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Case Report

Compound heterozygous delta beta thalassemia with IVS 1-5 (G>C) mutation presenting as thalassemia major phenotype

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ABSTRACT

Delta beta thalassemia is an unusual variant of thalassemia with elevated level of fetal hemoglobin (HbF). Unlike beta thalassemia, delta beta thalassemia heterozygotes have milder phenotype and homozygotes present as thalassemia intermedia phenotype. We report a 11-month-old male child who presented with severe anemia, and hepatosplenomegaly, thalassemia major phenotype. On evaluation was diagnosed as compound heterozygous for $\delta\beta^0/\beta$ thalassemia with IVS 1-5 (G>C) mutation. This case highlights the importance of genotyping of patients with δβ thalassemia and co-inheritance of δβ thalassemia deletion with point mutation for β-thalassemia results in severe clinical phenotype as thalassemia major.

Keywords: GAP PCR, Leucocytoses, Thalassemia major

INTRODUCTION

Delta beta thalassemia (δβ-thal) results from large heterogeneous deletions in the human β- globin gene cluster on chromosome 11. There is decreased or absent synthesis of the δ and β globin chains thus resulting in decreased Hb A and with increase in expression of fetal γ chain synthesis, resulting in the increased production of HbF. Unlike β-thalassemia, the clinical phenotype of δβ-thal is milder in both heterozygotes and homozygote patients. δβ-thalassemia is co-inherited most commonly with β-thalassemia due to IVS position 1-5 (G-C) mutation and alpha 3.7 deletion.[1] We hereby report an eleven-month-old baby with clinical phenotype of Thalassemia major and on evaluation of hematological parameters, high performance liquid chromatography (HPLC) and molecular studies was diagnosed as compound heterozygous delta beta/beta thalassemia.

CASE REPORT

An 11-month-old male child presented to our hospital with paleness of body and abdominal distention for 2 months. There was no history of bleeding from any site, rash, skin bleeds and jaundice. There was no history of prior blood transfusion. On examination, infant was afebrile and hemodynamically stable. He had severe pallor. Icterus was absent, there were no petechiae, purpura and lymphadenopathy. Frontal bossing was present. Per abdomen examination revealed distended abdomen, liver was palpable 7 cm below right costal margin, soft and non-tender and firm spleen 8 cm below left costal margin along its long axis. There was no ascites. Rest of the systemic examination was normal. A possibility of hemolytic anemia, probably thalassemia major was kept and child was investigated further.

Management and outcome

Investigations revealed hemoglobin 5.5 g/dL, total leucocyte count 280110/µL, differential leucocyte count of 11.6% neutrophils, 78% lymphocytes, 10.4% monocytes, platelets count of 1.66 lac/mm^3 with corrected reticulocyte count of 7.3%, red cell distribution width of 39.8, MCV of 71.2 fL, MCH 18.4 pg, MCHC 25.8 gm/dl, serum uric acid of 4.1 mg/dL, elevated LDH levels (900

U/L). Serum calcium was 9mg/dL and phosphorus 2.5 mg/dL. Liver function test were normal. Peripheral examination showed field full of nucleated red blood cells (>60% nucleated RBC), severely microcytic hypo chromic cells, with anis poikilocytosis and polychromasia. There was shift to left side in WBC and platelets count were normal. It is shown in Figure 1. Direct Coomb's test was negative. An HPLC analysis of patient and both parents were done and results are shown in Table 1. Based on HPLC of patient and both parents as shown in Figure 2, diagnosis of Thalassemia major (compound heterozygous for delta B^0/B thalassemia) was made. To confirm, molecular studies as GAP-PCR for high HbF syndrome was done which revealed heterozygous Delta beta inversion deletion. It was negative for Indian deletion, Asian deletion, HPHF3 deletion. ARMS PCR for beta thalassemia mutation was carried out and showed heterozygous IVS 1-5 (G>C). So, the final diagnosis of Compound heterozygous $\delta\beta^0/\beta$ thalassemia with IVS 1-5 (G>C) mutation was made.

Table 1: Hematological parameters and HPLC of patient and parents.

Variables	HbA2 (%)	HbF (%)	Hb (gm/dL)	MCV (fL)	Interpretation
Patient	4.4	94.7	5.5	71.2	Thalassemia major (compound heterozygous for delta B^0/B thalassemia).
Mother	5.0	1.7	9.7	63.8	Beta thalassemia trait.
Father	2.9	11.2	12.9	70.2	Heterozygous delta beta thalassemia.

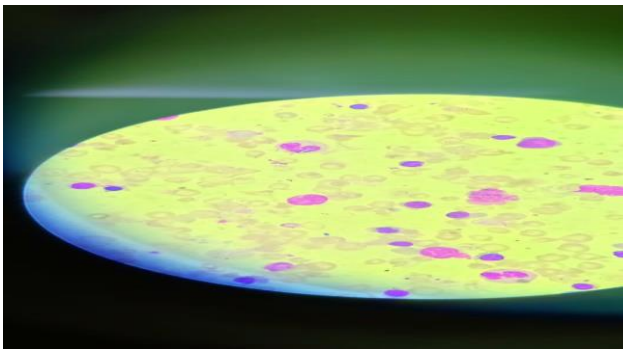

Figure 1: Peripheral smear of the patient.

