS B⁺thal and HbS B⁰thal). Infants with one abnormal beta chain gene are said to have a hemoglobin trait and are carriers for the disease; under most circumstances, they have no symptoms of the disease. Infants with two abnormal beta chain genes have disease.

The two cardinal pathophysiologic features of sickle cell disorders are chronic hemolytic anemia and vasocclusion (which results in ischemic tissue injury). The organs at greatest risk for injury are those with venous sinuses where blood flow is slow and oxygen tension and pH are low (spleen and bone marrow), or those with a limited terminal arterial blood supply (eye, head of the femur and humerus). The lungs, which receive deoxygenated sickle cells that escape from the spleen or bone marrow, may be at special risk for vasocclusion and infarction. No tissue or organ is spared from hypoxic injury, which may manifest as acute (e.g. painful events, acute chest syndrome) or insidious in onset (e.g. aseptic necrosis of the hips, sickle cell retinopathy). Acute and chronic tissue injury may ultimately result in failure of organs (for example, the kidney), particularly as the patient ages. Sickle cell disease affects growth; by about four years of age, height and weight growth rates are slowed.

Sickle Cell Anemia (HbSS) is the most clinically significant abnormal hemoglobin condition. It results when the gene for sickle hemoglobin is inherited from both parents. The predominant hemoglobin is Hemoglobin S (HbS). The infant appears normal at birth; however anemia develops in the first few months. The anemia is usually moderate to severe. Sickled cells trapped in the spleen can cause it to enlarge. Other complications include pain crises, splenic sequestration and sepsis. Organ damage may result in chronic morbidity such as pulmonary hypertension.

Sickle C Disease (HbSC disease) results when a gene for sickle hemoglobin S is inherited from one parent and a gene for hemoglobin C is inherited from the other. Painful episodes and vaso-occlusive problems are usually less severe in this condition than those associated with HbSS. Most affected children have persistent splenomegaly and aseptic necrosis occurs more frequently than in those with HbSS. Septicemia may occur. Retinal vascular changes, predominately in adolescents and adults, may lead to hemorrhage with retinal detachment. The hemoglobin concentration averages 9-10 g/dL, with the blood smear showing target cells and characteristic spindle-shaped red blood cells.

Hemoglobin C (HbC disease) is typically benign, producing a mild hemolytic anemia and splenomegaly. Sickling does not occur.

HbS in combination with other abnormal hemoglobins produces sickling disorders of varying degrees of severity. Several of these, including HbSD Los Angeles and HbSO Arab, present a clinical picture that is extremely difficult to distinguish from that of HbSS.

HbS in combination with thalassemia occurs when a person inherits a gene for HbS and a beta thalassemia gene; they interact to produce sickle cell disease called Sickle Beta Thalassemia. There are two forms of this disorder:

1. Sickle B⁺ thalassemia (HbS B⁺thal)
2. Sickle B⁰ thalassemia (HbS B⁰thal)

HbS B⁺thal can easily be differentiated from sickle cell anemia because of the presence of varying amounts of HbA. Differentiation of HbS B⁰thal from sickle cell anemia is more difficult and may require family studies, DNA analysis, or may be delayed until two years of age. Most individuals with HbS B⁺thal have preservation of splenic function and have fewer problems with infection, fewer pain episodes, and less end-organ damage. Their hemoglobin levels may be higher on average; splenic function is lost later in childhood, and splenomegaly is common into adulthood.

Patients with HbS B⁰thal may have very severe disease, which is almost identical to homozygous sickle cell anemia; in HbS B⁰thal, no HbA is made, so hemoglobin electrophoresis shows HbSF. The MCV is lower than in sickle cell anemia. Pain episodes, end-organ damage and prognosis may be similar to HbSS disease. Bone and retinal disease may even be worse when compared to homozygous sickle cell disease.

Incidence

Sickle cell disease affects an estimated 50,000 Americans and affects persons of many racial and ethnic backgrounds. Among infants born in the U.S., sickle cell disease occurs in 1 in every 375 African Americans, 1 in 3,000 Native Americans, 1 in 20,000 Hispanics, and 1 in every 60,000 Caucasians. Approximately 2 million Americans are heterozygous for hemoglobin S and hemoglobin A (normal adult hemoglobin). This carrier state, sickle cell trait (HbAS) is present in 8-10% of the African American population. Parents who are both carriers have a 25% probability with each pregnancy of having a child with sickle cell disease.

Clinical Features

Clinical presentations of sickle cell anemia include hematologic, infectious and vasocclusive crises.

