Hemoglobinopathies

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Outcome without screening:
Individuals affected with sickle cell disease have lifelong hemolytic anemia with acute and chronic tissue damage secondary to the blockage of blood flow produced by the abnormally shaped red cells. Additional clinical manifestations include episodic vaso-occlusive crises, functional asplenia, sepsis, infections, splenic sequestration, and bone marrow aplasia. Sickle cell disease can be lethal, especially in early infancy or childhood (10% mortality) because of overwhelming sepsis or splenic sequestration. Current predictions indicate an 85% chance that infants with homozygous sickle cell disease (HbSS) will survive to at least 20 years of age. Complications include cerebrovascular accidents, neurologic deficits, aseptic necrosis of bones, leg ulcers, serious infections, renal concentrating defects, neoproliferative retinopathy, delayed growth and sexual maturation.

The thalassemia syndromes are characterized by absent or deficient synthesis of one or more of the normal globin chains. This contrasts with the other hemoglobinopathies in which the variant hemoglobins are qualitatively or structurally abnormal. The major causes of mortality are iron overload and overwhelming infections following splenectomy, the former due to excessive iron deposition as a result of blood transfusions and increased gastrointestinal absorption. Excess iron deposited in the heart, pancreas, liver, and other organs damages tissue and leads to cardiac failure, arrhythmias, diabetes mellitus, and liver failure. Beta (β)-thalassemia trait generally is not detected in the newborn period, but anemia becomes evident in the first 1-2 years of life. Because It is associated with mild anemia and small red blood cell size, it is often confused with iron deficiency anemia. Homozygous beta thalassemia (beta thalassemia major) is a life-threatening condition that requires chronic transfusion and eventually iron chelation therapy to allow patients to lead a normal life. Clinically significant alpha (α)-thalassemia conditions are relatively rare in Tennessee, but can be responsible for fatal hydrops fetalis at birth and for Hemoglobin H disease, a lifelong chronic anemia. An increasingly common condition (related to increased number of persons from Southeast Asia in Tennessee) is Hemoglobin E-β thalassemia. This condition is associated with chronic anemia, which is sometimes severe enough to require chronic transfusion and/or splenectomy.

Incidence:
Hemoglobinopathies are among the most common genetic conditions in the world. Sickle cell disease is the most common hemoglobinopathy in Tennessee and approximately 1 in 12 African Americans are born with sickle cell trait (HbAS) and 1 in 350 are born with sickle cell disease (HbSS). There are three common types of sickle cell disease: Hemoglobin SS, which accounts for 65% of cases, Hemoglobin SC (approximately 25%), and Hemoglobin $S\beta^o$ thalassemia and Hemoglobin $S\beta^+$ thalassemia, which together make up 7 - 10% of cases of sickle cell disease. Although the sickle gene (hemoglobin S gene) is found in a number of ethnic groups throughout the world, including persons of Middle Eastern, Indian, and Mediterranean ancestry, in

Tennessee it occurs almost entirely in Blacks. Other inherited abnormalities of hemoglobin include alpha thalassemia, beta thalassemia, Hemoglobin C, and Hemoglobin E. The thalassemias are found in persons of Mediterranean, African-American, and Asian ancestry, whereas Hemoglobin C is found almost entirely in African-Americans and Hemoglobin E in persons from Southeast Asia. In some areas of the world the prevalence of these genes is very high, but the number of affected Tennesseans is relatively low.

Outcome with screening:
With screening, penicillin prophylaxis, and heightened vigilance, early death and morbidity from overwhelming sepsis are significantly decreased. Death from acute splenic sequestration and aplastic crisis may be prevented or reduced. Risks of disability are lowered by aggressive treatment of infection, dehydration, and cerebral thromboses. Long-term clinical outcomes of patients identified by newborn screening programs are unclear, because treatment remains prophylactic and symptomatic.

Causes of hemoglobinopathies:
The inherited disorders of hemoglobin fall into six groups:

1) Structural variants, such as HbS and HbC, related to single-amino acid substitutions (i.e., missense mutations),
2) Thalassemias, all characterized by a reduced rate of synthesis of one or more of the globin chains of hemoglobin,
3) Conditions in which fetal hemoglobin (Hb F) synthesis persists beyond the neonatal period known collectively as hereditary persistence of fetal hemoglobin (HPFH)
4) Unstable hemoglobins
5) Variants with altered oxygen affinity
6) M Hb variants

Screening test and confirmation:
Screening for the Hb variants and thalassemias is done to identify disorders such as those due to HbS and thalassemia. Newborn screening is done by high performance liquid chromatography (HPLC) performed on filter paper dried blood spots from a heelstick.

Treatment:
The primary rationale for newborn screening for sickle cell disease stems from the high morbidity and mortality associated with overwhelming blood stream infection due to pneumococcus. This results from early compromise of spleen function due to sickling in the spleen. Prior to the mid-1980s this was the leading cause of death in children with sickle cell disease, but a national study found that the use of penicillin prophylaxis was highly effective. Therefore, it is important to diagnose sickle cell disease shortly after birth, so that penicillin prevention can be started by age 2-3 months.

When sickle cell disease is suspected on newborn screening, an extremely high priority is placed on contacting the family so that their child can have confirmatory testing. If the second blood test confirms the diagnosis of sickle cell disease, an education program is initiated. This begins with the patient being seen and evaluated by a sickle cell nurse and pediatric hematologist. Detailed discussions with the family center on the inheritance and clinical significance of sickle cell disease and emphasize the need for two daily doses of liquid penicillin to prevent pneumococcal infection. Penicillin should be given on a regular basis at least until 5 years of age. Discussion also includes other significant complications of sickle cell disease that can occur early in life, including pneumonia, anemia, enlargement of the spleen, swelling of the

hands and feet, infection of the bone, and pain crises affecting various parts of the body. Children with sickle cell disease are seen in Hematology Clinic every 3 months for the first 2 years of life and every 6-12 months afterwards.

Immunization against pneumococcus, *H. influenzae*, and hepatitis infection should be given. Parent and patient education regarding rapid access to appropriate medical care for aggressive pain management, prompt recognition and early treatment of infections, management of dehydration and acidosis, blood transfusion therapy for selected problems (e.g., anemia and cerebrovascular events), and judicious use of oxygen reduce morbidity and mortality.

Special concerns and issues:
Of special concern is the marked clinical variability of sickle cell disease ranging from mild symptoms to more severe symptoms to death in early life. Clinical severity is influenced by the type of sickle cell disease present, e.g., HgbSC disease is usually milder than HgbSS disease. It is very important to differentiate sickle cell trait from sickle cell disease because the trait is rarely associated with any symptomatology and does not lead to shortening of life, whereas sickle cell disease is invariably associated with clinical problems and does lead to significant compromise of life span.

For all of the sickle cell conditions , a number of therapeutic options are now worth considering, depending on the clinical circumstances. These include the use of chromic transfusion, bone marrow transplantation (when a suitable donor is available), and therapy with drugs such as hydroxyurea, which stimulates increased production of fetal hemoglobin