Case Report

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A Rare Case Presentation of HbE/ β Thalassemia

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ABSTRACT

HbE/β thalassemia(HbE/β thal) genotype accounts for approximately one half of severe β thalassemia cases worldwide. The disorder shows marked clinical variability ranging from mild asymptomatic anemia to life threatening disease. Here, we report a case of a 2-year-oldboy from Bihar presenting with severe haemolytic jaundice. Complete haematological profile and Haemoglobin High Performance Liquid Chromatography(HbHPLC)using Biorad version was done of the patient along with the family was done to arrive at the diagnosis of this rare hemoglobinopathy.

Keywords: *Thalassemia, Heterozygous pedigree analysis*

Introduction

HbE/β thal genotype accounts for approximately one half of all severe β thalassemia cases worldwide.[1] The phenotypic variability of Hb E/β-thal and paucity of long-term clinical data, present challenges in providing definitive recommendations for the optimal management of patients. The disorder shows marked clinical variability ranging from mild asymptomatic anemia to life threatening disease. HbE variant results from a mutation in the beta globin chain where at the 26th position, glutamic acid is replaced by lysine. It tends to elute in A2 window within the retention time ranging from 3.3 to 3.9 min.[2] Genetic factors influencing the severity and clinical diversity of this disorder include type of beta-thalassaemia mutation, co-inheritance of alpha-thalassaemia, HbA levels, polymorphisms associated with increased production of fetal haemoglobin and co-inheritance with other hemoglobinopathies.[3] Other factors include increased serum erythropoietin levels and its response to age and HbE levels, malaria infestation, previous splenectomy and other environmental influences.[1]

Case Report

A 2-year-old male, resident of Bihar presented with complaints of abdominal distension, lethargy and irritability for six months. On physical examination, pallor and icterus was noted along with prominent frontal bossing. There was a positive history of passing dark coloured urine for four months. Peripheral smear showed moderate anisopoikilocytosis with predominantly microcytic hypochromic red blood cells with few target cells and polychromatic cells. Complete hemogram along with peripheral smear and biochemical findings revealed features of microcytic hypochromic anaemia with evidence of haemolysis. He had raised bilirubin levels (4.1g/dl), predominantly indirect bilirubin component (3.8g/dl) (Table 1). USG revealed mild splenomegaly with free fluid in peritoneal cavity. Based on clinical history and haematological findings, Hb HPLC of the patient was done which showed increased HbA2 (58.1%) and HbF (43.6%) levels with peak retention time of 1.18 and 3.65 minutes respectively. Following this, Hb HPLC of the parents was done and interpreted as heterozygous HbA/E in the father and ß thalassemia trait in the mother respectively. The probable clinical differentials were HbD/ ß^0 thalassemia, HbE homozygous and thalassemia intermedia. However, after proper family screening, relevant laboratory investigations and HPLC findings of the patient and family, a diagnosis of HbE/ß^0 thal was rendered.

Discussion

HbE/β thal is a major public health problem in Southeast Asia. Although some progress has been made toward a better understanding of its pathophysiology and clinical management, a great deal remains to be learned still. It is a relatively uncommon and clinically variable condition with symptoms varying from mild/ asymptomatic to severe complications. The pathophysiology of HbE/β thal is attributed to decreased HbE output and degree of globin chain imbalance along with other modifiers like coinheritance of alpha thalassemia.[1]

The highest frequencies are observed in India, Bangladesh and Southeast Asia, particularly in Thailand, Laos and Cambodia with estimated prevalence of around 40%, where it is common for individuals to inherit alleles for both Hemoglobin E (Hb E) and beta-thalassaemia.[4]

Table 1

Hematological Parameters	Value (Reference Range)
Hb	6.8 (11-14g/dl)
TLC	10,700 (5,000-15000/µl)
DLC	P-37%, L-55%, M-2%, E-6%
Platelet count	1.8 (2-4.9lakhs/cumm)
Reticulocyte count (Corrected)	5.8 (0.5-1.5%).
Biochemical Parameters	Value
Total Bilirubin	4.1(0.2-1.2 mg/dl)
Indirect Bilirubin	3.8(0.2-1.1 mg/dl)
SGOT	65(15-50U/L)

