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X-LINKED ADRENOLEUKODYSTROPHY: ROLE OF PROINFLAMMATORY CYTOKINES, ANTIOXIDANTS AND HEMATOPOIETIC CELL TRANSPLANTATION ON SOME PARAMETERS OF OXIDATIVE STRESS.

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Introduction: X-linked adrenoleukodystrophy (X-ALD) is an inherited disorder of peroxisomal metabolism, characterized by deficient β-oxidation of saturated very long chain fatty acids (VLCFA). Patients affected present a progressive brain and peripheral demyelination and adrenal cortex insufficiency, associated with accumulation of the VLCFA in tissues and biological fluids. X-ALD is characterized by heterogeneous clinical phenotypes, including adrenomyeloneuropathy (AMN) and cerebral childhood (CCER). Treatment options for X-ALD have been used in an attempt to achieve the main goals: stabilizing the adrenal insufficiency, decrease the concentration of VLCFA in plasma and demyelination in the brain. The hematopoietic stem cell transplantation is currently the most effective method for the therapy of CCER when detected in early stages of the disease and is the only method that improves cerebral demyelination. It has been demonstrated that several parameters of oxidative stress are altered in plasma, erythrocytes and fibroblasts of X-ALD patients, suggesting that it may explain at least part of the neurological impairment of these patients. Neurological damage in X-ALD seems to be mediated by activation of astrocytes and induction of pro-inflammatory cytokines such as tumor necrosis factor -TNFα- and interleukins - IL1β and IL6. Evidences of the function of antioxidants, such as N-acetylcysteine (NAC), can open an additional therapeutic approach to the currently employed.
Objective: This research aim to evaluate the role of pro-inflammatory cytokines and of hematopoietic stem cell transplantation on various parameters of oxidative stress in patients with X-linked adrenoleukodystrophy as well as to investigate the *in vitro* effect of NAC on DNA damage in leukocytes from individuals with X-ALD.
Materials and Methods: The subjects will be recruited in Medical Genetic Service of Clinical Hospital from Porto Alegre. Heparinized blood will be collected at the time diagnosis, before and after hematopoietic cell transplantation for X-ALD patients and controls matched for age and sex. It will be determined the malondialdehyde (MDA), total antioxidant reactivity (TAR), total antioxidant status (TAS), carbonyl group and sulfhydryl assay and quantified the cytokines (TNF-α, IL1β and IL6) in plasma. Quantification of cytokines will be performed by an immunoenzymatic method using a kit multiplex "Human Cytokine/Chemokine Multiplex Immunoassay", Millipore. The enzyme activities (superoxide dismutase, catalase and glutathione peroxidase) and glutathione (GSH) concentration will be measured in erythrocytes. Comet assay will be performed in leukocytes from whole blood treated with NAC. The data will be analyzed by T'Student test or ANOVA or by Mann Whitney and Wilcoxon. The correlation between parameters of oxidative stress, plasma levels of VLCFA and the concentrations of pro-inflammatory cytokines will be done by Pearson test. The correlation between oxidative damage to DNA and the other parameters mentioned above will be performed by Spearman's test. The research will be submitted to Ethical Comitte from Porto Alegre Clinical Hospital.
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