Sickle Cell Disease

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Key Points

- Sickle cell disease is an autosomal recessive condition caused by inherited mutations in the gene encoding the hemoglobin beta chain.
- Newborn screening programs in all states identify infants with sickle cell disease, so that antibiotic prophylaxis can be initiated as soon after birth as possible to prevent life-threatening infections.
- The clinical manifestations of sickle cell disease can be severe, and social and cultural barriers may affect patient management.

Learning Objectives

Participants will be able to:

- Explain the hemoglobin abnormality in sickle cell disease and how it is inherited;
- Identify medical complications associated with sickle cell disease;
- Describe barriers that may be encountered in the management of the patient with sickle cell disease.

Family History Issues

Sickle cell disease usually occurs in the absence of a family history of the disease. It is an autosomal recessive condition, meaning that both parents of an affected individual are carriers of a mutation for sickle cell disease. Such mutations can be transmitted from generation to generation with no affected individuals in the family. However, if two carriers have a child and the child inherits the sickle cell disease mutation from each parent, the child will have sickle cell disease.

Red Flags 

The diagnosis of sickle cell disease is suspected in infants or young children with painful swelling of the hands and feet ("hand-foot syndrome"), pallor,

jaundice, pneumococcal sepsis or meningitis, severe anemia with an enlarged spleen, or acute chest syndrome.

Case 34. Sickle Cell Disease Identified in Newborn Screening

Mr. and Mrs. H are called into their pediatrician's office to discuss the results of newborn screening tests on their one-week-old son. They have been notified that he has sickle cell disease. Mrs. H is distressed and wants to know how this could have happened, as there is no history of sickle cell disease in either her family or her husband's family. She is worried about her son's health.

Clinical Care Issues

Detection of sickle cell disease by newborn screening. Newborn screening programs identify infants with sickle cell disease and other hemoglobin abnormalities in every state in the U.S. (South Dakota and New Hampshire screen only selected populations or by request). The test for hemoglobinopathies is typically performed using isoelectric focusing on the newborn screening dried blood spot, to identify the abnormal hemoglobin that causes sickle cell disease. When an infant is identified to have sickle cell disease, treatment with prophylactic antibiotics can begin immediately to prevent potentially life-threatening pneumococcal infections.

Sickle cell disease. In most cases of sickle cell disease, the affected individual has two copies of hemoglobin S (S), an abnormal type of hemoglobin. In some cases, an individual has one copy of hemoglobin S and one copy of another abnormal hemoglobin, such as hemoglobin C (C). Under conditions of low oxygenation, red blood cells containing hemoglobin S become sickle shaped (crescent shaped) and cluster together, occluding blood vessels. Recurrent and widespread vascular occlusions lead to painful crises and injury to virtually every organ of the body, most significantly the spleen, brain, lungs, and kidneys. Damage to the spleen impairs immune function, making both children and adults more vulnerable to infections with encapsulated organisms such as pneumococcus. Treatment includes antibiotics to prevent and treat infection; supportive care, including pain medication and fluids during pain crises; blood transfusions; and management of specific complications. Bone marrow transplant has been

used successfully in cases of severe sickle cell disease, when an HLA-matched donor is available. The average life expectancy of an individual with sickle cell disease in the US has improved, with affected individuals living to their mid-40s (see *GeneReview*: Sickle Cell Disease).

Risk Assessment

The child who is newly diagnosed with sickle cell disease is at risk for pneumococcal infections, and faces the range of other clinical complications occurring with the disease. Appropriate clinical management includes antibiotic prophylaxis, routine monitoring, and rapid evaluation of pain, infection, and other clinical symptoms.

Genetic Counseling and Testing

When a child is diagnosed with sickle cell disease, both parents must be carriers and are therefore at risk of having additional affected children. Other family members may also be carriers. Genetic counseling provides an opportunity to discuss inheritance, recurrence risk, and genetic testing.

Explanation of autosomal recessive inheritance. If Mr. and Mrs. H seek more information about the genetics of sickle cell disease, they can be referred for genetic counseling. Such counseling may be particularly important if the couple is considering having more children and would like information regarding the availability of prenatal testing in future pregnancies.

A genetic counselor will explain to Mr. and Mrs. H that sickle cell disease is an autosomal recessive condition, caused by inheriting a mutation in the hemoglobin gene from each parent. When parents who are both carriers of a sickle cell disease mutation have children, the risk of having a child with sickle cell disease is 25% with each pregnancy. If desired, prenatal testing can determine whether the fetus has sickle cell disease.

Testing. Testing for sickle cell disease, or for sickle cell carriers, can be performed by hemoglobin electrophoresis, which will determine the presence of hemoglobin S and other abnormal types of hemoglobin. Prenatal diagnosis of sickle cell disease utilizes DNA-based testing to identify specific mutations in the hemoglobin gene associated with sickle cell disease.

Different forms of sickle cell disease. The three most common forms of sickle cell disease are referred to as S/S (the child inherits two hemoglobin S

mutations), S/C (the child inherits one hemoglobin S mutation and one mutation for another abnormal type of hemoglobin called "C"), and S/beta-thalassemia. In S/beta-thalassemia, the child inherits one hemoglobin S mutation and a mutation that results in reduced or absent production of beta hemoglobin, either a beta^0-thalassemia mutation (resulting in complete absence of hemoglobin beta chains) or a beta$^+$-thalassemia mutation (resulting in reduced production of hemoglobin beta chains). The combination of hemoglobin S and either hemoglobin C, beta^0-thalassemia or beta$^+$-thalassemia results in a clinical outcome that is similar to sickle cell disease, although S/C disease and S/beta$^+$-thalassemia lead to less severe manifestations than S/S or S/beta^0-thalassemia.