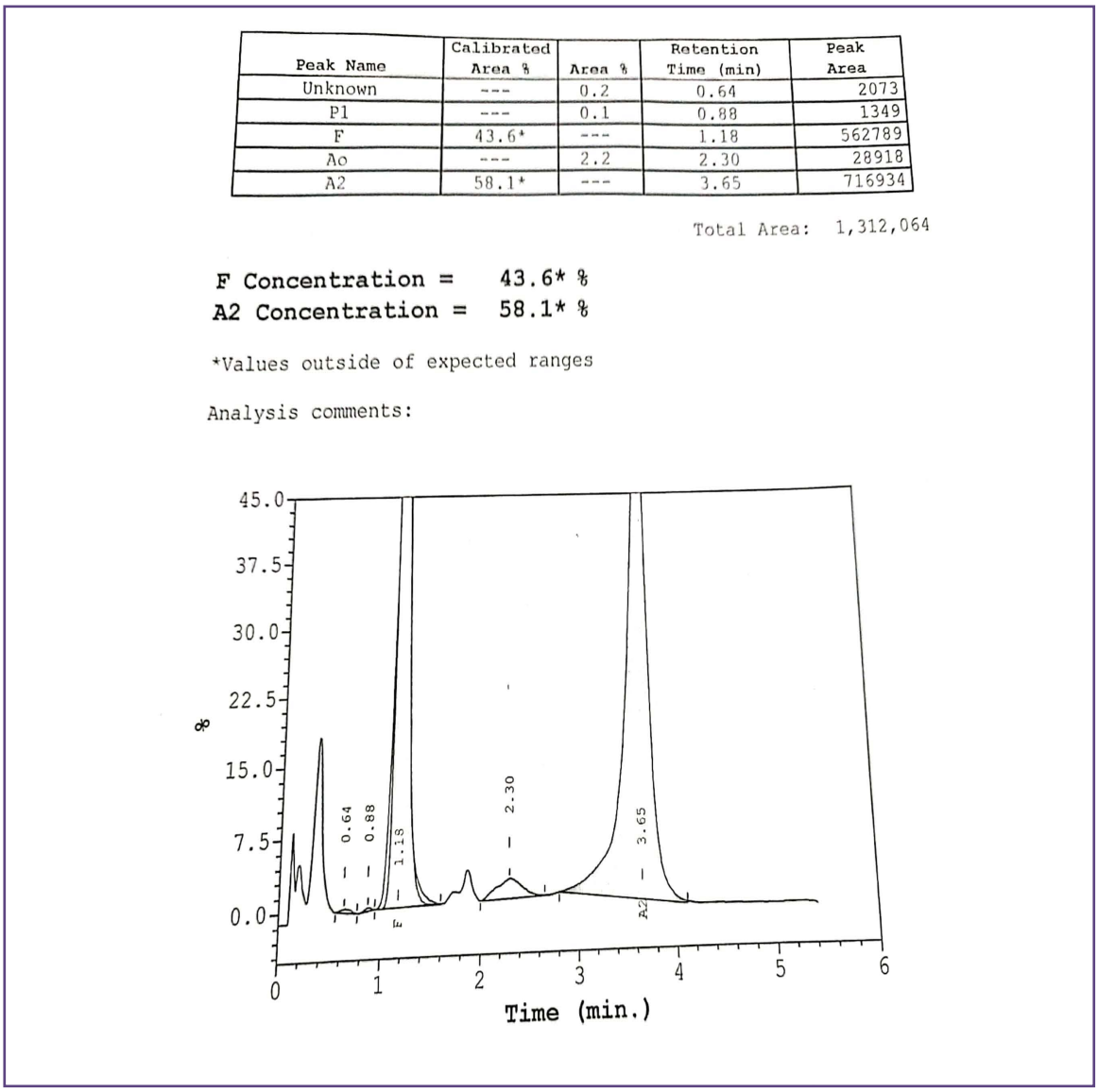

Fig. 1: HPLC graph of the patient.

