HEMOGLOBIN E DISEASE (Hb EE)

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 E disease have hemoglobin E (Hb E) with no Hb A. The IEF pattern of FE indicates hemoglobin disease. Abnormal IEF screens are validated by Hb fractionation using High Performance Liquid Chromatography (HPLC), which show the hemoglobin pattern with somewhat more accuracy.

Genetics and Heredity

Hb E is an inherited autosomal recessive variation of Hb A that occur in the beta (β)-globin protein chain of Hb A. The formation of Hb E occurs by substitution lysine for glutamic acid at codon 26 of the β-chain. Hemoglobin E disease (Hb EE) occurs when an infant inherits two copies of the Hb E variant gene, one from each parent. If both parents have the E trait, there is a 25 percent chance with each pregnancy that the child will inherit homozygous Hb EE. Disease with no Hb A may have either homozygous Hb EE or heterozygous Hb E/β-thalassemia (Hb E/β-thal). The best method to distinguish the results is to test both parents.

Prevalence

Hemoglobin E is believed to be the most common β-chain hemoglobin variant in the world. Prevalence is very high among persons from Southeast Asia, especially in Cambodia, Laos and Thailand. The borders of these countries are considered the “Hb E Triangle”. Hb E is also found in Vietnam, Malaysia, northeastern India, Bangladesh, Pakistan, Nepal and Sri Lanka. It is estimated that 30 million Southeast Asians are heterozygous for Hb E and 1 million are homozygous Hb EE. This variation began as a response to the selective pressure of malaria.

Pathophysiology

Hb E is a mildly unstable hemoglobin that denatures easily. The protein structure unfolds causing the original properties to diminish or not function properly. Homozygous Hb EE is a relatively mild disease and usually asymptomatic. The following signs and symptoms of the disease may occur:

- Target shaped red blood cells (up to 75% on smear)
- Microcytic red blood cells (mean corpuscular volume [MCV] of 67)
- Impairment of Hb E in reticulocytes
- Decreased hemoglobin concentration (Hgb approximately 12 g/dL)
- Hypoxemia due to reduced oxygen affinity of RBCs
**Homozygous Hemoglobin E (EE):**
Health problems are usually not associated with homozygous Hb E disease. It is usually considered clinically benign and requires no treatment. Individuals with Hb EE can vary in their symptoms. They may be asymptomatic or the following signs and symptoms may occur:
- Mild to moderate anemia
- Slight reduction of RBC survival
- Occasional splenomegaly

**Heterozygous Hemoglobin E/Beta (β)-thalassemia:**
The most serious Hb E syndrome is Hb E/beta-thalassemia (Hb E/β°-thal). Additional testing will be needed to differentiate between Hb EE and Hb E/β°-thal. Hb E/β°-thal disease can be life threatening and may include any of the following signs and symptoms:
- Moderate to severe microcytic anemia (Hgb 6 g/dl)
- Very low MCV
- Increased reticulocyte count
- Heart failure
- Splenomegaly
- Hepatomegaly
- Poor growth patterns

Individuals with Hb E/β+-thal have some Hb A and are more likely to have mild anemia and a non-palpable spleen. Those with Hb E/β°-thal have no Hb A present and will likely have more severe anemia with a palpable spleen and hepatomegaly. Treatment may include repeated blood transfusions.

**Essential Steps**

1. Inform the family of the confirmed Hb EE disease or Hb E/beta-thalassemia syndrome; explain the possible complications and interventions. Consider family referral to a genetic counselor.
2. If hemoglobin E disease is present, it is important to ensure that the infant does not also have beta-thalassemia. A complete blood count (CBC) with smear at 6 to 9 months of age will identify any of the β-thal components. If medical concerns arise or the infant is symptomatic, do the CBC with smear earlier.
3. Educate parents and caregivers regarding signs and symptoms.
4. Consult with a pediatric hematologist regarding patient evaluation and possible disease management.