Co-inheritance of α- and β-thalassemia in a Bangladeshi family

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Article Info

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Received: 20 May 2017
Accepted: 8 June 2017
Available Online: 9 June 2017

ISSN: 2224-7750 (Online)
2074-2908 (Print)

DOI: 10.3329/bsmmuj.v10i2.32708

Cite this article:
Rahman MM, Khan L. Co-inheritance of α- and β-thalassemia in a Bangladeshi family. Bangabandhu Sheikh Mujib Med Univ J. 2017; 10: 123-25.

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Available at:
www.banglajol.info

A Journal of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

Abstract

The double heterozygous state of α– and β–thalassemia is a relatively rare genetic disorder in Bangladesh which may alter the hematological indices and modify the phenotypic features of thalassemia. An 8 year old boy of a non-consanguineous couple who inherited both α– and β–thalassemia gene from his parents had presented with only mild anemia. Capillary hemoglobin electrophoresis showed the hemoglobin patterns which were in favor of the diagnosis of combined heterozygous alpha and beta thalassaemia carrier. Although molecular genetic study of the boy confirmed the presence of IVS 1–5 G>C point mutation for β–thalassemia but could not detect α–thalassemia gene as the sample was tested for only five most common α–thalassemia gene mutation which is not as much prevalent in Bangladesh. However, basing on the family screening and the hemoglobin pattern on capillary hemoglobin electrophoresis, it can be concluded that the boy is certainly carrying both α– and β–thalassemia gene.

Introduction

Thalassemias are a heterogeneous group of hemoglobin disorders resulting from either reduced or complete absence of synthesis of globin chains in hemoglobin tetramer.[1] Various types of mutations in α- and β–globin genes are responsible for the development of thalassemia. The thalassemia is widespread in Mediterranean region, Middle-East, China, Southeast Asia, and West Africa.[2] Clinical manifestations of α–thalassemia carrier or trait may be without symptoms but HbH disease and Hb Bart's hydrops fetalis manifest with various symptoms including intrauterine death in the later case. Gene deletions are usually the principal cause of α-thalassemia affecting one (α–thalassemia carrier), two (α–thalassemia trait), three (HbH disease) or four (Hb hydrops fetalis) of α –globin genes whereas point mutations in the β –globin gene sequence are the prime etiology for β–thalassemia.[3]

Approximately 6.5% of the world populations are carriers of inherited hemoglobin disorders. As per WHO report there are 3% carriers of β–thalassemia gene and 4% carriers of Hb E gene in Bangladesh.[4] No data is available regarding the prevalence of α thalassemia gene in Bangladesh. In India, α–thalassemia is also common and the occurrence of gene frequency is reasonably higher than β–thalassemia trait.[5] Though the exact frequency of α– and β–thalassemia is not well characterized in Bangladesh but from the prevalence of carrier rate in our neighboring countries, it is assumed that there is appreciably high frequency of β–thalassemia than α–thalassaemia. That's why, the co-inheritance of α– and β–thalassemia is rarely found. More so, limited molecular detection facilities of both α– and β–thalassemia hinders the accurate diagnosis of such co-inheritance. However, a study showed that 7.4% Bangladeshi individuals are carrying HbE/beta thalassemia gene.[6] The capillary hemoglobin electrophoresis in few cases permit the detection of hemoglobin Bart's which allows diagnosing the presence of co-inheritance of α– and β–thalassemia in Bangladesh.

Here, we present a case of co-inheritance of α– and β–thalassemia in a Bangladeshi boy whose one parent is a carrier of α–thalassemia and other parent is of β–thalassemia carrier. This is the first reported case in a Bangladeshi family and such documentation is essential for genetic counseling of the parents and to determine the reproductive risk of the family.

Case Report

An 8 year old boy, born to non-consanguineous young parents, had reported to a hematologist for weakness and anorexia. History revealed that, the boy was the only offspring of the parents and on physical examination no abnormality was detected except moderate anemia. Therefore, the boy was advised to do full blood count (FBC) including blood film examination. FBC showed hemoglobin 9.2 g/dL, red cell count 5.3 x 10^{12}/L, mean cell

volume (MCV) 58.1 fL, mean cell hemoglobin (MCH) 17.40 pg, mean cell hemoglobin concentration (MCHC) 30.0 g/dL, red cell distribution width (RDW) 14.1% and blood film showed microcytic hypochromic anemia. The patient was advised to investigate with capillary hemoglobin electrophoresis and serum iron profile. His serum iron profile (serum iron, total iron binding capacity [TIBC], serum ferritin) was within normal limit but capillary hemoglobin electrophoresis revealed Hb Bart's 22.3%, HbA 73.6% and Hb A_2 4.1% (Figure 1) indicated the provisional diagnosis of co-existing α– and β–thalassemia.

