Sickle Cell Carrier

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Key Points

- Carriers for sickle cell disease are individuals who have inherited one normal hemoglobin beta chain (A) and one sickle hemoglobin beta chain (S), described as hemoglobin A/S.
- Carriers for sickle cell disease are typically asymptomatic except under extreme physical conditions.
- In the past, the benign nature of the sickle cell carrier state was not understood. As a consequence, some sickle cell carriers suffered discrimination in access to employment and insurance because of assumptions that they were at increased risk for health problems.

Learning Objectives

Participants will be able to:

- Identify the medical complications that can occur on rare occasion in individuals who are carriers for sickle cell disease;
- Suggest testing options for an individual who is a sickle cell carrier and who is concerned about future offspring;
- Define the term "compound heterozygote."

Family History Issues

The relatives of an individual who has sickle cell disease are at increased risk of being carriers for sickle cell diseases. The parents and offspring have a 100% risk; healthy siblings (who do not have sickle cell disease) have a two-thirds risk. More distant family members may also be carriers for sickle cell disease.

Red Flags 

Individuals of African American ancestry have an 8-10% chance of being carriers for sickle cell disease and may wish to have testing for reproductive

counseling. Sickle cell disease also occurs among people whose ancestors come from Mediterranean countries, the Arabian peninsula, India, and some regions of Central and South America.

Case 35. A Mother Finds out that She and her Son are Sickle Cell Carriers

Mrs. G is a 35-year-old African American who is on maternity leave from her job as an interior designer. Her son was born three months ago. Both mother and baby are in excellent health. However, last month Mrs. G received a letter from the state newborn screening program, notifying her that preliminary testing indicated that her son may be a sickle cell disease carrier. Follow-up testing confirmed that her son has one copy of hemoglobin S, and is therefore a sickle cell carrier. Mrs. G was tested at the same time and is also a sickle cell carrier.

She is worried about the results and whether they pose a threat to her health or her son's health. She has also been told by her uncle not to tell her boss that she is a sickle cell disease carrier because she might be treated differently at work. She has made an appointment with her primary care physician to discuss her results.

Clinical Care Issues

Sickle cell carriers are individuals with one normal gene for beta hemoglobin (A) and one abnormal gene for beta hemoglobin (S), leading to the genotype A/S. Approximately 8-10% of African Americans are sickle cell carriers. The sickle cell carrier state also has an increased prevalence 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].

The sickle cell carrier state is different from sickle cell disease (S/S), in which two abnormal genes are present. In sickle cell disease, red blood cells become sickle-shaped (crescent shaped) and cluster together under low

oxygenation, occluding blood vessels. The condition causes chronic anemia. 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.

In contrast, sickle cell carriers are not anemic and have normal red cell indices. In general, the sickle cell carrier state is a benign condition that does not affect the health or longevity of the individual. However, individuals with sickle cell trait are at a slightly increased risk for a few specific medical problems.

- Painless hematuria occurs in 1-4% of individuals with sickle cell trait. This is usually not a significant problem.
- Pregnant women with sickle cell trait have an increased incidence of urinary tract infection.
- Although it is suspected that the risk for exercise-induced rhabdomyolysis (skeletal muscle breakdown) is increased in individuals with sickle cell trait, no direct causal evidence has been shown.
- Severe complications such as splenic infarction, pain episodes, and sudden death have been described as a result of extreme physical exercise, particularly at high altitudes or under heat stress. Such events are believed to be exceedingly rare, but may be of particular concern to athletes or in military basic training [Kark et al 1987, Eckart et al 2004].

Risk Assessment

Mr. and Mrs. G's risk of having children affected with sickle cell disease is dependent on Mr. G's testing results.

- If Mr. G is also a sickle cell carrier, they will have a 25% chance of having a child with sickle cell disease (S/S) with each pregnancy, a 50% chance of having a child who is a sickle cell disease carrier (A/S), and a 25% chance of having a child that did not inherit hemoglobin S from either parent (A/A).
- If Mr. G is not a sickle cell carrier, their offspring are not at risk of having sickle cell disease, but would still have a 50% chance of inheriting the sickle cell carrier state (A/S) from Mrs. G.

