REVIEW ARTICLES

HAEMOGLOBIN-E DISEASE IN CHILDREN: GLOBAL AND BANGLADESH PERSPECTIVE - AN UPDATE

RAHMAN AKMM[1], UDDIN MK[2], HOSSAIN MZ[3], AHMAD M[4], BEGUM RS[5], GHOSH AK[6], FATMI LE[7], DAS SR[8]

Abstract:

Haemoglobin E diseases are the most common structural haemoglobin variant with thalassaemic properties in the world population, reaching its highest frequency in South East Asia and also prevalent in Bangladesh. About 4.8 million people are carrier of this disorder in Bangladesh. Clinical presentations of Hb-E diseases are variable, ranging from asymptomatic to severe anemia with significant morbidity and mortality. Management includes regular follow up of growth and facial deformities, nutritional support, blood transfusion, splenectomy, iron chelation therapy, drugs to increase Hb F, bone marrow transplantation and gene therapy. The frequency of Hb E diseases are increasing day by day though there is no screening or prevention program for the diseases in Bangladesh. But many countries like Mediterranean and Western countries take initiative to prevent this type of diseases successfully by antenatal diagnosis, screening program, carrier detection and genetic counseling. Bangladesh needs such a type of program to combat these deadly diseases.

Key words: *Haemoglobin E, Haemoglobin E trait, Haemoglobin E diseases, HbE / â –thalassemia*

J Dhaka Med Coll. 2011; 20(1) : 193-198.

Introduction:

Haemoglobin E (Hb E), the fourth abnormal hemoglobin to be discovered, was identified in 1954. The first description of HbE / B – thalassemia was given in next year [1]. World wide it is one of the most common structural variants of hemoglobin[2, 3]. About one in 100 of the world population carries hemoglobin E [4]. World-wide there are over 56 million carriers and about 20,000 children are born each year with HbE / B-thalassemia. The gene is carried by an estimated 300 million people, virtually all residing on or near the South East Asian mainland [5]. In Northeast India and Bangladesh the prevalence rate is 30-40% but little is known about its natural history, the reasons for its clinical diversity, or its optimal management [6].Hb E is an inherited autosomal recessive variation of Hb A that occurs in the beta B globin chain of Hb A. The formation of Hb E occurs by substitution of lysine for glutamic acid at codon 26 of the B-chain[1,2]. Hemoglobin E is not only a structural variant but also synthesized inefficiently as compared with hemoglobin A, causing a clinical phenotype of mild form of B-thalassemia. The interaction of Hb E with B-thalassemia results in thalassemic phenotypes ranging from a condition like thalassemia major to thalassemia intermedia. The prevalence of hemoglobin E is higher than B-thalassemia. So Hob E/ B-thalassemia are prevalent in our country. But we are not aware about it. It is a common hematological problem in Bangladesh but it is not addressed properly till now. So we attempt to update our knowledge and attitude about the disease in this article.

1. Dr. A.K.M Matiur Rahman. Assistant Professor of Paediatrics, Dhaka Medical College, Dhaka.
2. Dr. Md. Kazim-Uddin. Associate Professor of Haematology, Northern International Medical College, Dhaka.
3. Dr. Mohammad Zaid Hossain. Assistant Professor of Medicine, Dhaka Medical College, Dhaka.
4. Dr. Mainuddin Ahmad, Associated Professor of Paediatrics, Dhaka Medical College, Dhaka.
5. Dr. Rashida Sadia Begum, Assistant Professor of Physiology, Dhaka Medical College, Dhaka.
6. Dr. Ashis Kumar Ghosh, Assistant Registrar, Paediatric Hematology and Oncology, Dhaka Medical College, Dhaka.
7. Dr. Lutfar Ehsan Fatmi, Professor of Paediatric Hematology and Oncology, Dhaka Medical College and Hospital.
8. Dr. Shishir Ranjan Das, Assistant Professor of Neonatology, Dhaka Medical College, Dhaka.

