

HbE β -Thalassaemia in Malaysia: Revisited

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Abstract

HbE β - thalassaemia is a public health problem in Malaysia and the most common type of thalassaemia seen in the Malays. It shows considerable diverse phenotypes. Complete molecular analysis to identify primary/ secondary alleles of thalassaemia and gene modifiers are arbitrary predictors of possible outcome of disease. Early diagnosis is important. Patients need to be classified as minor, moderate (TI) and severe. Clinical diagnosis requires careful observations over a period of time with good record keeping of growth, sexual maturation and quality of life. Patients with haemoglobin (Hb) levels less than 7 gm/dl should be treated as transfusion dependent β -thalassaemia major to prevent complications that occur progressively with advancing age. Hb levels less than 7 gm/dl show patients are destined to be short, have splenomegaly and skeletal abnormalities. Pre transfusion mean Hb levels kept between 9-10 gm/dl by transfusion will suppress bone marrow activity and decrease iron absorption through gastrointestinal tract.

Keywords: Thalassaemia; Haemoglobin E; Genetic modifiers; Genotype – phenotype diversity; Natural history; Treatment

Disorders of haemoglobin (Hb) chain synthesis are divided generally into three broad groups: Thalassaemia, Hb Variant and Hereditary persistence of foetal Hb (HPFH). Thalassaemia is a disorder of haemoglobin synthesis which is characterized by the absence or reduced synthesis of globin chain synthesis of Hb. The main forms of thalassaemia involve α and β globin chains. There are two forms of β -thalassaemia: β^0 – no β globin chain synthesis and β^+ – some β globin chain synthesis. Clinically β -thalassaemia presents as β -thalassaemia trait (β^0 or β^+), β -thalassaemia intermedia (β^+/β^+ ; β^+/β^0) and β -thalassaemia major (β^0/β^0). In Hb Variant, there is a structural defect where a point mutation in the β -globin gene results in replacement of an amino acid with an abnormal amino acid where reduced synthesis of this abnormal Hb leads to thalassaemia-haemoglobinopathy. In HPFH, there is a development defect where significant production of HbF continues through life.

The total population in Malaysia is estimated as 28 million. Malaysia is multiracial with three main races, the Malays (50.4%), Chinese (23.7%), Indians (7.8%) others (7.1%). Indigenous people (11%) are present in peninsular Malaysia (Orang asli) and also in east Malaysia (Sarawak and Sabah) [1]. Each ethnic group has its characteristic set of β -thalassaemia mutations. Thalassaemia is a public health problem in Malaysia [2].

The spectrum of β -thalassaemia mutations in Malaysia have been systematically delineated since 1984. Three common β -globin mutations that account for 73% of the mutations in Malays are HbE, IVS 1-5 (G to C), and IVS 1-1 (G to T). The 5 common β -globin mutations that account for 90% of the mutations in Chinese- Malaysians are CD 41-42 (-TCTT), IVS 654 (C to T), -28 (A to G), CD 17 (A to T) and CD 71/72 (+A) respectively [3-10].

Haemoglobin E (HbE) is the most common β -globin Hb variant in Southeast Asia where the trait reaches a frequency of 50% in many areas. Occurrence of HbE is highest on the Southeast Asian mainland in the border areas joining Thailand, Laos and Cambodia, the so called 'HbE triangle' [11]. In Malaysia, it is common in the Malays with carrier rate of 5% and higher prevalence in the Orang Asli of peninsular Malaysia. There are 10 Malays with HbE to one in Chinese - Malaysians. HbE is a structural β -globin Hb variant with a β^+ phenotype. The molecular defect a point mutation in exon 1 at codon 26 (GAG to AAG) of the β globin gene, results in substitution of lysine for glutamic acid. Activation of a cryptic splice site occurs in codons 24-27, where the abnormally spliced mRNA (1.5-8%) is non – functional and has

no globin chain formed at this site. The α /non- α ratio is 1.03-2.19 in HbE heterozygotes [12]. Thus, the β^+ phenotype is the consequence of reduced β -globin chain synthesis [13]. Factors that activate or reduce the amount of mRNA spliced at this cryptic splice site play a role in phenotype expression of HbE.

The interaction of HbE with β -thalassaemia results in HbE β -thalassaemia, an extremely heterogeneous clinical condition. Hb E β -thalassaemia is the most common form of β -thalassaemia in Southeast Asia. In 1954, the first description of Hb E β -thalassaemia appeared under the title of Mediterranean anaemia, a study of 32 cases in Thailand [14]. In Malaya, the first case of HbE was mentioned by Lehmann and Singh in 1956 [15]. In peninsular Malaysia, HbE β -thalassaemia is common in Malays and Orang Asli of peninsular Malaysia. In the indigenous people of Sabah, East Malaysia, the most common cause for transfusion dependent β -thalassaemia major is a homozygous state of the Filipino deletion and not Hb E β -thalassaemia.

