Hemoglobin E/Beta-Thalassemia

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Key Points

- The methods used in newborn screening for sickle cell disease also identify many other hemoglobin variants, some of which are clinically significant. Follow-up testing of the child and parents can help to determine the clinical implications of the screening result for the child and genetic risk to other family members, including future children.
- Hemoglobin E/beta-thalassemia is a hemoglobinopathy detected by newborn screening. In this condition, a person inherits a structural variant of the hemoglobin beta chain (hemoglobin E) from one parent and a hemoglobin variant causing decreased production of the hemoglobin beta chain (beta-thalassemia) from the other parent. Both variants are benign when they occur alone.
- The clinical course of individuals with hemoglobin E/beta-thalassemia varies widely, but typically involves anemia (often requiring blood transfusions) and hepatosplenomegaly, and may involve skeletal disease.
- Hemoglobin E and the beta-thalassemia carrier state are both common in Southeast Asians; as a result, Hemoglobin E/beta-thalassemia is seen most commonly in this population.

Learning Objectives

Participants will be able to:

- Appreciate the wide variability of clinical severity in hemoglobin E/beta-thalassemia;
- Explain the potential reproductive risks for the parent of a child with hemoglobin E/beta-thalassemia;
- Propose possible solutions to the language barriers experienced when providing counseling about a genetic condition to a non-English speaking couple.

Family History Issues

Because hemoglobin E/beta-thalassemia is inherited in an autosomal

recessive manner, both parents of an affected individual are obligate carriers for one of these hemoglobin variants. In most cases siblings have a 25% risk of inheriting the same condition. Parental testing is necessary to provide accurate recurrence risks.

Red Flags 

The diagnosis of hemoglobin E/beta-thalassemia is suspected in an infant or child less than two years of age with severe microcytic anemia and hepatosplenomegaly, and whose newborn hemoglobin results indicate E/beta-thalassemia, E trait or homozygous E, or who has not had newborn hemoglobin screening. Severely affected infants become progressively pale and have feeding problems, diarrhea, irritability, and recurrent fever. If left untreated, they fail to thrive. Milder cases present at a later age with anemia. A low MCV (mean corpuscular volume) and a normal or elevated RDW (red cell distribution width) on a complete blood count indicate a possible thalassemia.

Case 36. A One-Year-Old with Hemoglobin E/Beta-Thalassemia

TT is a one-year-old, previously well, Cambodian boy who moved with his parents from Cambodia to the United States at age six months. He was referred to the General Pediatric service because of lethargy and pallor. There was no history of blood loss or bloody or melanotic stools. TT is still breast fed several times per day and takes infant formula with iron. He eats rice, vegetables, and meats. His mother is 19 years old and has no other children. TT's father is 22 years old and is frequently away from home working as a shrimp farmer. TT and his mother are accompanied to the clinic by TT's American-born, 13-year-old uncle, who serves as translator.

Notable observations on physical exam included a palpable mass in the left upper quadrant and distinct pallor. A blood smear revealed microcytic (small), hypochromic (pale) red cells of distinctly variable size (anisocytosis), shape (poikilocytosis), and density (polychromasia). His hemoglobin was 5.6 gm/dL, MCV 56 fl, RDW of 26%, and reticulocyte count was slightly increased. His hemoglobin electrophoresis (isoelectric focusing) pattern

showed predominantly hemoglobins E and F (E greater than F) with no hemoglobin A. High-performance liquid chromatography (HPLC) found 55% hemoglobin E and 45% F. These findings, along with his clinical presentation, were determined to be consistent with a diagnosis of hemoglobin E/beta-thalassemia.

As the attending physician in the general pediatric clinic, you observe your resident attempting to explain the cause of the anemia in TT to his mother. The resident also tries to discuss the implications of TT's diagnosis for her future children. TT's mother seems uninterested in the entire discussion, but repeatedly acknowledges that she understands the explanations offered. However, she does mention that she doesn't understand how she could pass on a disease to her children since she is healthy. When the resident asks for permission to take a blood sample to determine her hemoglobin status, TT's mother becomes noticeably uneasy and politely refuses without explanation.

