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Case report 1

Diagnosing delta-beta thalassaemia in a resource poor setting

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Key words: delta-beta (δβ) thalassaemia, thalassaemia intermedia, high Hb F

Abstract

An eight-year-old girl presented with mild scleral icterus, pallor and hepatosplenomegaly. Her preliminary investigations revealed low haemoglobin (Hb) (94g/L), high reticulocyte count (3.5%), normal total bilirubin level and normal liver function tests. Her blood picture revealed evidence of chronic haemolysis. High performance liquid chromatography (HPLC) revealed markedly raised Hb-F (98.3%). Capillary electrophoresis revealed Hb-F of 99.2%. Acid elution test (Kleihauer test) showed pan-cellular distribution of Hb-F. Her parents were first cousins. Her mother's profile showed thalassaemic red cell indices with normal Hb-A2 and high Hb-F (13.3%). The father was not available for screening. The paternal grandmother's HPLC showed normal Hb-A2 and high Hb-F (6.8%). Based on clinical and laboratory findings and family screening results, the child was diagnosed as homozygous delta-beta (δβ)-thalassaemia presenting as thalassaemia intermedia.

Introduction

Thalassemias are a heterogenous group of inherited haematological disorders characterised by defects in the rate of production of globin chains[1]. Delta-beta (δβ)-thalassaemia results from a deletion in both the delta and beta genes on chromosome 11 resulting in decreased production of corresponding globin chains. Remaining gamma genes increase the production of gamma globin, thereby increasing the amount of foetal haemoglobin/Hb-F ($\alpha 2\gamma 2$). δβ-thalassaemia heterozygotes clinically show characteristics of thalassaemia minor. Because of the increased synthesis of Hb-F, homozygotes may give a clinical picture of thalassemia intermedia rather than thalassaemia major[1,2].

Case report

An eight-year-old girl with Tamil ethnicity presented to the paediatric department of base hospital Kalmunai-North, Sri Lanka, with a respiratory tract infection. Other than respiratory signs she had mild scleral icterus, mild pallor and hepatosplenomegaly (liver 3cm, spleen 4cm). She was short for her age, although not quite below the 3rd percentile line of the growth chart. On further inquiry, she has been icteric since 1½ years of age, but was not investigated before. She never had a blood transfusion. There was no known haematological disease in the family. Her parents were first cousins. She lived with her guardian, paternal grandmother as her parents were separated.

Her preliminary investigations revealed Hb-94g/L, WBC - 11.44×10^9/L, neutrophil count - 6.19×10^9/L and platelet count - 301×10^9/L. Her reticulocyte count was high (3.5%). Corrected reticulocyte count was 2.5% (3.5 × patient's PCV (32.2)/45). Liver profile was normal (SGOT - 26U/L, SGPT- 32U/L, Alkaline phosphatase - 202U/L). Serum total bilirubin was 1.2mg/dL (0.3-1.0 mg/mL) and direct bilirubin was 0.16mg/dL.

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Serum ferritin was 101ng/mL (7-140 ng/mL). Blood picture showed evidence of chronic haemolysis with hypochromic microcytic red cells, poly-chromatics, tear drop cells, target cells and few nucleated red blood cells (NRBC) (Figure 1).

Based on the preliminary investigation results, a chronic haemolytic anaemia was suspected. Her blood samples were sent to Medical Research Institute (MRI), Colombo, for further analysis. HPLC performed using a Bio-Rad Variant Hb Testing system with β-thalassaemia short programme done at MRI revealed markedly raised Hb-F (98.3%). Capillary electrophoresis (Sebia) was also per-formed which showed Hb-F of 99.2% (Figure 2). Acid elution test (Kleihauer test) showed pan-cellular distribution of Hb-F (Figure 3).

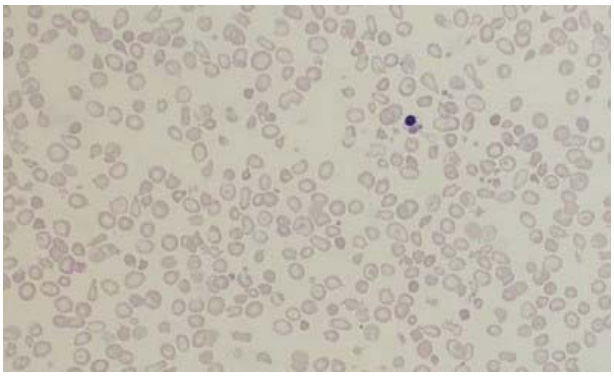

Figure 1. Blood picture of the proband showing evidence of chronic haemolysis with polychromatic cells, red cell anisopoikilo-cytosis, few NRBC.

