

SICKLE CELL DISEASE AND OTHER HEMOGLOBINOPATHIES

The term sickle cell disease (SCD) (OMIM database No. 603903)¹⁶² encompasses a group of genetic disorders characterized by chronic hemolysis and intermittent episodes of vascular occlusion that cause recurrent episodes of severe pain and a wide variety of other disease manifestations. Specialized comprehensive medical care markedly reduces mortality in infancy and early childhood by preventing some disease-related complications and limiting the severity and sequelae of others.

Newborn screening for SCD also identifies infants with nonsickle hemoglobinopathies, hemoglobinopathy carriers, and, in some states, infants with α -thalassemia.^{163,164} Newborn screening results and clinical manifestations for some of these conditions are outlined in Table 1. Guidance for follow-up and diagnostic evaluation of infants with these screening results has been published^{163,164} and is often provided by state newborn screening programs or their designated hemoglobinopathy consultants.

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TABLE 1 Newborn Screening for Conditions Other Than SCD

Incidence

Overall, SCD occurs in 1 of 2500 to 1 of 2000 US newborns.^{165,166} Its incidence is highest in persons of African, Mediterranean, Middle Eastern, Indian, Caribbean, and Central and South American ancestry. The disease occurs less commonly in other ethnic groups, including individuals of Northern European descent. Accurate incidence data for many groups are unavailable. SCD is estimated to occur in 1 of 346 black infants and in 1 of 1114 Hispanic infants in the eastern United States.¹⁶⁷

Clinical Manifestations

Most infants with SCD are healthy at birth and become symptomatic later during infancy or childhood. The most common clinical manifestation is musculoskeletal or abdominal pain, which occurs unpredictably and is often excruciating. Acute manifestations that may rapidly become life-threatening include bacterial sepsis or meningitis, splenic sequestration, acute chest syndrome, and stroke. Other acute complications include aplastic crises, priapism, and renal papillary necrosis. Chronic manifestations include anemia, jaundice, splenomegaly, hyposthenuria, hematuria, proteinuria, cholelithiasis, and delayed growth and sexual maturation. Avascular necrosis of the hip and shoulder, restrictive lung

disease, and leg ulcers may cause chronic disability. Pulmonary hypertension is a risk factor for early death. It is important to note that the severity of SCD varies widely, even among individuals with the same genotype.

Pathophysiology

Sickle hemoglobin is caused by a point mutation in the β -globin gene, which leads to an amino acid change that causes hemoglobin to polymerize when deoxygenated. Sick red blood cells are dehydrated and show oxidative damage and increased adhesion to endothelial cells. The cumulative effects of these cellular abnormalities are shortened red cell survival and intermittent episodes of vascular occlusion, which cause tissue ischemia and organ damage.

Inheritance

SCD is an autosomal recessive disorder. Heterozygous individuals have a generally benign, asymptomatic genetic carrier state, sometimes referred to as a sickle cell trait. Homozygous and compound heterozygous individuals have symptomatic disease. Four SCD genotypes (sickle cell anemia, sickle-hemoglobin C disease, and 2 types of sickle β -thalassemia [sickle β^+ -thalassemia and sickle β^0 -thalassemia]) account for most SCD cases in the United States.^{163,164,168} Less-common forms of SCD are caused by coinheritance of hemoglobin S with other hemoglobin variants such as hemoglobin D-Punjab and hemoglobin O-Arab.

Benefits of Newborn Screening

The primary rationale for newborn screening and presymptomatic diagnosis is prevention of mortality from pneumococcal sepsis and splenic sequestration during infancy and childhood.^{167,169–172} Prophylactic penicillin has been shown to reduce the incidence of pneumococcal sepsis by 84%¹⁷⁰ and is used in conjunction with pneumococcal conjugate and polysaccharide vaccines and urgent evaluation and treatment of febrile illness with parenteral antibiotics. Family education about signs and symptoms of splenic sequestration results in earlier detection and reduced mortality from that complication.¹⁶⁹ Data from a number of statewide newborn screening programs confirm that mortality from SCD during the first 3 to 4 years of life, historically as high as 20%, is virtually eliminated by universal screening and appropriate follow-up and treatment.¹⁷³

