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Thesis Abstract

Phenotypic expression of homozygous hemoglobin S in relation to β-globin haplotypes, glutathione *S*-transferase polymorphisms and detoxification enzymes

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Sickle cell anemia (SCA) shows a pathophysiology that involves multiple changes in sickle cell erythrocytes, vaso-occlusive episodes, hemolysis, activation of inflammatory mediators, endothelial cell dysfunction, and oxidative stress. These events complicate treatment and culminate in the development of manifestations such as anemia, pain crises and multiorgan dysfunction. The aim of this study was to evaluate, in SCA patients, oxidative stress and antioxidant capacity markers, correlating them to treatment with hydroxyurea (HU), β-globin haplotypes and glutathione *S*-transferase polymorphisms (*GSTT1*, *GSTM1* and *GSTP1*), in comparison to a control group (CG). The study groups were composed of 48 individuals without hemoglobinopathies (CG), SCA patients treated with HU [AF (+HU), N = 13] and untreated SCA patients [AF (-HU), N = 15], after informed consent. The groups were analyzed using cytological, electrophoretic, chromatographic and molecular methods and information from medical records. The *GSTM1* and *GSTT1* polymorphisms were determined by multiplex PCR, while the *GSTP1* polymorphism by PCR-RFLP. Biochemical parameters were measured using spectrophotometric methods [TBARS, TEAC and catalase (CAT) and GST activities] and a chromatographic method [glutathione (GSH)]. The fetal Hb (Hb F) levels observed in the SCA (+HU) group (10.9%) confirmed the already well-described pharmacological effect of HU, but the SCA (-HU) group also had high Hb F levels (6.1%), which may have been influenced by genetic factors not targeted in this study. We found a higher frequency of the Bantu haplotype (48.2%), followed by the Benin (32.1%) and also Cameroon haplotypes, rare in our population, and 19.7% of atypical haplotypes. The presence of Bantu haplotype was related to higher lipid peroxidation levels in patients, but also, it conferred a differential

response to HU treatment, raising Hb F levels in 52.6% (P = 0.03). The protective effect of Hb F was confirmed, because the increase in their levels resulted in a 41.3% decrease in lipid peroxidation levels (r = -0.74, P = 0.0156). The genotypic frequency of the GST polymorphisms observed was similar to that of other studies in the Brazilian population, and its association with biochemical markers revealed a significant difference only for the *GSTP1* polymorphism, where patients with genotype *V/V* showed higher GSH and TEAC levels (P = 0.04 and P = 0.03, respectively) compared to patients with genotype *I/I*. The TBARS levels were about five to eight times higher in the SCA (+HU) and SCA (-HU) groups, respectively, compared to controls, and HU produced a 35.2% decrease in lipid peroxidation levels in the SCA (+HU) group (P < 0.0001). Moreover, the SCA (+HU) group showed higher TEAC levels when compared to CG (P = 0.002). We did not find any significant difference in GST activity between the groups studied (P = 0.76), but CAT activity was about 17 and 30% lower in SCA (+HU) and SCA (-HU) groups, respectively (P < 0.00001). Plasma GSH levels were ~2 times higher in SCA patients than in the control group (P = 0.0005) and showed a positive correlation with TBARS levels, confirming its antioxidant function. HU treatment contributed to higher CAT activity and TEAC levels and lower lipid peroxidation, and its pharmacological effect showed a "haplotype-dependent" response. These findings may contribute to elucidating the potential of HU in ameliorating oxidative stress in SCA subjects.

Key words: Sickle cell anemia; Oxidative stress; Antioxidant capacity; Hydroxyurea

