SERA OF CELIAC PATIENTS WITH NEUROLOGICAL DISORDERS EVOKE A MITOCHONDRIAL-DEPENDENT APOPTOSIS IN HUMAN SH-Sy5Y NEUROBLASTOMA CELLS

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Background and Aims: Celiac disease (CD) may be associated with neurological manifestations in about 10% of cases. The nature of this association is unclear and thus the mechanisms underlying neurological impairment in CD remain unknown. In this study, we tested whether neuronal antibody positive sera from CD patients evoke neurodegeneration via apoptosis *in vitro*. **Methods**: Neuronal antibodies to central/enteric nervous system from CD patients with neurological disorders were detected by immunofluorescence. SH-Sy5Y cells were exposed to neuronal antibody positive sera and were processed for terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling (TUNEL) to detect apoptosis. Activated caspase-3, apaf-1, Bax and cytochrome *c* were identified by immunofluorescence. Cleaved caspase-8 and caspase-9 were evaluated by western blot. Mitochondrial respiratory chain complexes were analyzed in the mitochondrial fraction. **Results**: After 24 hours exposure to neuronal antibody positive sera, the percentage of TUNEL-positive nuclei of SH-Sy5Y cells (42.7%±3.8%) was significantly greater than that evoked by neuronal antibody negative sera (21.6%±2.2%; $p<0.001$), control sera or fetal calf serum (6.8%±2.0% and 3.3%±0.5% respectively; $p<0.001$). Apaf-1 and caspase-3 immunolabeled a greater proportion of cells exposed to positive sera than controls. Western blot demonstrated caspase-9, but not caspase-8, cleavage in positive sera. Mitochondrial respiratory chain complexes, except from citrate synthase, were significantly lower in cells treated with positive sera compared to controls. Cytochrome *c* and Bax showed reciprocal translocation (from mitochondria to cytoplasm and viceversa) after treatment with positive sera. **Conclusions**: The present study shows that neuronal antibodies in sera of CD patients with neurological disorders have the ability to evoke apoptosis in a human neuronal cell line, which may contribute to neurological impairment. Apaf-1 activation along with Bax and cytochrome *c* translocation suggest a mitochondrial-dependent apoptotic pathway. A better understanding of these complex mechanisms may help to elucidate the pathophysiology of neuronal dysfunction observed in neurological CD patients.