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Scientific comment

Comment on "Influence of βS-globin haplotypes and hydroxyurea on tumor necrosis factor-alpha levels in sickle cell anemia"☆

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Sickle cell anemia (SCA) is a monogenic disorder characterized by homozygous inheritance of an abnormal hemoglobin molecule, hemoglobin S (Hb S), due to the substitution of glutamic acid for valine at position 6 of the beta globin chain.[1,2] SCA is characterized by a variable clinical course and differences in response to medication, reflecting its complex pathophysiology and suggesting that it can be affected by modulator factors such as the haplotypes of the beta globin chain or fetal hemoglobin (Hb F) levels.[3,4]

The pathogenesis of SCA derives primarily from the polymerization of deoxygenated Hb S in red blood cells, leading to their deformability and rigidity. This sickling process, in turn, results in two primary pathological events: vaso-occlusion mediated by ischemia-reperfusion injury and hemolytic anemia. Both of these are thought to increase vascular inflammation, due to the numerous pro-inflammatory proteins in circulation playing a fundamental role in the activation of endothelial cells and leucocytes.[5,6]

In addition to an activated endothelium and leukocytosis, the inflammatory phenotype of SCA is characterized by high levels of acute-phase proteins and cytokines. SCA patients at steady state have chronically elevated levels of tumor necrosis factor alpha (TNF-α), interleukins (ILs) such as IL-1b, IL-6 and IL-8, C-reactive protein and soluble adhesion molecules. Several cell types contribute to the production of inflammatory mediators, including activated endothelial cells, leukocytes and platelets.[6-8]

TNF-α is a member of the TNF superfamily, which is composed of 19 ligands and 29 receptors and plays highly diversified roles in the body. All members of the TNF superfamily, without exception, have an inflammatory role, in part, through activation of the transcription factor, nuclear factor kappa B (NF-kB). TNF-α is the most important pro-inflammatory cytokine and is involved in cell growth and differentiation, cellular function, activation of endothelial cells and leukocytes, macrophage stimulation, affinity of leukocyte surface molecules and the survival of many cells.[9] Such characteristics make TNF-α an important risk factor in SCA.[10]

Pharmacological induction of Hb F is a potential therapeutic strategy for SCA. This is the case of hydroxyurea (HU), it increases the total intracellular hemoglobin, γ-globin mRNA and Hb F levels. There is also evidence that HU can act as a nitric oxide donor and increase cyclic guanosine monophosphate (cGMP) levels, which upregulate the translation of the γ globin. Therefore, HU increases erythrocyte volume and hemoglobin content and decreases the reticulocyte and white blood cell counts. The secondary benefits of HU are reduction of dehydration, exposure to phosphatidylserine and expression of adhesion molecules. All these factors reduce Hb S polymerization and make HU an important therapeutic agent for the prevention of vaso-occlusion and vasculopathies.[11,12]

In this edition of the *Revista Brasileira de Hematologia e Hemoterapia*, Laurentino et al. clearly show higher TNF-α levels in SCA patients compared to individuals without

☆See paper by Laurentino MR et al. on pages 121-5.

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hemoglobinopathies. Furthermore, the authors noted that the Bantu haplotype substantially influences the levels of this cytokine, elevating its plasma concentration. However, no difference was found regarding HU treatment.[13]

As previously reported by the same research group[14] and by other studies,[15-17] TNF-α levels are increased in SCA. This important finding supports the association between pro-inflammatory cytokine release and the clinical severity of SCA as these cytokines induce adhesion molecule activity in the endothelium.[18] Moreover, Laurentino et al. found higher TNF-α levels in individuals with the Bantu haplotype than those with the Benin haplotype.[13] These data not only reflect the severity of the disease but also the effect of haplotypes in modulating the SCA phenotype. The Bantu haplotype has been associated with higher disease severity and high incidence of organ, damage while the Benin haplotype is associated with an intermediate clinical course.[19]

Curiously, Laurentino et al. found lower TNF-a levels in Bantu/Benin individuals and not with the Benin/Benin haplotype.[13] This finding leads us to an important question: could this be the consequence of bias due to the small sample size or do homozygous haplotypes confer a worse clinical picture than double heterozygous inheritance?

Finally, Laurentino et al. did not observe any differences between the groups that received HU or not.[13] However, some studies have demonstrated variations in HU pharmacological response according to the β^S haplotype, with the Bantu haplotype being the most responsive to HU treatment due to a significant increase in Hb F levels and reductions in biochemical markers of oxidative stress.[4,20] Thus, this may mean that the difference between the HU treated and untreated groups in this study is masked by the inheritance of β^S haplotypes.