After analyzing the capillary hemoglobulin electrophoresis of the child his parents were requested to perform FBC, blood film examination and capillary hemoglobulin electrophoresis. FBC of the father, 43 year old, demonstrated hemoglobin 9.2 g/dL, red cell count 5.2 x 10^{12}/L, MCV 60.0 fL, MCH 17.80 pg, MCHC 29.6 g/dL, RDW 12.6% and blood film revealed the features of hereditary hemolytic anemia. Capillary hemoglobin electrophoresis showed Hb A 93.4, Hb F 1.4 and Hb A_2 5.2% indicating the diagnosis of β–thalassemia trait. FBC of the mother, 38 year old, revealed hemoglobin 11.4 g/dL, red cell count 4.4 x 10^{12}/L, mean cell volume 79.8 fL, mean cell hemoglobin 26.0 pg, mean cell hemoglobin concentration 32.5 g/dL, red cell distribution width 11.8% and blood film was non-specific. Capillary hemoglobin electrophoresis showed Hb Bart's 24.0, Hb A 74.1 and Hb A_2 1.9% commenting the diagnosis of α–thalassemia carrier.

Pedigree tree of the second and third generation was constructed (Figure 2) as the grandparents are not alive. Pedigree analysis showed that the father is a carrier of β–thalassemia, mother is α–thalassemia carrier and their son co-inherited both α- and β–thalassemia gene. For genotypic characterization of both α– and β–thalassemia gene, blood sample was collected from the boy and sent to SRL diagnostic centre, Mumbai, India for α– and β–thalassemia mutation study. Comment from the above mentioned diagnostic centre was that the individual is heterozygous for IVS 1–5 G>C point mutation confirming the presence of β–thalassemia gene but the five most common α-deletional mutations, prevalent among Indian populations, tested in this boy, were not detected. However, it didn't exclude the absence of α–thalassemia gene mutation because there are many rare mutations in alpha thalassemia which are not tested routinely what happened in this case. Finally, based on the hemoglobin pattern of the boy and his parents, it can be certainly concluded that the boy had co-inherited α– and β–thalassemia gene from his parents as both the parents clearly revealed the presence of heterozygous state for α– and β–thalassemia carrier.

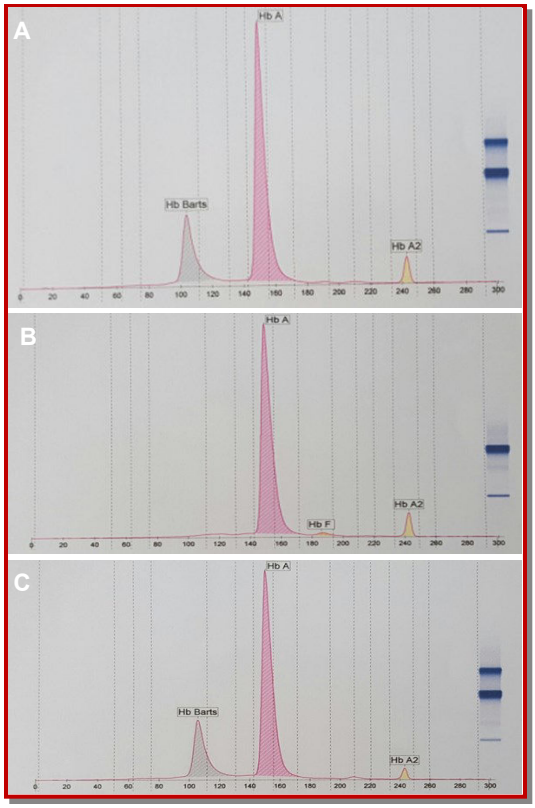

Figure 1: Hemoglobin patterns of the patient (A), father (B) and mother (C) on capillary hemoglobin electrophoresis

Discussion

Inherited disorders including thalassemias and hemoglobinopathies are passed from generation to generation and it is not usually curative till date but their early detection imparts important impact in the society through implementation of different types of preventive program. Carriers of gene for inherited hemoglobin disorders are usually

