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Case Report

Biochemistry Section

Incidental Identification of Possible Delta-Beta Thalassemia Trait in a Family: A Rare Cause of Elevated Hb F.

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ABSTRACT

Delta-Beta thalassaemia is an unusual variant of thalassaemia with elevated level of foetal haemoglobin (HbF). The clinical presentation of delta-beta thalassaemia is mild in both heterozygote and homozygote cases. We hereby describe a rare cause of elevated Hb F in a father and his two daughters. A 52-year-old diabetic male patient, on evaluation of chromatogram of cation exchange HPLC for HbA1c, we incidentally identified elevated Hb F of approximately 20%. Haematological investigation of the patient revealed decreased haemoglobin, normal RBC, leucocyte and platelet count, decreased MCV and MCH. Red cell morphology showed predominantly normocytic normochromic cells with mild anisopoikilocytosis, few microcytes and hypochromic cells seen. His liver function test was normal. Haemoglobin variant analysis revealed decreased Hb A (79.4%), normal Hb A2 (2%) and increased Hb F (19.75%). A possible diagnosis of heterozygous δβ-thalassaemia was considered. Since most laboratories perform HbA1c by cation exchange HPLC method, a careful evaluation of the chromatogram yields useful information. In our case, the elevated Hb F in a father and further careful evaluation of clinical and haematological parameters in the family members made us to possibly think of rare disorders like heterozygous Delta-Beta thalassaemia in the family and provide valuable genetic counseling.

Keywords: Foetal haemoglobin, Genetic counseling, Haemoglobin variant analysis

CASE REPORT

A 52-year-old diabetic male patient was routinely evaluated for blood glucose and HbA1c. On evaluation of chromatogram of cation exchange HPLC for HbA1c, we incidentally found elevated Hb F of 19.4%. Since Hb F is greater than 10%, the HbA1c was not reportable and patient was advised haemoglobin variant analysis for quantitative evaluation of Hb A, Hb A2 and Hb F. Haematological investigation of the patient revealed decreased haemoglobin, normal RBC, leucocyte and platelet count, decreased MCV and MCH. Red cell morphology showed predominantly normocytic normochromic cells with mild anisopoikilocytosis, few microcytes and hypochromic cells were seen [Table/Fig-1]. His liver function test was normal. Clinical evaluation of the patient revealed no signs and symptoms suggestive of anaemia, jaundice i.e., yellowish discoloration of skin, sclera (icterus), high coloured urine, hepatomegaly, splenomegaly, ascities. There was no previous history of hospitalization due to jaundice. Haemoglobin variant analysis revealed decreased Hb A (79.4%), normal Hb A2 (2%) and increased Hb F (19.75%) [Table/Fig-1]. In view of Haemoglobin variant analysis, hematological parameters and peripheral blood smear findings, a provisional differential diagnosis of heterozygous delta-beta thalassaemia was made. Screening of the family members was advised. The family history of the patient revealed two daughters of 19 and 15-year-old with no clinical signs and symptoms of anaemia or jaundice. After getting informed consent, we collected blood samples from his two daughters and his wife for haemoglobin variant analysis, complete blood count and liver function test. His wife did not have elevated Hb F or any other Hb variants. But both his daughters of 19 and 15 years old had decreased Hb A, normal Hb A2 and increased Hb F of 24% and 24.1% respectively. Haematological investigation for both daughters revealed decreased haemoglobin, normal RBC, leucocyte and platelet count, decreased MCV and MCH. Red cell morphology showed predominantly normocytic normochromic cells with mild anisopoikilocytosis, few microcytes and hypochromic cells were seen [Table/Fig-1]. Their liver function test was normal. In view of haemoglobin variant analysis, haematological parameters and peripheral blood smear findings, a provisional diagnosis of delta-beta thalassaemia trait was considered and genetic analysis was advised. The genetic analysis could not be performed due to financial constraints.