The current study provides information about the inflammatory status in SCA and shows the influence of the Bantu haplotype on the clinical course of the disease. It is clear that SCA phenotypes are modulated by other genetic factors and, therefore, further studies in this area should contribute to a better understanding of the disease and the treatment of patients.

Conflicts of interest

The author declares no conflicts of interest.

REFERENCES

1. Ingram VM. Abnormal human haemoglobins. III. The chemical difference between normal and sickle cell haemoglobins. Biochim Biophys Acta. 1959; 36:402-11.
2. Frenette PS, Atweh GF. Sickle cell disease: old discoveries, new concepts, and future promise. J Clin Invest. 2007;117(4):850-8.
3. Serjeant GR, Higgs DR, Hambleton IR. Elderly survivors with homozygous sickle cell disease. N Engl J Med. 2007;356(6):642-3.
4. Silva DG, Belini-Júnior E, Carrocini GC, Torres LS, Ricci-Júnior O, Lobo CL, et al. Genetic and biochemical markers of hydroxyurea therapeutic response in sickle cell anemia. BMC Med Genet. 2013; 14:108.
5. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet. 2010; 376(9757):2018-31.
6. Sparkenbaugh E, Pawlinski R. Interplay between coagulation and vascular inflammation in sickle cell disease. Br J Haematol. 2013;162(1):3-14.
7. Belcher JD. Activated monocytes in sickle cell disease: potential role in the activation of vascular endothelium and vascular-occlusion. Blood. 2000; 96(7):2451-9.
8. Pathare A, Kindi SA, Alnaqdy AA, Daar S, Knox-Macaulay H, Dennison D. Cytokine profile of sickle cell disease in Oman. Am J Haematol. 2004;77:323–8.
9. Aggarwall BB, Gupta SC, Kim JH. Historical perspectives on tumor necrosis factor and its superfamily: 25 years later, a golden journal. Blood. 2012;119:651-65.
10. Cajado CS, Cerqueira BA, Barbosa CG, Lyra IM, Adorno EV, Gonçalves MS. IL-8 e TNF-alfa: marcadores imunológicos no prognóstico da anemia falciforme. Gaz Med Bahia. 2010; 80:56-61.
11. Rees DC. The rationale for using hydroxycarbamide in the treatment of sickle cell disease. Haematol. 2011;96:488-91.
12. Ware RE, Aygun B. Advances in the use of hydroxyurea. Hematology Am Soc Hematol Educ Program. 2009;62–9.
13. Laurentino MR, Maia-Filho PA, Barbosa MC, Bandeira IC, Rocha LB, Gonçalves RP. Influence of βS-globin haplotypes and hydroxyurea on tumor necrosis factor-alpha levels in sickle cell anemia. Rev Bras Hematol Hemoter. 2014;36:121-5.
14. Bandeira IC, Rocha LB, Barbosa MC, Elias DB, Querioz JA, Freitas MV, et al. Chronic inflammatory state in sickle cell anemia patients is associated with HBB*S haplotype. Cytokine. 2014;65:217-21.
15. Malavé I, Perdomo Y, Escalona E, Rodriguez E, Auchustegui M, Malavé H. et al. Levels of tumor necrosis factor alpha/cachectin (TNF alpha) in sera from patients with sickle cell disease. Acta Haematol. 1993; 90(4):172-6.
16. Cajado C, Cerqueira BAV, Couto FD, Moura Neto JP, Vilas Boas W, Dorea MJ, Lyra IM, Barbosa CG, Reis MG, Goncalves MS. TNF-alpha and IL8:Serum levels and gene polymorphisms (308G>A and 251A>T) are associated with classical biomarkers and medical history in children with sickle cell anemia. Cytokine. 2011;56:312-7.
17. Veiga PC, Schroth RJ, Guedes R, Freire SM, Nogueira-Filho G. Serum cytokine profile among Brazilian children of African descent with periodontal inflammation and sickle cell anemia. Arch Oral Biol. 2013; 58:505-10.
18. Zhao B, Stavchansky AS, Bowden RA, Bowman PD. Effect of interleukin-1beta and tumor necrosis factor-alpha on gene expression in human endotelial cells. Am J Physiol Cell Physiol. 2003;284:C1577-83.
19. Padmos MA, Roberts GT, Sackey K, Kulozik A, Bail S, Morris JS, et al. Two different forms of homozygous sickle cell disease occur in Saudi Arabia. Br J Haematol. 1991;79:93-8.
20. Vicari P, De Barretto MA, Figueiredo MS. Effects of hydroxyurea in a population of Brazilian patients with sickle cell anemia. Am J Hematol. 2005;78:243-4.