Table I

Hematological parameters of the patient and his parents

Relation	Hb (g/dL)	RBC count (x10^{12}/L)	MCV (fL)	MCH (pg)	MCHC (g/dL)	RDW	Hb A (%)	Hb A_2 (%)	Hb F (%)	Hb Bart's (%)
Patient	9.2	5.3	58.1	17.4	30.0	14.1	73.6	4.1	-	22.3
Father	9.2	5.2	60.0	17.8	29.6	12.6	93.4	5.2	1.4	-
Mother	11.4	4.4	79.8	26.0	32.5	11.8	74.1	1.9	-	24.0

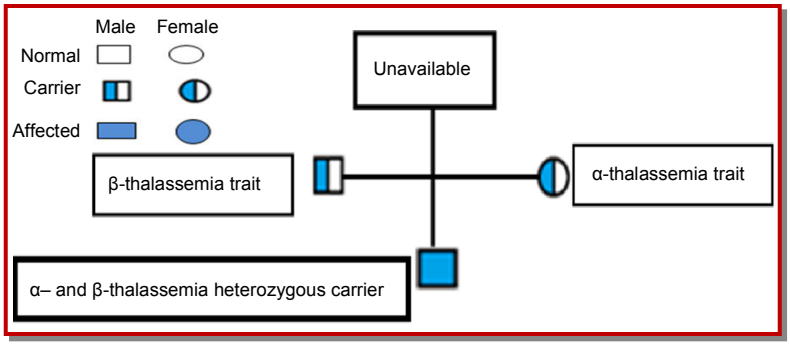

Figure 2: Pedigree of the boy

symptomless but if the gene transmitted to their progeny may have a risk to be diseased with highly variable symptomology.[7] Preventive screening program in case of combined heterozygous α– and β–thalassemia is not like other simple heterozygous or homozygous inherited hemoglobin disorders because such combination temper the FBC and Hb A_2 parameters in β–thalassemia trait. In such circumstances quantity of Hb A_2 may be reduced by α–thalassemia allele, but the reference range is yet higher than normal.[8, 9]

The boy (index case) was sent for hematologic evaluation by FBC and capillary hemoglobin electrophoresis. The hematological parameter of the boy and parents was shown in Table I. The boy who inherited both α– and β–thalassemia gene had Hb A_2 level (4.1%) just above the reference range (1.5–3.5%) in comparison to his father's Hb A_2 level (5.2%) who is a carrier of β–thalassemia gene. This finding indicated that the presence of α–thalassemia allele masked the hematological parameter of the boy who also inherited β–thalassemia gene.

Though α– and β–thalassemia mutation study only identified the β–thalassemia mutation (IVS 1-5 G>C point mutation) and could not detect the five (- $\alpha^{3.7}$, $\alpha^{4.2}$, α^{SEA}, FIL and THAI) most common α–thalassemia mutation in Indian population but negative result does not rule out the other known rare α–thalassemia mutation. From the family study it is almost clear that the boy had co–inherited both α– and β–thalassemia. Because the boy has both Hb Bart's (22.3%) and raised Hb A2 (4.1%) level. It is very difficult to detect α–thalassemia carrier and trait on gel Hb electrophoresis but capillary method may quantify the presence of Hb Bart's in the blood which is arbitrarily used to portend the genotype of α–thalassemia and the presence of Hb Bart's less than 25% in the blood indicate that the individual is suffering from α–thalassemia trait.[10] In the reported case, the amount of Hb Bart's is 22.3% and in the mother of the boy 24.0% indicating that they both are harboring α–thalassemia gene. Also the mother had low Hb A_2 level (1.9%) which is one of finding of α–thalassemia trait. As mutation study, which included only five common mutations prevalent in India, could not detect α–thalassemia mutation, it warrants carrying out test with more primers to detect rare known α–thalassemia mutation to arrive at a definitive diagnosis.

Conclusion

Though the heterozygous α– and β–thalassemia carrier is rare in Bangladesh but meticulous and careful interpretation of hemoglobin patterns on capillary hemoglobulin electrophoresis may enable the concerned physicians to take appropriate measures in such a way to reduce the incidence of such co-inheritance in Bangladesh.

Ethical Issue

Written and informed consent was taken from the parents for publishing this article.

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