Natural History of HbE β -Thalassaemia

The natural history of HbE β -thalassaemia has not been completely defined. Environmental factors, intercurrent infections, nutritional status and access to health care facilities have been confounding factors. Most studies reported are on hospitalized patients and miss out on mild cases in the population. HbE- β -thalassaemia can be confusing for both parents and doctors, as the picture varies so much from one patient to the next. Patients show considerable heterogeneity, both phenotypically and genotypically. Changing phenotypes make clinical studies difficult to do. In countries in Southeast Asia including Malaysia, molecular studies to identify gene modifiers are not available routinely. In the absence of guidelines on treatment and lack of understanding of the underlying mutations present, patients may be converted to transfusion dependency by regular blood transfusions.

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Clinical Severity and Diagnosis of HbE β thalassaemia

The diagnosis of HbE β -thalassaemia is largely clinical. A patient had to be symptomatic, transfusion dependent have Hb levels less than 7gm/dl for three consecutive months in absence of any concurrent infection to be considered as clinically severe. In this group, are patients who become symptomatic generally in the first year of life? In transfusion dependent β -thalassaemia major most patients are symptomatic in the first year of life as there is no HbA synthesis. In the majority of HbE β -thalassaemia, patients present after the 2nd year of life as HbE is present. In Malaysia, these patients get classified as HbE β -thalassaemia - intermedia. However, in this early age a patient with HbE β -thalassaemia may be seen in the presence of infection where the Hb level may reach levels <7 gm/dl. These patients may surreptitiously be converted to transfusion dependent β -thalassaemia major if the attending physician is not aware of the definitive diagnosis. A patient is defined as clinically mild if they were asymptomatic and had Hb levels 10-14 gm/dl. Majority of patients with HbE trait and β - thalassaemia trait will fall into this latter group. The patients that have HbE β -thalassaemia intermedia will fall between these groups. Thus, HbE β -thalassaemia intermedia refers to patients with clinical manifestations that are too severe to be minor (trait) and too mild to be β -thalassaemia major [16]. In Hb E β - thalassaemia, extreme diverse clinical phenotypes exist. Hb levels range from 5.5 to 11.0 gm/dl where the severity of anaemia is a consequence of the degree of ineffective erythropoiesis and peripheral haemolysis. In Malaysia, 2 clinical phenotypes are generally seen. Mild where the Hb levels are greater than 9.5 gm/dl, splenomegaly is mild and there is no requirement of blood transfusions. HbE with mild β thalassaemia mutations such as polyadenylation (AATAAA \rightarrow AATAGA) mutation is an example in this group. In the Chinese-Malaysians, the most common mutation is CD 41-42 (-TCTT). This latter molecular defect, a frame-shift mutation has a β^0 -phenotype resulting in total absence of HbA synthesis. Patients with HbE - β [FSC 41-42(-TCTT)] have clinically diverse manifestations as a consequence of modifying factors: they are either transfusion dependent or present as severe β -thalassaemia intermedia. The most common form of HbE β -thalassaemia in Southeast Asia and in Malaysia is HbE - β [IVS1-5 (G \rightarrow C)]. The IVS1-5 (G \rightarrow C) mutation has a β^+ - thalassaemia phenotype and is severe as there is only a minimal amount of HbA synthesis (2.7-5.8%). Patients in this group have a low mean Hb of 6.5 gm/dl, moderate to severe splenomegaly and skeletal abnormalities. Many are asymptomatic and adapt to this low Hb level [17]. Growth appeared to be normal until 5 years of age without blood transfusions. Growth deficiency and delayed sexual maturation become obvious after the age of 9 where 50% of the patients with HbE β -thalassaemia [IVS 1-5 (G to C)] by age 13 were below the 3rd percentile. Once sexual maturation occurs between 15-19 years of age, these patients are fertile, in the absence of blood transfusions and iron chelation therapy. Adults, however who had not been transfused had moderate thalassaemic facies, enlarged spleens and growth height age corresponding to 12-14 years. Thus, patients with Hb<7 gm/dl are short. However studies indicate that patients with Hb<7 gm/dl are destined to late complications. [18,19]. It is important that an early diagnosis is made to identify the mild, moderate [thalassaemia-intermedia (TI)] and severe types of Hb E β - thalassaemia.

The following key points are indicated in diagnosis [16,18-20].

