CASE REPORT

Identification of Delta-beta Thalassemia in a Family with Elevated Hb F: A Case Report

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Abstract:

Delta-beta Thalassemia is a rare variant of thalassemia with elevated Hb F. Heterozygous and homozygous state of delta-beta thalassemia present with features similar to Hereditary Persistence of Fetal Haemoglobin (HPFH) and beta thalassemia intermedia. Here, we describe a case of 8-month-old female child with anaemia and splenomegaly. Haemoglobin electrophoresis showed 100% HbF and no HbA and HbA2. Patient was put on haematinics and advised a repeat haemoglobin electrophoresis after completion of 1 year of age, and family screening. Hb electrophoresis of the patient at the age of 2 years mirrored the earlier findings and her father, mother and brother showed increased Hb F with normal HbA2 levels. A final diagnosis of homozygous delta-beta thalassemia in the case with sibling and parents being heterozygous delta-beta thalassemia trait was rendered. Haemoglobin electrophoresis with red cell indices forms an important diagnostic clue in differentiating delta-beta thalassemia from other thalassemia syndromes.

Keywords: Haemoglobin Electrophoresis, Delta-Beta Thalassemia, Foetal Haemoglobin, Anaemia, RBC indices

Introduction:

Delta-beta thalassemia is a rare form of thalassemia which results from deletion of both beta and delta globin genes located on chromosome 11, and compensatory increase in the gamma gene product formation [1]. The clinical presentation of delta-beta thalassemia is that of mild anaemia in heterozygous form, while the homozygous form presents with thalassemia intermedia like blood picture with thalassemic red cell indices, a raised foetal Haemoglobin (Hb F) and normal or low Hb A2 [2]. The definitive diagnosis is done by mutation analysis and is sub classified based on the different ethnic groups in which it is observed. A non-deletional mutation causing delta-beta thalassemia has also been reported in the recent times [3]. A close differential diagnosis of delta-beta thalassemia is Hereditary Persistence of Foetal Haemoglobin (HPFH) which also shows an increase in Hb F beyond infancy and presents with a mild normochromic anaemia [4]. Here we describe the haematological features of a young female child, her sibling and parents with delta-beta thalassemia with diagnostic perspective.

Case Report:

An 8 month old female child presented with complaints of recurrent infections. She was thinly built for age and had pallor and icterus. Liver was palpable 4.5 cm below right costal margin and spleen 3cm below left costal margin. Laboratory

investigations revealed mild indirect hyperbilirubinemia (0.8 mg/dl), anaemia (9.2 g/dl), reticulocytosis (5.3%) and a normal iron profile. Peripheral smear showed a microcytic hypochromic morphology with features of mild haemolysis. Osmotic fragility was normal and Coomb's test was negative. Haemoglobin electrophoresis showed a 100% Hb F, and no Hb A and A2 (Fig. 1). A diagnosis favouring thalassemia major was considered, however, keeping the mild anaemia and the age in consideration, a repeat Hb electrophoresis after completion of 1 year of age and family screening was advised. The patient came back after completing 2 years of age and the laboratory features were a mirror image of the previous data. Family screening showed both the parents and the sibling had a microcytic hypochromic anaemia, a raised Hb F and normal levels of Hb A2 (Fig. 2). Table 1 summarizes the laboratory features of the index case, sibling and both the parents. Based on these features diagnostic possibilities on the case included, homozygous beta thalassemia, homozygous delta beta thalassemia and a homozygous HPFH. Keeping in account the thalassemic blood indices, raised HbF and low/normal Hb A2 levels a diagnosis of homozygous delta-beta thalassemia was given in the patient while the brother and parents were labelled as heterozygous delta-beta thalassemia. Genetic testing was advised for confirmation of the diagnosis, however, could not be done owing to financial constraints.