Correspondence: Dr. A.K.M Matiur Rahman, Assistant Professor of Paediatrics, Dhaka Medical College, Dhaka. Cell Phone: +8801819242859, Email: pediatrics@yahoo.com

Genetics and Heredity:

Hb E is an inherited autosomal recessive variation of Hb A that occurs in the beta (â)-globin chain of Hb A. The formation of Hb E occurs by substitution of lysine for glutamic acid at codon 26 of the â-chain. Haemoglobin 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/beta-thalassemia (Hb E/â-thal). The best method to distinguish the results is to test both parents[4].

Pathophysiology:

Pathophysiology is complex which involves ineffective erythropoiesis, apoptosis, oxidative damage and shortened red cell survival time. Interaction between Hb E and B-thalassemia alleles is main determinant in pathophysiology. HbF level is strongest predictor of morbidity. HbE Trait may be co-inherited with B^0-thalassemia or B+thalassemia[7]. Hob E is known to be unstable in vitro and it is possible that this may contribute to the severity and variability in HbE/ B-thalassemia. The oxidative stress resulting from free ??chains within the HbE/ B-thalassemic red cell might result in the precipitation of HbE molecules, stressing the proteolytic capacity of the cell and further damaging its membrane. Small variations in oxidative stress and proteolytic capacity might provoke catastrophic precipitation of HbE and severe anemia[8]

Clinical Presentation:

The most common form of Hb-E diseases are Hemoglobin E trait (heterozygous state, genotype AE), Hemoglobin E disease (homozygous state genotype EE) and compound heterozygous form such as hemoglobin E/ β thalassemia (E/ β that) and sickle cell/ hemoglobin E disease (genotype SE).

Hemoglobin E Trait

Hemoglobin E Trait is defined by the heterozygous condition associating with one normal adult hemoglobin (HbA)- β gene and one variant hemoglobin EB gene [9]. Patient of hemoglobin E trait is an asymptomatic with no clinical relevance, except for the risk of compound heterozygous states with â thalassemia in the offspring.

Hemoglobin E diseases

Hemoglobin E diseases are an autosomal recessive disease. It occurs when an individual inherits two genes coding for hemoglobin E, one from each parent [11]. Hemoglobin E disease is defined by the coexistence of two b-E alleles (homozygous stats EE). At birth differential diagnosis of hemoglobin E diseases is E/ β thalassemia, which is always symptomatic after disappearance of HbF. Study of both parents is mandatory[9]. Individuals with the genotype EE are usually completely asymptomatic. There is usually no anemia and rarely any evidence of hemolysis [1]. The spleen is not usually enlarged. Otherwise a coexisting HbH disease ($?_{??}$thalassemia) must be considered.

Hb E/ β-thalassemia

Hb E/ β-thalassemia is the commonest form of severe thalassemia in the world and is most prevalent in the rapidly expanding and increasingly influential countries of Southeast Asia[1]. This compound heterozygous state is quite common in Thailand and occurs throughout a large part of Southeast Asia especially in Bangladesh. If one member of couple has hemoglobin E trait and the other has beta thalassemia trait, there is a 25% chance with each pregnancy that their child will co-inherit both traits. And this leads to a disease called hemoglobin E/ beta thalassemia in that child [8].

The severity of this compound heterozygous is variable, ranging from that of beta-thalassemia minor through thalassemia intermedia to thalassemia major. The most severely affected individuals are transfusion dependent and have liver enlargement and splenomegaly. Intermittent jaundice, growth failure and facial deformity. During pregnancy, patients may temporarily become transfusion dependant. Extramedullary hemopoiesis has sometimes led to spinal cord compression and brain tumor like clinical features.

Compound Heterozygotes (Sickle cell/ Haemoglobin E) SE disease

This variation is similar to sickle cell-C disease except that an element has been replaced in the hemoglobin molecule. This variation is often also seen in Southeast Asia populations. Hemoglobin SE disease is a form of sickle cell disease, which tends to be mild in childhood. However, adults with hemoglobin SE disease may experience complications including painful episodes, dysfunction of the spleen and anemia[10]. Mild chronic hemolytic anemia is common in this disorder but vesooclusive crises are rare, more frequent during pregnancy [7].

