Hemoglobinopathy screening in Utah identifies infants with hemoglobin disorders. Isoelectric Focusing (IEF), a screening process, separates, identifies, and quantifies each type of hemoglobin present in a sample. At birth there is normally more fetal hemoglobin (Hb F) than adult hemoglobin (Hb A) and is reported as FA. Infants with hemoglobin C disease have hemoglobin C (Hb C) with no Hb A. The IEF pattern of FC indicates hemoglobin disease. Abnormal IEF screens are validated by Hb fractionation using High Performance Liquid Chromatography (HPLC), which shows the hemoglobin pattern with somewhat more accuracy.

Genetics and Heredity

Hb C is an inherited autosomal recessive variation of Hb A that occurs in the beta (β)-globin protein chain of Hb A. The formation of Hb C occurs by substitution of lysine for glutamic acid at codon 6 of the β-chain. Hemoglobin C disease (Hb CC) is caused when an infant inherits two copies of the Hb C variant gene, one from each parent. If both parents have Hb C trait, there is a 25 percent chance with each pregnancy that the child will be born with Hb CC. Disease with no Hb A may have either homozygous Hb CC or heterozygous Hb C/β-thalassemia (Hb C/β-thal). Either diagnosis is associated with few clinical manifestations. The best method to distinguish the results is to test both parents.

Prevalence

Hemoglobin C disease is most often found in persons of West Africa, the Middle East, Southern Europe (Italy and Turkey), West India, Mexico, Central and South America and their descendants. About 2-3 percent of people of West Africa are heterozygous for Hb C. Homozygous Hb CC is rare and relatively mild. Individuals with Hb CC disease appear to have a normal life span in the industrialized countries of the Western World. However, this may not be true in the harsh environments of some Third World countries. These variations began as a response to the selective pressure of malaria.

Pathophysiology

Hb C (like Hb S) interacts more strongly with the erythrocyte membrane. This interaction results in the premature break down of red blood cells (RBC) and shortening of the RBC survival rate. This interaction also leads to RBC dehydration and an increase in mean cell hemoglobin concentration (MCHC). The following manifestations of Hb CC may be seen:

- Rod-shaped RBCs containing Hb C intracellular crystals
- Prominent Target cells (greater that 90% on smear)
- Microcytosis and Spherocytosis on smear
- Increased packed cell volume (approximately 25 to 30%)
- Mild hemolytic anemia (Hb levels 10 to 12 gm/dL)
- Moderate reticulocytosis (9 and 12 gm/dL)
- Reduced oxygen affinity
In hemoglobin C disease, straight-edged six-sided intracellular crystals may form, also known as crystalline inclusions. Hb F inhibits Hb C crystallization; therefore the tendency to form crystalline inclusions occurs in RBCs with a lower Hb F content. Hb C intracellular crystals are usually absent or rare in Hb C disease individuals who have an intact spleen.

**Homozygous Hemoglobin C:**
Hemoglobin C disease is usually clinically benign with no specific treatment required. Those individuals with homozygous Hb CC disease vary in symptomatology. They may be asymptomatic or have the following:

- Splenomegaly
- Aplastic crises
- Jaundice
- Folate deficiency
- Cholelithiasis
- Mild to moderate microcytic hemolytic anemia

Vaso-occlusive episodes with accompanying complications are not a feature of Hb C disease. Decreased mean corpuscular volume (MCV) facilitates passage of RBCs through the microcirculation. However, as a consequence of microcirculation abnormalities, rare individuals may have extensive retinopathy.

**Heterozygous Hemoglobin C/Beta (β)-thalassemia:**
Persons with heterozygous Hb C/β-thalassemia may be asymptomatic and have moderate hemolytic anemia. Those with Hb C/β+-thalassemia have some Hb A and are more likely to have mild anemia and a non-palpable spleen. Individuals with hemoglobin C/βº-thalassemia have no Hb A and the anemia and splenomegaly are more pronounced.

**Essential Steps**
1. Inform the family of confirmed Hb CC disease or Hb C/β-thalassemia; explain the possible complications and interventions. Consider family referral to a genetic counselor.
2. If hemoglobin C disease is present, it is important to ensure that the infant does not also have beta-thalassemia. A CBC with smear at 6 to 9 months of age will identify the β-thal components. If medical concerns arise or the infant is symptomatic, complete the CBC with smear earlier.
3. Hemolysis is usually very mild, so a nutritious diet should provide sufficient folic acid and supplementation unnecessary.
4. Consult with a pediatric hematologist regarding patient evaluation and possible disease management.

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