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COMPOUND HETEROZYGOSITY FOR HEMOGLOBIN E & B THALASSEMIA: A FAMILY STUDY FROM KERALA.

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Abstract:

Hemoglobinopathies are the most commonly seen monogenic disorders of blood creating a major genetic and public health problem worldwide. Hemoglobin E is a variant with a mutation in beta-globin chain of hemoglobin molecule. At least one million people around the world is having Hb E which can have either symptomatic or asymptomatic clinical presentation. The common abnormal hemoglobin variants prevalent in India are Hb S, Hb D, and Hb E. Hb S and Hb E are the prevalent in tribals of India[1] In Kerala HbS is the most prevalent abnormal hemoglobin which is most common among the tribals of Wayanad & Attapadi. HbE is very rare in Kerala while gene for beta thalassemia has been infrequently reported.[2,3] Early detection of haemoglobin E/β-thalassemia is important, because this compound heterozygous state is characterized clinically by thalassemia major in which affected individual may be symptomatic and transfusion dependent at an early age. This study focuses on 4 members of a family with compound heterozygosity for Hemoglobin E & beta thalassemia from Kerala.

Keywords: *Hemoglobin E, Beta thalassemia, compound heterozygous, HPLC*

Introduction

Hemoglobinopathies are one of the commonest recessive disorders seen globally. The burden hemoglobinopathies is of such a magnitude that it represents a major public health concern in most of the regions of Indian subcontinent. Hemoglobin E is the second most prevalent abnormal haemoglobin in the world and commonest one in Southeast Asia.[4] Carrier frequency of haemoglobin E/β-thalassemia is 60% in parts of Thailand, Laos, and Cambodia.[5] Of the several abnormal haemoglobins so far identified there are three variants Hemoglobin S, haemoglobin E and haemoglobin D which are predominantly prevalent in India[6]. Hemoglobin E is a structurally abnormal variant with a substitution of glutamic acid by lysine in the 26th position of the β-globin chain. Interaction of the structurally abnormal haemoglobin E with the disrupted synthesis of globin moiety leads to combination of two abnormalities, resulting in double heterozygosity of the disease. Etiology of hemoglobin E/β-thalassaemia is related to many factors including reduced β chain synthesis resulting in globin chain imbalance, ineffective erythropoiesis, apoptosis, oxidative damage and shortened red cell survival[7,8]. Since This double heterozygous condition presents with phenotypic instability in early life with remarkable clinical variability, ranging from a transfusion-dependent disorder similar to β thalassemia major to a transfusion independent form with mild symptoms, the treatment of this disease is often individualised.[9,10] Screening and accurate identification of hemoglobin variants have become increasingly important in early detection and prevention of hemoglobinopathies. This study highlights the rare occurrence of compound heterozygosity of an abnormal haemoglobin Hb E with β-thalassemia mutation from Kerala

Aim

Since hemoglobinopathies are a major genetic and public health problem in the state of Kerala, the present study aims to evaluate the detailed family study of compound heterozygous cases of haemoglobin E with β-thalassemia. A family with both HbE & beta thalassemia from Kerala is being presented. Present study also aims in proper understanding about the phenotypic heterogeneity of Hb E-beta thalassemia and in providing data about the clinical and laboratory features about hemoglobinopathies which will help in prevention strategies, genetic counselling and prenatal diagnosis about this inherited disease.

Case Presentation

This case study involves four members of a family from Kerala. The first member is a 35-year old female presented with history of jaundice and fatigue from childhood. She was a known case of anaemia who used to receive blood transfusions irregularly. She was been investigated sometimes back, records of which were not available. She was born out of a consanguineous marriage. She is married and had one child who had history of tiredness and fatigue. On examination she had pallor, Jaundice, haemolytic facies and hepatosplenomegaly and leg ulcer. Her 2 siblings died in early childhood cause of which were unknown. One brother had history of similar illness from childhood who also had received multiple transfusions., and mother also had history of tiredness and fatigue from early childhood. Her father is not alive who never had a history of similar illness.