Hematologic crises The anemia of sickle cell disease is due to the fact that, while normal red blood cells live about 120 days in the bloodstream, sickled cells have a life span of about 10 to 20 days. Because they cannot be replaced fast enough, the blood is chronically short of red blood cells. The infant appears normal at birth. Anemia develops in the first few months of life as production of fetal hemoglobin decreases and production of HbS increases. In the beginning, the anemia is usually mild, needing no treatment. As the infant gets older, transient aplastic crisis can occur. Because the life span of RBCs is greatly reduced in sickle cell disease, temporary suppression of erythropoiesis can result in severe anemia. Such transient aplastic crisis is typically preceded by, or associated with a febrile illness. Another result of the chronic hemolysis is a high prevalence of gallstones.

Infectious crises Infectious crises are due to the fact that infants and children with sickle cell anemia are particularly susceptible to infection due to *Streptococcus pneumoniae*, *Haemophilus influenzae type b*, *Mycoplasma pneumoniae*, *Staphylococcus aureus*, *E. coli*, and *Salmonella* species. Infection may manifest as pneumonia, meningitis, osteomyelitis, septicemia or other infections.

Vasocclusive crises Vasocclusion occurs when sickled RBCs obstruct the microcirculation, causing ischemia and resulting in pain. Vasocclusion is responsible for a wide variety of clinical complications of sickle cell disease, affecting bones (avascular necrosis of the head of the femur) joints and soft tissue (hand and foot syndrome), abdominal organs such as the spleen (enlargement and sequestration), the eyes (retinopathy), the kidneys (nephropathy), circulation to the extremities (leg

ulcers, the brain (stroke), the lungs (acute chest syndrome), and the heart (myocardial dysfunction secondary to hypoxia and RVH lung disease).

Complications of sickle cell disease include, but are not limited to sepsis, acute chest syndrome, splenic sequestration crisis, aplastic crisis, stroke, hand and foot syndrome, and painful episodes. **Any sign of illness in an infant with sickle cell disease is a potential medical emergency.**

Screening

Laboratory testing should detect most abnormal hemoglobin subtypes, even if the specimen is collected before 24 hours of age, unless the infant has had an exchange transfusion. Blood transfusions may cause false negative results. Newborn screening specimens should always be obtained prior to transfusing; however, if the infant has been transfused prior to the initial screening, a re-screen should be done 120 days after the transfusion.

Screening is performed by isoelectric focusing (IEF) of a hemolysate prepared from a dried blood spot. Hemoglobin “bands” are identified by a migration in the electrophoretic field. **Solubility tests (such as Sickledex) and the sickle cell preparation (with sodium metabisulfite) are often negative in the newborn period owing to presence of a high concentration of fetal hemoglobin (HbF), and cannot be used to confirm the presence of HbS in newborns and infants.**

Confirmatory Testing

The screening test is not diagnostic; confirmatory testing is by high-pressure liquid chromatography (HPLC).

Management

Consultation with a pediatric hematologist is essential to making a definitive diagnosis and should occur by 2 months of age. Follow-up in a pediatric sickle cell comprehensive care center is mandatory for patients with confirmed hemoglobinopathies.

Education about sickle cell disease should occur early on and should include all the infant’s caretakers. Caretakers should be taught the importance of maintaining good hydration, avoiding high altitudes and extreme hot or cold environments, and getting the child assessed by a healthcare provider at the first sign of impending illness. Prompt medical evaluation for fever and signs or symptoms of sepsis, splenic sequestration, aplastic crisis, stroke, hand and foot syndrome, acute chest syndrome, and painful episodes cannot be underestimated.

Prevention of infection as well as early treatment of minor infections is the best defense against serious infections such as septicemia, meningitis, pneumonia, and osteomyelitis. Antibiotic therapy for infection can be lifesaving. Infants with initial screening results suggesting sickle cell anemia should be started on oral penicillin prophylaxis while the phenotype is being confirmed. (This should be initiated by 2 months of age). Scientific studies have shown that prophylactic oral penicillin started early and maintained throughout childhood decreases the number of episodes of infection and deaths from infection. In addition to routine childhood immunizations, infants with sickle cell disease should receive:

- Pevnar at 2, 4, and 6 and 12-15 months of age.
- Pneumovax at 2 years of age.
- Hib Immunization beginning at 2 months of age
- polyvalent pneumococcal vaccine at age 2 years.
- hepatitis B virus immunization.

Emergency Management - Please see “Sickle Cell Emergency Management Guidelines”

Implications for Genetic Counseling

The most common abnormal phenotype identified through newborn screening is FAS which is presumably positive for sickle trait. Parents of infants with sickle cell trait have a chance of having an infant with sickle cell disease if both parents carry the gene for sickle hemoglobin. Further testing of both parents combined with genetic counseling can apprise parents of their chances of producing children affected with clinically significant disease.

