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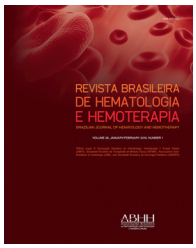

Scientific Comment

Comments on: "Clinical, hematological and genetic data of a cohort of children with hemoglobin SD"☆

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Sickle cell disease (SCD) is a group of genetic conditions related to the presence of a sickle hemoglobin (Hb S) mutation (HBB:c.20A>T). People with SCD can be homozygous for Hb S or can have compound heterozygosity for Hb S with other gene mutations.[1,2] Some hematologic features of SCD are listed in Table 1, but rare genotypes can also be found. Since the concentration of Hb S is a pathophysiological factor of disease severity, the presence of lower concentrations of Hb S due to double heterozygosity can determine phenotypic heterogeneity.[1,3] However, other genetic and environmental factors can also have an effect on the disease phenotype.[4]

Studies looking for abnormal hemoglobins (Hbs) in the Brazilian population have been performed since the 1950s.[5–8] However, the Brazilian Government Directive MS # 822/01 that regulates newborn screening for hemoglobinopathies, has promoted an increase of data about hemoglobinopathies in different Brazilian regions.[9–11] This associated with the use of isoelectric focusing electrophoresis (IEF) and high-pressure liquid chromatography (HPLC) as diagnostic methods, has enabled the identification of an increasing number of abnormal Hbs as well as compound heterozygous states of Hb S.[12–14] An example is a paper published in this issue of the Revista Brasileira de Hematologia e Hemoterapia that shows data on a cohort of children with hemoglobin SD pattern.[15]

Hb D is an abnormal Hb, which migrates to the same position as Hb S in electrophoresis at alkaline pH, and can be separated from Hb S in acid pH.[16–18] Several Hb D have been described in different racial groups, but the majority presented a point mutation in codon 121 of the β-globin gene, which results in the substitution of glutamic acid for glutamine (HBB:c.364G>C). This abnormal Hb is usually called Hb D-Punjab or Hb D-Los Angeles, however it can also be named Hb D-North Carolina, Hb D-Chicago, Hb D-Portugal, Hb D-Cyprus, and Hb D-Oak Ridge.[19–21] The estimated prevalence of Hb D-Punjab is 0.1 to 0.4% in African-Americans.[22] In Brazil, a study of African descendants showed a similar prevalence.[5]

Sometime after the discovery of Hb D-Punjab, the coinheritance of Hb D-Punjab and Hb S was identified in Caucasian patients with clinical and hematological manifestations similar to those of sickle cell anemia (SCA), because this mutation facilitates Hb S polymerization.[23–25] Further clinical studies confirmed the severity of the manifestations of this association and the need to treat these individuals as SCA patients by prescribing hydroxyurea when indicated.[21,26–29]

There are other types of Hb D due to different point mutations in the β-globin gene, such as Hb D-Iran (HBB:c.67G>C) and Hb D-Ibadan (HBB:c.263C>A). However, individuals with these mutations have normal hematologic values and do not suffer from vaso-occlusive complications, since their red cells do not sickle under physiologic conditions.[18,30,31]

Hb Korle-Bu (Hb KB) or Hb G-Accra (HBB:c.220G>A) is a frequent mutation in Sub-Saharan Africa.[32,33] This Hb has the same IEF mobility as Hb D-Punjab but can be differentiated by HPLC. Heterozygotes for Hb KB have no hematologic alterations, and individuals with double heterozygosis Hb S-Hb KB have normal red cells on blood smear and a benign clinical course, similar to sickle cell trait as Hb KB does not participate in the gelation of Hb S.[33,34]

Interestingly, the Hb KB mutation [beta73(E17)Asp→Asn] can occur in addition to the Hb S mutation [beta6(A3)Glu6Val]

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☆ See paper by Rezende et al. on pages 240–6.

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Table 1 – Hematological features of some sickle hemoglobinopathies.

Genotype	PCV (%)	Retic (%)	MCV (fL)	Hb F (%)	Hb A_2 (%)	% Variant	Severity[a]
SCA	25	8	90	5	3	>90% Hb S	++++
Hb SC disease	35	3	80	2	3	50% Hb S, 50% Hb C	++
S-β^0 thalassemia	27	7	82	7	5	90% Hb S	++++
S-β^+ thalassemia	38	2	70	2	6	5–30% Hb A	++
SCA-α thalassemia	30	6	78	5	5	>90% Hb S	+++
Hb SE disease	35	3	75	2	3	~30% Hb E	++
Hb SD disease*	20		86	1–10	2–4	45% Hb S, 45% Hb D	+++
Sickle cell trait	45	1	85	1	2	60% Hb A, 40% Hb S	⊖

SCA: sickle cell anemia; PCV: packed cell volume; Retic: reticulocyte count; MCV: mean cell volume; Hb: Hemoglobin.

[a] Severity of disease rated from most severe (++++) to absence of clinical events (⊖) includes complications related to sickle vaso-occlusion and hemolysis.

Table modified from 1 with * data obtained from 21,27,32.

in the same beta globin chain. In this case, this Hb with a double mutation is termed Hb C-Harlem (or Hb C-Georgetown) (HBB:c.20A>T, HBB:c.220G>A), because it migrates to the position of Hb C in cellulose acetate electrophoresis at alkaline pH. Individuals heterozygous for Hb C-Harlem are asymptomatic, but the coinheritance of Hb S and Hb C-Harlem has clinical manifestations similar to SCA.[20,32,35]

Researchers from India and the Middle East are the main authors of the few papers about Hb SD-Punjab; there are less data published about the association Hb S-Hb KB.[21,27–29,34,36–41] By studying two different groups of patients with Hb SD patterns, specifically Hb SD-Punjab and Hb S-Hb KB, Rezende et al. not only published important clinical data about the coinheritance of two rare Hb but also pointed out the importance of this differential diagnosis.[15]

Conflicts of interest

The author declares no conflicts of interest.

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