After investigating her blood parameters, we had further investigated her brother (member 2), mother (member3), son (member4) . The details are given below.

Table 1: Clinical features

Family Member	Age	Gender	Symptoms	Relevant History	Clinical findings
Member 1	35	Female	Jaundice. Tiredness	H/o multiple blood transfusions (Around 5 transfusions till date) H/o Leg ulcers	Pallor, Jaundice, hemolytic facies hepatosplenomegaly leg ulcer
Member 2	27	Male	Repeated attacks of jaundice. Severe tiredness	H/o multiple blood transfusions-35 transfusions till date. H/o Leg ulcers	Pallor, Jaundice hepatosplenomegaly. X ray skull - granular osteoporosis, widening of the diploe, thinning of outer table of skull
Member 3	65	Female	Asymptomatic	Nil	Pallor No Jaundice
Member 4	15	Male	Fatigue ,tiredness	Nil	Pallor No Jaundice

Table 2: Blood count and peripheral blood smear results

Family Member	Blood count	Other Relevant tests	Blood smear
Member 1	Hb - 4.1 g/d1 HCT -16.1% MCV-53.1 f1 MCH -13.7pg MCHC-25.5g/d1 RDW-29.1%	Total bilirubin- 4 mg/dl Direct bilirubin- 1.0mg/dl Reticulocyte count– 6.6% Sickling test – negative Osmotic fragility – decreased	Microcytic hypochromic anaemia with target cells. Polychromatic RBCs and nucleated RBCs present Kliehauer test - heterogenous distribution of hemoglobin F
Member 2	Hb - 4.8 MCV - 70 fl MCH - 19 pg. MCHC - 27 g/dl RDW - 32.7	Total bilirubin- 4.9 mg/dl Direct bilirubin- 1.3 mg/dl Reticulocyte count - 5.8% Sickling test - Negative Osmotic fragility - decreased	Microcytic hypochromic anemia, A few target cells, polychromasia, suggestive of hemolytic anemia Kliehauer test - heterogenous distribution of hemoglobin F

Member 3	Hb - 9.6 MCV - 59.6fl MCH - 20.1pg MCHC - 33 RDW - 14.2	Reticulocyte count – normal osmotic fragility – normal other tests- within normal limits	Microcytic hypochromic anemia
Member 4	Hb - 11.9 Hct -- 41.6 MCV - 64.0 MCH - 18.3 MCHC - 28.6 RDW - 16.8	Reticulocyte count – normal osmotic fragility – normal other tests- within normal limits	Microcytic hypochromic anemia

Table 3: Hemoglobin electrophoresis and HPLC results

Family Member	Cellulose acetate electrophoresis	Acid Citrate electrophoresis	High performance liquid chromatography
Member 1	Prominent band at region of A2/C/E with a faint band in the region of hemoglobin F.	Prominent band in the region of hemoglobin E No band at hemoglobin C region	Hb A2 -86.5 Hb F -7.9 Hb A0 -5.6
Member 2	Prominent band at position of A (recent transfusion) & another prominent band at A2/C/E	Prominent band in the region of hemoglobin E No band at hemoglobin C region	Hb A -10.2 Hb F -37.7 Hb A2 -52.1%
Member 3	Prominent A band Faint band at A2 No F band		Hb A – 93.7% Hb F – 1.1% Hb A2 – 5.2%
Member 4	Prominent A band Faint band at A2 No F band		Hb A – 93.9% Hb F – 1.1% Hb A2 – 5.0%