Clinical Care Issues

Hemoglobin E and beta-thalassemia

Hemoglobin E. Hemoglobin E is a structural variant of the hemoglobin beta chain and is the most common such variant among Southeast Asians. The gene frequency varies considerably between regions but is generally 1/10 to 1/20 and may reach as high as 1/2 in some regions near the intersecting borders of Cambodia, Thailand, and Laos. It is also prevalent in parts of the Indian subcontinent. In contrast, hemoglobin E is much less common in the Vietnamese population and is almost absent among the Chinese and Japanese populations.

Heterozygotes for hemoglobin E are clinically normal. Heterozygotes manifest only minimal changes in red blood cell indices, and on hemoglobin electrophoresis, 25%-30% of hemoglobin is hemoglobin E. Homozygotes for hemoglobin E are typically also clinically asymptomatic and may be only mildly anemic (see Table 1).

Beta-thalassemia syndromes. The beta-thalassemias are a heterogeneous group of disorders caused by mutations that result in decreased production of the hemoglobin beta chain. More than 200 causative mutations have been identified. The beta-thalassemia carrier state is common in many Mediterranean, Asian, and Middle Eastern populations, with each population having its own set of common mutations. In Asian populations, the beta-thalassemia carrier rate is 1/30 to 1/50.

Two general categories of beta-thalassemia mutations are characterized as beta^{+}-thalassemia, in which production of the hemoglobin beta chain is variably reduced, and beta^{0}-thalassemia, in which no hemoglobin beta chain is produced at all. The beta-thalassemia carrier state may result in mild anemia but is usually clinically asymptomatic. The presence of two beta-thalassemia mutations results in reduced or absent beta chains, leading to moderate to severe anemia. The severe form of the disease, thalassemia major, is due to homozygosity for mutations with a marked effect on beta-globin production (beta^{0} or beta^{+} with severe reduction in beta-globin). Its manifestations include severe anemia, enlarged liver and spleen, and failure to thrive. Onset of symptoms usually occurs by six to 12 months of age. If untreated, thalassemia major generally results in death by six years of age; blood transfusions and supportive care extend life to the mid-30s. Bone marrow transplant is now a potential option for more definitive therapy in those who have an HLA-matched donor. Individuals who are homozygotes or compound heterozygotes for mutations with less severe effects on beta-globin production have a variable but generally milder course, requiring only occasional blood transfusion. This condition is designated thalassemia intermedia.

Selective advantage of carrier state. Common gene variants are likely to reflect a survival advantage. Several hemoglobin variants are found more commonly in people from geographic areas where malaria is endemic. It is thought that the abnormal structure of the hemoglobin molecule protects against malarial infection, conferring a selective genetic advantage on carriers, with the result that the carrier state has been preserved in the gene pool.

Hemoglobin E/beta-thalassemia

Hemoglobin E/beta-thalassemia results from the inheritance of a hemoglobin E mutation from one parent and a beta-thalassemia mutation (either beta^{0} or beta^{+}) from the other parent. The severity of hemoglobin E/beta-thalassemia varies from mild to severe (see Table 1). Although, in general, severity of the disease is greater with beta^{0}-thalassemia mutations, the mutation type is not a reliable predictor of clinical course, and predicting clinical course is notoriously difficult.

- About half of individuals who have hemoglobin E/beta-thalassemia have severe manifestations that resemble thalassemia major, requiring regular blood transfusions to treat severe anemia. Without treatment,

this condition can result in lethargy, pallor, growth delay, developmental delay, and hepatosplenomegaly. The bone marrow expands in order to compensate for ineffective erythropoiesis, causing bones to become thin and brittle. Facial bones become distorted and characteristic facial features develop. Heart failure and infection are the leading causes of death among individuals with untreated thalassemia major, usually before the third decade. In developed countries, diagnosis is usually made early, allowing for early treatment before secondary complications occur.

- About half of individuals who have hemoglobin E/beta-thalassemia have symptoms similar to thalassemia intermedia, including pallor, jaundice, mild-to-moderate anemia, and hepatosplenomegaly. Blood transfusions are only occasionally needed. Other complications can include folic acid deficiency secondary to a high rate of erythropoesis; leg ulcers; gallstones; and thrombosis. Chronic anemia causes increased gastrointestinal iron absorption, leading to complications of iron overload. Other symptoms can present later, including decreased bone density and moderate-to-severe skeletal changes seen in severe cases.

