P-093 - SUBSTRATE REDUCTION THERAPY IN FIBROBLASTS OF MUCOLIPIDOSIS II AND III PATIENTS

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BACKGROUND: Mucolipidosis II and III (ML II and III) are autosomal recessive diseases caused by mutations in GNPTAB and GNPTG genes, causing defects in GlcNAc-1-phosphotransferase. This enzyme adds manose-6-phosphate residues in lysosomal hydrolases, which allows to enzymes entry in lysosomes. These diseases have no treatment, and we hypothesize that the use of substrate reduction therapy and immunomodulation may be a therapeutic approach.

METHODS: Fibroblast of 2 MLII/III alpha β and 2 MLIII gamma patients and 1 control were treated with 10µM Miglustat, 20µM Genistein and 20µM Thalidomide. Total proteins were extracted. ELISA and immunofluorescence confocal microscopy were performed to evaluate the presence and impact of heparan sulfate substrate. Enzymatic assay was carried out to evaluate the indirect impact of substrate reduction. RESULTS: The substrate reduction results were observed in all patients for all treatments, with a mean reduction of 25.05%, 33.07% and 35.57% in heparan sulfate for Genistein, Miglustat and Thalidomide respectively. The same was observed in immunofluorescence assay. In 60-70% of treatments, there was an increase in enzymatic activity, with averages of 102% (1-414%) in β-glucuronidase, 60% (1,58-246,87%) in α-Mannosidase and 27,89% (17,21-38,18%) in β-galactosidase. Miglustat treatment was more efficient with increases in 80% of the cases ranging from 2 to 414% of activity in the different enzymes.

DISCUSSION: The data present encouraging results, since increases above 10% of the residual activity of the enzyme may bring benefits in the phenotype of patients with inborn errors of metabolism. However the low sample size should be considered. Now, inflammatory response tests will be performed to evaluate and understand the results of treatment with Thalidomide. Support: CNPq, FIPE-HCPA, CAPES.