Hemoglobin E β-thalassemia: An increasingly common disease with some diagnostic pitfalls

Because of the extremely high gene frequencies for both hemoglobin E and β-thalassemia in many Asian populations, the compound heterozygous condition, hemoglobin E β-thalassemia, occurs frequently in this group. Indeed, recent evidence suggests that, globally, this will become the most important form of thalassemia in the near future.[1] It is also being encountered increasingly in countries with large Asian immigrant populations.

Although hemoglobin E β-thalassemia is a common disorder, there are still major gaps in our understanding of its pathophysiology. Because the mutation that causes the structural change in β-globin associated with hemoglobin E also activates a cryptic splice site in the first exon (coding region) on the β-

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globin gene, hemoglobin E is synthesized at a slightly reduced rate.[2] For this reason it results in the phenotype of an extremely mild form of β-thalassemia; heterozygotes are not anemic and have a very slightly reduced mean cell hemoglobin and mean cell volume, whereas homozygotes are slightly anemic and have red cell indices that resemble those of β-thalassemia heterozygotes. It is still not clear why this extremely mild form of β-thalassemia can interact with other β-thalassemia alleles to produce the severe phenotype of some forms of hemoglobin E β-thalassemia. Even more puzzling is the extraordinary clinical heterogeneity of this disease, which ranges from a mild, symptomless anemia to a life-threatening disorder that can lead to death from anemia in the early first years of life.[3] The phenotypic variability, the fact that the later course of the illness cannot be predicted in the first year or two of life, and the lack of knowledge of the natural history of the disease combine to make the management of hemoglobin E β-thalassemia particularly challenging.

Another problem posed by hemoglobin E β-thalassemia is that it is sometimes difficult to diagnose with certainty in the neonatal period. When hemoglobin analysis of a cord blood sample reveals predominantly fetal hemoglobin (hemoglobin F), small amounts of hemoglobin E, and the absence of hemoglobin A, it is difficult to determine whether the baby is homozygous for hemoglobin E, an extremely mild and clinically unimportant condition, or is a compound heterozygote for hemoglobin E and β-thalassemia, which may have much more serious clinical consequences. Although there are more sophisticated approaches to distinguishing between these conditions at the time of birth, they are available only in laboratories with particular expertise in identifying the thalassemias. For many centers that are faced with this problem, the only alternative is to carry out a family study and to determine the hemoglobin genotype of the baby's parents. As illustrated in the report of Krishnamurti et al.,[4] even this well-tried diagnostic approach can occasionally have pitfalls.

The distinction between homozygous hemoglobin E and hemoglobin E β-thalassemia at birth by a family study is usually straightforward: the parents of hemoglobin E homozygotes are both carriers of hemoglobin E, whereas, in the case of hemoglobin E β-thalassemia, one parent is a hemoglobin E carrier and the other is a β-thalassemia carrier. The parental genotypes may be more complicated, however. For example, hemoglobin E β-thalassemia may be inherited from a parent who is homozygous for hemoglobin E and a partner who is heterozygous for β-thalassemia. Very rarely, the condition is inherited from a parent who also has hemoglobin E β-thalassemia and whose partner is a carrier for either hemoglobin E or β-thalassemia.

These difficulties are well illustrated in the family reported by Krishnamurti et al.[4] A baby was found to have only hemoglobins E and F at birth and, because neither parent was anemic, was assumed to be a hemoglobin E homozygote. The baby's father appeared to be homozygous for hemoglobin E, whereas the mother was clearly a hemoglobin E carrier. It was only some months later, when the baby failed to thrive and became profoundly anemic, that it was realized that he was not, in fact, a hemoglobin E homozygote but had hemoglobin E β-thalassemia. A more detailed study of the father revealed that he, too, had hemoglobin E β-thalassemia of a very unusual variety: he was only mildly anemic, had only 4% fetal hemoglobin, and had extremely hypochromic and microcytic red blood cells. Although such a mild degree of anemia is not uncommon in hemoglobin E β-thalassemia, the extremely low level of fetal hemoglobin is very rare. The father's particularly mild disease has been ascribed to the coinheritance of a deletional form of α-thalassemia, which is known to modify the clinical course of hemoglobin E β-thalassemia.[5] Although it seems unlikely that this is the only reason for the particularly mild phenotype in the father of this child, it was not possible to identify any other ameliorating factors.

What are the practical lessons to be learned from these complex issues for pediatricians and obstetricians who have increasing numbers of Asians in their practices? First, every woman of this racial background should be screened for hemoglobin E and β-thalassemia at the antenatal clinic. If she is found to be a carrier for either trait, her partner should be similarly tested. If both parents have the hemoglobin E trait, their babies are at risk only for the homozygous state for hemoglobin E, an extremely mild condition. If one parent is a carrier for hemoglobin E and the other has the β-thalassemia trait, they should be counseled and the baby's blood should be examined at birth. If cord blood hemoglobin reveals only hemoglobins F and E, it is certain that the baby has hemoglobin E β-thalassemia. The baby should then be followed very carefully to decide whether transfusion and chelation therapy are required.

In rare cases in which one parent appears to be homozygous for hemoglobin E and the other is a heterozygote, it is important to be absolutely certain that the "homozygote" is not, in fact, a compound heterozygote for hemoglobin E and β-thalassemia. Although in most cases this distinction should be easy, because persons with hemoglobin E β-thalassemia are anemic and usually have levels of fetal hemoglobin in the 20% to 60% range, this may not always be the case; rarely, the two conditions may be very similar. As in the case described by Krishnamurti et al.,[4] there are, however, clues when an individual who appears to be a hemoglobin E homozygote may in fact have an unusual form of hemoglobin E β-thalassemia. These include a more severe degree of anemia, unusually marked hypochromia or microcytosis, and even a modest increase in fetal hemoglobin, which is unusual in the homozygous state for hemoglobin E. In these cases the parents should be referred to a center that can undertake globin gene analysis.

If at risk of inheriting hemoglobin E β-thalassemia, a baby should be kept under careful surveillance for at least the first 2 years of life. There is increasing evidence that the disease, particularly in its milder forms, may be manifested considerably later than other types of β-thalassemia. Furthermore, in assessing these babies in the first few months after birth, one must always remember that the presence of small amounts of hemoglobin A do not

rule out the diagnosis of hemoglobin E β-thalassemia. Although most of the β-thalassemia genes in Asian populations are associated either with no β-globin chain production (β^0-thalassemia) or with the output of only very small amounts of normal β chains (severe β^+-thalassemia), some forms of the disease are due to milder β-thalassemia mutations that result in higher levels of hemoglobin A production.[6]

In these days of DNA analysis and highly sophisticated approaches to protein separation, it is worth reminding clinicians that if they are uncertain about whether a baby is homozygous for hemoglobin E or has hemoglobin E β-thalassemia, they should include a careful examination of the blood film as part of their surveillance during the first year of life. The appearance of a population of red blood cells with the characteristic morphologic changes of severe β-thalassemia is highly suggestive of the diagnosis of hemoglobin E β-thalassemia.

Finally, if the pediatrician does diagnose hemoglobin E β-thalassemia early in life, it is important to continue to observe the infant carefully, not to offer a prognosis until the clinical course is clearly defined, and not to start a transfusion program unless the baby is failing to thrive or otherwise has symptoms. There is increasing evidence that some of these babies can grow and develop well without transfusion.

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