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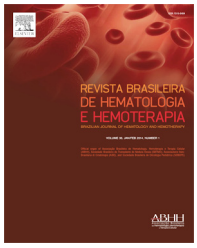

Scientific Comment

Fetal hemoglobin and hemolysis markers in sickle cell anemia☆

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It has been known for many years that high levels of fetal hemoglobin (Hb F) have an important clinical benefit in patients with sickle cell anemia (SCA). This knowledge was initially based on the observation that populations of Indian and Arabian SCA patients with high Hb F levels have a milder clinical form of the disease.[1] Later on, epidemiological studies demonstrated that patients with Hb F levels above 20% had consistently lower rates of recurrent clinical events such as vaso-occlusive crises, acute chest syndrome and hospitalizations, and patients with Hb F levels above 10% had reduced occurrence of aseptic necrosis and strokes.[2] A significant increase of 1.0 g/dL in hemoglobin levels in the high Hb F group was also noted, indicating a reduction in the rate of hemolysis.[2] A study of life expectancy in sickle cell disease (SCD) patients demonstrated an improved survival of patients with Hb F levels above 8.6% and an increased risk of early death in patients with low Hb F levels.[3]

The presence of Hb F in red blood cells (RBCs) alters contact between RBCs with hemoglobin S (Hb S) and inhibits the formation of polymers in deoxygenated RBCs. Hb F is produced by a fraction of RBCs denominated F-cells, which contain variable concentrations of Hb F.[4] Studies suggest that when F-cells contain around 10 pg of Hb F there is complete inhibition of polymer formation even when oxygen saturation is from 40% to 70%.[5] F-cells are RBCs that have a much longer survival than non-F-cells, with their survival being related to their Hb F content: the higher the Hb F content the longer the life span of F-cells.[6] The survival of non-F-cells is inversely correlated to the percentage of F-cells, possibly because patients with higher Hb F levels have better spleen function and thus have more efficient removal of non-F-cells from the circulation.

In the current issue of the Revista Brasileira de Hematologia e Hemoterapia, there is an article entitled "Pattern of hemolysis parameters and association with fetal hemoglobin in sickle cell anemia patients in steady state" by Moreira et al.[7] In this article the authors demonstrate the beneficial effects of elevated Hb F levels on hemolysis markers in SCA patients. When patients achieved Hb F levels above 10% they presented with significant reductions in reticulocyte counts and lactate dehydrogenase (LDH) levels. This increase in Hb F levels was achieved by treatment using hydroxyurea at doses that ranged from 0.5 to 1.5 g/day. Reduction of the rate of hemolysis in SCA patients is of vital importance in the prognosis of these patients. An observational multicenter study of 415 SCA patients who were followed-up for a median of 2.4 years reported that patients with an hemolytic component (assessed by measuring LDH, aspartate aminotransferase, total bilirubin and reticulocyte count) in the upper tertile presented over three times greater risk of death (Hazard ratio of 3.44).[8] Furthermore, the hemolytic component was positively associated with higher systemic pulse pressure, serum N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration, tricuspid regurgitation velocity and several other cardiac side effects.[8] There was also an inverse correlation between the rate of hemolysis and oxygen saturation as measured by pulse oximetry, which persisted after adjustment

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☆ See paper by Moreira et al. on pages 167-81.
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for hemoglobin concentration; patients on hydroxyurea therapy presented a significantly lower hemolytic component.[8]

Moreira et al.[7] also demonstrated that hydroxyurea therapy and subsequent elevation of Hb F levels was associated to reductions in arginase I levels. The lowest arginase I levels were seen in patients taking hydroxyurea at doses greater than 20 mg/kg/day. Arginase I is an enzyme that metabolizes L-arginine, the precursor of nitric oxide (NO). Therefore, the increased levels of arginase I seen in SCA patients contribute to a reduction in NO concentration. The findings of this study are in agreement with a previous study in which SCD patients on hydroxyurea therapy presented significantly lower arginase activity and higher NO synthase activity; a direct correlation between Hb F levels and the decrease in arginase activity was also observed.[9] These important findings indicate that hydroxyurea may have a beneficial effect in reducing arginase I levels and in the production of NO.

Conflicts of interest

The authors declare no conflicts of interest.

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