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SECTION 21.
MEDICAL SCIENCES AND PUBLIC HEALTH

Shuliatnikova Tetiana Volodymyrivna
MD, PhD., Associate Professor, department of pathological anatomy and forensic medicine
Zaporizhzhia State Medical and Pharmaceutical University, Ukraine

Tumanskyi Valerii Oleksiiovych
MD, DSc, Professor, department of pathological anatomy and forensic medicine, Vice-Rector for Research, Honorary Scientist and Engineering Worker of Ukraine
Zaporizhzhia State Medical and Pharmaceutical University, Ukraine

BRAIN TISSUE AMMONIA AND ALZHEIMER TYPE 2 ASTROCYTOSIS IN HUMAN LIVER CIRRHOSIS

Hepatic encephalopathy (HE) is among key manifestations of decompensated liver cirrhosis (LC) and is typical for 30-45% of patients [1], reducing their survival rate up to 2 years. The neurotoxic effect of ammonia is central in the pathophysiology of HE [2]. In astrocytes, high ammonia concentration with glutamate are metabolized in osmotically active glutamine, accumulation of which causes astrocytes swelling and subsequent generalized brain edema [3]. Despite the high prognostic value of HE in LC, its clinical diagnosis remains insufficient [4], herewith, postmortem determination of hepatogenic brain injury utilizes mainly the fact of the presence of so-called Alzheimer type 2 astrocytes (AA2) which were considered the hallmark of such pathology [5]. It was confirmed by neuroimaging methods earlier, that in patients with chronic and acute liver failure, ammonia brain concentrations increase significantly [6], hence, to our knowledge, there are no postmortem studies on this issue, making our present research very relevant.

The present study was aimed at comparing tissue ammonia level and Alzheimer type 2 astrocytes in the cerebral cortex, white matter, hippocampus, thalamus, striatum and cerebellum of the deceased patients with liver cirrhosis of different degree. The study was performed on the postmortem brain of 90 patients with non-alcoholic LC of classes A (n = 30), B (n = 30) and C (n = 30) according to Child-Pugh score, among which 65.55 % patients had HE of I-IV grades. Control group included postmortem brains of 30 patients died from acute cardiovascular insufficiency. For histochemical (HC) determination of ammonia in the paraffin brain sections, the protocol with Nessler's reagent proposed by Gutierrez-de-Juan et al. (2017) [7] was used. Ammonia level was assessed by the optical density of the HC+ ammonia precipitates using ImageJ software; numbers of Alzheimer's type 2 astrocytes (AA2) was counted.

HC method reveals region-dependent fine-grained expression of ammonia in control and cirrhotic groups. In control, a very low ammonia expression is observed with relatively higher values in cerebellum, thalamus, and striatum, ranked as negative by ammonia-scale. Increased ammonia expression is observed in compensated LC in the cortex, thalamus, striatum and cerebellum; in subcompensated LC - in all six brain regions. In decompensated LC, in cerebellum, thalamus and striatum ammonia expression is maximally increased (by 6.18, 5.72, and 5.50 folds, respectively). Significant correlations are present between patients' postmortem brain ammonia and in vivo blood total bilirubin, AST, ALT, albumin, leukocytic intoxication index. In compensated LC, increase in AA2 numbers is found in thalamus, striatum and cerebellum, which corresponds to weak degree. In subcompensated LC, moderate AA2-astrocytosis is found in cortex, thalamus and cerebellum, and weak AA2-astrocytosis - in striatum. In decompensated LC, pronounced AA2-astrocytosis is determined in the cortex, thalamus, striatum and cerebellum; moderate - in the white matter, and mild - in the hippocampus. There is a strong positive relationship between AA2-astrocytosis and ammonia level in thalamus, striatum, and cerebellum.

In conclusion, in the brain of cirrhotic patients, ammonia level in cerebellum, thalamus, striatum, and cerebral cortex directly correlates with the severity of LC according to Child-Pugh, reaching a maximum in LC of class C, and has significant correlations with in vivo blood levels of total bilirubin, AST, ALT, albumin, leukocytic intoxication index. With LC progression, AA2-astrocytosis becomes more pronounced in thalamus, cerebellum, striatum and cortex, which positively correlates with ammonia levels in these regions.

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