Diagnosis:

Laboratory method.

1. Estimation of haemoglobin:

Haemoglobin was determined by cyanmeth haemoglobin method. In this method, haemoglobin mixed with the potassium ferricyanide and potassium cyanide to form colored compound cyanameth haemoglobin (HicN). After the absorbance was taken in photoelectric colorimeter at a wave length of 540 nm. The absorbent of the complex is directly proportional to the haemoglobin concentration.

2. Blood count, blood film (PBF) and Haemoglobin Electrophoresis:

Haemoglobin E trait does not pose health concern[10]. Haemoglobin E trait may carry ? thalessemia conditions of varying severity. Blood film may be normal or may show hypochromia, microcytosis, target cells irregularly contracted cells, basophilic stippling. Electrophoresis at alkaline p^H on cellulose acetate shows that the variant HbE has the same mobility than that of the HbC and HbA_2. In HbE heterozygotes, the variant usually comprises 33% or less of total HbA. Individuals with less than 30% of HbE almost always have co existing ? thalessemia trait [9].

In *Haemoglobin E diseases* the blood count often resembles that of B thalassemia trait, with a normal hemoglobin concentration or very mild anemia and increased red blood cell, reduced MCV and MCH. MCHC is usually normal. The blood film usually shows hypochromia and microcytosis with variable numbers of target cells, basophilic stippling and irregularly contracted cells. Hemoglobin electrophoresis shows the major hemoglobin to be Hb E, with Hb E plus HbA_2 constituting 95-99% of total hemoglobin [9].

In *HbE/ B^0 thalassemia* the hemoglobin level is lower than the HbE disease. Hemoglobin electrophoresis show the presence of HbE, HbA_2 and HbF in case of HbE/ B^0 thalassemia and HbE, HbA, HbA_2 and HbF in case of HbE/ B^+ thalassemia [9]. It is possible to make diagnosis of E B-thalassemia even in neonates by Hemoglobin Electrophoresis. Prenatal Diagnosis can be done by Chorionic villus sampling [6].

In *Compound heterozygote SE disease* hemoglobin concentration may be normal or reduced.MCV is reduced. Reticulocytes count mildly elevated. The blood film shows target cells but sickle cells are uncommon. Hb S represents a large proportion of total hemoglobin than Hb E (around 65%). Hb F normal or slightly elevated [9].

Criteria for diagnosis of abnormal hemoglobin variants were based on identify an abnormal band on hemoglobin electrophoresis on cellulose acetate strip in tris-EDTA buffer (PH 8.6) by comparing the electrophoretic mobility (bands) of the test (Unknown).

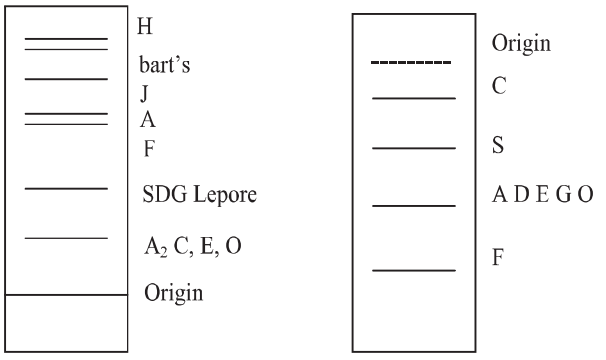

Fig: *Schematic representation of electro-phoresis mobility of normal and some of more common abnormal hemoglobin in cellulose acetate at PH 8.6 (left) and agar gel at PH 6.0 (right).*

Management of Haemoglobin E Diseases:

Haemoglobin E trait and Haemoglobin E diseases are asymptomatic. There is no anemia and rarely any evidence of hemolysis. Spleen is not usually enlarged. They do not suffer from iron overload but iron deficiency anemia. In pregnant woman iron therapy may needed. The Haemoglobin E carrier can donate blood[7].