Parameters	Father	Elder Daughter	Younger Daughter
AGE (years)	52	19	15
HAEMOGLOBIN (g/dl)	10.5	10.6	11.9
RBC COUNT (mil/µl)	4.60	4.51	5.03
HAEMATOCRIT (%)	33.0	32.7	37.5
MCV (fL)	71.8	72.5	74.6
MCH (pg)	22.9	23.4	23.6
MCHC (g/dl)	31.8	32.3	31.7
RDW (%)	16.5	16.4	14.9
PLATELET COUNT (thou/µl)	362	331	385
WBC COUNT (thou/µl)	7.4	6.2	9.0
HPLC	Hb A–79.4% Hb A2–2.0% Hb F–19.7%	Hb A–75 % Hb A2–2.3 % Hb F–24%	Hb A–75.1% Hb A2–2.3% Hb F–24.1%
TOTAL BILIRUBIN (mg/dl) DIRECT BILIRUBIN (mg/dl)	0.20 0.06	0.8 0.1	0.6 0.08
SGOT (IU/L) SGPT (IU/L) ALP (IU/L)	17 40 52	22 36 140	26 42 148
RBC MORPHOLOGY	RBCs are normocytic normochromic and exhibit mild anisopoikilocytosis. Few Microcytes and hypochromic cells seen.	RBCs are normocytic normochromic and exhibit mild anisopoikilocytosis. Few Microcytes and hypochromic cells seen.	RBCs are normocytic normochromic and exhibit mild anisopoikilocytosis. Few Microcytes and hypochromic cells seen

[Table/Fig-1]: Haematological Parameters of Patients With Delta-Beta Thalassaemia Trait

DISCUSSION

Foetal haemoglobin (Hb F) is a globular protein which contains two alpha and two gamma globin chains (α2 γ2). The Hb F levels decline

to less than 1% few months after birth. However persistence of high level of Hb F in adults is seen in conditions like Delta-beta thalassaemia and Hereditary Persistence of foetal haemoglobin (HPFH) [1,2]. Delta-beta thalassaemia is relatively a rare form of thalassaemia due to decrease in both beta and delta globin chain production [3,4]. It is usually due to deletion of delta and beta globin genes [5]. Nondeletional delta-beta thalassaemia has also been described which could be due to nucleotide substitutions in promoter region of Aγ and β-globin gene [5]. Deletional mutations responsible for delta-beta thalassaemia have been observed in different ethnic groups, including Turkish, Japanese, Black, Spanish, German etc [4]. Haematological investigations of heterozygous delta-beta thalassaemia usually have high RBC count, low MCV and MCH, normal or reduced HbA2 levels and increased amounts of foetal haemoglobin (Hb F). Homozygous delta-beta thalassaemia clinically present as thalassaemia intermedia with thalassaemic red cell morphology i.e., high RBC count, high reticulocyte with microcytic hypochromic anaemia with liver function test showing increased indirect bilirubin and reduced serum haptoglobin [6]. Homozygous delta-beta thalassaemia is also known as F-thalassaemia, normal A2 β-thalassaemia and β-thalassaemia type 2 [7].

In all the three cases described, there were no clinical signs and symptoms suggestive of anaemia, jaundice i.e. yellowish discoloration of skin, sclera (icterus), high coloured urine, hepatomegaly, splenomegaly, ascites etc. There was no previous history of hospitalization due to jaundice. Haematological investigations of all the three cases revealed low haemoglobin with normal leukocyte and platelet count with decreased MCV and MCH. Peripheral smear for red cell morphology showed predominantly normocytic normochromic cells with mild anisopoikilocytosis, few microcytes and hypochromic cells seen [Table/Fig-1]. Their liver function test was normal. Haemoglobin variant by HPLC revealed normal Hb A2 levels, decreased Hb A and increased Hb F in all three of them. The differential diagnosis of HPFH should be ruled out. The red cell morphology of all the three cases showed anisopoikilocytosis with mild microcytic hypochromic picture along with decreased MCV and decreased MCH pointing towards heterozygous delta-beta thalassaemia rather than HPFH in which case only normocytic normochromic picture would be observed [8,9]. Since most laboratories perform HbA1c by cation exchange HPLC method, a careful evaluation of the chromatogram yields useful information. In our case, the elevated Hb F in a father and further careful evaluation of clinical and haematological parameters in the family members made us to possibly think of rare disorders like heterozygous delta-beta thalassaemia in the family and provide valuable genetic counseling.

CONCLUSION

These cases of elevated Hb F by cation exchange HPLC in a family highlights the importance of careful evaluation of the chromatogram of cation exchange HPLC in considering rare disorders like Heterozygous delta-beta thalassaemia and Hereditary persistence of foetal haemoglobin to provide valuable genetic counseling.

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INFORMED CONSENT

Informed consent was obtained from all three participants included in the study.

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