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# HbE- Thalassemia: A case report

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**Abstract**
Thalassemia is a blood disorder passed down through families (inherited) in which the body makes an abnormal form or inadequate amount of hemoglobin. Hemoglobin is the protein in red blood cells that carries oxygen. The disorder results in large numbers of red blood cells being destroyed, which leads to anemia. Symptoms include fatigue, weakness, paleness and slow growth. Mild forms may not need treatment. Severe forms may require blood transfusions or a donor stem-cell transplant. Mild forms may not need treatment. Severe forms may require blood transfusions or a donor stem-cell transplant.

**Keywords:** HbE, beta globin, erythropoiesis, haemoglobinopathy, thalassemia, haemolysis

## 1. Introduction
Thalassemia is an inherited blood disorder that reduces the production of functional hemoglobin (the protein in red blood cells that carries oxygen). This causes a shortage of red blood cells and low levels of oxygen in the bloodstream, leading to a variety of health problems. There are two main types of thalassemia, alpha tha lacemia and beta tha lacemia. Signs and symptoms vary but may include mild to severe anemia, paleness, fatigue yellow discoloration of skin (jaundice), and bone problems. Beta thalassemia is caused by changes (mutations) in the HBB gene while alpha thalassemia is caused by mutations in the and/or HBA2 genes. Both are inherited in an autosomal recessive manner. Treatment depends on the type and severity of the condition but may include blood transfusion and/or folic acid supplements. Most people affected by beta thalassemia have mutations in both copies of the HBB gene in each cell. The parents of an affected person usually each carry one mutated copy of the gene and are referred to as carriers. Carriers typically do not show signs or symptoms of the condition; although some carriers of beta thalassemia develop mild anemia. When two carriers of an autosomal recessive condition have children, each child has a 25% (1 in 4) risk to have the condition, a 50% (1 in 2) risk to be a carrier like each of the parents, and a 25% chance to not have the condition *and* not be a carrier.

## 2. Case Report
A 7 yrs. old male patient visited department of pediatric nursing (civil hospital panipat in india). Family history revealed presence of thalassemia in one of his family members. Personal history was non-contributory. Patient was poorly built and nourished with short stature. He presented with complaints of Fatigue for 2 yrs., unusual size of head for 4 yrs. Yellowish discolouration of eyes for 8-9 months and abdominal discomfort and exertional dyspnoea for 8 months. His complaints started as mild fatigue. But these complaints were neglected. For the last 8- 9 months he is having jaundice, abdominal discomfort and exertional dyspnoea which made him to consult a doctor. No h/o recurrent infections or bleeding manifestations. No h/o blood transfusions. No h/o recurrent leg ulcers. No h/o loss of weight or appetite. He has 2 brothers and 3 sisters, of which 1 brother has h/o similar illness but not severe and not taking any treatment. No h/o surgeries in the family. On general examination he was conscious and oriented, Severe pallor (+), Mild icterus (+). No clubbing, cyanosis, lymphadenopathy or pedal oedema. PR-84/min, regular. BP– 110/70 mmHg. He was afebrile at the time of examination. Frontal bossing (+), Flat nasal bridge (+). On system examination: P/A- Liver palpable 3 cm below RCM with a Liver span- 15 cm, Massive splenomegaly (+) crossing the level of umbilicus. Other system examination was within normal limits. Investigations showed: TC–5600, DC- N76 L12, Hb–5.6, HCT–16.4, MCV-68, MCH-20.9, MCHC-30, RDW- 30.5, PLT4.8L, ESR –19, URE: Alb– nil, Sug– nil, UBG- (+++), RFT - 24/0.8, RBS–88, Na/K–136/4.1, TB/DB–7.3/1.0, TP/Alb8.6/5.1, ALT-25, AST- 32, ALP-122. Reticulocyte count- 5.8%, S. Ferritin-315 (23-322), Osmotic fragility test-negative. P. Smear showed Microcytic hypochromic anaemia, Microspherocytes and fragmented RBCs with evidence of haemolysis.

### Lab Investigation
Anaemia has been observed with Hb as low as 5.7 g/dL. The Mean Corpuscular Volume (MCV) has been approximately 72±6 fL and mean corpuscular Hb concentration (MCHC) has been 29±2 fL. The electrophoresis demonstrates both Hb E and Hb A with a marked range for the amount of Hb A. In neonates, DNA analysis is required to differentiate these two syndromes in neonates and is increasingly being used routinely for diagnosis of Hb E disorders.