- Hemoglobin E/beta-thalassemia can also occur in a mild form in which affected individuals usually do not develop clinically significant problems and require no treatment.

Table 1. Hemoglobin E and Hemoglobin E/Beta-Thalassemia

Genotype	Clinical Manifestations	Hemoglobin Electrophoresis
Hb E carrier (A/E)	None	Hb A and Hb E (with amount of Hb A > Hb E)
Hb E homozygote (E/E)	Mild anemia; may have no clinical manifestations	Hb E
Hb E/beta$^+$-thalassemia (E/beta$^+$)	Mild to moderate anemia	Hb E and Hb A (with amount of Hb E > Hb A); usually increased Hb F

Hb E/beta^0-thalassemia (E/beta^0)	Moderate to severe anemia; may be transfusion dependent	Hb E and increased Hb F

Adapted from Dumars et al 1969, Practical Guide to the Diagnosis of Thalassemia

Risk Assessment

The risk for TT's mother of having another affected child depends on her genetic status and that of TT's father. In order to assess this risk, testing of both parents is recommended. If each carries just one mutation (hemoglobin E in one parent and beta-thalassemia in the other), they will have a 25% risk of having a child with hemoglobin E/beta-thalassemia in each subsequent pregnancy. However, if one of the parents is homozygous for hemoglobin E, the recurrence risk is 50% with each subsequent pregnancy. Testing could reveal other hemoglobin abnormalities as well, most notably the alpha-thalassemia carrier state (a condition associated with decreased production of the alpha hemoglobin chain), which is also very common in the Southeast Asian population. If other abnormalities are present, further testing would likely be needed to determine potential reproductive outcomes.

Genetic Counseling and Testing

Counseling

Although a discussion with TT's mother about genetic risk is important, it may also be important to defer this discussion until after TT's care has been addressed and she has had the opportunity to adjust to TT's diagnosis of hemoglobin E/beta-thalassemia. The initial goal of counseling would be to inform of her of potential risks to future children, and of testing options that might clarify those risks, so that she could determine whether she wished to proceed with carrier testing.

A detailed discussion of recurrence risk in future children could occur via a referral to a medical genetics clinic that cares for individuals with hemoglobinopathies. Such a clinic can be located using the GeneTests Clinic Directory by searching for a hemoglobinopathy specialty clinic.

Counseling should also address risks for other family members. TT's aunts and uncles are at 50% risk of being carriers for either hemoglobin E or beta-thalassemia, depending on which mutation is maternal and which is paternal. In addition, when TT is old enough to be considering marriage or starting a

family, it would be appropriate to provide him with reproductive risk information. He will transmit either the hemoglobin E or the beta-thalassemia mutation to each of his offspring. The hemoglobin status of his reproductive partner will determine the risk to offspring.

Testing

Methods for beta-thalassemia and Hemoglobin E carrier testing include DNA testing and hemoglobin measurements, specifically hemoglobin electrophoresis or high-performance liquid chromatography (HPLC) followed by acid electrophoresis to distinguish between hemoglobin E and C which co-migrate (isoelectric focusing can distinguish between the two mutations without additional testing).

Molecular genetic testing of the gene encoding the hemoglobin beta chain (chromosomal locus 11p15.5) is available and may be useful in some cases. Testing can determine which beta-thalassemia mutation is involved, which could be helpful in the prediction of the clinical phenotype. Additionally, testing can be used for presymptomic diagnosis of other at-risk infants in the family, and if desired, prenatal diagnosis.

Of note, newborn screening includes testing for hemoglobinopathies in all states, using hemoglobin measurements. Testing is universal in most states; South Dakota and New Hampshire screen only selected populations or by request. However, unless the state also employs DNA testing, infants with hemoglobin E/beta^0-thalassemia cannot be distinguished from those with homozygous hemoglobin E. Further testing is needed to distinguish these genotypes, which have very different clinical implications (Table 1).

Interventions

Management of hemoglobin E/beta-thalassemia needs to take into consideration the range of severity observed. In severe cases resembling thalassemia major, affected individuals require regular blood transfusions and iron-chelation therapy. In moderate cases similar to thalassemia intermedia, transfusions may be needed occasionally. Folic acid supplementation is recommended due to extensive erythropoietic activity. Some patients require splenectomy. Patients may develop iron overload from increased gastrointestinal absorption of iron or from transfusions, and in such cases, iron-chelation therapy is administered. Bone marrow transplantation is considered in severe cases. Extensive guidelines for the management of thalassemia and hemoglobin E/beta-thalassemia are

available [Steinberg et al 2001, Thalassaemia International Federation].

