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IMMUNOHISTOCHEMICAL STUDY OF GFAP, GS AND AQP4 LEVELS IN THE POSTMORTEM BRAIN OF CIRRHOTIC PATIENTS

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One of the most dangerous liver cirrhosis-associated disturbances is hepatic encephalopathy (HE), defined as brain dysfunction caused by liver failure. HE manifests as a neuropsychiatric disorder and causes high rates of lethal outcome [1]. Current knowledge on HE is linked to hyperammonemia, neuroinflammation, oxidative/nitrosative stress, abnormal neurotransmission and brain edema of different degree [2]. It is considered that in HE, the most vulnerable cells in the brain appear astrocytes being the only cells to ammonia neutralization [3]. It was evidenced, that astrocytes reactively transformed and acquire Alzheimer Type II phenotype undergoing profound molecular remodeling [4]. Considering high heterogeneity of astrocytic populations in the brain [5], it would be efficient to discover features of the regional reactiveness of local astrocytes to the conditions of severe liver disease in different areas of the brain to find more sensitive among them. As a purpose of the present study we had the evaluation of GFAP, GS and AQP4 levels in different human brain regions in liver cirrhosis of different degree.

Materials and methods. Sectional material of 90 patients during lifetime suffered from liver cirrhosis of classes A, B and C according to Child-Pugh classification, including cases with HE of different grades. We examined postmortem material of the cortex, subcortical white matter, hippocampus, thalamus, striopallidum and cerebellum using H-E staining and immunohistochemical method for determination of GFAP, GS and AQP4 expression levels. Additionally, data from case histories as well as the histopathological study of livers was performed to identify the cirrhotic type, nature and grade. Control group included 30 cases of death from acute cardiac failure with intact liver and no any intoxication states.

Results. It was revealed that GFAP expression progressively decreased from class A to class C of liver cirrhosis in all studied brain regions. The alterations were region-specific with the most profound GFAP decline in the cortex and thalamus of cases of class C (6.74- /6.23-fold). GS expression showed the opposite trend dynamically increasing with aggravation of cirrhosis class. The highest values of GS were found in the cortical and thalamic regions in class C (4.34- /4.26-fold). AQP4 expression levels reflected analogous dynamics and elevated significantly with changing classes of cirrhosis. The most intense growth of AQP4 levels were characteristic for cortical and

thalamic areas in class C (4.25- /4.34-fold compared to control). Correlation analysis revealed that in class B and C of cirrhosis, changes of all three studied proteins were characterized by direct and inverse correlations. Thus, GS/AQP4 expression changes positively correlated with each other in all studied brain regions, however, changes of GFAP/GS and GFAP/AQP4 expression levels reflected inverse correlation.

Conclusions. During liver cirrhosis, local populations of astrocytes in different brain regions undergo profound molecular transformations reflecting their morpho-functional disability. Three critical proteins responsible for maintaining of cytoskeleton, cell shape, osmotic balance and brain water content are deeply altered in response to systemic and secondary intrinsic hepatotoxins and byproducts of abnormal metabolism. Spread violation of the principal physiological processes in homeostatic neuroglia might lead to disruption of the homeostasis in the whole brain and cerebral insufficiency in the conditions of acute-on-chronic liver failure. The most expressed protein alterations are recognized in the cortical and thalamic regions, indicating these areas as most sensitive to the action of detrimental factors of chronic liver insufficiency. The most prominent elevation of the noted proteins is characteristic for the last stage of liver cirrhosis when the action of systemic neurotoxins is the most expressed.

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