- Clinical diagnosis: This requires careful observations for a period of time before a decision is made. Proper records are mandatory.
- Early diagnosis is must as patients need to be counselled despite being asymptomatic. Follow up being life-long.

- Complete molecular diagnosis to identify the primary / secondary alleles of thalassaemia and also identify gene modifiers.

Clinical diverse phenotypes are the consequence of gene modifiers, environmental factors and access to health-care facilities. Gene modifiers identified provide arbitrary guidelines of genotype-phenotype correlation and possible clinical phenotypes [21,22]. The α and non- α globin chain imbalance results in ineffective erythropoiesis due to expression of the primary allele and other globin genes involved in the synthesis of globin chains of Hb. The primary gene modifiers are specific alleles that result in β -thalassemia. In Malaysia, studies indicate the major ethnic groups have its own set of common mutations and some rare ones [3-10]. The secondary modifiers are other globin genes that affect globin chain imbalance. These include genes in the alpha globin gene complex. Coinheritance of alpha-thalassemia ameliorates and triplication of the α - globin genes aggravates β -thalassemia. Amelioration occurring in those when 2 α globin - genes are deleted. Gene modifiers that increase HbF synthesis ameliorate Hb E β - thalassaemia intermedia. Hereditary persistence of fetal Hb (HPFH) synthesis and the inheritance of Xmn1 polymorphism [CD158 (C \rightarrow T)] (polymorphism of HBG2 at position -158) do this. However, it is only the homozygous state of this polymorphism that ameliorates the clinical condition. The alpha-haemoglobin-stabilizing protein (AHSP) plays a role in reducing the deleterious effects of excess alpha globin chains on red blood cells. AHSP expression was influenced by mean cell haemoglobin and HbF levels of HbE / β -thalassaemia patients in Malaysia [23]. In contrast, AHSP was not seen as a disease modifier of HbE- β -thalassaemia in Thailand [24]. Thus, AHSP expression as a modifier of thalassaemia may be population specific. Tertiary gene modifiers affect the disease process and not globin chain production. These include coinheritance of hemochromatosis gene, mutation in the promoter gene of bilirubin UPD-Glucuronyl transferase and bone metabolism (COL1A 1). A red cell membrane defect, hereditary ovalostomatocytosis present in the Malays reduces deformability of cells and with coinheritance of β -thalassemia increases red cell destruction in the spleen [20] (Table 1).

Treatment

Current treatment of Hb E β - thalassaemia in many countries in Southeast Asia including Malaysia in the absence of guidelines is done in a haphazard way and on demand transfusion is a feature in some [16,18-20,22]. The attending physician is in a dilemma: 'to treat or not to treat?'. Patients may be asymptomatic at Hb levels at <7 gm/dl in HbE β -thalassemia. However, studies have shown that complications are seen in this group in advancing-age in the absence of regular blood transfusions [19]. Complications that occur in the absence of blood

HbE β^0 -thalassaemia or HbE β^+ -thalassaemia
Ameliorate
HbE β^0 -thalassaemia or HbE β^+ -thalassaemia with α -thalassaemia
HbE β^0 -thalassaemia or HbE β^+ -thalassaemia with hereditary persistence foetal Hb (HPFH)
HbE β^0 -thalassaemia or HbE β^+ -thalassaemia with homozygous state of Xmn1 polymorphism [-158 (C to T)].
HbE β^0 -thalassaemia or HbE β^+ -thalassaemia with alpha haemoglobin stabilising protein (AHSP)
Aggravate
HbE β^0 -thalassaemia or HbE β^+ -thalassaemia with hereditary ovalostomatocytosis
HbE β^0 -thalassaemia or HbE β^+ -thalassaemia with triplication of α globin genes

Table 1: Molecular basis of HbE beta-thalassaemia.

transfusions are splenomegaly, bone deformities, extramedullary masses and leg ulcers. Progressive iron overload has been associated with liver disease (cirrhosis and hepatocellular cancer). Failure of commencement of therapy has resulted in splenectomy leading to increased risk of infection, hypercoagulable state, pulmonary hypertension and secondary heart failure. The common cause of death in HbE β -thalassaemia patients with splenectomy is infection. Splenectomy is no longer a recommended choice for treatment. Personalised therapy remains the treatment of choice for optimal care: This is targeted at quality of life, attainment of puberty, sexual maturation and prevention of complications that progressively occur with advancing age. In the puberty period, patients with HbE β -thalassaemia intermedia show benefit to regular blood transfusion to aid attainment of sexual maturation. The management of transfusion dependent β -thalassaemia major is well defined with recognised guidelines. HbE β -thalassaemia is a public health problem in Southeast Asia. There is urgent need for a concerted effort to produce guidelines to treat this condition in this region.

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