Sickle cell anemia: clinical diversity and beta S-globin haplotypes

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In sickle cell anemia (SCA), beta S-globin haplotypes represent the ethnic group or geographic region from which patients originated. The haplotypes include Senegal (SEN), Benin (BEN), Bantu or Central African Republic (CAR), Cameroon (CAM) and Arab-Indian (ARAB)[1,2]. Later, atypical haplotypes were described[3-5].

African-American patients with SCA mainly have the BEN haplotype[6]. In Brazil the main beta S-globin haplotype is CAR followed by BEN. In agreement with the historical origin of the afro-descendant population, the CAR haplotype is more common in the states of São Paulo[4,7-11], Rio de Janeiro[12-14], Minas Gerais[15], Pernambuco[16], Rio Grande do Norte[17], Ceará[18,19] and Pará[20,21]. The BEN haplotype is more frequent than CAR in Bahia in general[22,23], however, in Salvador (the capital city of Bahia), this frequency is different with similar frequencies for the CAR and BEN haplotypes[9,24,25] probably as a consequence of the domestic slave trade and subsequent internal migrations from other regions of Brazil.

Fetal hemoglobin (Hb F) is related to the haplotype and correlates with the clinical course of SCA. SEN and ARAB haplotypes produce the highest levels of Hb F and are associated with fewer clinical manifestations of SCA and with a lower occurrence of organ damage. BEN and CAM haplotypes exhibit intermediate levels of Hb F and clinical severity. However, the CAR haplotype is associated with lowest levels of Hb F and consequently with the worst clinical severity including a three-fold risk to develop stroke, renal failure, chronic lung disease with cor pulmonale, leg ulcers, and young adult death. The risk of acute chest syndrome (ACS), pain crises and infections is similar in individuals with the BEN or CAR haplotypes. In the USA, it has been reported that co-inheritance with the alpha-thalassemia gene has little influence in acute events during childhood[26-28].

Brazilian studies also found a correlation between SCA clinical manifestations, Hb F and the beta S-globin haplotype[8,9,13,19,25,29,30], including more vaso-occlusive crises[9,29], more infections[9] and slower growth[29] in the CAR haplotype, high levels of Hb F[13,19,25] and nitrites in the BEN haplotype[19], and increased risk of cerebrovascular disease (CVD) in children with the Bantu/atypical haplotype compared to other beta S-globin haplotypes[30]. Patients with the CAR/BEN haplotype had less painful crises compared to the other haplotypes[22]. Trials have shown no correlations between co-inheritance with alpha-thalassemia and clinical symptoms[8,9,22], however it may be associated with less infections[13] or with repeated acute pain crises[29].

Moreover, recent Brazilian publications have described that there are no correlations between beta S-globin haplotypes and the clinical course of SCA. Risk factors for conjunctival vessel alterations were lower hemoglobin and hematocrit levels and the SS phenotype and for retinal vessel alterations, risk was related to age over 17 years, however no correlation was found with Hb F, the beta-globin gene haplotype or alpha-thalassemia[10]. In a retrospective study in pediatrics, the mean Hb F level measured in over 2-year olds was lower in individuals with the CAR haplotype, but not statistically lower when compared to the BEN haplotype. One possible reason for this finding is that the Hb F may not have reached stable levels in these young children. Blood transfusions, ACT, acute spleen sequestration (ASS) and CVD were not significantly different between the different haplotypes[15]. Painful crises, ASS, hemolytic crises, hand-foot syndromes, ACS and infections were not related to the beta S-globin haplotype in another retrospective study of under 6-year-old children. Nevertheless, this lack of correlation could be due to the sample size, the number of heterozygous individuals, the miscegenation of the Brazilian population, and the multiplicity of the clinical expression in SCA[13]. It was not reported in these papers whether the patients (or how many patients) were receiving hydroxyurea (HU). If HU was being administered to SCA patients with the worst clinical symptoms, presumably those with the CAR haplotype, would this not explain the lack of clinical correlations between different beta S-globin haplotypes? A better response to HU was described in CAR haplotype patients in respect to increases in Hb F[31], but other trials did not support these results[32,33].

Chronic anemia and microcirculation disease of the renal medullary capillaries as a consequence of the physiopathology of SCA make renal damage a common complication. The incidence of renal disease is increasing as patient survival is improving. Children with

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SCA often develop hyposthenuria and increased glomerular filtration rates (GFR) at an early age, possibly contributing to the glomerular injury and renal insufficiency commonly seen later in life. Anemia, glomerular hyperfiltration, hypertension, microalbuminuria, proteinuria, nephrotic syndrome and microscopic hematuria are strong predictors of subsequent renal failure. Regarding haplotypes, the risk of renal failure in SCA is increased in patients who have the CAR beta S-globin haplotype[34]. The co-inheritance of alpha-thalassemia was associated with a lower prevalence of macroalbuminuria in SCA patients suggesting renal protection[35,36]. No association was found between albuminuria and beta S-globin haplotypes (CAR versus non-CAR haplotypes)[35,36]. An evaluation of the association between kidney dysfunction and haplotypes in 84 Brazilian sickle cell disease patients is published in this issue of the Revista Brasileira de Hematologia e Hemoterapia (RBHH) [37]. GFR, urinary concentrating capacity and urinary acidification were determined and there was no significant difference when comparing patients with the CAR/CAR and BEN/BEN haplotypes. However, there was a higher frequency of GFR between 60 and 120 mL/min among CAR patients. Despite initial data linking the CAR haplotype with renal failure, this data has not been confirmed over the years.

Survival in 102 over 60-year-old SCA patients from Jamaica was associated with female gender and higher Hb F but not with alpha-thalassemia or the beta-globin haplotype. The lack of effect of beta S-globin haplotype on survival may be explained by the high prevalence of the BEN haplotype in Jamaica. None received HU. Age-related changes were improvement of bone pain, increased serum creatinine and decreased hemoglobin levels. Renal failure affected 24% of SCA patients and was a major problem in this population[38]. In the USA, mortality in patients between 16 and 68 years while on HU therapy was shown to be mainly due to ACS (35%), but also due to multiple organ failure, stroke, end-stage renal disease, sepsis, cardiac arrhythmia, and pulmonary embolism. In this trial, homozygous BEN or heterozygous CAM haplotypes, possibly with more severe disease and organ damage, were significantly associated to death[39].

Although Hb F and beta S-globin haplotypes are widely studied as a genetic modulator for SCA, the diversity of the disease is not entirely explained. So, genetic polymorphisms that might explain the clinical diversity in SCA related to inflammation, vaso-regulation, blood coagulation, hemostasis, growth factors, cytokines and cytokine receptors, and transcriptional factors have been studied. Examples of polymorphism studies include the genes of the TGF-beta/BMP pathway suggesting that haplotypes in BMPR1B [a bone morphogenetic protein (BMP) receptor gene] are associated with higher GFRs in SCA[40], and the association of 844ins68, a genetic polymorphism of the cystathionine beta-synthase enzyme gene (CBS) and C677T MTHFR, a genetic polymorphism of the methylenetetrahydrofolate reductase enzyme gene (MTHFR) is a risk factor for vaso-occlusive episodes in SCD patients[41].

More studies on genetic polymorphisms are necessary to better understand SCA and if possible, to find genetic modulators of disease severity that could guide prognosis to determine preventive measures and the best treatment for acute and chronic organ damage.

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