

Identification of specific electron transport chain abnormalities in amyotrophic lateral sclerosis (ALS)

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Objective: To determine if flavine adenine dinucleotide (FAD) synthetase and related enzymes are implicated in the pathogenesis of amyotrophic lateral sclerosis (ALS).

Background: Autopsy studies in an ALS patient with an IgA monoclonal antibody (MAb) showed IgA presence in the surviving motor neurons and in addition, the antibody inhibited neuronal proliferation in culture. To further define this phenomenon, we identified the neuronal target antigen and determined the relevance of our findings to ALS in general.

Design/Methods: A neuroblastoma cDNA library was generated and screened with the IgA MAb. Reactive clones were identified as FAD synthetase. Quantitative RT-PCRs were performed on blood samples from 26 ALS and 30 control blood samples to determine mRNA expression levels of FAD synthetase and other electron transport chain enzymes or proteins, specifically riboflavin kinase (RFK), cytochrome C1 (CYC1), and succinate dehydrogenase complex subunit B (SDHB). All expression levels were measured against a control enzyme (GAPDH). As control, expression levels for a non-respiratory chain protein (beta-actin) were also measured. Statistical analysis was done using the non-parametric Mann-Whitney test.

Results: Index patient's IgA MAb reactivity to FAD synthetase was confirmed by ELISA and western blot with reactivity at serum dilutions over 1:100,000. Quantitative RT-PCR studies showed decreased mRNA expression of all measured electron transport chain enzymes or proteins. FAD synthetase expression levels were decreased in ALS samples compared to expression levels in controls ($p=0.0151$). Expression levels for RFK, CYC1, and SDHB were also significantly decreased in the ALS group ($p=0.0025$, $p=0.0002$, and $p<0.0001$ respectively). Expression levels for the non-respiratory protein beta-actin did not show significant difference between ALS and control groups ($p=0.2118$).

Conclusions/Relevance: Our data shows that a reduction in FAD synthetase and other related electron transport proteins, namely RFK, CYC1, and SDHB, is seen in patients with ALS. It is possible that this may have an effect on oxygen dependent metabolic pathways. Highly vulnerable cells such as the human motor neuron may be particularly susceptible to injury if there is sub-optimal oxidative metabolism. Further work is needed to confirm these findings and to determine the importance of mitochondrial dysfunction in ALS.