Peak Name	Calibrated Area %	Area %	Retention Time (min)	Peak Area
F	0.8	---	1.08	15721
Unknown	---	1.0	1.24	20721
P2	---	4.1	1.36	87605
Unknown	---	2.5	1.75	52655
P3	---	3.3	1.85	70655
Ao	---	62.3	2.47	1334781
A2	28.9*	---	3.65	559624

Total Area: 2,141,763

F Concentration = 0.8 %
A2 Concentration = 28.9* %

*Values outside of expected ranges

Analysis comments:

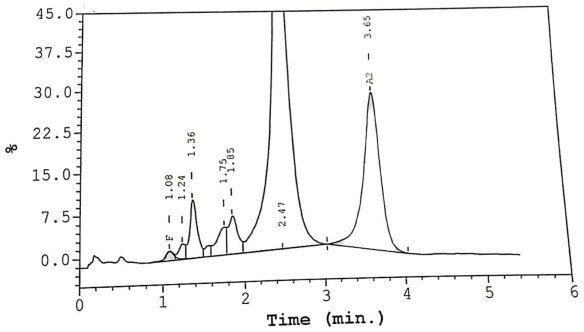

Fig. 2: HPLC graph of the father.

Peak Name	Calibrated Area %	Area %	Retention Time (min)	Peak Area
Unknown	---	0.1	0.99	898
F	0.9	---	1.09	9163
Unknown	---	1.1	1.25	11664
P2	---	3.9	1.37	42711
P3	---	6.1	1.74	66619
Ao	---	82.2	2.48	904255
A2	6.5*	---	3.64	64978

Total Area: 1,100,288

F Concentration = 0.9 %
A2 Concentration = 6.5* %

*Values outside of expected ranges

Analysis comments:

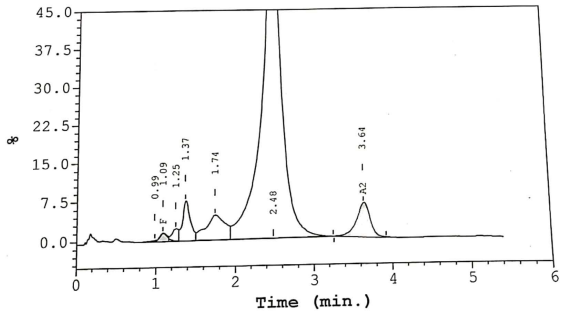

Fig. 3: HPLC graph of the mother.

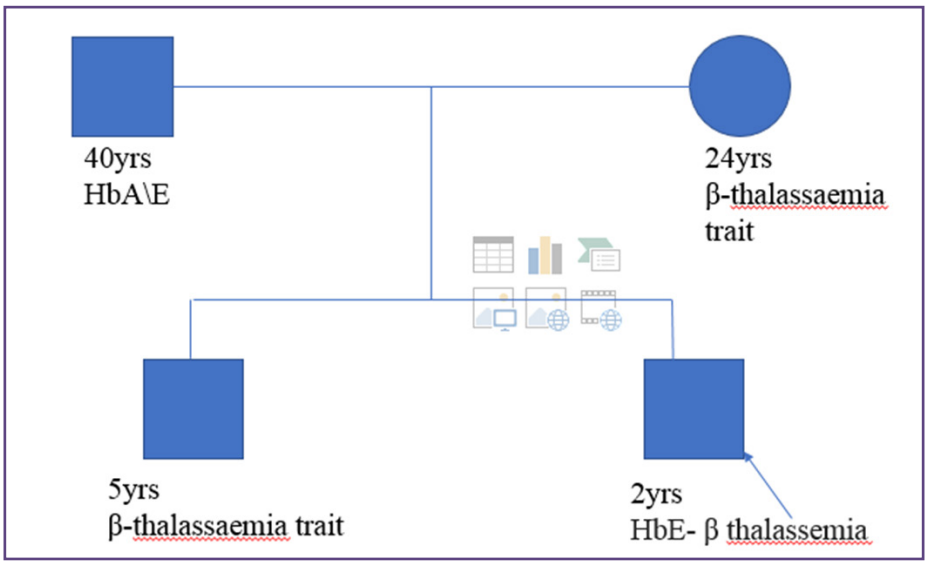

Fig. 4: Pedigree analysis of the patient.