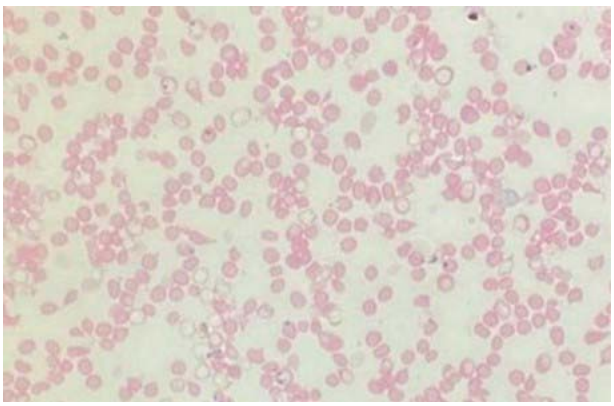

Figure 2. Kliehauer test of the proband showing pan-cellular distribution of Hb-F.

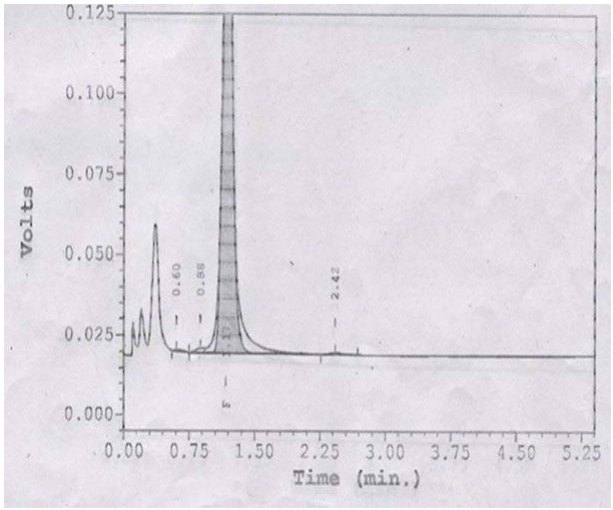

Figure 3. HPLC of the proband showing Hb-F of 98.3%.

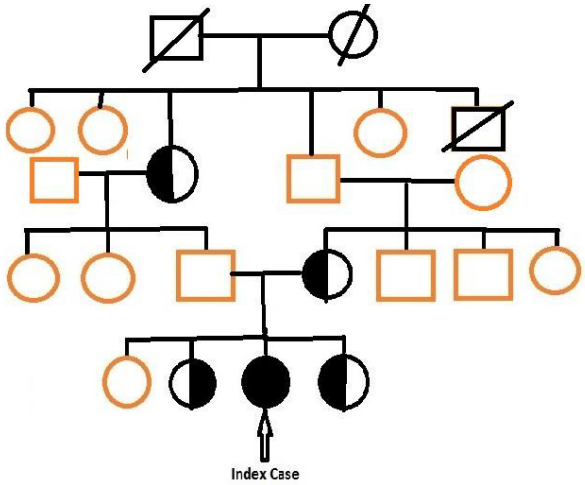

Figure 4. Family tree (Brown – not screened).

Family screening was arranged. Parents were not screened before. Her mother had thalassaemic red cell indices with normal Hb-A2 and high Hb-F (13.3%) suggestive of delta-beta thalassaemia trait. Father was not available for screening. Paternal grandmother had severe anaemia (Hb 39g/L), low red cell indices with normal Hb-A2 and elevated Hb-F (6.8%); suggestive of δβ-thalassaemia with coexistent severe iron deficiency. The profiles of two siblings were also compatible with δβ-thalassaemia trait. Their MCHC was low; suggestive of coexistent mild iron deficiency (Table 1).

Table 1. FBC/HPLC/capillary electrophoresis (CE) parameters of the proband, mother, siblings and paternal grandmother

Parameter	Proband (8 yrs)	Mother (43 yrs)	Sibling (18 yrs)	Sibling (7 yrs)	Paternal Grandmother (63 yrs)
RBC (FBC)	4.54	4.64	4.5	5.05	2.72
Hb (g/L)	94	100	87	93	39
MCV (fL)	63.0	69.6	66.4	60.2	55.9
MCH (pg)	20.7	21.6	19.3	18.4	14.3
MCHC (g/dL)	32.9	31	29.1	30.6	25.7
RDW-CV	21.2	22.1	23.7	23.4	25.2
(HPLC) HbA %	0.5	77.3	79.7	78.4	83.2
Hb A2 %	0	2.9	2.9	2.9	2.6
Hb F %	98.3	12.9	10.2	11.6	6.8
Kleihauer test	Pancellular distribution of Hb F	Hetero-cellular distribution of Hb F	Hetero-cellular distribution of Hb F	Hetero-cellular distribution of Hb F	Hetero-cellular distribution of Hb F
(CE) Hb A %	0.8	84.1	86.9	85.1	91.5
Hb A2 %	0	2.6	2.6	2.6	2.2
Hb F %	99.2	13.3	10.5	12.3	6.3
Diagnosis	Homo-zygous δβ thalassaemia	Hetero-zygous δβ thalassaemia	Hetero-zygous δβ thalassaemia	Hetero-zygous δβ thalassaemia	Hetero-zygous δβ thalassaemia

