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Scientific Comment

The compound state: Hb S/beta-thalassemia☆

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Sickle cell disease (SCD) results from a single amino acid substitution in the gene encoding the β-globin subunit (β6Glu > Val) that produces the abnormal hemoglobin (Hb) named Hb S. SCD has different genotypes with substantial variations in presentation and clinical course (Table 1).[1,2] The combination of the sickle cell mutation and beta-thalassemia (β-Thal) mutation gives rise to a compound heterozygous condition known as Hb S/β thalassemia (Hb S/β-Thal), which was first described in 1944 by Silvestroni and Bianco.[3]

The polymerization of deoxygenated Hb S (sickling) is the primary event in the molecular pathogenesis of SCD. However, this event is highly dependent on the intracellular Hb composition; in other words, it is dependent on the concentration of Hb S, and type and concentration of the other types of Hb. Therefore, the major primary genetic determinant of the severity of SCD is the genotype.[2,4–6]

Many different β-Thal mutations have been associated with Hb S, and the molecular basis of the thalassemia in Hb S/β-Thal individuals reflects the spectrum of β-Thal mutations observed in a particular population.[5,7–12] The heterogeneity of the β-Thal mutations leads to quantitatively different β-globin synthesis and consequently to different amounts of Hb A. This fact results in variable clinical manifestations, ranging from nearly asymptomatic to a severe condition similar to sickle cell anemia (homozygous Hb S).[3,13] There is no consensus about the classification of Hb S/β-Thal, but it is usually classified in two types: Hb S/β^0-Thal and Hb S/β^+-Thal.[2,4]

Hb S/β^0-Thal, in which the production of Hb A is abolished, is often clinically indistinguishable from sickle cell anemia. The thalassemia acts on sickled red blood cells, inducing microcytosis, hypochromia, and sometimes Hb F is elevated. This result in an improvement of the circulatory competence of these cells, a reduction of hemolysis, and a small increase in Hb concentration and in packed cell volume. However, these effects are not accompanied by any reduction in vaso-occlusive events, probably due to the great number of Hb S-containing red blood cells resulting in increased blood viscosity.[4,5]

A confusing diagnostic problem is the differentiation of Hb S/β^0-Thal from sickle cell anemia associated with α-thalassemia. Table 2 shows that hematologic and electrophoretic studies are unable to distinguish between the two conditions and so family studies and DNA analysis are needed to confirm the diagnosis.[5]

In Hb S/β^+-Thal, variable amounts of Hb A dilute Hb S and consequently inhibit polymerization-induced cellular damage. The Hb A levels vary from <5% to 45% of the hemolysate and higher levels of Hb A are usually associated with a milder phenotype.[5,8,12–15] However, because of the confounding influences of other genetic modifiers, such as γ-globin gene expression and α-thalassemia, a rigid genotype–phenotype correlation is difficult to establish.[5]

A classification of Hb S/β^+-Thal into Types I (Hb A: 1–7%), II (Hb A: 7–14%), or III (Hb A: 14–25%) according to the level of Hb A has been proposed.[3,14] However, this classification is not widely accepted and could be considered of little utility. Nowadays it is possible to define the β-Thal mutation exactly by molecular biology techniques, and determine the relationship between mutation and clinical manifestations.[5]

The determination of the β-Thal mutation in Hb S/β^+-Thal individuals was performed by Besilario et al. These authors studied four patients with an Hb A concentration above 38% and a very mild form of the disease, and identified two mutations for the first time in the Brazilian population.[16] It is important to point out that these cases could be wrongly interpreted as sickle cell trait, since they had no anemia, despite

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Table 1 – Sickle cell disease genotypes.

Severe sickle cell disease		
Sickle cell anemia (Hb S/S)	β6Glu > Val/β6Glu > Val	The most common form
Hb S/β^0 thalassemia	Multiple mutations	Most prevalent in the eastern Mediterranean region and India
Severe Hb S/β^+ thalassemia	Multiple mutations	Most prevalent in the eastern Mediterranean region and India
Hb S/O Arab	β6Glu > Val/β121Glu > Lys	North Africa, the Middle East, and the Balkans
Hb S/D Punjab	β6Glu > Val/β121Glu > Gln	Predominant in northern India
Hb S/C Harlem	β6Glu > Val/β6Glu > Val/β, β73Asp > Asn	Very rare
Moderate sickle cell disease		
Hb S/C	β6Glu > Val/β6Glu > Lys	25–30% cases of sickle cell disease of African origin
Moderate Hb S/β^+ thalassemia	Multiple mutations	Most in the eastern Mediterranean region
Mild sickle cell disease		
Mild Hb S/β^{++} thalassemia	Multiple mutations	Mostly in populations of African origin
Hb S/E	β6Glu > Val/β26Glu > Lys	Hb E predominates in southeast Asia
Very mild sickle cell disease		
Hb S/Hereditary Persistence of Fetal Hemoglobin	Large deletions of the β-globin gene complex	

Source: Modified from Rees et al.[1]

Table 2 – Laboratory differentiation of sickle cell anemia, sickle cell anemia/α-thalassemia, and Hb S/β^0-thalassemia.

Diagnosis	Level variation			Mean Hb F (%)
	Hemoglobin (g/dL)	MCV (fl)	Hb A2 (%)	
SCA	7–8	85–95	2.5–3.5	5
SCA/α-thalassemia	8–10	70–85	3.5–4.5	5
Hb S/β^0-thalassemia	8–10	65–75	4–6	9

Source: Modified from Steinberg et al.[5]

SCA: sickle cell anemia; MCV: mean corpuscular volume; Hb A_2: hemoglobin A_2; Hb F: hemoglobin fetal.

a little microcytosis, and that this incorrect diagnosis would reflect in the genetic counseling provided. In summary, this study reinforces the importance of molecular studies in our population, in order to enhance our knowledge about the disease in Brazil and consequently improve genetic counseling, follow up, and treatment.

Conflicts of interest

The author declares no conflicts of interest

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