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Editorial

Molecular Basis of Thalassemia Intermedia in Pakistan

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INTRODUCTION

The word thalassemia intermedia is a clinical definition in use for spectrum of clinical condition ranging in severity from the symptomatic carrier state to transfusion dependent patients. This mild phenotype may result from homozygosity for mild β thalassemia mutations, coinheritance with homozygous β thalassemia of α Thalassemia or hereditary persistence of fetal hemoglobin, compound heterozygosity for mild and severe β Thalassemia mutations, double heterozygosity for β Thalassemia and triple α globin gene arrangement or the presence of highly unstable hemoglobin (Hb) variants.

Thalassemia intermedia patients develop mild to moderate anaemia with average Hb level in steady state is 7-8g/dl. Thalassemia intermedia are usually associated with mild to moderate jaundice and hepato-splenomegaly. Patients with high Hb levels have no definite gross abnormalities in physical development and no thalassemic faces. Generally the patients have mild symptoms or rare symptom freebut complication do occur. Iron overload is always demonstrated by raised plasma ferritin level. Normally patients with β Thalassemia intermedia do not require blood transfusion except when they develop infections, which exacerbate the anaemia. Iron chelataion may not be necessary in very mild affected patients.

DIAGNOSIS

Age at presentation is one of the major clinical criteria for identifying patients with thalassemia intermedia. Patients affected by very mild forms may be recognized in the second decade of life or even later. Some patients present at two years of age with hemoglobin above 7 g/dL and do well clinically. Patients that grow normally at three years and do not develop evident bone changes without regular transfusions are definitely thalassemic intermedia. Some of these patients develop hyper-splenism and require splenectomy.

Hemoglobin level and composition is another important factor for diagnosis. Hb F is remarkably variable among patients, ranging from 5 to 100%. No direct correlation exists between total Hb and Hb F levels, suggesting that different mechanisms are responsible for γchain production.

MOLECULAR BASIS

Patients of thalassemia intermedia are either homozygous for a mild mutation (β^+/β^+), compound heterozygous for two mild mutations (β^+/β^+) or compound heterozygous for one mild and one severe mutation (β^+/β^0) as compared to the patients of thalassemia major who are homozygous for a severe mutation or compound heterozygous for two severe mutations (β0/β0).

DETERMINANTS

a) The $-158^{G}\gamma$ (C→T) substitution (Xmn-1polymorphism) is reported to be responsible for high HbF production. The inheritance of β thalassemia gene with Xmn-1 (+) haplotype is clearly associated with milder clinical phenotype. However, a single copy of this haplotype may not be enough to affect a sufficient increase in Hb F production in β^0thalassemia patients. In contrast, the Xmn-1 (+/-) has a significant affect on β^+ thalassemia patients and these patients have a milder phenotype.

b)The coinheritance of α-thalassemia is able to ameliorate the clinical course of homozygous β-thalassemia patients.Deletion of two αgenes is required to modify the excess of chains in β^0-thalassemia, since the deletion of a single gene has little effect on the phenotype.Deletion of a single gene can ameliorate the phenotype in carriers of β^+mutations.

c) Some forms of hereditary persistence of fetal hemoglobinand rare cases of β-thalassemiaare due to still unknown determinants not linked to the β-cluster. These determinants could modulate Hb F or Hb A production as well as stimulate α-chain proteolysis.

CLINICAL PROBLEMS

The chronic anaemia of thalassemia intermedia patients itself might lead to several clinical problems. Folic acid deficiency is a common problem of untreated patients.Splenomegaly caused by excessive RBCs breakdown and extramedullary hematopoiesis may exacerbate anaemia. Iron overload is a common feature even in untransfused thalassemia intermedia patients because of ineffective erythropoiesis, peripheral red cell breakdown and increased intestinal iron absorption.

TREATMENT

Continuous folic acid supplementation is recommended in all thalassemia intermedia patients. Splenectomy is the first therapeutic approach to consider to correct anaemia before starting regular transfusions.

Chelation therapy with desferrioxamine (DF) is obviously indicated when a transfusion regimen is started. It is even indicated in untransfused patients when iron overload is documented.

Although bone marrow transplantation has been performed in patients with thalassemia intermedia, this therapeutical approach should be evaluated case by case at present and cannot be proposed as standard therapy for all patients with a suitable marrow donor.

Thalassemia intermedia patients should potentially benefit more than their thalassemia major counterparts from pharmacological manipulation of the Hb switching proposed to increase Hb F. In the last few years it has been shown that several cytotoxic drugs – such as 5'- azacytidine (5'-Aza) and hydroxyurea are able to increase Hb F production in adult hemoglobinopathy patients. Hydroxyurea has been shown to be the most effective drug in sickle cell anaemia.Other drugs such as butyrate and short chain fatty acids can also achieve reversion of the Hb composition to fetal pattern.Recombinant human erythropoietins have also been in use in selected patients.

In Pakistan, β-thalassemia is one of the most common inherited Hb disorder. The five most common β-thalassemia mutations are IVI-5 (G→C) (37.7%), Codon8/9 (+G) (21.1%), 619bp del. (12.4%), IVS1-1 (G→T) (9.5%) & codon 5 (–CT) (9.1%).

In the northern areas, 83% of the children suffering from refractory anemias have β-thalassemia. The carrier frequency is estimated to be 5.4%, although the incidence of β-thalassemia varied from 1.4 to 8%. A high prevalence of this disease occurs in areas along the Arabian sea Coast in the South and the Khyber-Pakhtunkhwa (KPK) bordering Afghanistan, where people from the Middle East, the Mediterranean and central Asia have settled after invasion during various periods in history. The population is divided into Punjabi and Pashtoon in North, Balochi and Sindi in South. Furthermore, there are other ethnic groups, which may be grouped separately as Urdu Speaking, Gujratis and Memons who migrated to Pakistan after 1947 partition of the Indian Sub-continent from India. Many social factors such as a preference to marry within ethnic groups and consanguineous marriages, have contributed to the increased incidence of this disease in Pakistani population. Moreover, life expectancy and quality of life are very low for β-thalassemia patients, because of lack of public awareness about the disease and, also the provision of good quality care and blood screening increases the cost. Furthermore, the facilities for bone marrow transplantation are so far not available in the country.

Hence, all the thalassemia patients should be diagnosed molecularly before starting their blood transfusion to determine the course of their disease and for their properly management accordingly.

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