Oxidative status in sickle cell anemia

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HbS polymerization is a primary pathophysiological event in sickle cell anemia (SCA). Hydroxyurea (HU) is one important therapy that offers broad benefits to a select group of patients with severe symptoms. HU induces higher levels of HbF thereby inhibiting the polymerization of HbS, acts on red blood cell hydration, vascular wall adherence and suppresses granulocyte and reticulocyte counts.

It has been suggested that oxidative stress plays a key role in many pathophysiological disorders and thus has gained increasing attention. Imbalance between production and elimination of reactive oxygen species (ROS) can damage cell structures, including lipids, membranes, proteins and nucleic acids resulting in cell death or altered cell function. However, the role of free radicals is not fully known and most evidence is indirect; consensual reference ranges and interpretation are lacking.

Although results are sometimes contradictory, patients with SCA are shown to have high oxidative stress. Sickle cells spontaneously generate approximately two times more ROS compared to normal red blood cells; this is associated with endothelial dysfunction, inflammation and multiple organ damage and is related to the severity of clinical features.[1,2] In addition, multiple transfusions cause accumulation of pathological non-transferrin-bound iron that catalyzes the generation of ROS.

Monitoring oxidative stress involves different parameters associated to pro-oxidant and antioxidant biomarkers. Methods differ according to analytical practicability,

reproducibility, costs and clinical meaning, however recognized shortcomings of different methods must be taken into account.

Amounts of antioxidants are interesting parameters in themselves. The measurements of reduced glutathione (GSH) and its oxidized form glutathione disulfide (GSSG) have been considered useful indicators of the status of oxidative stress. A decrease in the GSH concentration and its antioxidant capacity has been associated with the pathogenesis of SCA. In the paper by Teixeira Neto PF et al., GSH levels were shown to be significantly higher in HU treated patients when compared to untreated patients suggesting a therapy-related antioxidant effect.[3]

HU was shown to significantly reduce lipid peroxidation levels in treated patients.[4] Some recent studies have shown that the HbF protective effect is primarily mediated by decreased intravascular sickling, resulting in reduced oxidative stress and also in increased nitric oxide bioavailability.[5] HU treatment may therefore be correlated to lower oxidative status and better antioxidative defense.

However, the use of an isolated biomarker to evaluate oxidative stress and measurement of individual antioxidants are not likely to be useful indexes of oxidative status. The oxidant-antioxidant balance involves biochemical reactions that require the evaluation of many endpoints.

The true relationship between oxidative status with HU treatment remains unclear and warrants further studies.

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