At least one of Mrs. G's parents is an obligate carrier of sickle cell disease. If

Mrs. G has siblings, they have at least a 50% risk of being a carrier of sickle cell disease, depending on whether one or both of their parents are carriers of sickle cell disease.

Genetic Counseling and Testing

If Mr. G is found to be a sickle cell carrier, genetic counseling can provide Mr. and Mrs. G with an opportunity to learn more about the inheritance of sickle cell disease and prenatal testing options.

Mr. G should be offered a hemoglobin electrophoresis to determine his carrier status. Such testing would also identify other beta hemoglobin variants such as hemoglobin C and beta-thalassemia. If Mr. G had another beta hemoglobin variant, Mr. and Mrs. G's offspring would be at 25% risk of being a compound heterozygote, a term used to describe an individual who inherited two different mutations in the same disease-causing gene. The clinical implications of the S/C genotype and the S/beta-thalassemia genotype are similar to the S/S genotype (see *GeneReview*: Sickle Cell Disease).

When both parents are carriers for sickle cell disease or other beta hemoglobin gene variants, prenatal diagnosis risk is possible using DNA analysis from fetal cells obtained by amniocentesis or CVS. Prior to prenatal diagnosis, both parents need to undergo DNA-based testing to identify the specific disease-causing mutations they carry.

Interventions

Preventive care. Sickle cell carriers who exercise regularly should take particular care to follow guidelines for safe physical exertion, such as avoiding dehydration; acclimatizing gradually to altitude, heat, and humidity; conditioning for several weeks before engaging in exhaustive exercise regimens; and refraining from extreme exercise during acute illness, particularly one involving fever [American College of Sports Medicine 1997].

Other clinical management. Typically, sickle cell disease carriers are asymptomatic and do not require specific clinical management. In rare cases, individuals may have problems with recurrent hematuria requiring medical intervention, transfusion, and iron therapy.

Ethical/Legal/Social/Cultural Issues

Historic misunderstanding and discrimination

Many early speculations about health risks associated with hemoglobin S were based on uncontrolled observations, anecdotal reports, or poor study designs in which carriers were not adequately distinguished from those with sickle cell disease. Some early testing techniques contributed to the misunderstanding because they identified red blood cell sickling, without separating carriers (heterozygotes) from those with sickle cell disease (homozygotes). As noted above in Risk Assessment, most carriers experience no health effects, and the available evidence indicates that hemoglobin S does not affect life expectancy. However, the sickle cell carrier state was described in some educational materials of the 1970s as a "milder form" of sickle cell disease. This confusion led many people with positive carrier test results to believe that their health was at risk.

Social stigma and discrimination also occurred. To the extent that people or organizations (such as employers) assume that sickle cell carriers have significant health problems, the information may be used adversely. Mrs. G's uncle may have recalled examples of employers placing unfair restrictions on hiring sickle cell carriers. For example, starting in the 1970s, sickle cell testing was used to exclude black employees from jobs as flight attendants, and many life insurers raised rates for people who were carriers of sickle cell disease. Like a number of other large employers, the Lawrence Berkeley Laboratory required black employees to undergo a pre-placement medical examination that included a test for sickle cell disease, as a condition of employment. In a landmark ruling, this testing program was struck down in court, more than 15 years after it had been initiated [US Court of Appeals 1998]. The court decision barred the use of a genetic test to discriminate in job placement or benefits unless the discriminatory action could be shown to be job related or dictated by business necessity; and on this basis the court barred the sickle cell screening program.

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**

References

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US Court of Appeals, Ninth Circuit (1998) Norman-Bloodsaw v. Lawrence Berkeley Laboratory. *Fed Report* 135:1260-76 [Medline]