Interpretations/Recommendations related to hemoglobin types that are reported for newborns

(The Hb pattern is always reported with the highest concentration first and the lowest concentration last)

Hb	Significance	Recommended Action(s)
FA	A: Normal adult Hb; F: Fetal Hb FA: Normal expected pattern for newborn	None. Please note that a normal newborn screen does not rule out B-thalassemia (thal) trait or certain types of B-thal major (B+/B ₀ or B+/B+)
FS	HbF and S; no A. Significant sickle cell genotype such as SS, S-β ₀ thal, S(γβ) ₀ thal; SS-αthal; rarely S-HPFH (Hereditary Persistence of Fetal Hb), which is benign	Referral to pediatric hematologist; repeat screen (filter) by 1 month of age; penicillin prophylaxis by 2 months of age. Penicillin mandatory if FS confirmed (unless HPFH); recommended prior to confirmation of FS
FSC	Hb F, S, and C; no A. Significant sickle cell disease; HbSC disease; milder than SS and S-β ₀ thal	Referral to pediatric hematologist; repeat screen (filter) by 1 month of age; ; penicillin prophylaxis by 2 months of age usually recommended for Hb SC disease
FS/β ₀ thal	Hb F and S; small amount of A (FSA); compatible with S-β ₀ thal, a significant, but least severe type of sickle cell disease	Referral to pediatric hematologist; repeat screen (filter) by 1 month of age; penicillin prophylaxis by 2 months of age usually recommended
FC	Hb F and C; no A. Compatible with homozygous Hb C (CC) or C-β ₀ thal. In childhood, CC causes mild anemia, low MCV, ± splenomegaly; C-β ₀ thal can cause moderately severe anemia, low MCV, and splenomegaly	Referral to pediatric hematologist; repeat screen (filter) by 1 month of age
F	HbF, no A. May be compatible with thal major (β ₀ /β ₀), homozygous HPFH, or delayed appearance of HbA	Referral to pediatric hematologist; repeat screen (filter) by 1 month of age
A or AF	HbA>F suggestive of RBC transfusion (Tx)	Repeat screen (filter) 4 months after last Tx
FAV	HbF and A with a variant Hb (V); may have clinical significance in childhood	Referral to pediatric hematologist suggested for anemia and/or persistence of variant Hb and identification desired; repeat screen (filter) by 6 months of age
FV	Hb F and a variant (V); no A; clinical significance more likely due to absence of HbA	Referral to pediatric hematologist; repeat screen (filter) by 1 month of age
BARTS	Fast moving Hb suggestive of α-thal trait or Hb H disease	Consultation with pediatric hematologist recommended
FAST MOVING Hb	Same as above or can be associated with another Hb disorder	Consultation with pediatric hematologist recommended

FE/A2	HbF and E and/or A2; no A; consistent with either homozygous Hb E (EE); mild anemia with low MCV or E-β0 thalassemia; moderately severe thalassemia syndrome that can be transfusion dependent	Referral to pediatric hematologist; repeat screen (filter) by 1 month of age
FD	Hb F and D; no A; consistent with either homozygous Hb D (DD); no anemia or D-β0 thalassemia; mild to moderate anemia, low MCV	Referral to pediatric hematologist recommended; repeat screen (filter) by one month of age; Hb D migrates to the same position as Hb S on cellulose acetate, pH 8.6, so Hb DD can be mistaken for SS if repeat electrophoresis done at a routine lab
FAE	Hb F, A and E; consistent with Hb E trait; no anemia, low MCV	Repeat screen (filter) by 6 months of age
FAD	Hb F, A and D; consistent with Hb D trait; no hematologic abnormalities	Repeat screen (filter) by 6 months of age
FAG	Hb F, A and G; consistent with Hb G trait; no hematologic abnormalities	Repeat screen (filter) by 6 months of age. Electrophoretic mobility same as Hb S on cellulose acetate; occasional misdiagnosis of sickle trait

It should be noted that the above Hb variants are those listed on the IEM laboratory information sheets for newborn screened in the state of NJ. Not included on the information sheets are some variants that can cause significant sickle cell syndromes, such as HbSD and Hb S-O Arab, and other variants such as Hb SE that can cause significant hemolysis. However these variants will result in an abnormal screen, which requires evaluation by a pediatric hematologist. The IEM screening laboratory will also perform IEF and HPLC on all family members of a newborn identified with an abnormal Hb screen for a fee of \$15 for the entire family.

References

Travis, Susan F. ". " Sickle Cell Newsletter December 2000, No 1 ed.: .

Travis, Susan F.. "Diagnosis of Sickle Cell Anemia and Other Hemoglobinopathies." Sickle Cell Newsletter September 2001, No. 2 ed.: .

Additional Information:

EMedicine

<http://www.emedicine.com/EMERG/topic26.htm>

The March of Dimes

http://www.marchofdimes.com/professionals/681_1221.asp

The Information Center for Sickle Cell and Thalassemic Disorders

<http://.sickle.bwh.harvard.edu/hemoglobinopathy.html>

For questions contact:

Newborn Screening and Genetic Services at (609) 292-1582

The Inborn Errors of Metabolism Laboratory at (609) 292-3090

March 2005