Condition: Hemoglobinopathies

Inheritance:

Autosomal recessive.

Genetic etiology:

Hemoglobinopathies include a diverse set of disorders due to mutation in the alpha or beta globin genes that encode the alpha and beta globin chains that contribute to adult hemoglobin. A variety of missense mutations in the beta globin chain lead to dysfunctional hemoglobin; the most common of these is the substitution of valine for glutamic acid responsible for sickle cell anemia. Mutations that lead to deficient production of alpha or beta globin result in thalassemia. In beta globin these involve mutations in the promoter, truncating, or splicing mutations, primarily. Because there are two alpha globin genes on each copy of chromosome 11, the most common alpha thalassemia mutations are deletions of one or both alleles; homozygosity for deletion of both alleles is lethal, and deletion of three of the four alleles leads to severe alpha thalassemia.

Frequency:

Hemoglobinopathies are most common in regions of the world where malaria is endemic; i.e., Africa, the Mediterranean, Middle East , and Southeast Asia. Hemoglobinopathies are now found worldwide in all ethnic groups, in part due to genetic admixture.

Clinical features:

Sickle cell anemia is characterized by a tendency for red blood cells to assume a sickle shape under conditions of low oxygen. Clinically, there is obstruction of blood flow through small vessels, with episodes of pain and tissue ischemia. Progressive damage to the spleen leads to susceptibility to infection. There is also a risk of stroke. Beta thalassmia leads to chronic anemia and splenomegaly, treated by transfusion, but complicated by iron overload. Alpha thalassemia is usually lethal if all four alpha globin genes are deleted, but deletion of three alleles leads to hemoglobin H disease, consisting of anemia and splenomegaly.

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Management:

Sickle cell crises are treated with hydration and pain medication. Antibiotic prophylaxis may prevent infection, and fevers should be evaluated and treated aggressively. Hydroxyurea may be beneficial, in part through stimulation of fetal hemoglobin production. Beta thalassemia is treated with transfusions and chelation to remove excess iron. Hydroxyurea may play a role in treatment of some patients. Hydrops fetalis due to deletion of all four alpha globin genes is not treatable; hemoglobin H disease may require transfusions. Bone marrow transplantation can be used in treatment of any of the hemoglobinopathies.

Genetic counseling:

Parents of affected child have 25% risk of recurrence. In populations with high carrier frequency, pseudodominant inheritance may occur. Genetic testing is possible, and in some populations carrier testing is offered.

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