Average HbE gene frequency in north east India is around 10.9%.[4] In a multicentre study conducted in Mumbai on 65,779 patients, HbE disease (homozygous HB E/Hb E-beta-thalassemia) accounted for 0.34% of cases.[2] In a study conducted in eastern India including 119,336 cases, the prevalence of HbE/β thal was 1.16 %.[5] Conversely, a study from western India showed a prevalence of 0.2%.[6] A study by Baruah MK et al and Mohanty D et al reported a prevalence of 2.14% and 0.19% respectively.[7,8] A study conducted previously in our institute showed a prevalence of 0.16%[9]

Diagnosis of HbE can be made through various modalities. Screening tests are osmotic fragility and dichlorophenolindophenol precipitation test. Bone marrow shows features of erythroid hyperplasia, dyserythropoiesis, increased macrophage activity and increased iron storage. Confirmatory tests include Cation exchange HPLC and capillary zone electrophoresis for specificity. Other ancillary techniques include flow cytometry, mutational studies and DNA analysis by multiplex allele specific PCR and amplification refractory mutation system-PCR.

HbE inheritance may present as homozygous (EE), heterozygous (AE) or compound heterozygous (in association with sickle cell anemia, β-thalassaemia and other disorders). When E allele interacts with a β thalassemia mutation in the compound heterozygous state, a variable range of haematological parameters is present, with Hb levels ranging from 3 to 11 g/dl.[3]

The severely affected patients are transfusion dependent and have hepatosplenomegaly, intermittent jaundice, growth retardation, delayed sexual maturation, facial deformity and malposition teeth owing to expansion of bone marrow cavity

At birth, infants with severe HbE/β thal are asymptomatic because HbF levels are high. HbF production decreases and is replaced by HbE at 6–12 months of age.[11] Compound heterozygotes for HbE and ß0thalassaemia have haemoglobin E representing 40–60% of total haemoglobin; In homozygous HbE, the percentage of HbE is usually 85–99%. Conversely, haemoglobin F is 30–60% in haemoglobin E/ß^0 thalassaemia, whereas, in homozygous haemoglobin E, it is less than 15%. [12] Overall, haemoglobin F is very variable, from 5% to 87%. [13] When haemoglobin A is present, it usually constitutes around 10% of total hemoglobin and HPLC shows haemoglobin E, A2 and F with minimal HbA levels in the case of HbE / ß0thalassaemia and Hb E, A, A2 and F in case of haemoglobin E/ ß+ thalassemia. [13]

HbE/β thal can lead to various complications like hypersplenism, susceptibility to infections, cardiac and pulmonary ailments and thromboembolism. Hemolysis related complications like jaundice, cholecystitis and cholelithiasis has also been reported. Repeated blood transfusions lead to iron overload leading to deposition in various organs and systemic complications like diabetes mellitus.[1] There is an urgent need for the prenatal diagnosis of thalassemia for preventing morbidity and mortality in new born and hence mitigating the burden of hemoglobinopathies in India. The important prerequisite for this disorder is to create awareness on the prevalence of ß-thalassemia in different ethnic groups and in different regions of the country. Education and timely screening

plays the most important part for the success of prevention programs for the control of thalassemia.

Conclusion

The remarkable variation and the instability of the clinical phenotype of HbE beta-thalassaemia suggests that careful tailoring of treatment is required for each patient, and that therapeutic approach should be re-assessed over a period of time. Hence, family screening is important for confirmation, exact characterisation and adequate management. Thus, compound heterozygous HbE/β thal should be considered as an alternative diagnosis in all patients with homozygous HbE disease who present with severe anemia.

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