Interaction between Hb SS and alpha Thalassemia (3.7 kb deletion): a familial study

Eliana Litsuko Tomimatsu Shimauti
Paula Juliana Antoniato Zamaro
Claudia Regina Bonini-Domingos

Biology Department, Laboratório de Hemoglobinas e Genética de Doenças Hematológicas, Universidade Estadual Paulista "Julio de Mesquita Filho" – UNESP, São José do Rio Preto, SP, Brazil

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Corresponding author:
Eliana Litsuko Tomimatsu Shimauti
Universidade Estadual de Maringá
Departamento de Análises Clínicas e Biomedicina
Av. Colombo, 5790 – Jardim Universitário
87020-900 – Maringá, PR, Brazil
Phone: 55 44 3011-4800
E-mail: eltshimauti@uem.br

www.rbhh.org or www.scielo.br/rbhh

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Both the clinical course and molecular alterations of sickle cell anemia (Hb SS) are highly distinct. Possible modulators of phenotypical variability have been documented, including alpha-thalassemia and beta S-globin gene cluster haplotypes.[1] The possible benefits of alpha thalassemia co-inheritance also affect hematological parameters.[2] The Hb S intracellular concentration seems to present direct dependence on the alpha-globin genotype. Thus, the association of alpha thalassemia and Hb SS minimizes the physiopathological effects in carriers of hemoglobinopathy S. Alpha thalassemia caused by the deletion of 3.7 kb of DNA ($-\alpha^{3.7}$) is the most common in Brazil.[3]

The present article reports the observation of different clinical and hematological profiles in two individuals from the same familial nucleus with Hb SS, one heterozygosis ($-\alpha/\alpha\alpha$) and the other homozygosis ($-\alpha/-\alpha$) for alpha thalassemia (3.7 kb deletion).

Patient 1, a 10-year-old boy ($-\alpha/\alpha\alpha$) and Patient 2, a 22-year-old woman ($-\alpha-\alpha$) are both mulattos. The diagnostic confirmation of Hb SS and for alpha thalassemia (3.7 kb deletion) were achieved by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP)[4] and multiplex PCR,[5] respectively. The concentrations of hemoglobinic fractions were determined by HPLC Variant™ equipment using the Beta Thal Short Program (Bio-Rad). Hematological parameters were obtained using a BC-300 PLUS automatic analyzer (Mindray). Blood samples were collected after receiving informed consent and according to the ethical principles established by Resolution 196/96 of the National Health Council.

Clinical data, obtained from an evaluation of medical records, are shown in Table 1. Patient 1 had been transfused 130 days prior and Patient 2, 3204 days prior to the blood collection for this study. They did not take hydroxyurea but took folic acid. Quantitative laboratorial data are shown in Table 2. As for the morphologic evaluation of red blood cells, hypochromia was only present in the Hb SS interaction with the $-\alpha/-\alpha$ genotype, and polychromatophilic macrocytes only in the interaction between Hb SS and the $-\alpha/\alpha\alpha$ genotype. Other alterations such as microcytosis, macrocytosis, polychromatophilic cells, drepanocytes, Howell-Jolly bodies, codocytes and erythroblasts were common in both. The haplotypes of both individuals were characterized as Bantu/Benin by PCR-RFLP.

Table 1 - Clinical characteristics of the Hb SS- $\alpha^{3.7}$ thalassemia coexistence observed

Clinical data	SS/($-\alpha/\alpha\alpha$)	SS/($-\alpha/-\alpha$)
Painful crises	No	No
Joint pain	Yes	No
Cholecystectomy	Yes	No
Splenectomy	No	Yes
Leg ulcers	Yes	No

Table 2 - Hematological data of the Hb SS- $\alpha^{3.7}$ interaction of Patients 1 and 2 with deletion of 1 and 2 alpha-genes, respectively

Hematological parameters	SS/($-\alpha/\alpha\alpha$)	SS/($-\alpha/-\alpha$)
Hemoglobin (g/dL)	7.6	9.0
Globular volume (%)	22.1	28.7
MCV (fL)	88.1	79.5
MCH (pg)	30.2	24.8
MCHC (%)	34.3	31.3
RDW (%)	17.7	14.2
Leucocytes (x 10^9/L)	14.0	9.7
Neutrophils (x 10^9/L)	6.1	4.9
Monocytes (x 10^9/L)	0.7	0.3
Platelets (x 10^9/L)	380	280
Hb S (%)	80.2	72.6
Hb A2 (%)	4.7	4.4
Hb F (%)	15.1	23
Reticulocytes (%)	12.1	6.3
Irreversible drepanocytes (%)	3.0	1.0

MCV = Mean corpuscular volume; MCH = Mean corpuscular hemoglobin; MCHC = Mean corpuscular hemoglobin concentration; RDW = Red cell distribution width

Both hepatobiliary complications and vasculopathy were seen in Patient 1 ($-\alpha/\alpha\alpha$), and splenomegaly were only observed in Patient 2 ($-\alpha/-\alpha$). As for the hematological effect, the homozygous patient for alpha thalassemia ($-\alpha/-\alpha$) showed a lower level of hemolysis, milder anemia, lower red blood cell indices as well as inflammation cell markers (granulocytes and monocytes) compared to the heterozygous patient ($-\alpha/\alpha\alpha$). Co-inheritance of alpha thalassemia and Hb SS is associated to lower risk of cholelithiasis[6] and a higher frequency of splenomegaly.[7] The benefits of this epistatic effect seem to increase with the number of $-\alpha^{3.7}$ gene deletions.

The results corroborate published data which report that the coexistence of

homozygosis for alpha thalassemia (3.7 kb deletion) with sickle cell anemia is a factor that modulates the clinical variability and hematological severity, demonstrating a diversity of manifestations even within a single family nucleus.

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