Factors Associated in Production of Raised Gama Globin Chain in HbE/ β-Thalassemia – A Review

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Abstract: HbE/β-thalassemia genotype represent approximately 50% of all severe β-thalassemia worldwide and is the commonest form of thalassemia in many Asian countries, predominantly prevalent in North-Eastern region exhibiting phenotypes that range from severely symptomatic and transfusion-dependent anaemia in early life to a asymptomatic and clinically 'silent' condition that is ascertained by chance in middle age. Assay of m-RNA in cell free system clearly shows a deficiency of m-RNAin heterozygous β-thalassemic bone marrow. Compensation for defective β-chain synthesis by the β-chain locus on the unaffected chromosome in β-thalassemia heterozygotes have been reported. Some genotypic factors have been reported to affect the synthesis of γ-chain, such as 3’HS1 (+179 C→T) polymorphism, the (AT)x(NY)(AT)z motif in the 5’HS2 site, the (AT)x(AG) motif in the -540 region of the β-globin gene, GATA-1 (26), and heme-regulated initiation factor 2 alpha kinase (HRI). Also genetic variation at three major loci - XmnI-HBG2, HBS1L-MYB intergenic region on chromosome 6q23 and variation of rs11886868(T→C) in the BCL11A gene chromosome 2p16 has account for relatively large proportion (20-50%) of the phenotypic variation in HbF levels. HbF levels in HbE/β-thalassemia, and other β-thalassemia syndromes, results from increased erythropoietin levels leading to bone marrow expansion, and possibly increased F-cell production, combined with ineffective erythropoiesis giving a survival advantage to F cells. Among the known genetic factors XmnI, DNA sequence variation(C→T) at position -158 upstream of the G γ globin gene is one of the gene polymorphism that influence HbF production.

Keywords: Gama Globin, HbF, Xmn-I, HbE, Thalassemia

1. Introduction

Hereditary hemoglobinopathies and thalassemias are the worldwide prevalent heterogenous group of autosomal recessive disorders. Amongst the variant structural hemoglobin, HemoglobinE (HbE, B 26 GAG-AAG) is the most common β-thalassemichemoglobinopathy in Southeast Asian population. Similarly, thalassemias arises due to transcriptional failure of globin synthesis with a corresponding decrease or absence in the amount of functionally active protein resulting in an abnormal Hb ratio(α: nona). The HbE gene can interact with β-thalassemic gene and result in double heterozygous state which may exhibit phenotypic manifestations of β-thalassemia major or β-thalassemia trait.

HbE/β-thalassemiagenotype represent approximately 50% of all severe β-thalassemia worldwide and is the commonest form of thalassemia in many Asian countries, predominantly prevalent in North-Eastern region of India imposing a major genetic health problem. The affected individual may have phenotypes that range from severely symptomatic and transfusion-dependent anaemia in early life to a asymptomatic and clinically ‘silent’ condition that is ascertained by chance in middle age. Manifestations of HbE/β-thalassemia include refractory anaemia, splenomegaly and bony deformities, sometimes unexplained jaundice, variable degree of iron overload, depending on severity of anaemia and transfusion requirement, hypercoagulable states (post-splenectomy), pulmonary hypertension and cardiopulmonary disease.

The genetic mechanisms causing reduction of α-globin synthesis in the α-thalassemias and of β-globin synthesis in the β-thalassemia’s have been models for the study of other genetic diseases. Weatherall (1981) hypothesized that the hallmark of β-thalassemia is defective β-globin synthesis, which leads to imbalanced globin chain production and an excess of α-chains which aggregate in red-cell precursors, and cause abnormal cell maturation and their premature destruction in the bone marrow. Pathophysiology due to chain imbalances within the thalassemicerythropoietic precursors resulting in ineffective erythropoiesis and medullary as well as intravascular hemolysis, perhaps as a result of oxidative processes and resulting apoptosis-like events during erythroid development was explained by Schrier (1994). Assay of m-RNA in cell free system clearly shows a deficiency of m-RNAin heterozygous β-thalassemic bone marrow. It has been proposed that in β-thalassemia heterozygous there is compensation for defective β-chain synthesis by the β-chain locus on the unaffected chromosome. It has also been suggested that there is a compensatory reduction in α chain synthesis or that possibly both this mechanism may be operative.

In a recent study it has been shown that a highly expressed protein called Alpha Hemoglobin Stabilizing Protein (AHSP) can act as a chaperone for free α-chains and prevent their precipitation as it is highly expressed in hemoglobin-synthesizing erythroid precursors. AHSP acts as a secondary compensatory mechanism to balance the excess α-globin chain in β-thalassemia after the formation of HbF. Thus it can be said that AHSP is a modifier for phenotypic severity in HbE/β-thalassemia patients.

Foetal haemoglobin, HbF(α2Y2) is one of the major Hb during the foetal life and gradually in diminishing trend, and finally reported in the adult Hb comprising up <2%. HbF level is considered to be one of the major diagnostic criteria in detection of HbE/β-thalassemia.

Some genotypic factors have been reported to affect the synthesis of γ-chain, such as 3’HS1 (+179 C→T)
polymorphism (23), the (AT)xNry(AT)y motif in the 5′HS2 site (24), the (AT)x(CT) motif in the -540 region of the β-globin gene (25), GATA-1 (26), and heme-regulated initiation factor 2 alpha kinase (HRI) (27). Also genetic variation at three major loci - XmnI-HBG2 (28,29), HBS1L-MYB intergenic region on chromosome 6q23 and variation on rs11886868(T→C) in the BCL11A gene (30,31) on chromosome 2p16 has account for relatively large proportion (20-50%) of the phenotypic variation in HbF levels (32).

HbF levels in HbE/β-thalassemia, and other β-thalassemia syndromes, results from increased erythropoietin levels leading to bone marrow expansion, and possibly increased F-cell production, combined with ineffective erythropoiesis giving a survival advantage to F cells. (33)

Baruah et al(2014) reported that the HbF level in HbE/β-thalassemia patients (HbF30.7±10.1) was found to be statistically significant when compared to HbF levels of HbE homozygous (HbF=4.6±3.1) and subjects with normal hemoglobin pattern (HbF=0.5±0.7) (34).

Study by Premawardhena et al in the HbE/β-thalassemia patients in the Sri Lankan patients noted a significant correlation within a narrow range of haemoglobin values between the steady state hemoglobin and the absolute level of haemoglobin F (r=0.7, p=0.001). Relation between concentration of erythropoietin and haemoglobin(r=0.66, p=0.0001) and a decline in erythropoietin response with age (r=0.56, p=0.0001) was found to be statistically significant in the HbE/β-thalassemic patient. Erythropoietin correlation within a narrow range of haemoglobin values. As a consequence, augmented γ-globin gene expression or HbF production can ameliorate the clinical severity of these common hereditary disorders.

References


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