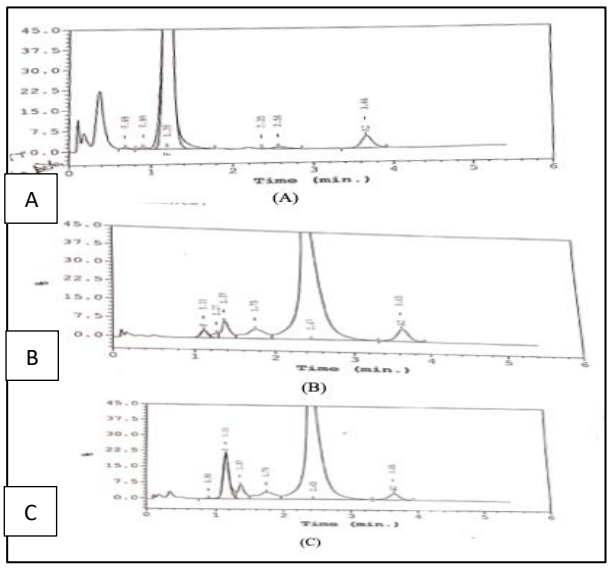

Figure 2 (A, B and C): Hemoglobin HPLC of child showed markedly raised fetal hemoglobin (94.7%) and HbA2 (4.4%), hemoglobin HPLC of mother of fetal hemoglobin (1.7%) and increased HbA2 (5%) and hemoglobin HPLC of father showed fetal hemoglobin (11.2%) and increased HbA2 (2.9%).

DISCUSSION

Delta beta thalassemia results from large deletions in delta and beta genes in the beta globin cluster located on chromosome 11. It is characterized by reduced adult hemoglobin with persistent expression of fetal hemoglobin throughout adult life. High levels of fetal hemoglobin (Hb F) ameliorate the symptoms of β-thalassemia by increasing the hemoglobin concentration of the thalassemic red cells and decreasing the accumulation of unmatched α-chains which cause ineffective erythropoiesis. Hereditary persistence of fetal hemoglobin (HPFH) also has overlapping features of δβ-thal but the level of expression differs. Individuals with HPFH are asymptomatic with normal red cell indices, pan cellular distribution, have higher levels of HbF i.e., 17-30% in heterozygotes and 100% in homozygotes. Homozygous δβ-thal has thalassemia intermedia phenotype because of high HbF (100%). In heterozygous state, there is reduced synthesis of δ and β chains and behaves as thalassemia trait with microcytic hypo chromic red cell indices and HPLC showing HbF 5-20%.[2] Heterozygous δβ thalassemia needs to be differentiated from other high HbF syndrome (HPFH, homozygous β thalassemia major and double heterozygosity for δβ-thalassemia.[2] In present case the infant presented with clinical phenotype of thalassemia major, red cell indices and high Hb F on HPLC suggesting β thalassemia major. However, on evaluation of hematological parameters and HPLC study of parents, it was found that mother had β thalassemia trait but father had normal hemoglobin with microcytic hypo chromic red cells on smear, normal HbA_2 and elevated Hb F on HPLC, thus suggestive of heterozygous δβ thalassemia. Molecular studies revealed IVS 1-5 (G>C) mutation in the child suggestive of point mutation in β globin gene. More than 40 different types of deletions in δβ -thal or HPFH have been reported and these mutations are specific for different ethnicities. Mutations responsible for δβ- thalassemia have been

observed in different ethnic groups, including Turkish, German, Japanese, Black, Sicilian and Spanish type deletion mutations.[3] Though Hb electrophoresis of index case and parents with markedly elevated HbF may suggest possibility of high HbF syndrome as in our case but molecular characterization of gene deletion is imperative. Nandkarni et al studied red cell indices and GAP PCR in 55 adults with increased Hb F levels on HPLC study. 46/55 individuals were characterized for the molecular defect. The authors reported 27% cases of δβ-thal, 47.2% cases of HPFH-3 mutation and 9% with Chinese deletion.[4]

Coinheritance of δβ thalassemia or HPFH with other factors like alpha and β-thalassemia has been documented in the literature recently. Galanello et al reported that patients with double heterozygous δβ thalassemia with β mutation had more severe clinical phenotype as compared to the δβ patients without β mutation.[5] Pandey et al studied 52 adult patients with raised HbF levels, and reported 5/18 δβ-thalassemia cases with alpha 3.7 deletion with thalassemia intermedia phenotype and 3/18(%) cases with IVS 1-5 (G-C) mutation who had severe anemia, jaundice and transfusion dependency. Hariharan et al screened 5 deletions and 1 inversion-deletion in 192 individuals by GAP PCR and correlated the genotype with hematological indices and clinical phenotype of the patients.[6] The 138/192 individuals were found to be heterozygous for β-globin cluster deletions, of which the Asian Indian inversion-deletion was found to be the most frequent variation (39.9%). The authors observed that if Hb F above 25% HPFH-3 is more likely. Also, 4 individuals in their study had point mutation for β thalassemia and uncharacterized β-globin cluster gene deletion. The mean age was 7.2 years±5.6 and mean Hb F% 89.1%±13.4%. The case in present report also had high Hb F at 94%, uncharacterized β-globin cluster gene deletion and point mutation for β thalassemia.

CONCLUSION

This case highlights the importance of genotyping of patients with δβ thalassemia and co-inheritance of δβ thalassemia deletion with point mutation for β-thalassemia results in severe clinical phenotype as thalassemia major. Molecular characterization of patients with delta beta thalassemia may aid in providing appropriate management and pre natal counselling.

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