Ethical/Legal/Social/Cultural Issues

Cultural issues and refusal of hemoglobin testing

We cannot know why the mother of TT declined hemoglobin testing without obtaining further information either from her or from other knowledgeable sources. She might have refused testing because of a concern about the cost of testing, particularly if her family lacks health insurance. Or she may not have fully understood the recommendation for testing because of language barriers. She might have wished to consult with other family members or friends before proceeding to testing, or might have understood the testing option and made an informed decision not to pursue it.

Because it is traditional in many Asian cultures to show respect — or even deference — toward physicians, an Asian patient or parent's nod may not necessarily indicate understanding or agreement. The resident may have been puzzled by Mrs. T's refusal of the blood test because it did not seem to fit with her agreeable demeanor throughout the conversation. In this case, the resident could explain the value in knowing her hemoglobin status. The resident can also explain that having the test is not needed to treat her son and that it can be deferred to a later date if desired.

Ovecoming language/cultural barriers

The role of TT's 13-year-old uncle as translator puts him in the difficult position of being responsible for accurate communication of serious medical information to his sister and of her questions and concerns to the health care provider. His role as translator is particularly questionable when sensitive issues, such as genetic risk, are being discussed. Sometimes a family member is used as a translator because there are no other interpreters available. However, a lack of adequate interpreter services could interfere with the provision of good quality care to TT and his family. A first step in addressing this problem might be to defer the discussion of genetic risk until appropriate translator services are available (as well as to allow time for TT's mother to adjust to TT's illness).

Culturally, the best approach is to have a trained interpreter from the Cambodian culture who can work with the family and the physician to help each understand the other's perspective. The physician needs to understand the meaning of the illness to TT's family, what the family members think

may have caused the illness, and what treatment and counseling they would like. The exploration of causation (illness attribution) ideally should incorporate an understanding of the thoughts and feelings of family members about possible complementary and alternative medical approaches, including religious and spiritual rituals and traditions [Barnes et al 2000].

Conversely, TT's parents need to understand genetic transmission of hemoglobin E/beta-thalassemia sufficiently to make an informed decision about carrier testing and other potential testing options, such as prenatal diagnosis in a future pregnancy. Concepts of genetic transmission and its implications in US medical care may be challenging to convey in this situation. Therefore, assistance from a trained interpreter would be recommended.

Culturally appropriate patient education materials may be helpful in facilitating the discussion. Materials that demonstrate concepts through drawings and illustrations may assist TT's mother in understanding the genetics of hemoglobin E and beta-thalassemia. Some brochures on thalassemia-related conditions have been translated specifically for Cambodian patients, including one developed by the Northern California Comprehensive Thalassemia Center.

Resources

- ***GeneReview:* Beta-Thalassemia**

- **GeneTests Clinic Directory**
  Locate a hemoglobinopathy specialty clinic.

- **Cooley's Anemia Foundation**
  129-09 26th Ave, Suite 203
  Flushing, NY 11354-1131
  Phone: 718-321-2873; 1-800-522-7222
  Fax: 718-321-3340
  Email: info@cooleyanemia.org
  Hemoglobin brochures in 5 languages

- **National Library of Medicine Genetics Home Reference**
  Beta-thalassemia

- **Thalassaemia International Federation**
  PO Box 28807
  2083 Nicosia, Cyprus
  Phone: 357-2-319129
  Fax: 357-2-314552
  Email: thalassaemia@cytanet.com.cy

- **Northern California Comprehensive Thalassemia Center**
  Children's Hospital Oakland
  Department of Hematology/Oncology
  747 52nd Street
  Oakland, CA 94609
  Phone: 510-428-3885 x4398
  Email: info@thalassemia.com

- **Washington State Department of Health**
  Hemogolobin E Fact Sheet (pdf)
  Fact sheets available on many hemoglobinopathies, translated into several languages

- **GeneTests Online Medical Genetics Information Resource**

- ***GeneReviews*, GeneTests Online Medical Genetics Information Resource**

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