Management of HbE B-thalassemia is similar to homozygous B-thalassemia. In these patients with Hb >7gm% without complications, long term folic acid is recommended. Many may benefit from hydroxyurea therapy which decreases ineffective erythropoiesis and increases haemoglobin with or without increase in HbF. During childhood regular follow up of growth and facial deformities, hemoglobin level, prophylaxis and treatment of infection sources are essential. Daily oral penicillin is recommended. Indications for regular transfusion are persistently low haemoglobin (< 7gm/dl), significant skeletal abnormalities and marked extramedullary hematopoiesis.

Complications are usually due to iron overload, hence regular iron chelation is recommended. Endocrinopathy secondary to hemosiderosis may require exogenous hormonal therapy. Splenectomy is indicated when there is high transfusion requirement 3and evidence of hypersplenism. Bone marrow transplantation has very rare indications and high morbidity and mortality. Recombinant erythropoietin alone or associated with hydroxyurea may be useful in reducing transfusion requirements, in improving quality of life and in diminishing hemopoietic ectopic extramedullary masses. Periodic assessment of serum ferritin, calcium, T_4, TSH, RBS, LFT etc. aids in proper management. In those with hypogonadism, serum testosterone or estradiol levels should be assessed[6].

Counseling the family:

01. 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.
02. 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 B – thalassaemia components. If medical concerns arise or the infant is symptomatic, CBC with smear should be done earlier.
03. Educate parents and care givers regarding signs and symptoms.
04. Consult with a pediatric hematologist regarding patient evaluation and possible disease management.

Bangladesh Aspect:

Haemoglobin E (beta26Glu—> Lys) is the most common hemoglobin variant in Southeast Asia [12]. World wide it is one of the common structural variants[5]. According to the World Health Organization (WHO) report estimates that about 3.0% of populations are carriers of Beta Thalassemia and 4.0% are carriers of Hb-E in Bangladesh, which means that there are about 3.6 millions carriers of beta thalassemia and 4.8 millions carriers of Hb-E[13]. More over the percentage of HbE patients are increasing day by day because a dynamic model of the three genes (involving HbA, HbE and-thalassemia) suggest that the HbE gene is replacing the-thalassemia gene in most Southeast Asian populations[14]. The detection of hemoglobin E is important for the antenatal diagnosis of disorders of globin chain synthesis because its interaction with B thalassaemia produces a compound heterozygous state that varies in severity from thalassaemia minor to, more often, thalassaemia intermedia or thalassaemia major. Many of the countries in which hemoglobin E is prevalent have under-resourced laboratories and expensive and relatively difficult techniques such as high performance liquid chromatography (HPLC) and haemoglobin electrophoresis are available only in major centers. Nevertheless, the detection of haemoglobin E is important if social and economic burden of hemoglobinopathy is to be avoided [15]. Hemoglobin-E, which is quite common in Bangladesh, has no definite data regarding carrier status of the hereditary

hemoglobin disorder exist. No screening programme had ever been taken in any population group [13]. No doubt the total scenario is alarming for Bangladesh because patients doubly heterozygous for HbE and beta thalassemia are substantially more symptomatic than patients heterozygous for either disease [5]. Therefore, in a prevention and control program, rapid, accurate, and inexpensive screening protocols to identify carriers of Hb E and other hemoglobinopathy (?²?- thalassemia. â- Thalassemia), especially in a prenatal population at risk for Hb disorders, are essential[16]. Although antenatal diagnosis is central to the control of a hemoglobinopathy, screening programs form an important and integral part of the programs. Several Mediterranean and western countries have achieved a significant change for the control of Thalassemia in the homozygote population since the last two decades. Other countries which also have such control programs include Canada, Israel, Turkey, Thailand, Lebanon West Bank and Gaza Strip, Malaysia, China, Iran, Egypt, and Pakistan[5].

A screening policy exists in Cyprus to reduce the incidence of thalassemia which since the program's implementation in the 1970s (which also includes pre-natal screening and abortion) has reduced the number of children born with the hereditary blood disease from 1 out of every 158 births to almost zero[17]. The ultimate goal of hemoglobin E screening is to prevent severe forms of the disorder, namely hemoglobin E-thalassaemia. This has been achieved in Hong Kong by an antenatal screening program for pregnant women that incorporate carrier detection, genetic counseling and prenatal diagnosis. There are merits therefore to develop a screening program in the community for carriers detection to be given both the time and genetic information of reproductive significance to plan their future family. Needless to say, public education is also an important element in ensuring success of preventive program [18]. The importance of screening programs lies in the fact that they also provide a platform for increased awareness and education regarding thalassemia in the screened population and the associated population group including parents, teachers, friends, siblings, and employees [19].

