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Double heterozygous for hemoglobin E and Beta thalassemia: A case study

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Abstract

Haemoglobinopathies and thalassemias are inherited conditions, being diagnosed with increasing prevalence in India. An accurate diagnosis of β -thalassemia carriers, homozygous patients, double heterozygous patients and identification of different structural hemoglobin variants is important for epidemiological studies as well as for management and prevention of the major hemoglobin disorders. The phenotypic variability of Hb E/ β -thalassaemia and the paucity of long-term clinical data, present challenges in providing definitive diagnosis and management of such patients. This case was clinically labelled as Thalassaemia intermedia and was confirmed as Double heterozygous for HbE and Thalassaemia. Family study was also done.

Keywords: CE-HPLC, Hemoglobin E, Hb E/ β -thalassemia

Introduction

Haemoglobinopathies are genetically important hematological disorders affecting millions of people worldwide. The cumulative gene frequency of hemoglobin pathies in India is 4.2%^[1]. There are many electrophoretic and chromatographic approaches for estimation of HbA₂ and Hb F but cation exchange HPLC (CE-HPLC) using automated dedicated machines like the Variant II Hb testing system have become the method of choice for these Investigations^[2]. HbE is usually seen in South-east Asians and eastern and North-eastern states of India including Bihar. Heterozygous (HbAE) and homozygous (HbEE) forms are clinically mild or asymptomatic, whereas double heterozygous HbE--thalassemia is more symptomatic; mostly presenting as thalassemia intermedia clinically and sometimes with even thalassemia major phenotype^[3].

Uncommon double heterozygous states may be encountered with increasing incidence in future, particularly in places with a confluence of people with diverse sociocultural and ethnic background^[3]. The documentation of these type of cases may help in antenatal counseling of β -Thalassaemia and HbE carrier parents.

Case presentation

A 15 year old female patient presented with chief complaints of easy fatigability & breathlessness; with monthly requirement of blood transfusion. Patient was previously clinically labelled as thalassemia intermedia. Patient had undergone splenectomy. Clinically patient showed pallor 3+ and Thalassaemia like frontal bossing. Peripheral smear picture showed moderate microcytic, severe hypochromic RBCs, moderate anisopoikilocytosis, elliptocytes, tear drop cells, many target cells, polychromatic RBCs, few fragmented RBCs and Howell Jolly bodies. Total WBC count was 68400/cmm, 660 NRBCs/100 WBCs were seen; corrected WBC count was 9000/ cmm. Platelets on peripheral smear were increased. Hb was 5.8gm%, RBCcount-3.06 million/ml, PCV-20%, MCV-67%, MCH-18.10pg, MCHC-26.62% and RDW-36%. Sickling solubility test was negative; reticulocyte count was 7%.

Differential diagnoses to be considered were Thalassaemia and Haemoglobinopathies Hb-high performance liquid chromatography (HPLC) was done using Bio-Rad Variant II and the corresponding Beta-Thalassaemia Short Program, (Bio-Rad laboratories, Inc. Hercules, California, USA) to rule out underlying hemoglobinopathy. It revealed HbF-28.8%, HbA₀-4.9%, HbA₂-61.4%, D window-absent, S window-absent, C window-absent. HPLC findings of mother showed HbF-0.5% and HbA₂ 25.9%, HbA₀ 61.8% Father's study could not be done, as he refused to give blood sample.

HPLC findings of sister of the patient showed normal values; HbF-1% and HbA2 -2.9%, HbA0-86.6% Considering the two differential diagnoses.

Thalassemia v/s Haemoglobinopathies

HbA2 is never so high in any condition. Only HbE coelutes with HbA2.

Besides HbE, the other Hbs eluting in the A2 window include Hb Lepore, Hb D-Iran, G-Coushatta., but agarose gel Hb electrophoresis (pH 8.6) was done and it confirmed double heterozygous state; revealed two bands corresponding at the position of Hb A2 /E and the other at Hb F.

So the case was concluded as Double heterozygous for HbE and Thalassemia, mother was HbE trait and Sister was normal, Father's sample was not available; he would be β Thalassemia trait.

Table 1

	Patient	Mother	Sister
Hb A0%	4.9	61.8	86.6
HbA2%	61.4	25.9	2.9
HbF%	28.5	0.5	1
Diagnosis	Double heterozygous for HbE and Thalassemia	HbE trait	Normal

Discussion

The coinheritance of two different haemoglobinopathies is a rare occurrence [4]. These disorders, which were mainly confined to certain areas, religions, castes and tribes particularly with endogamous norms of marriages, are now widely prevalent all over the world. This is because of the ever increasing migration of people from one place to another and the mixing of different communities through marriages [5].

Hb E/ β -thalassaemia results from co-inheritance of a β -thalassaemia allele from one parent and the structural variant Haemoglobin E from the other. Haemoglobin E results from a G→A substitution in codon # 26 of the β globin gene, which produces a structurally abnormal haemoglobin as well as activates a cryptic splice site, resulting in abnormal messenger RNA (mRNA) processing [6].

The inherited disorders of haemoglobin, particularly the β -thalassemias and their interaction with haemoglobin E (HbE) and haemoglobin S (HbS) are a considerable health problem in India and contribute significantly to morbidity and mortality [7].

Its phenotype ranges from mild anemia to severe transfusion-dependency necessitating splenectomy in many patients [8].

The marked expansion of erythropoiesis is responsible for much of the pathology of the disease, including hepatosplenomegaly, extramedullary hematopoiesis, bony deformities, growth retardation and delayed sexual maturation. Splenomegaly often develops in severely affected patients. In the past, splenectomy was routinely performed in an attempt to increase hemoglobin levels [8].

Clinical phenotypes of Hb E disorders particularly Hb E/ β -thalassaemia is quite variable [7]. Individuals with the Hb E Trait are usually not anemic and have no symptoms. Hematological investigations of these individuals reveal mild microcytosis, hypochromia and erythrocytosis as seen

with the β -thalassaemia trait. However, identification of these individuals is of crucial importance as they may be transmitters of the abnormal gene, giving rise to various combinations of haemoglobinopathies and thalassemias in their progeny [1].

Among 120 cases of thalassemias and abnormal hemoglobins, Sinha *et al.* [9] reported 66.9% and 15.9% cases of thalassemias and Hb E disorders, respectively. In another study; as part of the antenatal screening program for thalassemias and haemoglobinopathies, 5.8% of pregnant women were found with the β -thalassaemia trait and 0.8% with the Hb E trait [10].

In another study, 10 (0.16%) patients were diagnosed as Hb E- β thalassemias [4]. Patient showing a peak at the HbA2/E position with increased HbA2 level (>15%) and increased Hb F level (5 - 87%) was labelled as a double heterozygous state of Hb E and β -thalassaemia [1].

Thus, uncommon double heterozygous states may be encountered with increasing incidence in future, particularly in places with a confluence of people with diverse sociocultural and ethnic background.

Learning points

1. The documentation of these cases may help in antenatal counseling of Thalassemia trait and HbE trait parents. Thus, premarital and antenatal screening should be mandatory to prevent the birth of offspring with β thalassemia major.
2. Moreover, knowledge of common Hb patterns in a particular region helps to formulate appropriate preventive and therapeutic strategies.
3. Although, haemoglobin chain disorders require combination of techniques, HPLC is a cost effective and powerful tool for characterization of these disorders.
4. This study also highlights the importance of hematological parameters (Hb, RDW and RBC count) in elucidation of double heterozygous haemoglobinopathies from much commoner variants of haemoglobinopathies, particularly in under resourced areas.

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