Sickle cell carriers. Family members of Mr. and Mrs. H have an increased risk of being carriers. The siblings of Mr. and Mrs. H have a 50% risk of being carriers of sickle cell disease. Family members of reproductive age can be offered hemoglobin electrophoresis testing to determine their carrier status.

Carriers of sickle cell disease are sometimes referred to as having sickle cell "trait." Most carriers experience no health effects, and the available evidence indicates that the carrier state does not affect life expectancy. Among African Americans, the carrier rate is between 7% and 10%, leading to a sickle cell disease prevalence of approximately 1/500 births. Sickle cell disease also occurs with varying frequency among people whose ancestors come from Mediterranean countries (such as Greece, Turkey, and Italy), the Arabian peninsula, India, and some regions of Central and South America. In a California newborn screening study, the carrier rate for hemoglobin S was one in 14 in African Americans, one in 176 in Native Americans, one in 183 in Hispanics, one in 360 in Middle Eastern groups, one in 625 in whites not of Middle Eastern origin, and one in 1336 in Asians [Lorey et al 1996].

Interventions

Preventive care. Infants with sickle cell disease have an increased risk for pneumococcal infections and sepsis. Prophylaxis with penicillin and vaccination can help prevent this complication. Routine well-child care focused on the needs of a child with sickle cell disease is also important. If available, referral to a clinic providing services for children with sickle cell disease may provide the family an opportunity to learn more about medical management and community resources.

The use of hydroxyurea, an anti-tumor drug, has shown promising results on

some adults with sickle cell disease by reducing the frequency of severe pain, acute chest syndrome, and the need for blood transfusions. Hydroxyurea induces the formation of fetal hemoglobin (hemoglobin F) — a hemoglobin normally found in the fetus or newborn — which, when present in older individuals with sickle cell disease, prevents sickling.

Other clinical management. Treatment of painful crises relies on analgesic medication and oral and intravenous fluids to maintain intravascular volume and prevent complications from small vessel occlusion. Blood transfusions are used to treat anemia as well as complications of the disease such as spleen enlargement and strokes. Patients who experience multiple or severe episodes of splenic sequestration may require splenectomy.

Bone marrow transplant has been used for some patients with severe disease, when an HLA-matched donor is available. More details of care are outlined in the *GeneReview*: Sickle Cell Disease; comprehensive guidelines are available from NHLBI: The Management of Sickle Cell Disease.

Ethical/Legal/Social/Cultural Issues

The parents in this case are coping with their newborn son's diagnosis of sickle cell disease, and beginning to learn about the potential clinical complications and shortened life span. Some social and cultural concerns may include:

- **Adjusting to the diagnosis.** It is always difficult for parents to absorb information about serious health problems in their newborn. A sickle cell disease clinic or a community-based sickle cell disease organization provides access to expert medical professionals as well as other affected individuals and their families. Even if such a clinic is not available, interaction with other affected families can help the couple to learn about the diagnosis and may best address the family's worry over their son's condition. Parents may also benefit from counseling to help them to address their feelings related to having a child with an inherited condition.
- **Sharing information with relatives.** Other family members could be carriers of sickle cell disease, including the siblings of Mr. and Mrs. H. The couple should be encouraged to tell their relatives about the hereditary basis of sickle cell disease. Some relatives, especially those of reproductive age, may wish to have testing to determine if they are

carriers. However, sharing information about genetic risk may be difficult for some families, because of concerns about stigma within the family.

- **Barriers to care.** Several barriers may impede the management of patients with sickle cell disease. Historically, racial discrimination has been a prominent feature of the US healthcare system [Reynolds 2004], and perhaps because of this history, African Americans are less likely than white Americans to trust their health care provider [Boulware et al 2003]. In addition, African Americans are more likely to face cultural and economic barriers in accessing health care [Smedley et al 2002].

  For patients with sickle cell disease, the variability and unpredictability of pain may create an additional barrier to adequate health care. Pain from sickle cell disease is difficult to characterize and is often under-treated [Smith et al 2005, Bonham 2001]. Patients may be seen by health care providers as seeking excessive narcotic pain medications, potentially leading to adversarial relationships and mistrust.

  Understanding these barriers may help clinicians provide high-quality care to patients with sickle cell disease. A family-centered care approach, which seeks to ensure active involvement of the family in education and decision-making processes, may also help to create a supportive health care environment for the patient.

Resources

- **Sickle Cell Disease Association of America, Inc**
  200 Corporate Pointe, #495
  Culver City, CA 90230-8727
  Phone: 310-216-6363; 1-800-421-8453
  Fax: 310-215-3722
  Email: scdaa@sicklecelldisease.org

- **American Sickle Cell Anemia Association**
  10300 Carnegie Avenue
  Cleveland Clinic
  Cleveland, OH 44106

Phone: 216-229-8600
Fax: 216-229-4500
Email: irabragg@ascaa.org

- **NHLBI: The Management of Sickle Cell Disease**
- **Medline Plus: Sickle Cell Anemia**
- **National Library of Medicine Genetics Home Reference**
  Sickle cell disease
- **GeneTests Online Medical Genetics Information Resource**
- ***GeneReview*: Sickle Cell Disease**

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