Based on clinical and laboratory findings and family screening results, she was diagnosed as homozygous δβ-thalassaemia. Genetic testing was advised for confirmation of the diagnosis, however, could not be done owing to financial constraints. Counselling was done. Possibility of requiring occasional blood transfusions in the future, especially with concurrent infections, surgery and pregnancy were explained. Folic acid prophylaxis was started. Thyroid functions, USS-Abdomen and 2D-ECHO were arranged.

Discussion

Delta-beta (δβ)-thalassaemia is a rare form of thalassaemia, observed in many ethnic groups, including Mediterranean populations (Italians, Greeks and Turks)[1,2,3]. It is rarely detected in Sri Lanka.

Delta-beta (δβ)-thalassaemia results from a deletion in both delta and beta genes on chromosome-11 resulting in decreased production of delta and beta globin chains. A compensatory increase in gamma chain production causes a rise in Hb-F ($\alpha 2\gamma 2$) levels. Hb-F is the major haemoglobin during intrauterine life. Hb-F levels fall progressively to values close to adult level (1%) during the first two years of life[1,3]. Persistence of high levels of Hb-F after the first year of age is seen in haemoglobin variants like hereditary persistence of foetal Hb (HPFH) and thalassaemia syndromes. An Hb-F of >50% as in our index case, has been observed in homozygous β-thalassaemia major and intermedia, homozygous HPFH and homozygous δβ-thalassaemia[3]. β-thalassaemia major patients usually present in the first year of life with severe anaemia and they depend on blood transfusions for survival. HPLC of β-thalassaemia major shows only Hb-F and Hb-A2[1,2,3.4]. β-thalassaemia intermedia patients present with haemolysis during intercurrent infections and surgeries, but they are not dependent on regular blood transfusions. HPLC of β-thalassaemia intermedia shows elevated Hb-F with low Hb-A, Hb-A2 is also elevated[1]. In the present case, β-thalassaemia major and intermedia was excluded by clinical presentation and HPLC findings. Other differential diagnoses for markedly elevated Hb-F with lack of Hb-A are homozygous δβ-thalassaemia and homozygous HPFH[1]. Homozygotes of HPFH are clinically normal[1,5,6]. Homozygous δβ-thalassaemia patients are generally in a compensated hemolytic process. In the present case, the patient's clinical picture and HPLC findings are compatible with homozygous δβ-thalassaemia.

Family screening is always helpful in confirming the diagnosis of complicated haemoglobinopathies[1]. In the present case, the mother and the siblings showed thalassaemic red cell indices, with normal Hb-A2 and high Hb-F, with heterocellular distribution shown in Kleihauer test. Normal Hb-A2 level excludes β-thalassaemia trait in this family. The differential diagnoses for asymptomatic cases with high Hb-F of <30% and normal Hb-A2 are heterozygous δβ-thalassaemia and heterozygous HPFH. Presence of low red cell indices with high Hb-F of 5-20%, which is heterocellularly distributed in red cells are suggestive of δβ-thalassaemia trait. Presence of normal red cell indices with high Hb-F of 15-30% with a pan-cellular distribution in red cells is suggestive of HPFH trait[1]. The mother and the siblings had thalassaemic red cell indices with Hb-F of 10-15% compatible with δβ-thalassaemia trait[1,8,9,10].

In the present case father was not available for screening; but paternal grandmother was screened and her profile was compatible with δβ-thalassaemia trait. The father may be having δβ-thalassaemia trait possibly inherited from his mother. The paternal grandmother and the maternal grandfather are siblings. The mother of the proband may have inherited the gene from her father.

This case highlights the importance of screening for thalassaemia before marriage, especially when the marriage is between blood relatives and the couple originates from a thalassaemia prevalent area. Knowledge on clinical picture, haematological and HPLC findings of different thalassaemias and supportive tests are always useful in differentiating haemoglobinopathies especially when genetic facilities are not freely available. Family screening is also helpful in confirming the diagnosis of complicated cases.

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