Conclusion:

It is evident that the hereditary hemoglobin disorders are quite common in Bangladesh and these disorders are inherited as autosomal recessive mendelian pattern affecting both male and females. So we can not avoid this disease. The most of the population are usually asymptomatic, do not require treatment and leads a reasonably good quality of life but they are dangerous because possibility to give birth of homozygous or double heterozygous children. This is a health threat nationally as well as in global situation.

References:

1. Rees DC, Porter JB, Clegg JB, Weatherall DJ. Why are hemoglobin F levels increased in Hb E/β-thalassemia? Blood 1999; 94: 3199-3204.
2. Bunn HF, Forget B. Hemoglobin: molecular, genetic and clinical aspects. Philadelphia: Saunders; 1986. 425-7.
3. Ali MAM, Quinlan A, Wong SC. Identification of haemoglobin E by the isopropanol solubility test. Clin Biochem 1980; 13: 146-8.
4. Hemoglobin E disease. Fact sheet for health care providers. Utah department of health, Salt Lake City. 208; 8: 2.
5. Thomas M. Hemoglobin E in Indochinese Refugees. West J Med 1982; 137: 186-90.
6. Manawa Q, Sadashiva U, Malagi NN, Thobbi AN. Hemoglobin E â+-Thalassaemia- a case report from Bijapur, South India. Al Ameen J Med Sci 2009; 2: 20.
7. Vichinsky E. Changing pattern of thalassemia worldwide. Ann N Y Acad Sci 2005; 1045: 18-24.
8. Itano HA, Bergren WR, Sturgeon P. Identification of a fourth abnormal human hemoglobin. J Am Chem Soc 1954; 76: 2278.
9. Bachir D, Galacteros F. Hemoglobin E. Orphanet Encyclopedia 2004; http://www.orpha.net/data/patho/GB/uk-HbE.pdf [Accessed on 22.12-2010.
10. Bojanowski J. Hemoglobin E trait. Children's Hospital Oakland Comprehensive Thalassemia Center.Oakland 2005.
11. Quinn P, Arnold D. Genetics and Newborn screening. Springfield. IIIinois Department of Public Health; 2006.

12. Kishore B, Khare P, Gupta RJ, Bisht S, Majumdar K. Hemoglobin E disease in North Indian Population: a Report of 11 cases. Hematology 2007; 12(4): 343-7.

13. Rahman MJ, Rahman MH. Prevention & control strategy of thalasssemia in Bangladesh. Orion Med J 2003; 16: 13.

14. Flatzl G. Hemoglobin E: distribution and population dynamics. Biomedical and Life Sciences 2004; 3: 189-234.

15. Chapple L, Harris A, Phelan L, Bain BJ. Reassessment of a simple chemical method using DCIP for screening for hemoglobin E. J Clin Pathol 2006; 59 :74-6.

16. Sanchaisuriya K, Fucharoen S, Funcharoen G. Reliable screening protocol for thalassemia and hemoglobinopathies in pregnancy - an alternative approach to electronic blood cell counting. Am J Clin Pathol 2005;123:113-8.

17. Leung TN, Lau TK, Chung TKH. Thalassaemia screening in pregnancy. Curr Opn Obs Gynecol 2005; 17: 129-34.

18. Sin SY, Ghosh A, Tang LCH, Chan V. Ten years' experience of antenatal mean corpuscular volume screening and prenatal diagnosis for thalassaemias in Hong Kong. J Obstet Gynaecol Res 2000; 26: 230-8.

19. Cao A, Rasatelli MC, Gallanello R. Control of beta-thalassaemia by carrier screening genetic counseling and prenatal diagnosis: The Sardinian experience. Ciba Found Symp 1996; 197: 137-51.