Abstract: PB2532

Title: VARIABLE HEMATOLOGICAL AND CLINICAL PHENOTYPES IN DOUBLE HETEROZYGOTES OF BETA-THALASSEMIA AND TRIPLICATED ALPHA-GLOBIN GENES

Abstract Type: Publication Only

Session Title: Thalassemias

Background:

The excess of unpaired alpha-globin chains is a major determinate of hematological and clinical severity of beta-thalassemia. In beta-thalassemia heterozygotes, the coinheritance of additional alpha-globin genes, most commonly through double heterozygosity for a triplicated alpha-globin gene allele, may exacerbate the clinical and hematological phenotype.

Aims:

We present the clinical and hematological findings in a cohort of cases with co-inheritance of a triplicated alpha-globin gene allele and heterozygous beta-thalassemia.

Methods:

Following analysis of alpha and beta globin genotypes 43 cases were referred to our thalassemia clinic with mild to moderate anemia for phenotypic evaluation and clinical follow-up.

Results:

Data are summarized in Table I. All patients had the $\alpha\alpha\alpha^{anti\text{-}3.7}$ allele and were heterozygotes for a β-thalassemia mutation. The most common *HBB* variant was HBB:c.118C>T (CD39 C>T) (32.6%). Mean Hb levels were 10.1±1.3 g/dl (male 10.6±1.2 g/dl; female 9.8± 1.3 g/dl), with a median of 9.95 g/dl (range: 7.1–12.8 g/dl) (male: 10.75 g/dl; female: 10.75 gr/dl). Five cases (11.6%), had less than 9 gr/dl hemoglobin. Nineteen (44%) had splenomegaly and two had undergone splenectomy with improvement of clinical status. Four cases (9%) had cholecystectomy. Other morbidities included hypothyroidism (3 cases), diabetes mellitus (1 case), osteopenia (6 cases) and osteoporosis (2 cases). Five cases had more than 3 transfusions due to pregnancy, splenectomy or infections. All transfused cases had severe beta-thalassemia variants. Five cases developed iron overload and received iron chelation therapy, one of whom was additionally homozygous for the p.Cys282Tyr (C282Y) variant of the *HFE* gene. Of note is that 35/42 cases carry a null *HBB* variant and overall 40/42 cases had severe *HBB* variants.

Summary/Conclusion: Double heterozygosity for a beta-thalassemia and a triplicated alpha-globin gene underlies a variable clinical phenotype, ranging from thalassemia minor to thalassemia intermedia of moderate severity, potentially modified by other genetic and environmental factors. These findings indicate that all double heterozygotes should be routinely referred for long-term hematological and clinical follow-up even when presenting with thalassemia minor at initial diagnosis.

Table 1. Genotypes and hematological profiles of 43 patients.

Male, n (%)	18 (41.8%)
Female, n (%)	25 (58.1)
Current age (mean ±sd), years	32 ± 0
Age of Diagnosis (mean ±sd), years	20.5±19.4
Age of Diagnosis, (median; range), years	15 (0.5-73)
Genotype of beta mutation	**n (%)**
HBB:c.118C>T (CD39 C>T)	14 (32.6)
HBB:c.92+1G>A (IVSI-1 G>A)	9 (20.9)
HBB:c.315+1G>A (IVSII-1 G>A)	5 (11.6)
HBB:c.20delA (Cd6 del A)	4 (9.3)
HBB:c.17_18delCT (Cd5 del CT)	4 (9.3)
HBB:c.93-21G>A (IVSI-110 G>A)	3 (6.9)
HBB:c.92+6T>C (IVSI-6 T>C)	2 (4.7)
HBB:c.92G>C, p.Arg30Thr	2 (4.7)
Hematological parameters (mean±sd)	
Hb (gr/dl)	10.1±1.2
Ht (%)	32.8 ± 3.6
MCV (fL)	62.2 ±7.0
MCH (pg)	19.2 ±1.7
MCHC (g/dl)	30.7 ±1.4
RET (%)	2.9 ±3.6
Ferritin (µg/L)	201 ±224.1
HbA2 (%)- range	5.08 ±0.8 (3.3-7)
HbF (%) - range	5.5± 6.1 (0-30)

Keywords: Globin gene, Complications, Thalassemia, Phenotype