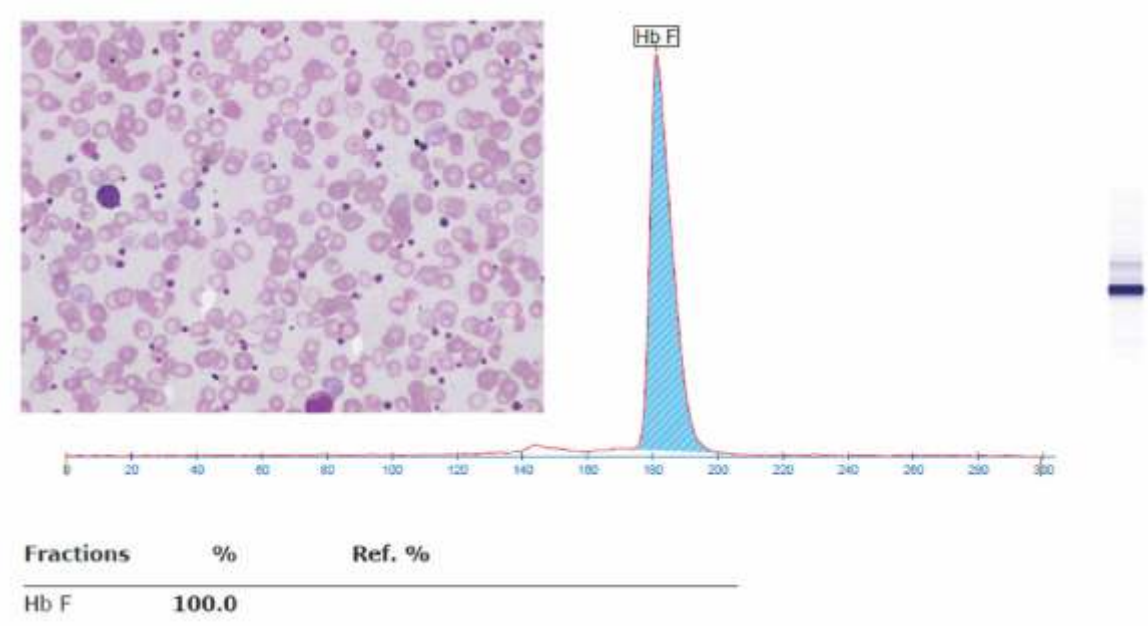

Fig. 1: Peripheral Smear of the Case Shows Microcytic Hypochromic Anaemia with Polychromasia And Target Cells (Leishman, 100x). Haemoglobin Electrophoresis Reveals Presence of 100% Hb F.

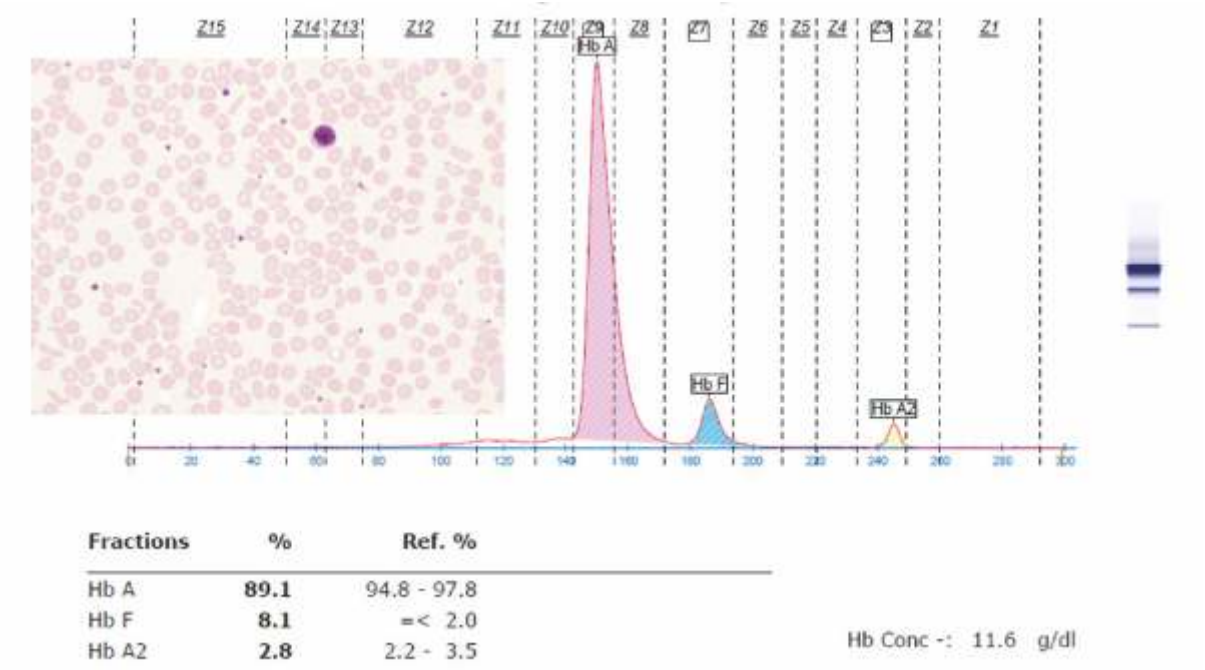

Fig. 2: Peripheral Smear of the Father with Mild Anaemia and Microcytosis (Leishman, 100x). Hb Electrophoresis Shows an Increased Hb F with Normal Hb A2.

