DOI 10.36074/grail-of-science.25.11.2022.53

EXPRESSION OF THE WATER CHANNEL PROTEIN AQUAPORIN-4 IN THE BRAIN DURING HUMAN LIVER CIRRHOSIS

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Hepatic encephalopathy (HE) is a frequent complication of liver cirrhosis, manifesting as a neuropsychiatric syndrome ranging from cognitive deficits to coma. HE pathophysiology is linked to elevated brain ammonia and neuroinflammation [1]. Astrocytes are central brain cells responsible for ammonia detoxification and during acute HE are characterized by severe swelling [1]. Aquaporin-4 (AQP4) is a central protein of astrocytes, predominant water channel in the brain, which undergo alteration in response to hyperammonemia [2]. Studies have evidenced that AQP4 which is enriched in astrocytic perivascular end-feet and responsible for the brain water homeostasis, can be either upregulated or reduced in acute and chronic liver diseases accompanied by hyperammonemia [2]. Despite the controversial findings, it was supposed that AQP4 alteration may play a principal role in cytotoxic and/or vasogenic edema formation occurring during HE [3]. This statement needs further arguments to uncover the mechanisms that control edematous changes during liver cirrhosis in humans. Thus, the present study aimed to study of AQP4 level in 6 brain regions of cirrhotic patients in the course of liver cirrhosis. For this, we examined postmortem material of 90 cirrhotic patients of classes A, B and C according to Child-Pugh classification. Immunohistochemically, using rabbit polyclonal anti-AQP4 (Thermo Scientific, USA), we studied cortex, subcortical white matter, hippocampus, thalamus, striatum and cerebellum. Additionally, data from case histories were analyzed. It was revealed that AQP4+ labeling in all studied regions in control was related to the membranes of perivascular and parenchymal astrocytic processes of individual astrocytes and AQP4 expression appeared to be the highest in the hippocampus and the lowest in the white matter. In cirrhotic groups, AQP4 expression altered in growing manner and correlated with liver cirrhosis aggravation. Increased AQP4 expression was associated with labeling of cell body's plasmalemmas and increased numbers of positive cells in all studied regions, which

caused moderate-to-weak homogenous staining of neuropil. Class A demonstrated increased AQP4 in all studied regions with the highest values in the striatum – 2.62-fold and the least in the cerebellum – 1.66-fold. In class B, AQP4 elevation gained maximal indications of 3.73-fold increase in thalamus, 3.37-fold in the cortex and the least increase in hippocampus – 2.41-fold. The highest increase of AQP4 was observed in the class C. Cortical and thalamic regions showed the most prominent elevation, respectively: 4.25-fold and 4.34-fold. The least AQP4 elevation was related to cerebellum: 2.92-fold. AQP4 expression differed significantly in all pairs of subsequent cirrhotic classes in the white matter, thalamus, striatum and cerebellum. In the cortex and hippocampus, AQP4 levels differed significantly between A vs. B and A vs. C, but not between B vs. C classes.

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