### Clinical Presentation
HbE Disease Presents in 3 Forms Namely
- Heterozygous State (Genotype AE or HbE trait)
- Homozygous State (Genotype EE or Hb E disease).
- Compound Heterozygous states.
- Hb E Beta Thalassemia (E Thalassemia).
- Sickle Cell/HbE Disease (SE Genotype).

The most serious Hb E syndrome is Hb E β0- thalassemia. The compound heterozygote state of Hb E βthalassemia results in a variable phenotype ranging from a complete lack

of symptoms to transfusion dependency. Approximately, one-half of the patients are phenotypically similar to patients with thalassemia major who require regular transfusion therapy and the other half resembles thalassemia intermedia. The pathophysiology of Hb E βthalassemia is complex. Ineffective erythropoiesis, apoptosis, and oxidative damage are central components of the disease and its shortened red cell survival. The interaction between Hb E and β-thalassemia alleles is the main determinant in the pathophysiology. Hb F level is the strongest predictor of morbidity. However, the basis of increased Hb F is usually unknown. The degree of severity is also affected by the type of β-thalassemia mutation. Co-inheritance of αthalassemia mutations decrease the globin chain imbalance and improve the anaemia. This occurs in fewer than 15% of patients. Triplicated or quadruplicated α-globin genes increase the severity of E-thalassemia and occur in approximately 4% of the population.

The clinical course of E β-thalassemia is punctuated by acute and chronic complications that may cause serious morbidity and mortality. The marked expansion of erythropoiesis is responsible for much of the pathology of the disease including hepatosplenomegaly, extramedullary haematopoietic masses, growth retardation, delayed sexual maturation and bone deformities. Splenomegaly often develops in severely affected patients. Iron overload in nontransfused patients is common secondary to increased gastrointestinal absorption of iron. End-organ failure secondary to iron overload may not be suspected because the serum ferritin level is disproportionately low.

WBC and Platelets normal. USG abdomen revealed borderline hepatomegaly and massive splenomegaly. HPLC showed Hb A2- 67% and Hb F-29% and these findings are suggestive of HbE-Homozygous state. But HbE alone will not produce this much severe clinical presentation. So, we proceeded with Hb electrophoresis and which showed Hb fractions Hb A-6.7%, Hb F- 34.2%, Hb E- 53.2%, Hb A2-5.9% and these findings were suggestive of compound heterozygosity for HbE/Beta Thalassemia. So, we kept the final diagnosis as congenital haemolytic anaemia- HbE/Beta Thalassemia Heterozygous state. Treated with packed cell transfusions to raise the Hb.

## Discussion

Haemoglobin (Hb) E is one of the world's most common and important mutations.It has replaced β-thalassemia as the most common Haemoglobinopathy in many countries. The World Health Organization (WHO) estimates that in Thailand at least 100,000 new cases of Hb E β-thalassemia are expected in the next few decades.High estimates are predicted for India, Sri Lanka, Malaysia and Southern China. The phenotype for patients with similar mutations can range from asymptomatic to transfusion dependent.Hb E is formed by a substitution of glutamic acid by lysine at codon 26 of the β-globin gene as a result of a splice site mutation on exon 1 of the beta-globin gene. This mutation also activates a cryptic mRNA splice site, which results in reduced synthesis of the β-E chain and leads to a thalassemia phenotype. Hb E has a weakened α/β interface, leading to some instability during conditions of increased oxidant stress. Hb E trait has no clinical significance. Patients may have mild microcytosis without anaemia.The red cell morphology may show targeting and may be similar to other thalassemia traits or mild thalassemia intermedia conditions. It is known to be unstable at high temperatures. The crystal structures of HbA2 and HbE have been established at 2.20 and 1.74 angstroms resolution, respectively. This is the reason why HbE is filtered along with HbA2 in HPLC. So, to differentiate between these two (HbE and HbA2), we need Hb electrophoresis. Hb E β+-thalassemia may have an extremely variable laboratory picture. They usually have a mild anaemia of approximately 9.5 g/dL. However, significant ranges of Cardiopulmonary disease is the most common cause of death in Hb E β-thalassemia. Patients with Hb E β-thalassemia are excellent candidates for agents directed at elevating Hb F production. A small increase in the steady-state haemoglobin concentration might be of major clinical benefit.

## Conclusion

HbE is a common abnormal Hb variant, which is an unstable form. Homozygous condition usually asymptomatic and almost silent and it becomes manifested when it mingles with Thalassemia. So high degree of suspicion and evaluation is needed, especially when the patient is coming from a prevalent area.

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