Screening

Most newborn screening programs use isoelectric focusing to separate hemoglobins eluted from dried blood spots. A few programs use high-performance liquid chromatography (HPLC) or cellulose acetate electrophoresis as the initial screening method. Most programs retest screening specimens with abnormal results using a second complimentary electrophoretic technique, HPLC, immunologic tests, or DNA-based assays. The sensitivity and specificity of isoelectric focusing and HPLC are excellent,¹⁶⁷ but results and interpretation can be confounded by extreme preterm birth or previous blood transfusion.^{163,174}

Hemoglobins identified by these screening methods are reported in order of quantity. Because more fetal hemoglobin (HbF) than normal adult hemoglobin (HbA) is present at birth, most normal infants show FA results. Infants with SCD also show a predominance of F at birth; FS, FSC, or FSA are the most common results in children with SCD.

Follow-up and Diagnostic Testing

Infants with screening results indicative of possible SCD (FS, FSC, FSA) should have confirmatory testing of a second blood sample accomplished before 2 months of age. Confirmatory testing is performed by isoelectric focusing, HPLC, hemoglobin electrophoresis (cellulose acetate and citrate agar), and/or DNA-based methods.¹⁶⁴ Most infants with screening results that show HbFS have sickle cell anemia, but other possibilities include sickle β^0 -thalassemia, sickle $\beta\beta$ -thalassemia, and hereditary persistence of fetal hemoglobin, a benign condition. For this reason, testing of parents or DNA analysis may help clarify the diagnosis in selected cases. For infants with probable sickle cell disease, the selection of diagnostic tests and the interpretation of results ideally should be supervised by an expert in the diagnosis of hemoglobin disorders in childhood.

Family testing to identify carriers, for the purpose of defining an infant's diagnosis and/or providing genetic education and counseling, requires a complete blood cell count and hemoglobin separation by electrophoresis, isoelectric focusing, and/or HPLC.^{164,168} Individuals with hemoglobin variants such as S, C, and E are identified readily. Most individuals with heterozygous β -thalassemia show a decreased mean corpuscular volume (MCV) and increased levels of hemoglobin A₂ and/or hemoglobin F. Thus, accurate quantitation of hemoglobin F and hemoglobin A₂ is needed if the MCV is decreased or borderline decreased. Solubility testing is inadequate and should never be used for carrier testing, in part because it will not identify individuals with the hemoglobin C trait and β -thalassemia.

Brief Overview of Disease Management

SCD is a complex disorder with multisystem manifestations that require specialized comprehensive care to achieve an optimal outcome.¹⁶⁸ Family and patient education about the genetics, clinical manifestations, and treatment of SCD and its complications are important, particularly because prompt recognition of potentially life-threatening complications reduces morbidity and mortality. Important health maintenance issues include prophylactic medications, particularly prophylactic penicillin (should be started no later than 2 months of age), and timely immunizations, especially with the pneumococcal conjugate and polysaccharide vaccines. Periodic comprehensive medical evaluations facilitate documentation of important baseline physical findings and laboratory values, detection of signs of chronic organ damage, and development of individualized patient care plans. Timely and appropriate treatment of acute illness is critical, because life-threatening complications can develop rapidly. Some patients, including those who have suffered a stroke or who are identified as being at high risk of stroke by transcranial Doppler ultrasonography screening, receive chronic blood transfusions to prevent stroke and other complications. Selected patients with frequent or severe disease manifestations may benefit from hydroxyurea therapy and/or may be considered for stem cell transplantation, particularly if there is an HLA-matched sibling donor. Guidelines for the management of SCD were published recently.^{168,175}

Current Controversies

Because SCD is more prevalent in some racial and ethnic groups than others, some programs initially implemented selected or targeted screening rather than testing all newborn infants. However, experience with targeted screening showed a rate of missed cases as high as 30%, in part because of difficulties identifying infants' race or ethnicity. In addition, targeted compared with universal screening incurs additional costs and exposes screening programs, nurseries, and physicians to increased litigation risk for the preventable morbidity and mortality that results from delayed diagnosis. For these and other reasons, universal screening is strongly recommended and has been implemented in all 50 states, the District of Columbia, and the US Virgin Islands.

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