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EXPRESSION OF PTGER4, CNR1, AND CNR2 IN SICKLE CELL ANEMIA: INFLUENCE OF HYDROXYUREA AND HEMOLYSIS BIOMARKERS

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Introduction: Sickle cell anemia (SCA) is a severe monogenic hemoglobinopathy characterized by chronic hemolysis, recurrent vaso-occlusive crises, and persistent systemic inflammation. These processes are mediated by cellular stress and oxidative damage, which activate inflammatory pathways such as the PTGS2 gene cascade and the production of prostaglandins. Inflammatory responses may also be related to receptors such as the prostaglandin E receptor 4 (PTGER-4) and the cannabinoid receptors. The endocannabinoid system is shown as a relevant modulator of both nociceptive signaling and inflammatory responses, with receptors expressed by the genes CNR1 and CNR2, as well as the prostaglandin E2 receptor PTGER4, playing key roles in these mechanisms. Hydroxyurea (HU) remains the cornerstone of disease-modifying therapy, reducing hemolysis and exerting anti-inflammatory effects through multiple mechanisms, like the increase of fetal hemoglobin levels, which may influence the expression of genes involved in these pathways. **Objectives:** The objective of this study is to understand how HU modulates these molecular targets to specify their therapeutic potential and variability among patients. **Material and methods:** We compared the expression of PTGER4, CNR1 and CNR2 genes of 5 AA patients and 5 SS patients treated with HU. In order to support our data, we analyzed the levels of neutrophils and Indirect Bilirubin (BI) of 196 patients before and after treatment with Hydroxyurea from HEMORIO. **Results:** In the primary cohort, no statistically significant differences were observed in the expression of PTGER4, CNR1 and CNR2 between HU-treated HbSS patients and HbAA controls ($p > 0.05$). In contrast, in the larger cohort, HU use was associated with significantly reduced BI (median: $0,37 \pm 0,08$ without treatment vs. $0,72 \pm 0,07$ mg/dL treated, $p < 0.05$) and neutrophil (median: $4,20 \pm 0,17$ vs. $4,75$

$\pm 0,45$ / μ L, $p < 0.05$) compared to untreated patients, confirming its impact on hemolysis and systemic inflammation.

Discussion and conclusion: Although no significant differences were observed in PTGER4, CNR1 and CNR2 expression between HU-treated HbSS patients and HbAA controls, the biochemical analysis revealed meaningful hematological modulation in the independent cohort. HU-treated patients presented significantly lower absolute neutrophil counts and reduced indirect bilirubin levels compared to untreated patients. These findings align with the known pharmacological effects of HU leading to decreased hemolysis and attenuation of systemic inflammation. Neutrophils reduction is particularly relevant because neutrophil activation contributes to vaso-occlusive events and endothelial dysfunction in sickle cell anemia, while lower indirect bilirubin indicates reduced extravascular hemolysis and oxidative stress. HU considerably modulates key markers of inflammation and hemolysis, as demonstrated by lower neutrophil counts and reduced indirect bilirubin in treated patients. These effects may attenuate the inflammatory signaling that would otherwise upregulate PTGER4, CNR1 and CNR2 expression, explaining the lack of observed differences between groups. Future studies should evaluate these gene targets in patients untreated with HU, which may be difficult when HU is the best available option for treatment of SCA and integrate additional inflammatory biomarkers to clarify the interplay between hemolysis, immune activation, and gene regulation in sickle cell anemia.

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FENÓTIPOS HEMOLÍTICO E INFLAMATÓRIO EM ADULTOS COM DOENÇA FALCIFORME

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Introdução: As manifestações clínicas da doença falciforme (DF), apesar de estarem diretamente relacionadas à mutação da hemoglobina S (HbS) e consequente hemólise, dependem também de outros fatores incluindo um fenótipo inflamatório característico. **Objetivos:** Identificar fatores genotípicos e laboratoriais de adultos com doença falciforme (DF) e Acidente Vascular Cerebral (AVC) comparados a pacientes sem AVC. **Material e métodos:** Trata-se de um estudo de coorte retrospectivo que analisou 1795 exames laboratoriais de 320 pacientes com DF, idade ≥ 18 anos de ambos os sexos. Dados foram coletados de prontuários médicos, no período de junho de 2014 a junho de 2024. Aprovado pelo Comitê de Ética em Pesquisa. **Resultados:** A coorte de pacientes era de 53,1% do sexo feminino ($n = 170$). A distribuição genotípica revelou: genótipo 74.7% SS ($n = 239$), 17.5% SC ($n = 56$), 5.0% S β^0 ($n = 16$) e 2.8% S β^+ ($n = 9$). A prevalência de AVC foi de 10.3% ($n = 33$).