Table 1: Haematological Parameters of the Case and Family

Parameter	Case (at presentation)	Case (at follow up)	Brother	Father	Mother
Age (years)	8 months	2	5	37	33
RBC count (x10^6/µl)	4.33	4.38	4.8	5.37	4.89
Hb (g/dl)	8.1	9.1	10.5	11.6	10.5
MCV (fl)	66.1	67.1	68.7	65.5	69.5
MCH (pg)	20.3	20.8	21.8	20.3	21.5
RDW (%)	27.4	21.0	24.3	20.3	19.6
Hb electrophoresis					
Hb A (%)	0	0	79.7	89.1	87.1
Hb A2 (%)	0	0	2.8	2.8	2.8
Hb F (%)	100	100	17.5	8.1	10.1

Footnote: RBC- Red blood cell, Hb- Haemoglobin, MCV- Mean corpuscular volume, MCH- Mean corpuscular haemoglobin, RDW- Red cell distribution width

Table 2: Differential Diagnosis and Distinguishing Features of Haemoglobinopathies with a Markedly Elevated HbF [2, 4, 5]

Feature	Homozygous delta-beta thalassemia	Homozygous HPFH	Homozygous beta thalassemia
Anaemia	Mild, compensated	Mild, compensated	Severe
MCV	Decreased	Normal	Decreased
RDW	Increased	Normal	Increased
Reticulocyte count	Increased	Normal	Increased
RBC morphology	Microcytic hypochromic, Polychromasia, Target cells	Normocytic normochromic, Few target cells	Microcytic hypochromic, Target cells, nRBCs, polychromasia, RBC inclusions
Kleihauer-Betke test	Heterocellular distribution of Hb F	Pancellular distribution of HbF	Heterocellular distribution of HbF
Hb A	Decreased	Decreased	Decreased
Hb A2	<2%	<2%	>5%
Hb F	Upto 100%	Upto 100%	Upto 95%
Transfusion dependence	No	No	Yes

Footnote: MCV- Mean corpuscular volume, RDW- Red cell distribution width, RBC- Red blood cell, Hb- Haemoglobin, HPFH- hereditary persistence of fetal haemoglobin

Discussion

Delta-beta thalassemia is primarily caused by deletion mutations in the beta and delta globin chain genes, resulting in decreased production of corresponding globin chains. This caused a decrease in the amount of HbA and HbA2; however, a compensatory increase in the gamma chain production causes a rise in the HbF levels [1, 5]. It can express in a homozygous or heterozygous fashion. Heterozygous patients present with a mild anaemia similar to beta thalassemia trait and are termed as delta-beta thalassemia trait, while the homozygous patients can show a picture similar to thalassemia intermedia, hence termed delta-beta thalassemia disease [2, 6].

Hb F levels stabilize after 1 year of age, and an adult level is reached by the age of 2 years. Persistence of high levels of HbF after 1 year of age is seen in haemoglobin variants like HPFH and thalassemia syndromes. An HbF of >50% has been observed with homozygous beta thalassemia, homozygous HPFH and homozygous delta-beta thalassemia [4, 7]. Red cell indices and haemoglobin electrophoresis are useful tools in evaluation of such cases and reaching a diagnosis. Homozygous beta thalassemia and delta-beta thalassemia present with thalassemic red cell indices, namely erythrocytosis, anaemia, a reduced Mean Corpuscular Volume (MCV), Mean Corpuscular Haemoglobin (MCH) and increased Red Cell Distribution Width (RDW). Homozygous beta thalassemia presents with severe anaemia, features of haemolysis on the peripheral smear, whereas homozygous delta-beta thalassemia and homozygous HPFH show a mild degree of anaemia. In addition, the HPFH even in its homozygous form presents with a normocytic normochromic anaemia [3, 4]. Along with an elevated Hb F, Hb electrophoresis shows an elevated HbA2 in homozygous beta thalassemia while a reduced or normal levels of HbA2 in homozygous delta-beta thalassemia and HPFH. Another differentiating feature is distribution of HbF in the red blood cells, which is pancellular in HPFH whereas, heterocellular in beta and delta-beta thalassemia and can be demonstrated by Kleihauer-Betke acid elution test [7]. Table 2 summarises the various differential diagnosis and distinguishing features.

Delta-beta thalassemia, in its heterozygous form, presents with anaemia and thalassemic indices and can be differentiated from beta thalassemia intermedia and trait based on Hb A2 values, which are within normal range in cases of heterozygous delta-beta thalassemia and increased in latter [6, 8]. In the present scenario, both the parents and sibling have features of heterogeneous delta-beta thalassemia, whereas the index case had features of homozygous delta-beta thalassemia. It is imperative to differentiate it from other haemoglobinopathies as these patients do not require transfusion support, and thus are saved from future iron overload and growth abnormalities. Genetic testing is a confirmatory test for diagnosis of haemoglobinopathies with diagnostic tests ranging from polymerase chain reaction to DNA sequencing. These tests, however, are high end and not readily available in a resource limited diagnostic set up. Haemoglobin electrophoresis by high performance liquid chromatography or capillary zone electrophoresis help in determination of Hb fractions, provide a diagnostic clue, and help in planning appropriate management [4].

Conclusion:

Delta-beta thalassemia is rare in the Indian subcontinent. Case reports similar to the present case highlight the necessity of screening during pre and perinatal periods, and will help to understand the various clinical features as well as biochemical and haematological parameters aiding the pathologist and the clinician to suspect delta-beta thalassemia trait and disease.

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