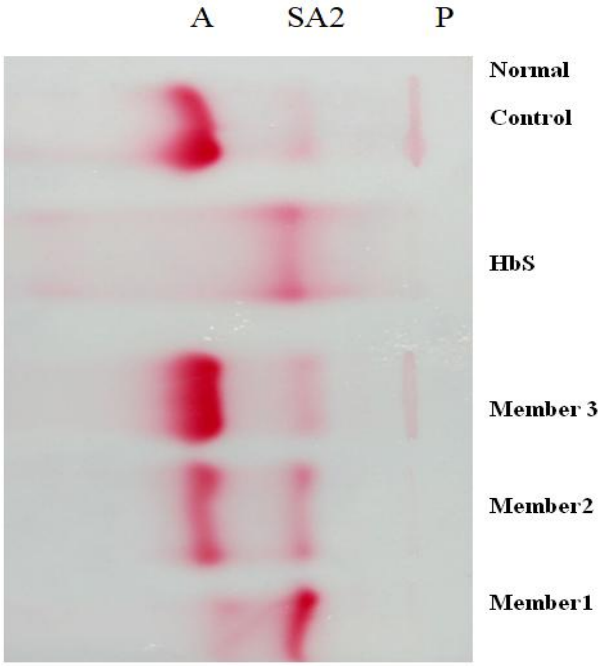

Figure 1: Electrophoresis at pH8.6

Discussion

Patients with Hemoglobin E-β-thalassemia manifest variable clinical, haematological and prognostic profile. Hemoglobin E is the second most prevalent hemoglobin variant after Hb S. Homozygotes (Hb EE) are clinically asymptomatic, prominent microcytosis with a usual MCV of 55 to 65 fl and hemoglobin electrophoresis showing >90% HbE. Heterozygotes (Hb AE) are silent carriers of E gene. They are clinically silent, and electrophoresis shows 20- 35% of Hb E. In compound heterozygotes (Hb E thal) clinical picture & electrophoresis variable & depends on the severity of associated β thalassemia.

North Kerala has a prevalence of Hemoglobinopathies, particularly HbS, sporadic cases of HbE and infrequent cases of beta – thalassemia. However, a compound heterozygote for HbE and beta – thalassemia is being reported for the first time. The patient born of consanguineous marriage, were found to have thalassemic facies and symptoms of variable severity. She had a significant band at the position of HbA2/C/E on cellulose acetate electrophoresis which was quantitated further on HPLC. From HPLC there are possibilities of a hemoglobin other than A2 because Hb A2 usually shows maximum values up to 10, but in the patient, it was 86.5%. The patient showed a faint band of HbF and no HbA band. Citrate agar electrophoresis at acid pH showed that the abnormal hemoglobin present was Hemoglobin E. Member 2 had similar haematologic investigation results with band at HbA due to the five units of blood transfusion received within the last four months of investigation. So, both the siblings were compound heterozygotes for HbE and beta-thalassemia. Member 3 and 4 showed increased levels of HbA2 indicating the presence of beta-thalassemia minor. The gene for thalassemia had therefore come from the mother and that of HbE possibly from father, who is no more and so could not be tested. The other four surviving siblings were found to be normal

Member1 - Hb E β thalassemia

Member2 - Hb E β thalassemia

Member3 - β thalassemia trait

Member 4 - β thalassemia trait

CONCLUSION

Hemoglobinopathies and thalassemia are among one of the major genetic and public health problems in India. These genetic abnormalities impose a high degree of morbidity among infants and children, adolescent girls, pregnant woman etc. causing death. In India, Hb E is mostly restricted to the northeastern states of India with mean frequency of 10.59%, highest 22% in West Bengal and 50 to 80% in Assam[11.] Compound heterozygosity for hemoglobinopathies is an uncommon entity. This disorder has got a variable clinical presentation, ranging from a mild and asymptomatic anemia to a life-threatening clinical illness requiring transfusions from early childhood. The phenotypic variability of Hb E/β-thalassemia and the paucity of long-term clinical data, present challenges in providing definitive guidelines for treatment of patients. Major causes influencing the severity of this disorder include the type of beta-gene mutation, the co-inheritance of alpha-thalassemia, high level of hemoglobin F and history of previous infection with malaria. There is a paucity of adequate literature available on the occurrence of double heterozygous state for hemoglobinopathies in Kerala. Present study will help to understand in depth about the clinical presentation of compound heterozygous hemoglobinopathies in the state and will also be useful for genetic counseling, prenatal diagnosis and future molecular studies about this inherited disease

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