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ENLARGED PERIVASCULAR AND EXTRAPERIVASCULAR (PERICELLULAR AND NEUROPIL) EDEMATOUS SPACES IN THE BRAIN TISSUE DURING HUMAN SEPSIS-ASSOCIATED ENCEPHALOPATHY

Sepsis-associated encephalopathy (SAE) is defined as diffuse cerebral dysfunction during sepsis without direct brain infection, which clinically features by alteration of consciousness up to coma [1, 2]. In sepsis, both LPS and cytokines can induce brain endothelial cells (BECs) activation [3] and expression by them numerous adhesion molecules, secretion of proinflammatory cytokines and NOS, that followed by primarily non-disruptive changes of the BBB [4] with increased permeability and vasogenic brain edema development [5]. In these conditions, perivascular Virchow-Robin spaces surrounding blood vessels up to capillary level in specific vascular brain regions [6] can be enlarged (EPVSs), while perivascular astroglia endfeet are also frequently swollen and their membranes can be detached from the vascular/parenchymal basement membranes and contribute to the EPVSs [4]. Extraperivascular tissue spaces (ExPVTSs) which appear during edematous processes, can be represented by swelled pericellular (perineuronal) astrocytic satellites and their neuropil/perisynaptic processes, as well as by astrocytes with clasmatodendrosis and those which are in the decaying state. It is believed that in SAE, brain edema is mostly related to the loss of autoregulation of blood supplying triggered by systemic hemodynamic failure rather than disruptive BBB [4, 5]. It was reported earlier that SAE brain has been shown to be more sensitive to systemic factors in certain regions, including the cerebral cortex, white matter, and hippocampus [7, 8]. To specify edematous changes in the mentioned brain structures in comparison with other regions we studied postmortem brains of deceased patients with abdominal sepsis and SAE (SAE group, n=35), and control deceased patients (n=30) who died from acute heart failure without toxic-metabolic pathologies. 57.14% of SAE patients were diagnosed with sepsis-associated liver injury (SALI). The mean area of edematous tissue spaces (EPVS and ExPVTSs) (μm^2), as well as the portion of each parameter

(%) from the total edematous tissue area was calculated in the cerebral cortex of four lobes, subcortical white matter, hippocampal dentate gyrus, thalamus, striatum, and cerebellum. The median area of edematous tissue spaces in SAE group appeared significantly ($p<0,05$) larger compared to control: in the cortex – 9.38-fold, white matter – 9.43-fold, hippocampus – 8.84-fold, thalamus – 10.47-fold, striatum – 9.98-fold, cerebellum – 10.02-fold respectively. At the same time, the portion of the EPVS significantly exceeded the portion of the ExPVTSs in SAE brain regions: in the cortex – 65.74% vs 34.26%, white matter – 74.55% vs 25.45%, hippocampus – 81.73% vs 18.27%, thalamus – 54.24% vs 45.76%, striatum – 59.31% vs 40.69%, cerebellum – 57.53% vs 42.47%. These results declare that SAE associates with obvious and predominantly perivascular tissue edema widespread in six brain regions. Prevailing portion of EPVSs above ExPVTSs presumably indicate that vasogenic mechanism is central in pathophysiology of the brain edema in SAE. The less significant difference between EPVSs and ExPVTSs in the thalamus, striatum and cerebellum in SAE might indicate more expressed perineuronal and perisynaptic astrocyte swelling conditioned by predominant accumulation of tissue ammonia in these regions, which was evidenced in the brain of septic patients associated with SALI by our recent study [8]. Also these results are in line with experimental and human data on increased expression of the main water channel of the brain, astrocytic AQP4, in the aforementioned regions of the septic brain [9].

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